Fourth Edition

Pediatric Critical Care

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Preface

On publishing this Fourth Edition of *Pediatric Critical Care,* we are struck by how much the milieu of pediatric critical care medicine and the content of this textbook have changed over the last 2 decades. The first edition of *Pediatric Critical Care* appeared in 1992, only 5 years after the first Pediatric Critical Care Medicine certification examination. In fact, the first table of contents for *Pediatric Critical Care* was constructed to encompass the American Board of Pediatrics' original content specifications for pediatric critical care medicine. Since then, most of the authors and editors of *Pediatric Critical Care* have survived recertification and are now actively engaged in "Maintenance of Certification." However, the value of a comprehensive textbook such as *Pediatric Critical Care* remains constant; it continues to provide a comprehensive overview of pediatric critical care medicine for those working in the field.

That noted, the content of *Pediatric Critical Care* has certainly evolved through these four editions. Cardiopulmonary physiology still represents comfort food for most intensivists. Those concepts remain as fundamental as ever. However, the virtual explosion of molecular biology has fueled the expectation of personalized medicine. When the first edition of *Pediatric Critical Care* appeared, the Human Genome Project was just getting underway. Today, whole genome mapping is common in research, and, in the near future, it will probably become an element of the medical record.

Reanimation was once a comic book fantasy. Today, extracorporeal life support has become an integral component of cardiopulmonary resuscitation in many hospitals. Since the first systemic pulmonary shunt was performed in 1943, the advances in pediatric cardiac surgery and postoperative care have been nothing less than spectacular, including the growth of pediatric cardiac intensive care as a new focused subspecialty. A parallel pattern of subspecialization seems to be appearing in pediatric neurocritical care. Similarly, pediatric critical care medicine has clearly played a role in improved survival of hematology/oncology and hematopoietic progenitor cell transplantation patients.

At the time of the first edition of *Pediatric Critical Care,* family-centered care was merely an interesting and controversial concept. Now parents routinely contribute information during rounds to help inform the daily care plan. Pulmonary artery catheters were once in common use, often placed by cut-down vascular access. Today, a pediatric critical care medicine fellow is more likely to encounter a pulmonary artery catheter in a simulation laboratory, yet is skilled in vascular ultrasonography and echocardiography, techniques that facilitate placement of vascular catheters on the first pass and provide three-dimensional visualization of complex cardiac anatomy. Before the new millennium, pediatric and adult patients with hypoxemic respiratory failure were commonly supported by using tidal volumes of 10 to 15 mL/kg. Chest tube insertion equipment and draining systems were typically ordered to the bedside on initiation of mechanical ventilation because pneumothorax was an anticipated and frequent complication. Similarly, catheter-associated bloodstream infections were a troublesome and not unexpected complication of central venous catheterization. Meanwhile, over the past 20 years, there has been a remarkable decline in deaths from sudden infant death syndrome, and infants of ever-greater prematurity have survived.

Two publications, "To Err is Human: Building a Safer System" and "Crossing the Quality Chasm" would not appear until the twenty-first century and have ushered in a new hospital paradigm of continuous quality improvement.

Although there have been huge advances in knowledge of the molecular pathophysiology of sepsis since the first edition of *Pediatric Critical Care,* basic critical care principles remain paramount: early detection; early, vigorous hemodynamic resuscitation; and early antibiotics—simple concepts that clearly save lives. Success in the field of pediatric critical care medicine has allowed a change in outcome focus of interventional clinical trials from death to long-term morbidity. Particularly over the last decade, pediatric critical care medicine has seen the emergence of clinical research networks that will continue to foster translation of important basic research into practice.

With the publication of the Fourth Edition of *Pediatric Critical Care,* the editors note that new challenges continue to emerge for practitioners, particularly in a field that is now overtly international in scope. Worldwide, roughly 25 children still die of sepsis every minute. Obesity now complicates the neurogenic-inflammatory-endocrine stress response to critical illness. A growing population of children with acquired immunodeficiency increasingly find their way into the pediatric intensive care unit, as do an increasing number of children with chronic complex conditions.

As in the past, although in debt to many, we remain particularity grateful to our families, friends, and colleagues who have been patiently supportive through three revisions of this textbook. We thank our new section editors as well as the hundreds of authors who have contributed to the success of this and former editions of the textbook. Lastly, we thank the members of the multidisciplinary teams who make pediatric critical care medicine work and the patients and families who allow us into their lives at a time when they are most vulnerable. Being a pediatric intensivist remains an amazing, challenging, rewarding, humbling, and privileged occupation.

We hope this Fourth Edition of *Pediatric Critical Care* will help nurture our evolving specialty.

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Chapter 1

History of Pediatric Critical Care

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"In critical care, it strikes one that the issues are three: realism, dignity, and love."

Jacob Javits, 1986 (United States Senator)

PEARLS

- There are many heroes in medicine and in pediatric critical care medicine, but most of the courage awards go to our patients and their parents.
- The evolution of pediatric critical care medicine has been a long process of progress in ventilation and resuscitation, physiology and anatomy, anesthesia, anesthesiology, neonatology, pediatric general and cardiac surgery, and pediatric cardiology.
- The role of nursing is absolutely central to the evolution of critical care units.
- Pediatric critical care physicians have made remarkable achievements in the understanding and treatment of critically ill children.
- Until the 1950s and 1960s, intensive care units were organized by grouping patients with similar diseases. In the 1960s, neonatal intensive care units began to group children according to age and severity of illness, and pediatric intensive care units followed this example.
- The development of sophisticated interhospital transfer services was significant in reducing mortality and morbidity of critically ill children, and "retrieval medicine" holds great promise for future improvements in care.
- We have seen great progress in the national and international organization of pediatric critical care medicine as well as in education and research in the field.
- Better and increased use of technology has advanced the care of critically ill children but has also created an environment with increasing errors, complications, and sequelae and a greater need for humane, caring environments for the patients and their families.

In his book *Retrospectroscope: Insights into Medical Discovery,*[1] Dr. Julius H. Comroe Jr, wrote about the courage to fail. He concluded there is no single definition of courage but that it comes in different sizes, each with its own definition. There are four sizes.

Courage, Size 1: "This, the largest size…..The person voluntarily involves himself in an action (or sometimes inaction) that places *himself* in grave peril such as loss of life, liberty, or pursuit of happiness. Courage, Size 1…also bars as a motive any possible gain, material or otherwise, to the individual should he fail or succeed, and postulates that if he succeeds, he wants the gain to be for someone else."

Examples of Courage, Size 1 awards go to James Carroll, William Dean, and Jesse Lazear (a former house officer of W. Osler),[2] who all volunteered to be bitten by yellow fever-infected mosquitoes to prove the mosquitoes were the human-to-human vector of the disease. They proved it and Lazear died. Also Werner Forssmann, who in 1929 introduced a catheter into his own right atrium in order to improve diagnosis for treatment of certain disorders, not knowing whether the tip would cause ventricular fibrillation.[2,3] He received little acclaim for this breakthrough until 1956, when he won the Nobel Prize.

Courage, Size 2: "Size 2…… differs from Size 1 in that the investigator… is not the one who takes the risk, in initial experiments the subject is usually a close member of his family, even one of his children…An example is Lady Montague who having survived an attack of smallpox in the early 1700s, long before Jenner (cowpox) had her children inoculated with pus from patients suffering from virulent smallpox. Another is Edward Jenner who vaccinated his first son Edward with cowpox and then injected him with pus from smallpox patients on five or six occasions to prove he was immune. He then vaccinated his second son Robert.

Courage, Size 3: "This is similar to size 1, in that the individual puts his own life at risk instead of that of another…, the risk is a grim one, and considerable benefits to mankind would surely accrue if his mission should be successful. It ranks below Sizes 1 and 2 because his act is motivated by assured fame and fortune if he succeeds. There are no examples of this in medicine, but Charles Lindbergh's 1927 transatlantic flight is an example in aviation.

Courage, Size 4: "Size 4 medals go to patients who, informed by specialists they have advanced disease and statistically have only weeks, months, or years to live, elect to undergo a previously untested operation or other form of therapy…It might benefit them or lead to earlier death." Examples are the first man (1925) to have bilateral sympathectomy for very high arterial blood pressure; Dr. James Gilmore (1933), the first patient to have one whole lung removed surgically at a single operation; the family of the first patient to receive insulin; the first patient to receive penicillin; and the family of the first "blue baby" operated on by Blalock.

†Deceased.

Some physicians may get Courage, Size 4 awards when they face intense professional criticism and loss of professional esteem for their efforts, such as Dr. Ludwig Rehn, a German surgeon, who in 1896 repaired a 1.5 cm stab wound of the right ventricle of a young man, saving his life. He did this despite a pronouncement in 1883 by the dean of European surgery, Billroth, who warned others not to try. Some patients (or parents) get Courage, Size 4, awards for the willingness to try a procedure or treatment despite knowing this has met with repeated failure. For example, in 1948 Claire Ward, a 24-year-old woman, was the fifth patient to be operated on by Dr. Charles Bailey in Philadelphia for mitral stenosis. This operation had previously been reviewed and proclaimed unsuccessful, and, when Bailey revived it, his first four patients died. Mrs. Ward traveled to Chicago by train 10 days after the operation, went on to live for 23 more years, and gave birth to two children.

Some physicians may have nothing to lose but may get a Perseverance, Size 1 award for continued effort. For example, there are Zoll's attempts at converting ventricular fibrillation by the closed-chest technique; the first three patients died before his first success. Others include Smythe and Bull, who pioneered neonatal ventilation (see below).

Although we in pediatric critical care have plenty of physician "heroes" we admire and appreciate, none get Courage Size 1, 2, or 3 awards. Rarely, we encounter those worthy of Size 4 awards for having risked their professional standing. By far and away, more of our Courage, Size 4 awards go to patients and parents who have had the courage to fail when presented with bleak prognoses and offered only untested or previously unsuccessful procedures or therapies.

Definitions

An important early principle of pediatric critical care medicine (PCCM) is centralization of resources and expertise. Currently, we have highly trained individuals and sophisticated technology in specialized physical spaces. In the future, we may see these highly trained individuals extending their services into additional sites to address the problems of sick children earlier in their illness.

Definition of a Pediatric Intensive Care Unit

In the 1983, Guidelines for Pediatric Intensive Care Units (PICUs)[4] (updated 1993[5] and 2004[6]) the committee defined a PICU as "…a hospital unit which provides treatment to children with a wide variety of illnesses of life-threatening nature including children with highly unstable conditions and those requiring sophisticated medical and surgical treatment." Randolph et al.[7] have expanded this definition, stating, "A PICU is a separate physical facility or unit specifically designated for the treatment of pediatric patients who, because of shock, trauma, or other life-threatening conditions, require intensive, comprehensive observations and care."

Definition of Pediatric Intensivist

Randolph et al.[7] define a pediatric intensivist (in the United States) as "…any one of the following: (a) a pediatrician with subspecialty training in PCCM and subspecialty certification from the American Board of Pediatrics (ABP); (b) a pediatric anesthesiologist with special competency in critical care with subspecialty certification from the American Board of Anesthesiology; (c) a pediatric surgeon with special competency in critical care with subspecialty certification from the American Board of Surgery; or (d) a physician (as above) eligible for subspecialty certification by their respective board." Similar requirements for training exist or are in development elsewhere in the world.

History of Critical Care

Resuscitation and Ventilation

The key to understanding the present practice of intensive care for children lies in knowing the history of scientific study of cardiorespiratory anatomy and physiology and of the discovery of techniques to support ill patients. Although one could think our current practice suddenly emerged with the late twentieth-century technical discoveries, Downes and Todres have skillfully reminded us[3,8] that accomplishments in the development of resuscitation and ventilation that we take for granted today date back to the Bible, and numerous events and contributions led to our current practice. In a biblical story,[9] Elisha resurrected a young boy who was dead when, " …he climbed onto the bed and stretched himself on top of the child, putting his mouth to his mouth, his eyes to his eyes, and his hands to his hands, and as he lowered himself onto him the child's flesh grew warm….Then the child sneezed and opened his eyes." In 117 CE, Antyllus performed tracheotomies for patients with upper airway obstruction.[10] Paracelsus, a sixteenth-century Swiss alchemist and physician, first provided artificial ventilation to both animals and dead humans using a bellows,[10] and Andreas Vesalius, a Flemish professor of anatomy, in *De Humani Corporis Fabrica* reported ventilating open-chest dogs and pigs using a fireplace bellows in 1543.[11-13]

The French obstetrician Desault, in 1801, described how to successfully resuscitate apneic or limp newborns by digital orotracheal intubation with a lacquered fabric tube and then blowing into the tube.[3] In 1832, Dr. John Dalziel in Scotland developed a bellows-operated intermittent negative-pressure device to assist ventilation,[14] In 1864, Alfred F. Jones, of Lexington, Kentucky, built a body-enclosing tank ventilator, and in the 1880s, Alexander Graham Bell developed a "vacuum jacket" driven by hand-operated bellows.[14] In 1876, Woillez, in Paris, built what was probably the first workable iron lung, which was strikingly similar to the respirator introduced by Emerson in 1931.[14] Braun developed an infant resuscitator, as described by Doe in 1889, which was used successfully in 50 consecutive patients. A respirator developed by Steuart in Cape Town, South Africa, in 1918 apparently successfully treated a series of polio patients, but he did not report it.[14]

In 1888, Joseph O'Dwyer, a physician working at the New York Foundling Hospital who was concerned about the severe death rate in croup and laryngeal diphtheria, instituted the manual method of blind laryngeal intubation. *Despite severe criticism from associates and the other practitioners, he persisted in the use of this technique.* He assembled a series of sized tubes for the palliation of adult and pediatric laryngeal stenosis and, with George Fell, devised a method of ventilation with a foot-operated bellows connected by rubber tubing to the endotracheal tube (Figure 1-1).[12] O'Dwyer may deserve a Courage, Size 4 award for his work.

In 1898, Rudolph Matas of New Orleans adapted the Fell-O'Dwyer technique to perform chest wall surgery and, in the early 1900s, George Morris Dorrance of Philadelphia used the technique to perform resuscitations.[12] In 1910, at the Trendelenburg Clinic in Leipzig, two thoracic surgeons, A. Lawen and R. Sievers, developed a preset, electrically powered piston-cylinder ventilator with a draw-over humidifier. It was used with a tracheotomy tube during and after surgery and for a variety of diseases.[3] Over a long career, Chevalier Jackson (1858-1955), a surgeon at Temple University in Philadelphia, developed the techniques for laryngoscopy, bronchoscopy, and tracheotomy.[3]

In 1958, Peter Safar published work in which he showed the longstanding resuscitation technique of chest-pressure arm-lift was virtually worthless and, in effect, went back to Elisha and proved jaw thrust and mouth-to-mouth resuscitation superior.[15] Soon after, W.B. Kouwenhoven and James Jude at Johns Hopkins published work on the effectiveness of closed-chest cardiac massage.[16] Beck and his team, in 1946, had demonstrated open-chest electrical defibrillation, and, in 1952, Zoll and his team proved the efficacy of external defibrillation and, in 1956, the effectiveness of external cardiac pacing.[17]

Anesthesia

The evolution of PCCM is tightly linked with the demand for postoperative care for infants and children with conditions needing complex surgery. The evolution of anesthesia allowed surgeons to develop the techniques to address the problems of these patients.

In 1842, Crawford W. Long, a University of Pennsylvania Medical School graduate practicing medicine in rural Georgia, observed that bruises encountered by participants during "ether frolics" caused no pain when they occurred during the "exhilatory" effects induced by inhalation of vapor. This also occurred when nitrous oxide was inhaled. Both of these agents, at the time, were inhaled for their hallucinatory effects in the United States. Long utilized this serendipitous observation to provide ether to James Venable and incise a cyst from his neck, without pain. This was 4 years before Morton's demonstration of the use of ether at Massachusetts General Hospital in 1846. In 1849, Long reported his experience with his third patient, an 8-year-old boy who had a diseased toe, which was amputated without pain in 1842.[18]

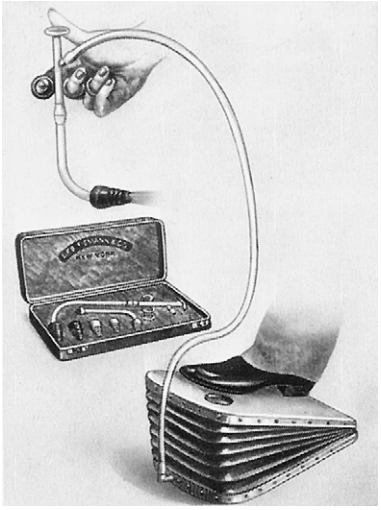

Figure 1–1. The Fell-O'Dwyer Respiratory Apparatus. *(Reproduced with permission, Blackwell Scientific Publications, Oxford.)*

The widely publicized public demonstration of the use of ether by the dentist William T.G. Morton took place at the Massachusetts General Hospital on October 16, 1846. Dr. John Collins Warren removed a mandibular tumor, without the patient experiencing pain. This great success was quickly picked up and used by John Snow in London and later by Friedrich Trendelenburg in Leipzig, who first used anesthesia via an endotracheal tube in 1869.[19]

Anatomy and Physiology

What seems simple and obvious today took a great deal of time, effort, and insight to understand. Downes[3] has provided a thorough review of this topic, and we briefly note here some of the contributions that advanced medicine and enabled the development of cardiorespiratory support and, eventually, intensive care. Andreas Vesalius (1514-1564), the Flemish anatomist, corrected many previous mistakes in anatomy and provided positive-pressure ventilation via a tracheotomy tube to asphyxiated fetal lambs. Michael Servetus of Spain (1511-1553) correctly described the pumping action of the heart's ventricles and the circulation of the blood from the right heart through the lungs to the left heart. *He was burned at the stake for his views* and thus deserves a Courage, Size 1 award. Matteo Realdo Columbo (1515?-1559) described the pulmonary circulation and the concept that the lungs added a *spirituous* element to the blood by the admixture of air. William Harvey (1578-1657), with his genius and *perseverance,* published *De Motu Cordis* (On the Motion of the Heart)[20] in 1678. Since he did not yet have the microscope available, he could not see the capillaries and thus could not include the mechanism for transfer of blood from the arterial to the venous system of the pulmonary circulation. Capillaries were described by Marcello Malpighi (1628-1694, Italian) in *De Pulmonibus* (On the Lungs) in 1661. Thomas Willis (1611-1675) and, eventually, William Cullan (1710-1790) led the way to understanding the role of the nervous system as the site for consciousness and the regulation of vital phenomena. Richard Cower (1631-1641) proved it was the passage of blood through the lungs, ventilation of the lungs, and gas exchange with blood that vivified the blood and turned it red. Stephen Hales (1677-1761) measured blood pressure with a brass tube connected to a 9-foot glass tube in a horse. Joseph Black (1728-1799) identified carbon dioxide as a gas expired from human lungs. Karl Wilhelm Scheele (1742-1785) isolated oxygen, as did Joseph Priestley (1733-1804), who named it *dephlogisticated air* and determined its vital role in supporting combustion. Antoine Laurent Lavoisier (1743-1794) identified oxygen as the vital element taken up by the lungs that maintains life and gave it its name, but its essential role in physiology and biochemistry was clarified much later. Joseph Lister (1817-1916), one of the founders of modern histology, reasoned that bacteria were the source of pus in rotten organic material and used carbolic acid in surgical fields to eliminate bacteria. This technique improved patient outcomes for wounds and after surgery. Along with the discovery of antibiotics, antiseptic technique was an important step in patient care. Nonetheless, imperfect antiseptic technique, sepsis, inflammation, and the consequences of multiorgan failure are still a major portion of what pediatric intensivists deal with today. Felix Hoppe-Seyler (1825-1895) described the transportation of oxygen in blood by hemoglobin. Robert

Koch (1843-1910) developed his postulates in 1882. William Konrad von Röntgen (1845-1923) discovered x-rays. Scipione Riva-Rocci (1863-1937), in 1846, measured blood pressure using the sphygmomanometer, and Nikolai Korotkoff, in 1905, introduced his auscultation method.[3] In the present day, cardiac catheterization, echocardiography, computerized tomography, and magnetic resonance imaging have enabled clinicians to delve into anatomy and physiology in the living patient with relative ease.

History of Pediatric Critical Care

Pediatric Anesthesiology

The development of PCCM rests on the efforts of pediatric anesthesiologists, as well as pediatric general and cardiac surgeons, and neonatologists. In fact, most of the original PICUs were founded by pediatric anesthesiologists (Table 1-1).[3,8,21-28] Much depends on the definition of a PICU, very much a moving target in the early days, with units eventually evolving from separate areas within recovery rooms and adult units to separate freestanding PICUs. In addition to those noted in Table 1-1, there were probably others which are not as well documented.

Pediatric General and Cardiac Surgery

The pioneering efforts of Dr. William E. Ladd (1880-1967) at Boston Children's Hospital (BCH) in developing many of the techniques to operate on noncardiac congenital malformations and Dr. Robert Gross, also at BCH, to operate on congenital cardiac lesions (7-year-old Lorraine, coarctation of the aorta, August 23, 1938) were instrumental in developing their surgical fields and demonstrating the need for good postoperative care. Dr. C. Everett Koop trained there for 6 months and then returned to Children's Hospital of Philadelphia (CHOP) where he, with the help of nursing staff, developed the first neonatal surgical intensive care unit in 1956. This was staffed by Dr. Leonard Bachman (anesthesiology) and his colleagues. Dr. Bachman's young associate, John J. Downes, subsequently set up the PICU in the hospital in 1967. Dr. C. Crawfoord in Sweden repaired a coarctation of the aorta in 1945, and Drs. Alfred Blalock (surgeon) and Helen Taussig (cardiologist) with Mr. Vivien Thomas (laboratory assistant) at Johns Hopkins created the subclavian-to-pulmonary artery shunt for tetralogy of Fallot, also in 1945. Dr. John Gibbon at Jefferson Medical College Hospital in Philadelphia performed the first successful open-heart surgery (for atrial septal defect) using cardiopulmonary bypass in 1953.[3] As the surgical procedures became more invasive, the need for improved postoperative support of all organ systems advanced rapidly. Although some surgeons believed the success or failure of treatment was solely determined in the operating room, others credited improved survival to better postoperative care.

Neonatology

Pediatric critical care owes a great debt to fellow neonatal pediatricians.[3,8,29] In the 1880s and 1890s special care nurseries were developed in Paris, and in 1914, the first premature infant center in the United States was opened at Michael Reese Hospital in Chicago by Dr. Julius Hess (1876-1955). In Canada, Dr. Alfred Hart performed exchange transfusions in 1928, and in 1932, Drs. Louis Diamond, Kenneth Blackfan, and James Batey at BCH described the pathophysiology of hemolytic anemia and jaundice of erythroblastosis fetalis; in 1948, the same team performed exchange transfusions using a feeding tube inserted in the umbilical vein. In the 1950s and 1960s, Dr. Geoffrey Dawes at the Nuffield Institute for Medical Research at Oxford University began work, using fetal and newborn lambs, to describe the circulation of mammalian neonates. This work was continued, and the fetal transitional circulation further elucidated, by Dr. Abraham Rudolph and colleagues at the Cardiovascular Research Institute (CVRI) of the University of California, San Francisco (UCSF).

Dr. Clement Smith at Boston Lying-In Hospital published his textbook of neonatal physiology in 1945, and in 1959, a research fellow at Harvard, Dr. Mary Ellen Avery (with mentor Dr. Jere Mead) discovered the deficiency of alveolar surfactant in lungs of newborns dying from respiratory distress syndrome (RDS). Dr. L. Stanley James from New Zealand was recruited to Columbia in New York by Dr. Virginia Apgar (anesthesiology) in the 1960s and helped confirm the work of Dr. Dawes. In the 1960s, neonatologists altered the practice used in adult ICUs of cohorting patients with similar diseases by establishing units with infants with a variety of life-threatening conditions and shifted from supportive care to more invasive measures to treat organ failure.

In 1959, Drs. Peter Smythe (pediatrician) and Arthur Bull (anesthesiologist) had the first real success in long-term mechanical ventilation of neonates, treating infants with neonatal tetanus for 4 to 14 days using tracheotomy and a modified Radcliff adult ventilator.[30] Up until that time, infants were not given ventilatory support for more than a few hours using manual ventilation. There were no pediatric ventilators, humidifiers, or blood gas analysis. Dr. Smythe had to overcome these obstacles by innovation. On July 13, 1957, he began intermittent positive-pressure ventilation on a baby with neonatal tetanus at Groote Schuur Hospital, with the assistance of anesthesiologist Bull. This was truly a landmark event in the evolution of PCCM. There are three interesting points to be made about their work. First, although considered a success story in that it was the first time infants survived long-term positive-pressure mechanical ventilation, the first 7 of 9 patients died. Eventually their survival rate reached 80% to 90%. Surely Smythe and Bull deserve Perseverance, Size 1 awards. Second, they commented that, "No praise can be too high for the nursing staff, who were all student nurses and without any special training." And third, Dr. David Todres, a medical student at the time, administered intramuscular curare to these patients. Dr. Smythe moved to Red Cross Children's Hospital when it opened in 1958, and established a 6-bed neonatal tetanus unit.

In 1963–1964 in Toronto, Drs. Paul Swyer, Maria Delivoria-Papadopoulos and Henry Levison were the first to successfully treat premature infants with RDS with positive-pressure mechanical ventilation and supportive care.[31] They emphasized the importance of a full-time team, *including dedicated nurses and therapists* as well as physicians. In 1968, Dr. George Gregory and colleagues demonstrated greatly improved survival with the addition of continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP) to the mechanical ventilation regimen.[32] However, as always, progress in treating a disorder leads to unforeseen complications and new disorders, and successful treatment of RDS led to

Table 1–1 Early Pediatric Intensive Care Units and Programs

Year	Institution/Location	Medical Director(s)	Director(s) Specialty
1955	Children's Hospital, Goteborg, Sweden	G. Haglund	Pediatric Anesthesiology
1961	St. Goran's Children's Hospital, Stockholm, Sweden	H. Feychting	Pediatric Anesthesiology
1963	Hospital St. Vincent de Paul, Paris, France	J.B. Joly G. Huault	Neonatology Neonatology
1963	Royal Children's Hospital, Melbourne, Australia	I.H. McDonald J. Stocks	Pediatric Anesthesiology Pediatric Anesthesiology
1964	Alden Hey Children's Hospital, Liverpool, England	G.J. Rees	Pediatric Anesthesiology
1965	Children's Hospital District of Columbia, Washington, DC	C. Berlin	Pediatrics
1967	Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	J.J. Downes	Pediatric Anesthesiology
1968	Children's Hospital Calvo Mackenna, Santiago de Chile	E. Bancalari	Pediatrics
1969	Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania	S. Kampschulte	Pediatric Anesthesiology
1969	Yale-New Haven Medical Center, New Haven, Conn.	J. Gilman N. Talner	Pediatric Anesthesiology Pediatric Cardiology
1971	Massachusetts General Hospital, Boston, Mass.	D. Shannon I.D. Todres	Pediatric Pulmonology Pediatric Anesthesiology
1971	Hospital for Sick Children, Toronto, Canada	A. Conn	Pediatric Anesthesiology
1971	Long Island Jewish Hospital, New York	B. Holtzman	Pediatric Pulmonology
1971	Montefiore Hospital, New York	R. Kravath	Pediatric Pulmonology
1972	Sainte Justine Hospital, Montreal, Canada	M. Weber A. Lamarre	Pediatrics Pediatric Pulmonology
1972	Children's Hospital "Dr. R. Gutierrez," Buenos Aires, Argentina	J. Sasbon	Pediatrics
1972	Children's Hospital "Pedro Elizade," Buenos Aires, Argentina	C. Bonno	Pediatrics
1972	Sick Kids, Edinburgh, Scotland	H. Simpson	Neonatology
1974	Red Cross Children's War Memorial Hospital, Cape Town, South Africa	M. Klein	Pediatric Pulmonology
1974	Great Ormond Street Children's Hospital, London, England	D. Matthews	Pediatrics
1975	Private Hospital, Uruguay	M. Gajer	Pediatrics
1975	National Children's Hospital Medical Center, Washington, DC	P.R. Holbrook A. Fields	Pediatrics Pediatrics
1975	Children's Medical Center, Dallas, Texas	D. Levin F. Morriss	Pediatrics Pediatrics/Pediatric Anesthesiology
1976	Hospital Infantil La Paz, Madrid, Spain	F. Ruza	Pediatrics
1977	Johns Hopkins Medical Center, Baltimore, Maryland	M.C. Rogers	Pediatrics/Pediatric Anesthesiology
1977	Sheba Medical Center, Israel	F. Barzilay	Pediatrics
1977	Children's Hospital of San Diego, San Diego, California	B. Peterson	Pediatrics/Pediatric Anesthesiology
1977	Hospital das Clinicas, Sao Paulo, Brazil	A. Wong	Pediatrics
1978	Sophia's Children's Hospital, Rotterdam, The Netherlands	E. van der Voort H. van Vught	Pediatrics Pediatrics
1978	Children's Hospital of Los Angeles, Los Angeles, California	E. Arcinue	Pediatrics
1979	University of Minnesota Hospital, Minneapolis, Minn.	B. Fuhrman	Pediatrics
1980	Moffett Hospital, San Francisco, California	G. Gregory	Pediatric Anesthesiology
1980	Children's Hospital Boston, Boston, Mass.	R. Crone	Pediatrics/Pediatric Anesthesiology

Adapted from references 3, 8, and 21 through 28.

survivors with chronic lung disease, retinopathy of prematurity, and hypoxic brain injury. When Morriss and Levin were first working in Dallas they complained that the beds were taken up by chronic patients. One of the pediatricians commented, "Before you started doing this, we didn't have chronic patients." This was an early observation still relevant today: Pediatric intensive care allows successful treatment of disorders previously considered hopeless, but may also result in a population of children with long-term problems that also require study and clinical attention.

Pediatric Cardiology

As previously indicated, the vision of Dr. Taussig in devising a method to treat "blue babies," in cooperation with pediatric cardiac surgeons, led to infants and children who survived surgery and then needed postoperative care. This sequence has been well documented by Dr. Jacqueline Noonan.[33] She notes that, "Much success of the surgery can be attributed to a group of pediatric intensivists, pediatric intensive care units, improved ventilatory support, and trained respiratory therapists." Advances in technology, especially for imaging, have allowed clinicians to "see" into living patients with astounding accuracy. Increased understanding of anatomy and physiology has led to improved surgical care for children with very complex problems. Perhaps ironically, some recent developments in cardiac catheterization and interventional radiology have enabled clinicians to treat many lesions without surgery, improving outcomes without the need for open-heart surgery and potentially difficult postoperative intensive care. The burgeoning growth of techniques, both interventional and surgical, has resulted in many centers creating specific cardiac intensive care units often run by pediatric cardiac intensivists, although not without some controversy in the world of PCCM.

Poliomyelitis

The interwoven history of resuscitation and ventilation, anesthesia, anatomy and physiology, pediatric anesthesiology, pediatric general and cardiac surgery, neonatology, and pediatric cardiology all come together in an astounding story of the treatment of paralytic polio and respiratory failure ("bulbar polio"). The confluence of great scientific and clinical minds and the organizational efforts of physicians, nurses, and technicians addressing the needs of polio patients rapidly led to the creation of PICUs. In 1929, Philip Drinker, an engineer, Dr. Louis Shaw, and Dr. Charles F. McKhann published their experience with a mechanical ventilator which was an electrically powered negative-pressure body tank, eventually termed the "iron lung" by a now unknown journalist (Figure 1-2).[34] On October 12, 1928, an 8-year-old girl with polio and difficulty breathing was admitted to BCH. On October 13, her respiration was failing and she was placed in the respirator at low pressure. She improved and was taken off the device, but on October 14, she was comatose and cyanotic and was placed back in the respirator at high pressures. She regained consciousness and a little later asked for ice cream. "Most of the people who witnessed the scene were in tears."[14] Even though this patient died on October 19, with necropsy findings of poliomyelitis and bronchopneumonia, the device subsequently saved the lives of a student nurse at Bellevue Hospital in New York and a Harvard College student at Peter Bent Brigham Hospital.

As dramatic as this was, it seems to be overshadowed by the remarkable polio epidemics in Los Angeles in the early 1950s and in Copenhagen in 1952.[14] Writing in 1953,[35] H.C.A. Lassen, Chief Epidemiologist of the Department of Communicable Disease, Blegdam Hospital, Copenhagen, describes treating 2772 patients for polio between July 24 and December 3, 1952. Of these, 866 patients had paralysis and 316 of these were in respiratory failure. Of the 316, 250 eventually underwent tracheotomy. Previously, starting in 1948, such patients underwent tracheotomy and suctioning for secretions without ventilatory support, but all died. Of the 15 patients treated with a mechanical respirator without tracheostomy, five patients, one adult and four children, survived. During the first month of the 1952 epidemic, of the 31 patients with respiratory paralysis, 27 died, for a mortality rate of 85% to 90%. Thereafter they consulted Dr. Bjorn Ibsen, an anesthesiologist, who suggested tracheotomy, rubber-cuff tubes, and manual positive-pressure ventilation ("iron lungs" were not commonly available in Europe at the time) using a rubber bag. From August 28 to September 3, 1958, they were admitting 50 patients a day, 12 of whom had respiratory failure and were admitted *to a special unit for respiratory care.* In this unit they had as many as 70 cases at once in respiratory failure. There were 200 patients admitted to the unit who underwent tracheotomy, manual positive-pressure ventilation with 50% oxygen, and suctioning. They employed 200 extra nursing

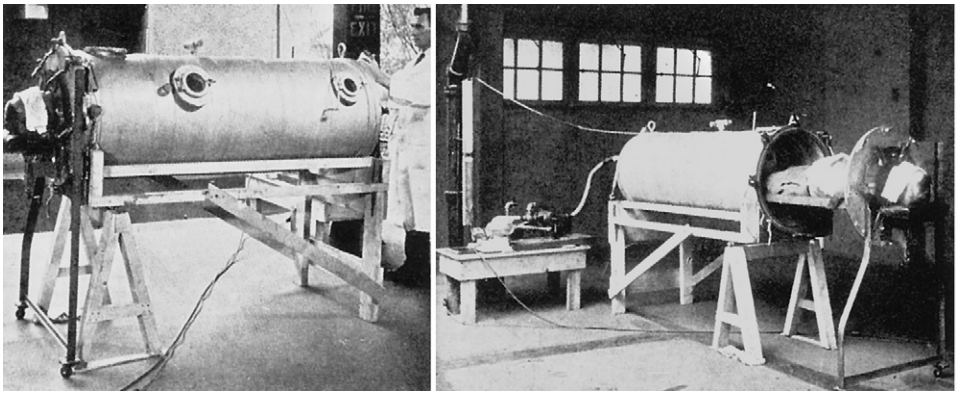

Figure 1–2. The Drinker negative-pressure mechanical ventilator. *(Reproduced with permission, Blackwell Scientific Publications, Oxford.)*

auxiliaries (students and aides), 200 medical students at a time each working 8-hour shifts to provide manual ventilation (1000 in all), and 27 technicians per day to care for the patients.[35-37] The mortality decreased from 90% to 40%. Ibsen adds that the first patient was a 12-year-old girl with paralysis of all four extremities and atelectasis of the left lung, who was gasping for air and drowning in her own secretions. She had a temperature of 40.7° C and was cyanotic and sweating. The tracheotomy was done under local anesthetic and a cuffed endotracheal tube was inserted. During the procedure she became unconscious. They connected her to the ventilator but could not ventilate her. He then gave 100 mg of pentothal IV and she collapsed, her own respirations stopped, and he could then provide manual ventilation. She then developed signs of carbon dioxide retention even with full oxygenation (rise in blood pressure, skin clammy, and sweating), and she again started her own respirations with gagging and bucking. Secretions began to pour out of her mouth and nose. This was relieved in a few moments with increased ventilation but then her blood pressure dropped and she appeared to be in shock. He gave a blood transfusion and her condition improved, with her skin becoming warm, dry, and pink, "Which always makes an anesthesiologist happy." A chest radiograph showed atelectasis of the left lung and she was placed on a mechanical positive-pressure ventilator, after which all the signs of underventilation recurred, along with cyanosis. She was given supplemental oxygen and her color improved, but she still showed signs of carbon dioxide retention. Manual ventilation was started and she improved.[36]

He concluded that tracheotomy with local anesthetic without an endotracheal tube in place was too difficult. The patients were anxious, vomited, aspirated, and had airway spasms. Few survived, so they started doing the tracheotomies earlier with endotracheal intubation and anesthesia and had great success.[36,37] Another change in strategy was that patients from outlying areas were being sent in ambulances without sufficient attendants and airway care and arrived moribund. They started to send teams in ambulances out to the pick up the patients in the countryside, with marked improvement ("retrieval teams"). This was the beginning of an important aspect of PCCM that many believe still has great potential for improving care in the future and which remains far from fully implemented. They also started passing stomach tubes for nutrition and the rubber-cuffed tubes were replaced with a silver cannula. Even with all the improvements he concludes, "Naturally we ran into a lot of complications."[37]

They also received help from other bright people who were focusing their efforts on treating polio. The clinical biochemist Poul Astrup developed a method to measure carbon dioxide, and C.G. Engstrom constructed a volume-preset positive-pressure mechanical ventilator. This spectacular and thrilling story resulted in a cohort of patients in respiratory failure in a single geographical area being cared for by full-time physicians, nurses, and technicians.

Although these units tended to disband after the summer-fall polio season, they led to the creation of full-time units, the first of which was described by Dr. Goran Haglund in 1955, at the Children's Hospital of Goteberg, Sweden.[23] He called the unit a Pediatric Emergency Ward. The patient who inspired Dr. Haglund to organize the unit was a 4-year-old boy who was operated on in 1951 for a ruptured appendix. Postoperatively, he lapsed into a coma and the surgeon declared they had done all they could and he would die of "bacteriotoxic coma." The anesthesiologist offered to help and the boy was intubated, given manual positive-pressure respiration with generous oxygen, tracheostomized, and given a large blood transfusion. After about 8 hours, the bowels started to move, and 4 hours later he was out of coma. After 20 hours, he had spontaneous respiration and had been successfully treated for respiratory insufficiency and shock. The unit had 7 acute care beds, 6 full-time nurses and 15 nursing assistants, with 24-hour coverage. In the first 5 years, the team treated 1183 infants and children, with a mortality rate of 13.6%. Haglund goes on to state, "But what we did was something else. It was the application of the basic physiology to clinical practice. Our main purpose was not to heal any disease, it was to forestall the death of the patient. The idea was—and is—to gain time, time so that the special medical and/or surgical therapy can have desired effects."[23] (Morriss and Levin[38] took this approach in organizing the first edition of their textbook in 1979.) He was also careful to point out that, "There are few jobs more exacting, demanding, and taxing than emergency nursing. Our nurses and nurse assistants are tremendous. They must be!"[23]

Nursing

As has been shown, the dissemination of the knowledge and skills that the anesthesiologists had developed in the operating room to postoperative recovery rooms, surgical and medical wards, and eventually to geographically defined units, permitted improved treatment of patients with a variety of disorders, only some of which required surgical intervention. Among the diseases treated were polio in the 1920s to 1950s, tetanus in the 1950s and 1960s, and Reye syndrome in the 1970s and 1980s.[3] These epidemics, along with developments in neonatology, pediatric general and cardiac surgery, and pediatric cardiology created a demand for greater services for more unstable patients. The events paralleled those in the world of adult critical care, with early intensive care units opened in 1923 at Johns Hopkins in Baltimore, a three-bed unit for postoperative neurosurgical patients directed by Dr. W.D. Dandy,[10,39,40] in 1953 at North Carolina Memorial Hospital in Chapel Hill, North Carolina, in 1954 at Chestnut Hill Hospital, Philadelphia, in 1955 at the Hospital of the University of Pennsylvania in Philadelphia,[41] and 1958 at Baltimore City Hospital (Dr. Peter Safar) and Toronto General Hospital (Dr. Barrie Fairley).[3]

Although many sources emphasize the role of advanced technology in the creation of adult, neonatal, and pediatric ICUs,[3,24] it is interesting to consider the important role of nursing in this evolving process. Porter,[42] as well as others, reminds us of the vital role of nursing in triage and organization of care for patients by degree of illness. Long before the organizational efforts just described, Florence Nightingale (1820-1920) organized the military hospital at Scutari in 1854, during the Crimean War, to provide more care to the most severely injured soldiers by grouping them together. Although the care consisted mostly of better hygiene and nutrition, the mortality rate dropped from 40% to 2%.[43] These efforts were continued in the United States by Dorothea Dix (1802-1887) and Clara Barton (1821-1912), the "Angel of the Battlefield," during the American Civil War, and when Barton brought the Red Cross to America in 1882. It was Nightingale who provided the definition of nursing as "helping the patient to live."[42,43] Fairman and Kagan[41] conducted an interesting study looking

at the creation and evolution of an adult intensive care unit by researching the historical records and interviewing the people involved at the Hospital of the University of Pennsylvania from 1950 to 1965. They emphasize that there really was no new equipment, only the migration of existing equipment from the operating room to the wards. In fact, some nurses remembered that they did not really have much in the way of equipment at all, even monitors. Certain social factors and the need for nurses were much more influential in forming geographically defined units away from the operating room or recovery room. Most patients at that time were operated on for gallbladder disease, appendectomies, and tonsillectomies. Poor patients were admitted to the ward postoperatively and wealthier patients were admitted to private or semi-private rooms and hired, at their own expense, private-duty nurses to care for them. This resulted in a two-tier system, with poorer patients having little postoperative care. Then a shortage of private-duty nurses occurred; many private-duty nurses refused to work nights, weekends, and holidays, and nurses with less training worked "off-shifts." Surgeons and families complained they could not get care, and of course the poorer patients did not receive adequate care at all. The hospital, to save money, (the average cost per patient per day for recovery room care in 1960, at Baltimore City Hospital, was $50 to $80)[44] demanded more from existing hospital nurses, tried to hire more private-duty nurses at family expense, and failing that, shifted some semiprivate patients to the ward. This resulted in complaints of noise (from patients) on the ward and understaffing to the point of safety concerns. One of the patients became disconnected from a ventilator and died unnoticed.

There was a move by nurses for better training, improved safety, and better staffing, as well as for more specialized rooms to organize the care of the sickest surgical and medical patients in architecturally distinct areas at no extra cost to the patients. This resulted in the creation of the Fifth Special Unit, closure of obsolete wards, and a more egalitarian admission policy to the special unit. There developed a shared sense of adventure between nurses and physicians in the ICUs, which seemed like experimental laboratories. Similar development was mirrored in PICUs, and the camaraderie and spirit were evident. The ICU nurse in adult, neonatal, and pediatric units rose to the top of the ladder in the hospital hierarchy. As one graduating Dartmouth Medical School student said in his class address, "When I started on clinical rotations I needed to learn how to function in the hospital. In order to do this I needed to understand the hierarchy in the institution. It quickly became apparent to me that the ICU nurse was at the very top of the pecking order."[45]

Several other references to the central importance of nursing in creating and enabling intensive care to develop have been cited.[3,8,23,30,31,42] As Fairman and Kagan[41] conclude, "…powerful social contextual forces, such as workforce and economics, architectural changes, and an increasingly complex hospital population—rather than new technology—supported the development of critical care."

Pediatric Critical Care

Getting Started

As we have seen, geographically defined PICUs, directed by specific medical and nursing personnel, emerged in the 1950s and 1960s and gathered momentum in the 1970s. These early units were heavily influenced by pediatric anesthesiologists (Table 1-1). But even in the 1970s, the future of these units and the role of pediatricians in them were far from certain.

We all owe a great deal to the efforts and leadership of Drs. Downes, Todres, Shannon, and Conn. The first physician-directed multidisciplinary PICU in North America was established at Children's Hospital of Philadelphia (CHOP) in January, 1967, as an outgrowth of a hospital-wide respiratory intensive care service.[3] The unit consisted of an open ward of six beds equipped with bedside electronic monitoring (electrocardiography, impedance pneumographic respiratory rate, and two direct blood pressure channels) and respiratory support capabilities. An adjacent procedure room could serve as an isolated seventh bed. An intensive care chemistry laboratory, manned 24 hours per day by a technician, was located next to the unit with a pass-through window for handing blood samples and receiving written reports. The nurses were assigned full-time to the unit, and most had previously served in the recovery room or the infant ICU for patients on the cardiac surgery or respiratory intensive care services. Dr. Downes was the medical director and worked closely with two other anesthesiologists, Dr. Leonard Bachman, Chief of Anesthesiology, and Dr. Charles Richards, an allergist/pulmonologist, Dr. David Wood also shared duties and call. One of four pediatric anesthesiology/critical care fellows was in or immediately available to the PICU on a 24-hour basis. Rounds with the nurses, fellows, and anesthesiology staff physician on service were conducted each morning and late afternoon. They were most fortunate to have close relationships with Dr. C. Everett Koop (Chief of Surgery and strong supporter of critical care), Dr. William Rashkind (the father of interventional pediatric cardiology), Dr. John Waldhausen (one of the nation's few full-time pediatric cardiac surgeons and a creative thinker), and Dr. Sylvan Stool (a pioneer in pediatric otolaryngology), as well as the support of numerous pediatric and surgical consulting staff and house officers. In 1971, at the Hospital for Sick Children in Toronto, Dr. Alan Conn resigned as director of the department of anesthesiology to become director of a new multidisciplinary 20-bed PICU, by far the largest and most sophisticated unit in North America. The establishment of this unit and a critical care service culminated a decade of efforts by Dr. Conn and his associates. They were able to cohort critically ill older infants and children in one geographic area that was not a postanesthesia recovery area. This advanced complex was the forerunner of units developed in major pediatric centers throughout North America over the following decade.[3] Also in 1971, Dr. David Todres, an anesthesiologist, and Dr. Daniel Shannon, a pediatric pulmonologist, founded a 16-bed multidisciplinary unit for pediatric patients of all ages at the Massachusetts General Hospital.[3,8] Each of these units also established vibrant training programs in critical care medicine and conducted clinical research. Among their numerous accomplishments, Dr. Conn became a noted authority on the management of near-drowning victims, and Dr. Todres pioneered long-term mechanical ventilation for children at home with chronic respiratory failure. These early PICUs and their training programs had a favorable impact on mortality and morbidity rates—particularly those associated with acute respiratory failure—and led to the development of similar units and programs in most major pediatric centers in North America and Western Europe during the 1970s and early 1980s.

In 1966, after internship, Dr. Max Klein joined Drs. H. de V. Heese and Vincent Harrison in a two-bed neonatal research unit at the Groote Shuur Hospital in Cape Town. Over the course of the next 2 years and more, their research resulted in many significant papers, not the least of which was "The Significance of Grunting in Hyaline Membrane Disease,"[46] demonstrating that oxygen tensions fell when infants were not allowed to grunt. This provided the rationale for the application of CPAP, an artificial grunt, to these patients. By 1969, pediatric patients at Red Cross War Memorial Children's Hospital with respiratory failure (e.g., Guillain-Barré) were ventilated on the wards and deaths were common. There was no centralized facility for older children. He encouraged Dr. Malcolm Bowie (consultant) to start a six-bed ICU, or "high-care ward," originally in collaboration with the anesthesiology staff. In 1971, Dr. Klein did a year of adult pulmonary fellowship with Professor M.A. de Kock at the University of Stellenbosch and then 2 years at the CVRI, UCSF. When he returned to Cape Town in 1974, he combined the neonatal tetanus ward of Dr. Smythe and the six-bed ICU of Dr. Bowie into the first full-time PICU in South Africa. An important aspect of the effort was that, at the time, the hospital was racially segregated. It took Dr. Klein *25 years of persistent effort* to create a nonsegregated PICU. He is truly deserving of a Perseverance, Size 1 award.[47]

The path to providing care for the sickest patients on a full-time basis remained unclear for an extended period. Subsequent early leaders in the field each carved out his own path. Dr. Daniel Levin completed pediatric cardiology and neonatology fellowships to learn how to take care of sick children, but found few chairmen interested in hiring an "intensivist." Dr. Nicholas Nelson, Chairman of Pediatrics at Penn State University Medical School in Hershey, would permit him to work at developing a PICU on the side, but he did not think it would work. A few years later he hand wrote a letter to Levin, actually apologizing and indicating that he now believed that in the near future, children's hospitals would be nothing but ICUs and most other patients would be cared for as outpatients. In 1974, Dr. Abraham Rudolph, one of Dr. Levin's mentors, inscribed his new book, *Congenital Diseases of the Heart,* "Wishing you the best in your chosen career as an 'intensivist" (quotes his). A career as a pediatric intensivist was far from a sure thing. In 1975, Drs. Levin and Frances Morriss (pediatrics and pediatric anesthesia) were recruited to Dallas by Dr. Theodore Votteler, Chief of Surgery and a former trainee of Dr. Koop, and by Heinz Eichenwald, Chairman of Pediatrics, to start a PICU at Children's Medical Center of Dallas.

In 1970, when Dr. Peter Holbrook finished medical school, he had been exposed as a student to the work of Dr. John Downes at CHOP. He also knew he wanted to work full-time taking care of the sickest children, but during his residency at Johns Hopkins he was discouraged by prominent pediatricians and told by some of the earliest leaders in the field that he needed to become an anesthesiologist. Dr. Peter Safar at Pittsburgh, however, welcomed him as a fellow in critical medicine in a personalized program to prepare him for PCCM. Dr. Safar told him, "We've been waiting for you."[27] In 1975, Dr. Holbrook and pediatrician Dr. Alan Fields, who also trained in Pittsburgh, went to Children's Hospital National Medical Center, as pediatricians in the Department of Anesthesia, to run their PICU.

Dr. Bradley Fuhrman finished his residency in 1973 and did both pediatric cardiology and neonatology fellowships to master both cardiovascular and pulmonary life support. In his words, "it seemed like the best route at the time."[48] After finishing the fellowships, he started the first PICU at the University of Minnesota Hospital in 1979.

Dr. Mark Rogers recognized the lack of senior supervision of interns during his pediatric residency in Harvard-affiliated hospitals. Like many of the early intensivists he was discouraged that junior people were left in charge of the sickest children. He subsequently studied pediatric cardiology and then chose to complete an anesthesiology residency. He was appointed director of Pediatric Intensive Care at Johns Hopkins after his residency. There were so few of this new breed of "intensivist" that many became directors right after completion of residency or fellowship. At the beginning, no one wanted to be responsible for pediatric intensive care.[28]

Dr. Bradley Peterson[49] went into the military service after his pediatric and neonatology training and then took an anesthesiology residency at Stanford. Upon completion of the latter, he opened the PICU at Children's Hospital of San Diego in 1977. Dr. George Lister[50] had many of the same experiences and thoughts as a resident at Yale. He found sicker older children scattered around the hospital without an organized approach to their care. He studied cardiorespiratory physiology and improvised a training program at the CVRI to gain the background and knowledge to take care of critically ill children. Post-cardiac surgery infants were cared for in the NICU and older children in the adult ICU, at Moffett Hospital. He started his attending career there in 1977 in the combined adult-pediatric ICU and, due to the director's illness, quickly found himself as the co-director of the unit.[51]

Eventually more and more pediatricians decided to devote their careers to being members of a multidisciplinary team taking care of the sickest children in hospitals on a full-time basis. In 1975, the CHOP program started to accept PCCM trainees who were pediatricians without anesthesia residency. The field grew rapidly in the late 1970s and 1980s.

During this time period, Calvin[39] indicated there was a struggle for authority in adult units, with some clinicians trying to change the culture of intensive care from one in which each different service cared for its "part" of the patient to one in which a full-time service was consistently available, and cared for the whole patient, with the help of consulting specialties. Although this conflict was probably worse in units for adults, it was certainly a prominent issue in PICUs as well.[27]

The Present

Although the field of PCCM was undergoing a period of rapid growth, it faced several problems. These were: (1) the need for a common "home" or national structure in which to meet and communicate; (2) acceptance or validation of pediatric critical care as a subspecialty; (3) education within the field; and (4) academic credibility with meaningful research.

A small group of interested people met at the Society of Critical Care Medicine (SCCM) National Education Forum in San Francisco in 1979 to discuss structure and a home.[27,52] There were about 15 people present, and memories have faded, but Drs. Holbrook, Gregory, Downes, Raphaely, Vidayasagar, and Levin were among them. It was decided to petition the SCCM to form a section of pediatrics. The society had no

subsections, but the petition was successful, and the pediatric section was formed in 1981.[3] In 1981, Dr. James Orlowski, with the support of others, petitioned The American Academy of Pediatrics (AAP) to form a section of Pediatric Critical Care or Intensive Care Medicine within the AAP. Although there was some controversy and some within the AAP wanted the new section to be housed within in an existing section (such as Anesthesiology, Emergency Medicine, or Diseases of the Chest), the petition was successful and the section began in 1984.[52] These organizations provided structure, places to meet, and opportunities to discuss common goals and concerns. Increasing international investment in pediatric intensive care was recognized with the first World Congress of Pediatric Intensive Care in Baltimore in 1992 and foundation of the World Federation of Pediatric Intensive Critical Care Societies (WFPICCS) in Paris in 1997 by Dr. Geoffrey Barker and others, providing a global platform for the field.[28]

Acceptance and legitimization were reflected in, and enhanced by, establishment of a new sub-board of Pediatric Critical Care Medicine of the American Board of Pediatrics in 1985, and the first certifying examination occurred in 1987.[53] Certification provided clear guidelines for hospital credentialing of PCCM physicians[54] and in 1989, special requirements for training in PCCM were developed by the American College of Graduate Medical Education (ACGME) with formally accredited programs first recognized in 1990.[53] In 1983, a committee of the SCCM developed guidelines for PICUs,[4] which have been regularly updated.[5,6]

In 1979, Ross Planning Associates indentified 150 PICUs of four or more beds, and another 42 were thought to exist (total 194).[3] Only 40% had a pediatric intensivist available at all times. Forty percent had fewer than seven beds and only one half had transport systems. By 1995, there were 306 general PICUs and in 2001 there were 349. Of these, 94% had a pediatric intensivist on staff. Pediatrics ward beds decreased by 22.4% between 1980 and 1989, by 10.8% between 1990 and 1994, and by 15.7% between 1995 and 2000. During the same three time periods, PICU beds increased by 26.2%, 19.0% and 12.9%, respectively.[7] The first subboard examination in 1987 certified 182 PCCM subspecialists. By 2006, there were 1454. In 1983-1984 there were 32 PCCM training programs, and the ACGME accredited 28 of them in 1990. By 2008, there were 62 PCCM training programs.[53] The number of fellows enrolled in PCCM has increased by 40.8% since 1997 (2006 figure) and the percent of women fellows increased from 39.6% to 44.6% from 1997 to 2006, peaking at 45.4% in 2000-2001. Eighty-five percent of applicants intended to work exclusively as intensivists.[54]

Education within the field has progressed rapidly. Educational programs at the annual SCCM, AAP, Pediatric Academic Societies, and American Thoracic Society meetings have been supplemented by a unique volunteer effort, started in 1983 by Dr. Hector James, a pediatric neurosurgeon from San Diego, and continued by Dr. Peter Holbrook in 1984, called the Pediatric Critical Care Colloquium (PCCC). National and regional organizations around the world conduct many other specialty-specific meetings. There have been many textbooks in the field in many languages including texts specifically for PCC nurses (Table 1-2). Through the efforts of members of the SCCM, that society's journal, *Critical Care Medicine*, and WFPICCS, a new journal, Pediatric Critical Care Medicine, began in 2000, edited by Patrick Kochanek.[81]

Academic credibility that results from meaningful scientific research has come slowly. In the early days, intensivists were mostly consumed by clinical and administrative responsibilities, but high-quality science, addressing a broad range of problems, has gradually emerged. Huge amounts of effort and money in PCCM have gone into clinical trials in attempts to improve therapy, but have failed to deliver on some promises[24] such as liquid ventilation,[82,83] recombinant bacterial/permeability–increasing protein ($rBPI_{21}$),[84] and activated protein C.[85] This may have as much to do with the incredibly difficult task of performing large clinical trials on very sick children as the validity of the concept or experimental design.

In the early 1990s, the Pediatric Critical Care study group was formed and led by Dr. Gregory Stidham of LeBonheur Children's Hospital.[24] In 1998, Dr. Adrienne Randolph initiated a clinical trials group with early assistance from Drs. Jacques Lacroix and Douglas Willson, that was initially formed to assist each other with oversight and conductance of three multicenter trials[86-88] and which subsequently evolved into the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI). By directly applying the already successful programmatic model of research developed by the Canadian Critical Care Trials Group (CCCTG),[89,90] PALISI has grown and prospered due to the cooperative volunteer spirit of the more than 70 North American member units, with[91] many publications in high-quality journals, ongoing funded clinical trials and observational studies, and active new protocol development. The Virtual PICU started in 2000, and Drs. Randall Wetzel of Children's Hospital of Los Angeles and Thomas Rice of The Children's Hospital of Wisconsin have created a massive database for research and quality control.[24] In Canada, the "Pediatric Interest Group" was created in the year 2000 within the CCCTG by Drs. Jacques Lacroix, James Hutchison, and Haresh Kirpalani, with the help of the Canadian Institutes of Health Research.[92]

In April 2004, the National Institute for Child Health and Human Development established funding (renewed in 2009) for the first network supporting pediatric critical care research, the Collaborative Pediatric Critical Care Research Network (CPCCRN), "To initiate a multicentered program designed to investigate the safety and efficacy of treatment and management strategies to care for critically ill children, as well as the pathophysiologic basis of critical illness and injury in childhood."[93] In the first 5 years, a number of landmark studies including observational studies on bereavement, opioid tolerance, and pertussis were initiated as well as several interventional trials, including a randomized controlled trial of immune prophylaxis and a study developing and testing a functional status outcomes scale. The NIH has also supported research in PCCM through the Pediatric Critical Care Scientist Development Program (PCCSDP), a K-12 program funded by the Eunice Kennedy Shriver National Institute of Child Health Development to support the development of young physician scientists in pediatric critical care. The PCCSDP entered its second project period in 2009, under the continuing direction of Dr Michael Dean at the University of Utah.[94]

The growth of education and research in PCCM has coincided with better care for children. In addition to the examples of diseases such as polio, tetanus, and Reye Syndrome that were stimuli for forming the subspecialty, examples such as the decrease in mortality from septic shock help demonstrate the improvement. During the period from 1958 to 1966, the

Table 1–2 Textbooks in Pediatric Critical Care Medicine

1st Edition	Title	Editors	Ref #
1971	*The Care of the Critically Ill Child*	R. Jones, J.B. Owen-Thomas	55
1971	*Pediatric Intensive Care: Manual*	K. Roberts, J. Edwards	56
1972	*Nelson's The Critically Ill Child: Diagnosis and Medical Management*	J. Dickerman, J. Lucey	57
1979	*A Practical Guide to Pediatric Intensive Care*	D. Levin, F. Morriss, G. Moore	38,58-60
1980	*Tratado de Cuidados Intensivos Pediatrucos* (Textbook of Pediatric Intensive Care)	F.J. Ruza	61
1984	*Nursing Care of the Critically Ill Child*	M.F. Hazinski	62
1984	*Textbook of Critical Care*	W.K. Shoemaker, W.L. Thompson, P.R. Holbrook	63
1984	*Pediatric Intensive Care*	E. Nussbaum	64
1985	*Temeas em Terapia Intensiva* (Issues in Pediatric Intensive Care)	J. Piva, P. Carvalho, P. Celiny Garcia	65,66
1985	*Critical Care Pediatrics*	S. Zimmerman, J. Gildea	67
1987	*Pediatric Intensive Care*	J.P. Morray	68
1988	*Pediatric Intensive Care*	M. Rogers	69
1992	*Pediatric Critical Care*	B.P. Fuhrman, J.J. Zimmerman	70
1993	*Textbook of Pediatric Critical Care*	P.R. Holbrook	71
1994	*Urgences & Soins Intensif Pediatriques*	J. Lacroix, M. Gauthier, F. Beaufils	72
1995	*Critical Heart Disease in Infants and Children*	D.G. Nichols, D.E. Cameron, W.J. Greeley, D.W. Lappe, R.M. Ungerleider, R.C. Wetzel	73
1996	*Critical Care of Infants and Children*	I.D. Todres, J.H. Fugate	74
1996	*Critical Care Nursing of Infants and Children*	M.A. Curley, J. Bloedel-Smith, P.A. Moloney-Harmon	75
1997	*Illustrated Textbook of Pediatric Emergency & Critical Care Procedures*	R.A. Dieckmann, D.H. Fiser S.M. Selbst	76
1997	*Paediatric Intensive Care*	N.S. Morton	77
2001	*Manual de Cuidados Intensivos Pediatricos*	J. Lopez-Herce Cid, C. Calvo Rey, M.J. Lorente Acosta, A. Baltodano Aquero	78
2005	*Cuidudo Intensivo Pediatrico y Neonatal*	J. Forero, J. Alarcon, G. Cassalett	79
2007	*Pediatric Critical Care Medicine: Basic Science and Clinical Evidence*	D.S. Wheeler, H.R. Wong, T.P. Shanley	80

mortality of gram-negative bacteremia in patients less than 16 years of age at the University of Minnesota was 60% in medical and 40% in surgical patients.[95] The mortality in septic shock was 95%. Now is it less than 10% and continues to be a major focus of clinical and research attention.

Drs. Murray Pollack and Timothy Yeh have shown us how to study severity-adjusted mortality in pediatrics and demonstrated that patients do better[96] when cared for by pediatric intensivists. Dr. Debra Fiser's group[97] has shown us there is improvement in mortality in patients with respiratory disease. Although many would attribute the improvements to technology and scientific advances, Dr. Yeh and others remind us it is possible that the presence of a full-time team and attention to a few basic principles rather than great investment in exotic high-technology solutions improves outcomes.[98] This is echoed by Dr. Frank Shann, who has two rules of PCCM: Rule 1 is "the most important thing is to get the basics exactly right all of the time"; Rule 2 is "organizational issues are crucially important.[28] Yeh as well as Ibsen[37] and Richard Orr have emphasized the important contributions of regionalization and the quality of PCCM transport teams in improving outcomes.[99,100]

The Cost of Success

Everything comes at a cost. In the field of PCCM, as in many others, advances have lead to increased cost, chronic disease, medical errors, and dehumanization of patients. The spiraling cost of medicine in general and intensive care in particular are well known and have been well presented by Dr. Downes[3] so will not be discussed further here.

As mentioned earlier, most intensivists are fully aware of and are distressed by the increased population of chronic patients who have prolonged PICU stays and frequent readmissions. Most of these patients did not exist previously; they died. Although we return many sick children to complete health, many children who would have died previously now live with chronic neurologic, respiratory, cardiac, and renal disease and residual problems from surgery, oncologic disease, and other causes.

Medical errors come in many forms. In addition to the well-publicized problems with staff fatigue, the tremendous complexity of the patients and environment makes individual errors a frequent occurrence. In addition, many systemic errors occur, not due to individual staff members' mistakes or fatigue but due to overarching issues such as equipment design and use, treatment regimens, communications, inherent problems with medications, and others. These have been well documented in neonatology by Drs. Silverman[101] and Robertson.[102-104] Well-intentioned, but in some cases not well-designed or reasoned, interventions have caused a great deal of morbidity and mortality. Many approaches that for long years were thought to be correct are now thought to be harmful, useless, or incorrect (e.g., normalizing $PaCO_2$ and PaO_2,[105] and transfusing patients from hemoglobins of <10 g/dL to >12 or 13 g/dL[87]).

In an extremely technical, frenetic environment, dehumanization of patients is always a danger. The story of intensive care for children has moved from triumph to triumph. However, in the process, the public has perceived that although medicine has succeeded on the technical level, it has lost much of its human touch, becoming more impersonal and forbidding. Some have stated that medicine has lost its way, although clinicians have started to reclaim this lost heritage of caring and compassion. This has been particularly true in end-of-life care, with the combined expertise of both intensivists and palliative care-givers. Pediatric intensivists have come to the realization that caring for critically ill children requires the simultaneous gathering of information in two areas. One is the disease itself, which includes the symptoms, signs, investigations, and clinical management. The other is the context of illness, which is the patient's and family's agenda of concerns, expectations, feelings, and thoughts that are unique to each individual and family. An intensivist acts to bring about a positive good or benefit to the patient; however, experience in the PICU has shown that conflicts arise when the presumption to save life (a good) requires interventions that may cause undue suffering. The more aggressive are the efforts to reverse illness, often the more suffering is inflicted on the patient. This leads to a situation where the physician begins to question how far to pursue these procedures. These ethical dilemmas are increasingly receiving the attention of intensivists. Ethics committees have been helpful in providing the health care team with important perspectives in approaching these difficult issues. Early on we asked, "How to do procedures," then we asked "When to do procedures," and increasingly we have asked, "Should we do procedures?"

In many units an increasingly diverse patient population has sensitized intensivists to the need to understand and respect individual cultural differences. Stereotyping a particular culture fails to respect individual differences. Increasingly, care is centered on the patient and family in recognition of the effects of personal spiritual/religious, cultural, and family values on patients' illness and recovery and in coping with the end of life. In many PICUs, chaplains are brought to the bedside and become part of the intensive care team.

The addition of child psychiatrists and social workers to the PICU consulting team has helped families and children cope with the severe and devastating effects of critical care illness. For the health care team, the long hours of stressful work and the occasional feelings of despair and frustration that all the hard work is not making a difference lead to emotional distress and a sense of loss of fulfillment in their professional lives. Understanding this problem and helping the team to realize they are making an important difference and are valued will reduce burnout and enhance staff morale. To illustrate the importance of knowing that one's effort does make a difference in people's lives, the following letter received by one of the nursing staff after a visit to the family at home stated,

"In the almost 3 weeks that we were in the pediatric ICU (PICU), we witnessed two deaths besides our son's….We know that death is part of your job and therefore must be dealt with as each sees fit….it seems funny that we'd be so happy to see people we barely know but your visit and the effort you took to come signifies a great deal. It meant that you DID care about our baby. And the solace received from your caring was—and is—immense. Special thanks for that….Please do not feel that your encouragement helped to give us false hope. Hope is what got us through those 3 weeks. Despair could wait."

One way we have attempted to support patients and families is to include families as members of the team by having them present at rounds with their child.[106] This effort allows the family, and often the patient, to hear what the team has to say and to ask questions, both of which empower the family and build trust.

Around the World

We have alluded to the many contributions of people around the world to the evolution of PCCM, both through innovative treatment of specific diseases (e.g., polio[3,14,35,36] and tetanus[30]), and in organizing and creating PICUs (see Table 1-1), and education (see Table 1-2).[107] What follows below are the varied contributions from many places, using a geographical approach.[8]

Canada

At the Hospital for Sick Children in Toronto, Dr. Alan Conn, anesthetist-in-chief, had the vision of developing an ICU utilizing his anesthesiology skills. In 1971, he took on the position of full-time director of critical care and initiated a flourishing clinical and research program. Dr. Conn was followed by Dr. Geoffrey Barker, who continued to promote the unit as one of the leading PICUs in the world. Dr. Barker's vision of the need to bring together intensive care from many parts of the world led to his directorship of the WFPICCS, which has done much to foster the development of pediatric critical care in countries around the world and to bring the skills and experience so vital in this practice to the benefit of multiple countries. In Montreal, the first patient was mechanically ventilated outside the postoperative recovery room in 1965, in what would later be named the PICU. This unit was first run by Dr. Paul Stanley, a pediatric cardiac surgeon. A medical PICU was created in 1972 by a pediatrician, Dr. Michel Weber, and pulmonologist Dr. André Lamarre. The units were merged in 1982. Drs. Marie Gauthier and Jacques Lacroix (Université de Montreal) and John Gordon (McGill University) were very active in the development and implementation in 1992 of a fellowship program in PCCM supervised by the Royal College of Physicians and Surgeons of Canada.[92]

Africa

Dr. Pat Smythe, a pediatrician working with Dr. Arthur Bull, an anesthesiologist at the Red Cross Children's War Memorial Hospital in Cape Town, South Africa, conceived a brilliant

therapeutic plan to treat infants afflicted with tetanus from infected umbilical cord stumps. This was the first successful long-term mechanical ventilation of sick infants. A dedicated group of nursing aides caring for these infants played a crucial role in their survival. Monitoring these infants depended on close observation of chest movement and visualization of cyanosis. Routine blood gas analyses had not yet entered the scene. The Severinghaus electrode (Pco_2) appeared in 1959 and the Clark electrode (Po_2) in 1961. However, using the Van Slyke method on a sample of end-tidal gas provided a measure of Pco_2. This labor-intensive method, which was performed by the pediatric resident, was applied somewhat infrequently! In combination with the efforts of Dr. Christiaan Barnard (cardiac surgery) and Dr. Jannie Louw (general surgeon) during the 1950s and 1960s, this experience led to the logical step of applying these principles of ventilator-supported care to the other critically ill infants and children, which followed later with the designation of a special unit for critically ill children in 1974 with full time intensivists. Dr. Max Klein with Drs. Louis Reynolds, Jan Vermeulen, Paul Roux, Cass Matola, and later Andrew Argent assumed this role with distinction. Dr. Klein's commitment to psychosocial issues in the care of patients was exemplary. His vision went beyond the PICU. In an excellent home-care tracheostomy program of 60 to 70 children, he, with nurse Jane Booth, were successful in ensuring the care of these children despite dreadful home conditions. In talking with him about the program, Dr. Todres recalled his enthusiasm for the need to have these children nurtured away from the hospital, and his staff provided these children with visits to the public gardens![47,108]

Asia: Japan

In the 1960s, Dr. Seizo Iwai, Chief of Anesthesia at the National Children's Hospital in Tokyo, was the first Japanese physician to introduce long-term mechanical ventilation and arterial blood gas analysis of critically ill infants, fostering a tradition of anesthesiologists taking care of every critically ill child outside of the operating room if a child should need their expertise. He was a strong force in developing a close relationship with other Asian countries and invited trainees from those countries to promote the teaching and development of pediatric critical care. His close working relationship with Drs. Conn and Barker in Toronto, Canada, paved the way for Dr. Katsuyuki Miyasaka to study in Philadelphia with Dr. Downes. Dr. Miyasaka returned to Japan in 1977 and, in October 1994, opened the first geographically distinct PICU in Japan at the National Children's Hospital and founded the Japanese Society of Pediatric Intensive Care. He continues to foster the development of a new generation of pediatric intensivists and to play a major role in facilitating this process.[109]

India

Development of neonatal and pediatric critical care in India has been described in detail before.[110] As in the developed countries, the discipline of neonatology and neonatal critical care preceded the development of the discipline of pediatric critical care in India. NICUs in India were established in 1960s, first at All India Institute, Delhi, and subsequently at teaching hospitals in major cities.

Today almost all major cities in India have NICUs providing different levels of intensive care. The well-established NICUs provide care on a par with NICUs in the Western countries. They are equipped to provide inhaled nitric oxide therapy and to manage complex cases including extremely low birth weight, surgical, and cardiac surgical cases. The outcome results are very encouraging.[111]

The first PICUs were established at major postgraduate centers (Delhi, Chennai, Chandigarh, Mumbai, and Lucknow) nearly two decades after the development of NICUs.[112] A special interest group of the Indian Academy of Pediatrics (IAP) working in PICUs was formed in 1997, and the Section of Pediatric Intensive Care was formed in the Indian Society of Critical Care Medicine (ISCCM) in 1998.[113] The Pediatric Critical Care Council (PCCC), a joint body of the Intensive Care chapter of the IAP and the Pediatric Section of the ISCCM,[114] provides the professional practice guidelines for pediatric critical care for the practitioners and the hospitals, and has initiated fellowship training programs in recognized units.[115] Today, PCCM is the fastest growing pediatric subspecialty in India. The growth of PICUs had been mainly in the private sector, although major government teaching hospitals are also improving the PICUs in their hospitals.

Prompt access to the available critical services is critical for pediatric patients. A study at a Children's Hospital in Hyderabad, Andhra Pradesh, India has shown that patients travel long distances (up to 500 km) to seek pediatric critical care, with survival inversely proportional to the distance traveled.[116] To overcome these difficulties, a bold and innovative statewide patient transport program, the Emergency Management and Research Institute (EMRI), was started in 2005 with a fleet of 70 ambulances deployed in the state of Andhra Pradesh, India.[117] The public-private collaborative organization has 2500 staff including EMTs, support staff, and associates, and a call center in the capital city of Hyderabad. A call using number 108 from any phone in the state gives access to ambulance service in the remote parts of the state. After 5 years, EMRI has a fleet of 652 ambulances and covers 23 districts and attends to over 4500 emergency calls per day. The EMRI center is linked to 331 private and public hospitals throughout the state and because of its success, the model is being adopted in other states of the country.[118]

Replicating this success elsewhere in India and the developing world will have an immense impact on resource needs. In view of the high birth rates (annual births of 25 million) and large pediatric population (35% of total or approximately 300 million) the required number of NICU and PICU beds will be enormous. It would therefore be prudent that all District hospitals (750 in the country) be upgraded to provide good level II services to meet the needs of rural communities.[119]

Although the development of PICUs is essential for overall improvement in child survival of the developing countries, the high cost of intensive care limits patients' access to PICU services. A recent study in Papua New Guinea demonstrated that the use of pulse oximetry in addition to clinical signs before initiating antibiotics, according to a World Health Organization (WHO) protocol, decreased mortality by 30%.[120] Similar low-cost innovative approaches may meet the demands of critical care in the developing world. It is therefore important to train health care personnel in early detection of infants at risk, for example, for respiratory distress, and in early initiation of treatment that would reduce the need for admissions to PICUs.

Australia and New Zealand

As in the United States and Canada, Australian PICUs started forming in the early 1960s, arising out of postoperative recovery wards with congenital heart surgery. In 1963, Drs. John Stocks and Ian McDonald in Melbourne introduced postoperative respiratory support with prolonged nasal intubation. Other units followed in Adelaide, Perth, Sydney, and Brisbane. An important contribution to the development of intensive care was the use of plastic endotracheal tubes for prolonged intubation and ventilation. Dr. Bernard Brandstater, an Australian working in Lebanon, reported prolonged intubation as an alternate to the tracheostomy at the First European Congress in Anesthesia in 1962. The first report of prolonged intubation in 50 patients was described in the *British Journal of Anesthesia* in 1965 by Drs. McDonald and Stocks.[121] Australian pediatric critical care is highly regionalized in tertiary university services supported by sophisticated retrieval services. Until 1991, all critically ill children in New Zealand received care in adult ICUs. The first PICU opened in December 1991 at the Starship Children's Hospital in Auckland.

Since 1996, all units have contributed outcome and other data to the Australian and New Zealand Pediatric Intensive Care Registry. The registry has evolved into a multicenter trials research group, affiliated with the Australian and New Zealand Intensive Care Society Clinical Trials Group. Recent evidence utilizing various scoring systems including the registry-developed PIM (Pediatric Index of Mortality) score reveal that outcomes in the region are better than predicted.[122] A formalized training scheme evolved during the 1990s and a separate College of Intensive Care Medicine will control all training in intensive care for the region from 2010 onwards.[123,124]

Europe

In Europe, pediatric intensive care followed shortly after the poliomyelitis epidemic in Denmark in 1952. Even in the early years, it was recognized that children had a higher mortality than adults in these poliomyelitis respiratory units; thus separate PICUs were developed in Uppsala and Stockholm in the 1950s. In 1955, Dr. Goran Haglund, an anesthesiologist, established the first PICU for infants and children at the Children's Hospital in Goteborg in Sweden. In 1961 Dr. Hans Feychting, a pediatric anesthesiologist, established the first PICU in Stockholm, Sweden, and became recognized as a pioneer in the development of pediatric intensive care in Europe. He introduced many of the skills that had been developed for the operating room and were later applied to pediatric intensive care.

In France, in July 1963, a newborn presented with tetanus and was admitted to l'Hôpital des Enfants Malades of Paris. Shortly afterward, Dr. Gilbert Huault opened the first multidisciplinary PICU, in Saint Vincent de Paul Hospital. This unit was the first pediatrician-directed PICU in Europe; it soon became a major influence on the development of ICUs, and in it, Drs. Francois Beaufils and Denis Devictor were to play an important role in the further development of critical care practice in pediatrics.

In Britain, in 1964, the first PICU was opened by Dr. G. Jackson Rees, an anesthesiologist, at the Alder Hey Children's Hospital in Liverpool. Other units soon followed, essentially serving as areas allowing prolonged postoperative support. Dr. Todres worked in such a unit at the Hospital for Sick Children, Great Ormond Street, London, in 1966. Although not designated "a pediatric ICU," in essence it was a unit that operated in this manner. This experience formed the foundation of intensive care practice that followed, with primary attention to conditions that led to failure of ventilation and circulation. Here Dr. David Hatch was instrumental in developing a PICU that provided outstanding clinical care and research.[125,126]

In Spain, a pediatrician, Dr. Francisco Ruza, had started working in neonatal surgical intensive care in 1969. By 1976, he opened a multidisciplinary medical-surgical PICU for older infants and children at the "Hospital Infantil La Paz" in Madrid. This center, directed by Dr. Ruza, has served as a major training center for pediatric intensivists not only from Spain but from South America as well.[127]

The first PICUs in The Netherlands were established in the late 1970s and early 1980s at the Sophia Children's Hospital in Rotterdam, the Wilhelmina Children's Hospital in Utrecht, and the Emma Children's Hospital at the Academic Medical Center in Amsterdam. In 1995, a section on Pediatric Intensive Care Medicine was founded by the Dutch Pediatric Association, which certifies the training of nearly all Dutch pediatric intensivists in fellowship programs. The PICUs are multidisciplinary, and all are part of university teaching hospitals. A nationwide transport system to connect this centralized care system of pediatric critical care was developed. Dr. Albert Bos in Amsterdam and Dr. Edwin van der Voort in Rotterdam continue to foster the highest standards of pediatric critical care. Units were opened in Germany[128] and Slovakia[129] as well as in many other places at that time.

Israel

Although located in the Middle East, Israel has traditionally been part of the European scientific organizations. The first PICU in Israel was established in 1977 by Dr. Zohar Barzilay as a five-bed facility located within the Children's Hospital at Sheba. Now, 32 years later, Israel has 12 PICUs and two cardiac PICUs. Extracorporeal membrane oxygenation services as well as cardiac transplantation are provided nationwide as part of the national health insurance program. A special chapter in Israel pediatric critical care medicine belongs to the Palestinian pediatric population. About 30% of the patients in many of the PICUs in Israel come from the Palestinian Authority. Palestinian physicians trained in PCCM in Israel established the first PICU in Gaza.[130,131]

Latin America

In Argentina, the first PICU was established in Dr. Ricardo Gutierrez Children's Hospital in Buenos Aires in 1969 as part of a general surgery ward. In 1972, Dr. Jorge Sasbon became the first staff director of the PICU. In 1972, a PICU was set up in Pedro de Elizalde Children's Hospital under the guidance of Dr. Clara Bonno, and the unit has been a pillar of the specialty in Argentina.

Critical care progressed steadily, and the first liver transplant in a pediatric patient was performed in 1987. With the introduction of international fellowships, physicians were able to travel abroad for further training in units in Toronto, Pittsburgh, Madrid, and London. The J.P. Garrahan National Pediatric Hospital was inaugurated as a tertiary center in 1987, and has developed a sophisticated PICU under the direction of Dr. Jorge Sasbon.

In Brazil in the 1970s, epidemics of polio and meningococcal disease with high mortality led to the creation of small units for the care of these patients, attended to by personnel with skills and technical resources (although they were scarce). These units were the precursors of PICUs later established at Hospital das Clínicas São Paolo by Dr. Anthony Wong (1977), at Hospital São Lucas in Porto Alegre by Dr. Pedro Celiny (1978), and in Rio de Janeiro. At the same time, neonatal intensive care was developing, and the model of the NICU was transferred to the care of critically ill children in the 1980s. In 1982, Dr. Jefferson Piva opened a 13-bed PICU at Hospital da Criança Santo Antonio in Porto Alegre.[132]

In 1984, the first Brazilian Pediatric Intensive Care Congress in São Paolo took place. These congresses continue annually. At the three major tertiary centers in São Paolo, Rio de Janeiro, and Porto Alegre, government agencies actively support research programs. Pediatric intensivists in the Brazilian Pediatric Society and the Brazilian Critical Care Society worked together to establish the subspecialty, with examination certification commencing in 1990. Brazil's intensivists also are active in cooperative efforts with other Latin American intensive care societies. One of the pioneers of development of pediatric critical care in Latin America was Dr. Mauricio Gajer, a dedicated physician from Uruguay. Dr. Gajer, with the stimulus of Professor Ramon Guerra, created the first PICU in Uruguay in 1975. He traveled to France, where he worked with Professors Huault and Beaufils. After returning to Uruguay he created the first private ICU in Uruguay. With his enthusiasm to bring all Latin American pediatricians together in the cause of critical care, he organized the first Latin American Pediatric Intensive Care Congress in Uruguay in 1993, which led to development of the Pediatric Intensive Care Society. In Colombia, Pediatric Intensive Care started in the early 1960s, with postoperative care of cardiovascular patients in the Clínica Shaio of Bogotá, with adult cardiologists in charge. In the 1970s the cardiovascular patients were taken care of by Dr. Merizalde, a pediatrician with training in pediatric cardiology. In 2007, the first pediatric critical training started in Bogotá, and 2 years later there are five programs in three cities.

In 1956, in the Luis Calvo Mackenna Children's Hospital in Santiago, Chile, a single-bed postoperative care unit was started by Drs. Helmut Jager (cardiac surgeon) and Fernando Eimbecke (cardiology). In 1968 this evolved into a five-bed PICU started by Dr. Eduardo Bancalari who was later joined by Drs. Patricio Olivo and Jaime Cordero (pediatricians). In the 1970s, Dr. Carlos Casar started a PICU at the Roberto del Rio Children's Hospital in Santiago, Chile and was later joined by Dr. Bettina von Dessauer (pediatrician).[133] There was no formal training in PCCM and these pediatricians devised individual programs to prepare themselves for taking care of sick children. Intensivists there have devoted great effort toward developing transport systems to overcome the impact of Chile's difficult geography.

In a similar fashion, the first intensive care unit in San Jose, Costa Rica was opened in 1969 as a postoperative cardiac care unit. It was initially a nine-bed unit run by anesthesiologists and surgeons. Eventually pediatricians, without special PCCM training, became involved. Dr. Aristides Baltodano was the first formally trained (Toronto) pediatrician to work in intensive care in Costa Rica, joining the staff in 1982. They now have a 22-bed multidisciplinary unit with more than 1000 admissions per year.[134]

Our Heroes

As previously noted, there are people in medicine who deserve Courage, Size 1 awards. These include, but certainly are not limited to, Dr. Jesse Lazear (yellow fever), Michael Servetes (pumping action of the heart), and a Guatemalan physician, Dr. Juan Francisco Pratesaba, who refused to stop treating wounded guerilla soldiers who presented themselves to his clinic during the civil war. He disappeared shortly thereafter, and was tortured and killed.[135] There are no Courage, Size 1 awards in PCCM. There are Courage, Size 4 awards (e.g., O'Dwyer) and probably many Perseverance, Size 1 awards (e.g., Smythe and Bull, and Klein). Certainly our most prominent awards are Courage, Size 4 to our patients and their families.

But we do have "heroes" by other measures, who have been recognized for their contributions to the field by their peers and organizations. These include the international pioneer awards of the WFPICCS (Box 1-1), the distinguished career awards of the Section on Critical Care of the AAP (Box 1-2), the chairs of the PCCM sub-board (Box 1-3), pediatric intensivist presidents of SCCM (Box 1-4), chairs of the

Box 1–1 International Pioneer Awards World Federation of Pediatric Intensive Care Societies*

Alan Conn, Canada
John Downes, United States
Hans Feychting, Stockholm, Sweden
Maurico Gajer, Uruguay
Gilbert Huault, France
Seigo Iwai, Japan
Max Klein, South Africa
John Socks, Australia

*Awarded Montreal, 2000

Box 1–2 Distinguished Career Awardees, Section on Critical Care, American Academy of Pediatrics

1995: I. David Todres, MD
1996: John Downes, MD
1997: Peter Holbrook, MD
1998: George Gregory, MD
1999: George Lister, MD
2000: Russel Raphaely, MD
2001: Murray Pollack, MD
2002: Daniel Levin, MD
2003: Ann Thompson, MD
2004: Bradley Fuhrman, MD
2005: J. Michael Dean, MD
2006: David Nichols, MD
2007: Ashok Sarnaik, MD
2008: Patrick Kochanek, MD
2009: Jerry Zimmerman, MD
2010: M. Michelle Moss, MD

Critical Care Executive Committee of the AAP (Box 1-5), chairs of the pediatric section of the SCCM (Box 1-6), and those honored by the SCCM (Box 1-7); and there are many more to come.

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Box 1–3 Chairs, Pediatric Critical Care Medicine Subboard, American Board of Pediatrics*

1985-1987	Peter Holbrook, MD
1988-1990	Bradley Fuhrman, MD
1991-1992	Thomas Green, MD
1993-1996	Ann Thompson, MD
1997-1998	Daniel Notterman, MD
1999-2001	David Nichols, MD
2002-2003	Jeffrey Rubenstein, MD
2004-2004	Alice Ackerman, MD
2005-2007	Donald Vernon, MD
2008-2009	Karen Powers, MD

*Medical Editor, 1985-2004, George Lister, MD

Box 1–4 Pediatric Intensivists, Presidents of Society of Critical Care Medicine

1982	George Gregory, MD
1984	Dharampuri Vidyasagar, MD
1988	Peter Holbrook, MD
1992	Russel Raphaely, MD
2001	Ann Thompson, MD
2004	Margaret M. Parker, MD

Box 1–5 Chairs, Executive Committee, Section on Critical Care Medicine, American Academy of Pediatrics

1984-1987	Russel Raphaely, MD
1987-1990	Fernando Stein, MD
1990-1992	J. Michael Dean, MD
1992-1996	Kristian Outwater, MD
1996-2000	Timothy Yeh, MD
2000-2004	M. Michele Moss, MD
2004-2008	Alice Ackerman, MD
2008-2010	Donald Vernon, MD

Box 1–6 Chairs, Pediatric Section, Society of Critical Care Medicine

1980-1981	Peter Holbrook, MD
1981-1983	Russel Raphaely, MD
1983-1984	Bernard Holtzman, MD
1984-1985	Bradley Furhman, MD
1985-1986	Frank Gioia, MD
1986-1987	Timothy Yeh, MD
1987-1988	Fernando Stein, MD
1988-1989	Thomas Rice, MD
1989-1991	Ann Thompson, MD
1991-1994	J. Michael Dean, MD
1994-1996	Debra Fiser, MD
1996-1998	Tom Green, MD
1998-2000	Daniel Notterman, MD
2000-2002	Richard Brilli, MD
2002-2004	M. Michele Moss, MD
2004-2006	Stephanie Storgion, MD
2006-2008	Edward Conway Jr, MD
2008-2010	Vicki Montgomery, MD

Box 1–7 Pediatric Award Recipients, Society of Critical Care Medicine

Shubin-Weil Master Clinician/Teacher: Excellence in Bedside Teaching Award

1990	John J. Downes, MD
1993	Alan I. Fields, MD

Grenvik Family Award for Ethics

1993	Robert D. Truog, MD
1999	I. David Todres, MD

Distinguished Service Award

2002	Patrick M. Kochanek, MD
2004	Ann E. Thompson, MD
2007	Margaret M. Parker, MD
2009	Richard J. Brilli, MD
2009	Alan I. Fields, MD

ACCM Distinguished Investigator Award

2002	Murray M. Pollack, MD
2007	Patrick M. Kochanek, MD

Barry A. Shapiro Memorial Award for Excellence in Critical Care Management

2010	M. Michele Moss, MD

Lifetime Achievement Award

2010	John J. Downes, MD

Devictor, Gideon Eshel, Bradley Fuhrman, George Gregory, Mary Fran Hazinski, Peter Holbrook, Max Klein, Patrick Kochanek, Jacques LaCroix, George Lister, M. Michele Moss, David Nichols, Bradley Peterson, Jefferson Piva, Arnold Platzker, Bala Ramachandran, Adrienne Randolph, Francisco Ruza, Hirokazu Sakai, David Schell, Fernando Stein, Ann Thompson, James Thomas (reviewer), Dharmapuri Vidyasagar, Gary Williams, Douglas Willson, Timothy Yeh, the AAP, and the SCCM.

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References are available online at http://www.expertconsult.com.

Chapter 2

The Intensivist in the New Hospital Environment: Patient Care and Stewardship of Hospital Resources

Margaret M. Parker

PEARLS

- Effective teamwork is essential for optimal care of the critically ill child in the setting of limited resources.
- Communication and collaboration among members of the health care team improve the quality and efficiency of patient care.
- The intensivist, as "captain of the ship," must manage the clinical care of the critically ill child and the organization of the intensive care unit to make optimal use of limited resources.

Intensive care units (ICUs) create an environment in which critically ill patients can be supported and many lives can be saved. By their very nature, ICUs are resource intensive with respect to both technology and the need for skilled health care providers. A large percentage of hospital costs are attributed to the ICU. As the cost of health care increases, the need to manage the resources of the ICU as efficiently and effectively as possible increases in importance as well.

Many studies in the literature have reported that management of the ICU and critically ill patients by intensivists increases survival rates and decreases resource utilization.[1-4] In addition to improvement in resource utilization, Gajic et al.[3] reported that the presence of a critical care specialist was associated with improved staff satisfaction, an important consideration when considering the increasing staffing limitations. Not all studies have reported a benefit in outcome, however. In sharp contrast to the many studies showing improved outcomes associated with intensivist staffing, Levy et al.[5] reported that patients managed by intensivists had a higher risk of death than did those who were not managed by them. It is not clear why this study had such disparate results from previous studies, but one likely reason is that the study design was very different from that of previous studies, as were the definitions used.[6] The systematic review by Pronovost et al.[1] defined high-intensity staffing as the ICU policy requiring that the intensivist have responsibility for care for all of the patients in the ICU (closed ICUs) or that there be a mandatory consultation by an intensivist. In the study by Levy et al.,[5] the involvement of the intensivist was elective (i.e., not decided at the unit level but by the choice of the attending physician). According to the definition by Pronovost et al.,[1] ICUs that allow the choice of whether to involve an intensivist are low-intensity staffing models. The effect of intensivists in low-intensity–staffed ICUs has not been studied adequately. Levy et al.[5] did a separate analysis of no-choice ICUs versus choice ICUs and reported that the mortality rate was higher in the no-choice ICUs, raising the question again as to whether intensivist staffing may increase mortality rates, although a mechanism by which this outcome might occur is not apparent. The preponderance of available studies continues to show a benefit of management by an intensivist.

Unlike adult critical care units, nearly all pediatric ICUs have trained pediatric intensivists who manage most (if not all) of the patients. In the United States, only about 30% of the adult ICUs are staffed by trained intensivists. Regionalization of trauma services for adults has improved outcomes of trauma patients.[7] Regionalization has been recommended as a way to improve the care of critically ill or injured adults and children, although the barriers to regionalization are far greater for adults than for children.[8,9] Regionalization effectively puts limited resources together to maximize the effectiveness and availability of these resources to a greater number of patients, although at the expense of travel for many patients and their families.

Organization and Quality Issues

During the past 2 decades, the cost of health care in the United States has increased dramatically, with hospital costs increasing more rapidly than other cost indexes. Controlling critical care medicine costs will be an important issue as health care reform is discussed. Critical care consumes an increasing proportion of hospital beds as the acuity of hospital inpatients increases. Although the cost of critical care is rising, the proportion of national health expenses used in critical care medicine has decreased over time.[10,11] Different methods for calculating critical care medicine costs create some discrepancies in the estimates of these costs, making it difficult to ensure that efforts to control costs are really effective.

The ICU provides support to a variety of services that could not be offered without ICU care, such as cardiac surgery and transplantation. Defining the ICU as the cost center gives a very different picture of the expense of ICU care than would attributing the costs of such patients to the services that use the ICU. Similarly, attributing some of the revenue that such services generate to the ICU and critical care physicians rather than solely to the surgical service per se provides a different view of the value of the ICU to the institution. Different strategies for controlling costs have potential benefit but often have unintended consequences. Shifting costs from the ICU to the supporting hospital services further complicates efforts to account for accurate ICU costs. True critical care medicine cost containment is extremely difficult, if not impossible.[12]

Today's intensivist must be knowledgeable about the economic aspects of managing the ICU and balance economic realities with the needs of the critically ill patient. Controlling costs of care without compromising the care of the patient requires a multitude of administrative and clinical skills. Close attention to both clinical details and financial considerations is necessary to meet these dual challenges. The intensivist needs to demonstrate flexibility and adaptability in order to navigate the business aspects of critical care while providing the best possible care for the patient.

Effective multidisciplinary care requires developing a teamwork model in the ICU. True teamwork recognizes the importance of the role of each member of the team and requires respect and trust for the other professions represented on the team. Effective communication between all members of the health care team and the patient/family cannot be overemphasized. A collaborative partnership with shared responsibility for maintaining communication and accountability for patient care includes the recognition that no one provider can perform all parts of patient care; the whole team is much more effective than each member of the team alone. True teamwork is a complementary relationship of interdependence.[13]

An effective team is critical to both the clinical and financial health of the ICU.[14] Good teamwork requires a number of skills. A team performance framework for the ICU requires communication, leadership, coordination, and team decision making. Effective team leadership is crucial for guiding effective team interactions and coordination. Leadership performance can be measured; the leadership performance of attending intensivists is associated with accomplishment of daily patient goals.[15] Important leadership characteristics include communication skills, conflict management, time management, acknowledging others' concerns and one's own limitations, focus on results, setting high standards, and showing appreciation for the work of the team.

Quality improvement is an important part of ICU management. The intensivist must be responsible for leading and ensuring quality improvement efforts. The Institute of Medicine's "six aims for improvement" are safety, effectiveness, equity, timeliness, patient centeredness, and efficiency.[16] These aims are certainly relevant to pediatric critical care practice and can provide a framework for improving quality in the pediatric ICU (PICU). Acuity scores have been used as tools for measuring quality in the ICU. It is important for the intensivist to understand the various available scoring systems and how they can be used to ensure appropriate use of these tools.[17]

The use of clinical pathways has been shown to improve efficiency of care and decrease resource utilization.[18] The intensivist, as leader of the team, must ensure that these guidelines are developed with input from all members of the ICU team to optimize acceptance and smooth implementation of such guidelines. Standardization of care increases the likelihood that every patient will get the appropriate treatments at the right time. A common objection to standardization is that ICU patients are too complex or too different to be able to standardize their care. However, some aspects of care should be provided to most, if not all, patients and can be overlooked easily if they are not standardized. One example is insertion of central venous catheters using full-barrier precautions to prevent line-associated bloodstream infections. Checklists are helpful to remind all members of the team to carry out the "routine" steps every time. In the case of a patient who has a contraindication to "standard" care, the contraindication should be documented. In an environment that is increasingly complex, ensuring reliability in processes of care is exceedingly difficult. Standardizing the processes means that everyone on the team knows what to expect. Empowering every member of the team to speak up if he or she observes an unsafe condition further increases the safety of the patient and the reliability of care.

A systematic review by Carmel and Rowan[19] described eight organizational categories that may contribute to patient outcome in the ICU. These factors include staffing, teamwork, patient volume and pressure of work, protocols, admission to intensive care, technology, structure, and error. Pollack and Koch[20] demonstrated that organizational factors and management characteristics can influence health outcomes in the neonatal ICU. The intensivist, as captain of the ship, is responsible for ensuring that these important organizational factors are optimized in the ICU.

Manpower Issues

By its very nature, critical care is an intense and stressful field. Optimal clinical care and management in the ICU depends first and foremost on the availability of sufficient numbers of trained critical care professionals. Shortages of all types of critical care providers are an increasing concern. The Society of Critical Care Medicine, the American College of Chest Physicians, and the American Thoracic Society performed a manpower analysis of critical care specialists in 1997 and projected an increasing shortage of intensivists during the next 2 decades.[21] These three professional societies, along with the American Association of Critical-Care Nurses, further reviewed the available literature to identify causes of the shortage of critical care professionals and possible approaches to redesigning critical care practice.[22] These groups recommended common standards across the critical care field to promote uniformity and quality, use of information technology to promote standardization and improve efficiency, government incentives to attract health care professionals to critical care, and sponsorship of research defining the optimum role for intensive care professionals in the delivery of critical care. In an interesting study that looked at intensivist/bed ratio, Dara and Afessa[23] reported that differences in intensivist/bed ratios from 1:7.5 to 1:15 were not associated with differences in mortality rates, but a ratio of 1:15 was associated with increased ICU length of stay. Shortages of intensivists, which lead to higher numbers of patients per intensivist, may further limit the availability of ICU beds by increasing the

length of stay. Although these projects and the resulting documents were primarily aimed at critical care services for adults, the need for which will unquestionably increase markedly as the population ages, there are similar and equally pressing shortages of well-trained pediatric critical care professionals.[24] The pediatric intensivist needs to be aware of the importance of the health care professional as one of the most important resources of the PICU.

A matter that is at least as concerning as the physician shortage in the ICU is the increasing shortage of critical care nurses. As the supply of nurses decreases, the nurse/patient ratio in many ICUs increases. Increasing the number of critically ill patients a nurse must care for has negative effects on both patient care and on nursing morale and job satisfaction.[25,26] Decreased morale leads to increased turnover and the loss of experienced and highly skilled nurses. This situation, in turn, places patients at increased risk.

The presence of a pharmacist on rounds in the ICU has been shown to reduce drug errors and improve patient safety. Pharmacists are another group of critical care professionals who are in increasingly short supply.[27]

With the increasing shortage of intensivists has come consideration of other ways to provide adequate numbers of practitioners to care for critically ill patients. Hospitalists provide a substantial amount of critical care in the United States. One study reported that after-hours care in the PICU by hospitalists was associated with improved survival rates and shorter length of stay compared with care by residents.[28] Numerous studies have looked at the role of nurse practitioners and physician assistants as physician extenders in the PICU.[29-31] These practitioners can effectively complement the physician staff in the ICU, especially as resident work hours decrease.

Summary

Health care costs continue to increase and will likely do so until there is meaningful health care reform in the United States. Critical care consumes a large, although not increasing, share of health care costs. With the increasing complexity of management of the critically ill patient, careful management of the very limited resources available to promote optimal outcomes is increasingly important. The pediatric intensivist must be skilled in the management not only of the critically ill child, but also in the administration of the PICU and the appropriate use of all of its resources. Effective teamwork will be the key to ensuring optimal care in the face of limited resources.

References are available online at http://www.expertconsult.com.

Chapter 3

The Nurse in Pediatric Critical Care

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PEARLS

- Nursing's unique contribution to patients within the health care environment is that nurses create safe passage for patients and families.
- Nurses coordinate the patient's and family's experiences by their continuous attention to the person who exists underneath all the advanced technology that is being employed.
- Building a humanistic environment that endorses parents as unique individuals capable of providing essential elements of care to their children lays the foundation for family-centered care.
- Caring practices are a constellation of nursing activities that are responsive to the uniqueness of the patient/family and create a compassionate and therapeutic environment with the aim of promoting comfort and preventing suffering.
- Excellence in a pediatric critical care unit is achieved through a combination of many factors and is highly dependent on a healthy work environment.
- Studies have demonstrated that a stable, established, and proficient nursing workforce improves patient outcomes.
- A successful critical care professional advancement program recognizes varying levels of staff nurse knowledge and expertise and fosters advancement through a wide range of clinical learning and professional development experiences.
- Technical training alone is insufficient in meeting patient and family needs in the critical care environment.

Pediatric critical care nursing has evolved tremendously over the years. The nurse is the singular person in the pediatric critical care unit who creates an environment in which critically unstable, highly vulnerable infants and children benefit from vigilant care and who coordinates the actions of a highly skilled team of patient-focused health care professionals. Pediatric critical care nursing practice encompasses staff nurses who provide direct patient care, nursing leaders who facilitate an environment of excellence, and professional staff development that ensures continued nursing competence and professional growth. This chapter discusses the essential components of pediatric critical care nursing practice.

Describing What Nurses Do: The Synergy Model

The synergy model describes nursing practice based on the needs and characteristics of patients and their families.[1] The fundamental premise of this model is that patient characteristics drive required nurse competencies. When patient characteristics and nurse competencies match and synergize, optimal patient outcomes result. The major components of the synergy model encompass patient characteristics of concern to nurses, nurse competencies important to the patient, and patient outcomes that result when patient characteristics and nurse competencies are in synergy.

Patient Characteristics of Concern to Nurses

Every patient and family member brings unique characteristics to the pediatric intensive care experience. These characteristics—stability, complexity, predictability, resiliency, vulnerability, participation in decision making, participation in care, and resource availability—span the continuum of health and illness. Each characteristic is operationally defined as follows.

Stability refers to the person's ability to maintain a steady state. Complexity is the intricate entanglement of two or more systems (e.g., physiologic, family, and therapeutic). Predictability is a summative patient characteristic that allows the nurse to expect a certain trajectory of illness. Resiliency is the patient's capacity to return to a restorative level of functioning using compensatory and coping mechanisms. Vulnerability refers to an individual's susceptibility to actual or potential stressors that may adversely affect outcomes. Participation in decision making and participation in care are the extents to which the patient and family engage in decision making and in aspects of care, respectively. Resource availability refers to resources that the patient/family/community bring to a care situation and include personal, psychological, social, technical, and fiscal resources.

These eight characteristics apply to patients in all health care settings. This classification allows nursing to have a common language to describe patients that is meaningful to all care areas. For example, a critically ill infant in multisystem organ failure might be described as an individual who is

unstable, highly complex, unpredictable, highly resilient, and vulnerable, whose family is able to become involved in decision making and care but has inadequate resource availability.

Each of these eight characteristics forms a continuum, and individuals fluctuate at different points along each continuum. For example, in the case of the critically ill infant in multisystem organ failure, stability can range from high to low, complexity from atypical to typical, predictability from uncertain to certain, resiliency from minimal reserves to strong reserves, vulnerability from susceptible to safe, family participation in decision making and care from no capacity to full capacity, and resource availability from minimal to extensive. Compared with existing patient classification systems, these eight dimensions better describe the needs of patients that are of concern to nurses.

Nurse Competencies Important to Patients and Families

Nursing competencies, which are derived from the needs of patients, also are described in terms of essential continua: clinical judgment, clinical inquiry, caring practices, response to diversity, advocacy/moral agency, facilitation of learning, collaboration, and systems thinking.

Clinical judgment is clinical reasoning that includes clinical decision making, critical thinking, and a global grasp of the situation coupled with nursing skills acquired through a process of integrating formal and experiential knowledge. Clinical inquiry is the ongoing process of questioning and evaluating practice, providing informed practice on the basis of available data, and innovating through research and experiential learning. The nurse engages in clinical knowledge development to promote the best patient outcomes. Caring practices are a constellation of nursing activities that are responsive to the uniqueness of the patient/family and create a compassionate and therapeutic environment with the aim of promoting comfort and preventing suffering. Caring behaviors include, but are not limited to, vigilance, engagement, and responsiveness. Response to diversity is the sensitivity to recognize, appreciate, and incorporate differences into the provision of care. Differences may include, but are not limited to, individuality, cultural practices, spiritual beliefs, gender, race, ethnicity, disability, family configuration, lifestyle, socioeconomic status, age, values, and alternative care practices involving patients/families and members of the health care team. Advocacy/moral agency is defined as working on another's behalf and representing the concerns of the patient/family/community. The nurse serves as a moral agent when assuming a leadership role in identifying and helping to resolve ethical and clinical concerns within the clinical setting. Facilitation of learning is the ability to use the process of providing care as an opportunity to enhance the patient's and family's understanding of the disease process, its treatment, and its likely impact on the child and family. Collaboration is working with others (i.e., patients, families, and health care providers) in a way that promotes and encourages each person's contributions toward achieving optimal and realistic patient goals. Collaboration involves intradisciplinary and interdisciplinary work with colleagues. Systems thinking is appreciating the care environment from a perspective that recognizes the holistic interrelationships that exist within and across health care systems.

These competencies illustrate a dynamic integration of knowledge, skills, experience, and attitudes needed to meet patients' needs and optimize patient outcomes. Nurses require competence within each domain at a level that meets the needs of their patient population. Logically, more compromised patients have more severe or complex needs; this in turn requires the nurse to possess a higher level of knowledge and skill in an associated continuum. For example, if a patient is stable but unpredictable, minimally resilient, and vulnerable, primary competencies of the nurse center on clinical judgment and caring practices (which include vigilance). If a patient is vulnerable, unable to participate in decision making and care, and has inadequate resource availability, the primary competencies of the nurse focus on advocacy/moral agency, collaboration, and systems thinking. Although all the eight competencies are essential for contemporary nursing practice, each assumes more or less importance depending on a patient's characteristics. Optimal care is most likely when there is a match between patient needs/characteristics and nurse competencies.

Clinical Judgment

Clinical judgment, that is, skilled clinical knowledge, use of discretionary judgment, and the ability to integrate complex multisystem data and understand the expected trajectory of illness and human response to critical illness defines competent nursing practice. In critical care, the novice nurse focuses on individual aspects of the patient and the environment. As expertise develops, the nurse develops a global understanding of the situation. The expert nurse anticipates the needs of patients, predicts the patient's trajectory of illness, and forecasts the patient's level of recovery. Evolving clinical expertise creates safe passage for patients. The very best nursing care often is invisible, as it should be, because untoward effects and complications are prevented. Nursing's unique contribution to patients within the health care environment, which encompasses all nursing's competencies, is that nurses create safe passage for patients and families. Safe passage may include helping the patient and family move toward a greater level of self-awareness, knowledge, or health; transition through the acute care environment or stressful events; and/or a peaceful death.

Clinical Inquiry

Clinical inquiry optimizes the delivery of evidence-based care. Studying the clinical effectiveness of care and how it affects patient outcomes provides information that helps balance cost and quality. Quality improvement methods include use of multidisciplinary teams that work together to help systems operate in a way that promotes the best interests of patient care. Collaborative practice groups working with clinical practice guidelines (CPGs) provide the opportunity to initiate evidence-based interventions.

CPGs—that is, patient-centered multidisciplinary and multidimensional plans of care—help the team provide evidence-based practice and improve the process of care delivery. CPGs ensure practitioner accountability, encourage coordinated care, decrease unnecessary variation in practice patterns, improve quality and cost-effective services, and provide a means to systematically evaluate the quality and effectiveness of practice in moving patients toward desired outcomes. Effective CPGs are driven by patient needs and help provide

evidence linking interventions to patient outcomes. CPGs help guide the appropriate use of resources, limiting interventions. Evidence-based guidelines can help to eliminate interventions that do not benefit patients but frequently are steeped in tradition and opinion.

Caring Practices

Caring practices bring clinical judgment to view. Caring practices are activities that are meaningful to the patient and family and enhance their feelings that the health care team cares about them. Families equate caring behaviors with competent behaviors. Families trust that nurses will be vigilant. Vigilance, which includes alert and constant watchfulness, attentiveness, and reassuring presence, is essential to limit the complications associated with a patient's vulnerabilities.[1]

Nurses coordinate the patient's and family's experiences by their continuous attention to the person who exists underneath all the advanced technology that is employed. This steady attention can make an important difference for patients by helping patients and their families better tolerate the experience of critical illness. This aspect of practice, our presence with patients, is unique to the profession of nursing.[1] For example, in working with patients with head injuries, caring nurses acknowledge the person by surrounding them with their possessions, such as family pictures and cards from friends, and their favorite music. Nurses talk with their unresponsive patients, orienting them and telling them what is going on, which preserves the patient's "humanness." Occasionally a patient responds as evidenced by as an increase in heart rate or blood pressure, a decrease in intracranial pressure, or the shedding of a tear. Nurses take this level of communication one step further by teaching this process to family members so they too can interact with their critically ill loved one.

Pediatric critical care nurses, more than any other intensive care unit (ICU) nursing subspecialty, have made significant progress in integrating family-centered care into the practice of critical care. Building a humanistic environment that endorses parents as unique individuals capable of providing essential elements of care to their children lays the foundation for family-centered care. Family-centered care is more than just providing parents with unlimited access to their children.[1]

Nursing research provides the foundation for this change in practice. Based on nursing research, we know that parents have the need for hope, information, and proximity; to believe that their loved one is receiving the best care possible; to be helpful; to be recognized as important; and to talk with other parents with similar issues. Pediatric critical care nurses have gone beyond the identification of family needs to illustrating interventions that patients and families find helpful.[1] We provide families with what they need to help their child. Parents believe the most important contribution pediatric critical care nurses make is to serve as the "interpreter" of their critically ill child's responses and of the pediatric ICU environment.

Response to Diversity

Response to diversity honors the differences that exist in the people we are and in the individuals we care for. At a minimum, it requires that care be delivered in a nonjudgmental, nondiscriminatory manner. Effective communication with patients and families at their level of understanding may require customizing the health care culture to meet the diverse needs and strengths of families. Skilled nurses foresee differences and beliefs within the team and negotiate consensus in the best interest of the patient and family.

Advocacy/Moral Agency

Moral agency acknowledges the particular trust inherent within nurse-patient relationships, a trust gained from nursing's long history of speaking on the patient's behalf in an effort to preserve a patient's "lifeworld" (Hooper, personal communication, 1996). The holistic view of the patient that nurses often possess is a reflection of moral awareness.

When a cure is no longer possible, nurses turn their focus to ensuring that death occurs with dignity and comfort. Nurses "orchestrate" death, supporting parents and family members through the death of their loved one. Nurses often coordinate the experience for patients and families when death is imminent. This most intimate aspect of nursing care is a profound contribution to humankind.[2]

Pediatric critical care nurses provide critical support of the practice of family presence during procedures and resuscitation. Including family members during pediatric resuscitation is not a universal practice. However, one study established that the parents who were able to be present during their child's resuscitation collectively believed that their presence provided comfort to their child and themselves.[3] Parents who were not able to stay regretted not being able to comfort their child in the final moments of his or her life. The study authors advocated that policies be developed to facilitate parental presence during resuscitation. A study of physicians ascertained that most respondents encouraged family members to be present during their child's resuscitation.[4] The majority of physicians believed that being there was helpful to parents and that physicians should be prepared for this practice. Nurses take on the essential accountability of preparing families to stay with their child.[5]

Facilitator of Learning

Nurses facilitate learning so that patients and their families become knowledgeable about the health care system and can make informed choices. Teaching is an almost continuous process that involves helping the patient and the family understand the critical care environment and therapies involved in critical care. Also essential is reinforcement of the patient's experience and how, most likely, the infant or child will cope with the ICU experience. This education provides patients with the capacity to help themselves and for parents to help their infants and children.

Collaboration

Collaboration requires commitment by the entire multidisciplinary team. A classic study done by Knaus et al.[6] found an inverse relationship between actual and predicted patient mortality and the degree of interaction and coordination of multidisciplinary intensive care teams. Hospitals with good collaboration and a lower mortality rate had a comprehensive nursing educational support program that included a clinical nurse specialist and clinical protocols that staff nurses can independently initiate. The American Association of Critical-Care Nurses Demonstration Project also documented a low mortality ratio, low complication rate, and high

patient satisfaction in a unit that had a high perceived level of nurse/physician collaboration, highly rated objective nursing performance, a positive organizational climate, and job satisfaction and morale.[7]

Systems Thinking

Nurses are constantly challenged to design, implement, and evaluate whole programs of care, manage units where programs of care are provided, and determine whether the health care system is meeting patient needs.[8] These vital components require a patient-centered culture that stresses strong leadership, coordination of activities, continuous multidisciplinary communication, open collaborative problem solving, and conflict management.[9] For many years nurses have learned to manipulate the system on behalf of their patients; however, systems thinking[10]—that is, the ability to understand and effectively manipulate the complicated relationships involved in complex problem solving—is a new but necessary skill in taking overall responsibility for the caregiving environment.

Managing complex systems is essential to creating a safe environment. Nurse-patient relationships commonly occur around transitional periods of instability brought about by the demands of the health care situation. Helping patients make transitions between elements of the health care system—for example, into and out of the community—requires systems knowledge and intradisciplinary collaboration.[11]

Optimal Patient Outcomes

According to the synergy model, optimal patient outcomes result when patient characteristics and nurse competencies synergize. The study of many patient outcome measures is appropriate, including physiologic, psychological, functional, and behavioral outcome measures, as well as symptom control, quality of life, family strain, goal attainment, utilization of services, safety, problem resolution, and patient satisfaction.[12] A "nurse-sensitive" outcome, a term first coined by Johnson and McCloskey,[13] defines a dynamic patient or family caregiver state, condition, or perception that is responsive to nursing interventions. Brooten and Naylor[14] note: "The current search for 'nurse-sensitive patient outcomes' should be tempered in the reality that nurses do not care for patients in isolation and patients do not exist in isolation." Outcomes have been described at three levels: patient, provider, and system.

Patient Level Outcomes

Major patient level outcomes of concern to pediatric critical care nurses include hemodynamic stability and the presence or absence of complications. Outcomes related to limiting iatrogenic injury and complications of therapy demonstrate the potential hazards present in illness and in the critical care environment. Patient/family satisfaction ratings are subjective measures of health and/or the quality of health services. Patient satisfaction measures involving nursing typically include technical/professional factors, trusting relationships, and education experiences.[15] Patient-perceived functional change and quality of life are multidisciplinary outcome measures. Linking patient satisfaction, functional status, and quality of life is important because the three factors often are related.

Provider Level Outcomes

Provider level outcomes include the extent to which care/treatment objectives are attained within the predicted time period. Nurses coordinate the day-to-day efforts of the entire multidisciplinary team. The nurse's role as the coordinator of numerous services is essential for optimal patient outcomes and shorter lengths of stay. As discussed, nurse–physician collaboration and positive interaction is associated with lower mortality rates, high patient satisfaction with care, and low nosocomial complications.[6,7]

System Level Outcomes

Critical care units must manage resources and maintain quality as collaboratively defined by both users and providers in the system. The goal is high-quality care at moderate cost for the greatest number of people. Important patient-system outcome data include recidivism and costs/resource utilization. Recidivism, that is, rehospitalization and readmission, is repeated work that adds to the personal and financial burden of providing care. In addition to patient and system factors, nurses can decrease the patient's length of stay through coordination of care, prevention of complications, timely discharge planning, and appropriate referral to community resources. Reducing length of stay and tracking emergency department visits and rehospitalization ensure that cost shifting is not occurring.

Nightingale Metrics

One population-specific approach to measurement of nurse-sensitive outcomes is the Nightingale Metrics.[16] This program was developed so that bedside nurses could be actively involved in identifying nurse-sensitive metrics important to their unique patient and family population. Nurses give care in an environment that supports the capacity of the patient and family to heal. Much of nursing is preventive care that often is not measured; thus care is often invisible. When measuring outcomes, it is important to measure the invisible aspects of nursing that have a tremendous impact on patients. For example, invisible are the large numbers pressure ulcers that never develop because of good nursing care. The Nightingale Metrics reflect current standards of care, are based on evidence, and are measurable (Box 3-1).

Box 3–1 Pediatric Intensive Care Unit—Nightingale Metrics

- Pain and sedation scores every 4 hours
- In patients with a central venous line, changing the dressing every 7 days
- Establishment of a nutrition plan within 24 hours of admission
- Pressure ulcer bundle: If patient is immobile, documentation of position change every 2 hours and positioning of heels off the bed; if not on bed rest, documentation of patient being out of bed or held in parent's or nurses' arms
- Ventilator-associated pneumonia bundle: Head of bed elevation at 30 to 45 degrees; documentation of oral hygiene twice in 24 hours; peptic ulcer prophylaxis (in patients not receiving tube feedings); discussion of extubation readiness test on rounds; daily holiday from sedation or chemical paralysis
- "Time to critical intervention": response to panic laboratory value, the time intervals from sending specimen to laboratory to first intervention to correct laboratory value

Leadership

Excellence in a pediatric critical care unit is achieved through a combination of many factors and is highly dependent on effective leadership.[17] Numerous studies have demonstrated the importance of leadership in creating an environment where both nurses and patients can flourish. Effective leaders help diverse groups work together in harmony.[18]

Specialized units such as pediatric critical care units require staff with the expert knowledge and skill required to meet the multifaceted needs of patients and families. A healthy work environment should improve retention and recruitment. A study was done to determine the incidence of ICU nurses' intention to leave their jobs because of working conditions and to identify factors predicting this phenomenon.[19] Nurses were divided into two groups: (1) those intending to leave because of working conditions, and (2) others (e.g., those not leaving or retirees). Work environment was measured by investigating seven subscales: professional practice, staffing/resource adequacy, nursing management, nursing process, nurse/physician collaboration, nurse competence, and a positive scheduling climate.

A total of 2323 nurses from 66 hospitals and 110 critical care units in the United States completed surveys. Seventeen percent (n = 391) reported that they intended to leave their position in the coming year. Of those, 52% (n = 202) stated that the reason for their planned departure was working conditions. The authors of the study determined that improving the professional practice environment and clinical competence of the nurses as well as sustaining new nurses may decrease turnover and help secure an established and proficient workforce.[19]

The literature validates that an established and proficient workforce improves patient outcomes. A study conducted by Aiken et al.[20] observed the effect of nurse staffing levels on patient outcomes and factors affecting nurse retention. A total of 10,184 nurses from 168 hospitals were surveyed. The results concluded that after adjusting for patient and hospital characteristics, each additional patient per nurse was associated with a 7% increase in the likelihood of dying within 30 days of admission and a 7% increase in the odds of failure to rescue (death subsequent to a complication that develops and was not present at admission). In addition, after adjusting for nurse and hospital characteristics, each additional patient per nurse was associated with a 23% increase in the odds of burnout and a 15% increase in the odds of job dissatisfaction.

Aiken and colleagues[21] have continued their work by assessing the net effects of work environments on nurse and patient outcomes. Using data from the 168 hospitals and 10,184 nurses, they investigated whether better work environments were related to lower patient mortality and better nurse outcomes independent of nurse staffing and the education of the RN workforce in hospitals.[21] Work environments were considered based on the practice environment scales of the Nursing Work Index. Three of the five subscales studied were nursing foundations for quality of care; nurse manager ability, leadership, and support; and collegial registered nurse/physician relationships. Outcomes studied included job satisfaction, burnout, intent to leave, quality of care, mortality, and failure to rescue. Aiken and colleagues found that a higher percentage of nurses working in hospitals with unsupportive care environments reported higher burnout levels and dissatisfaction with jobs. They also found that work environment had a significant effect on plans to leave their units. When all patient and nurse factors were taken into account, the likelihood of patients dying within 30 days of admission was 14% lower in hospitals with healthier care environments. These findings support the observation that nursing leaders have at least three major opportunities to boost nurse retention and patient outcomes. These opportunities include increasing nurse staffing; using a more highly educated nurse workforce; and enhancing the work environment.

One of the best examples of a work environment that champions the nurse at the bedside is Magnet Hospital designation. Data demonstrate that hospitals that use the structure for magnet designation achieve significant improvements in their work environments.[21] Hospitals that have even some of the magnet characteristics illustrate improved nurse and patient outcomes. Characteristics of magnet hospitals that have the most impact on nurse and patient outcomes are investments in staff development, superior management, frontline manager supervisory skill, and good nurse/physician collaboration.[21]

The importance of a healthy work environment cannot be stressed enough as the means to ensure a viable, competent, and caring workforce. Nurses look for a culture that respects the nurse's experience, skills, abilities, and unique contributions. The standards for a healthy work environment as established by the American Association of Critical-Care Nurses (AACN) are skilled communication, true collaboration, effective decision making, appropriate staffing, meaningful recognition, and authentic leadership.[9]

Beacon Award

The Beacon Award for Critical Care Excellence, created by AACN, distinguishes adult critical care, adult progressive care, and pediatric critical care units that attain high-quality outcomes. This prestigious Award provides the critical care community with a means of recognizing achievements in professional practice, patient outcomes, and the health of the work environment.

A pediatric critical care unit can achieve the Beacon Award by meeting several criteria in the areas of recruitment and retention; education/training/mentoring; evidence-based practice/research; patient outcomes; healing environment; and leadership/organizational ethics. All of these areas provide a comprehensive view of any given ICU. To date, 17 pediatric critical care units have received the Beacon Award for Critical Care Excellence (M. Herigstad, personal communication, 2010).

Professional Development

A critical aspect of development for the nurse is the ability to advance and be recognized professionally. A successful critical care professional advancement program recognizes varying levels of staff nurse knowledge and expertise and fosters advancement through a wide range of clinical learning and professional development experiences. Essential components of this program include an orientation program, a continuing education plan, in-service education, and an array of other opportunities for clinical and professional development. Unit-based advancement programs are most effective when they are

linked to the nursing department's professional advancement program.

A professional advancement program that recognizes and rewards evolving expertise contains elements of both clinical and professional development strategies. The synergy model's ability to describe a patient–nurse relationship that optimizes patient and family outcomes illuminates the various dimensions of critical care nursing practice that require attention from a development perspective.[1,22] The impact of these contributions can be measured based on the nurse's level of expertise, and professional development strategies can be focused to have an impact on patient care.

By combining the nurse competencies identified in the synergy model and the behaviors identified in Benner's levels of practice,[23] a continuum of expertise can be described that matches behavior with practice levels. It focuses recognition and reward on clinical practice. The impact of expert nurses on patient outcomes is presented in quantitative and financial parameters that can be understood throughout the health care system. The model links clinical competencies to patient outcomes.

Nurses require a broad body of knowledge to meet patient and organizational needs. This requirement necessitates a lifelong process of professional development targeted to specific levels of clinical practice. Nurses can choose from many learning options, such as academic education, continuing education, participation in research, collaborative learning, case studies, and simulations. Nurses view the presence of continuing education, both as learning in the unit and in-service education, as very important.[24]

Staff Development

The goal of nursing staff development programs is safe, competent practice. Comprehensive programs provide the critical resources to support and promote practice. In addition, professional nursing standards of practice, health care laws, regulations, and accreditation requirements focus on the components of competent patient care to protect the health care consumer. The establishment of a staff development program that is linked to clinical practice is key to the success of professional nurse development.

Critical care staff development programs can be designed to educate staff nurses within the competencies of the synergy model.[1] The program builds on the nurse's prior education and professional nursing experience, which facilitates attainment and maintenance of competence. Concepts intrinsic to the educational process and to critical care nursing are used as a framework around which professional development opportunities are organized. Once defined on the basis of a unit's patient population, the organizing framework serves as the structure within which all critical care nursing staff development programs are designed.

Technical training alone is no longer sufficient to meet the care delivery needs of the nurse in the critical care environment. Critical care nurses require broad knowledge and expertise in areas such as communication, critical thinking, and collaboration.[9] They need to attain the diverse skills necessary to meet the complex needs of their patients and families.

The theory and science required to meet the synergy competencies includes topics such as disease processes, nursing procedures, cultural differences, moral and ethical principles and reasoning, research principles, and educational learning theories. This information can be presented through a variety of methods, including lectures, written information, posters, self-studies, or computer-based technology. However, it is essential that the information be related to realistic clinical situations. Clinical scenarios, case studies, and simulations that represent the dynamic and ambiguous clinical situations nurses encounter daily are most effective.[25]

Bedside teaching is particularly helpful in the development of clinical judgment and caring practice skills. Expert nurses are role models for many of the competencies delineated by the synergy model. Novice nurses learn by watching these expert nurses and emulating their behaviors. Clinical teaching also enables the novice practitioner to gain experience with unfamiliar interventions in a safe and protected environment. Communicating and validating clinical knowledge focuses learning, positively affects patient outcomes, and adds to the total body of nursing knowledge.[25]

Information about research and research utilization builds clinical inquiry and system thinking skills. Demystifying research, outcome, and quality processes contributes to the development of these key skills. Use of journal club formats and supporting staff involvement in research develop clinical inquiry skills. Building knowledge in the areas of health care trends and political action expand system thinking skills. Development of critical thinking skills and problem solving skills also assists with development of system thinking.

Nurses acquire facilitation of learning skills by incorporating communication development into their professional development plan. Presenting clinical teaching strategies and helping staff to determine learner readiness and assess understanding are included in the development of facilitation of learning. The importance of developing patience, flexibility, and a nonconfrontational style is reinforced.

Negotiation, conflict resolution, time management, communication, and team building are components of collaboration skills. Role playing, role modeling, and clinical narratives are methodologies that have been used to develop collaboration skills.

Nurses learn technical skills and scientific knowledge in many ways, but caring practices and advocacy are developed only through relationships that evolve over time.[26] Nurturing professional relationships with experienced staff promotes the novice's integration into practice. Expert nurses who share their clinical knowledge and coach other nurses have a tremendous impact on novice nurses. Nurses who coach are in their roles because they are able to clinically persuade and guide situations. They demonstrate expert skills and expedite the ongoing clinical development of others.

A variety of staff development programs exist, but most fall into three general categories: orientation, in-service education, and continuing education programs.

Orientation

Orientation programs help acclimate new staff to unit-based policies, procedures, services, physical facilities, and role expectations in a work setting. A specific type of orientation program that has developed in response to the nursing

shortage is the critical care internship program. These programs have been developed as a mechanism to recruit and train entry-level nurses. They are designed to integrate nurses with little or no nursing experience into the complex critical care environment. They provide extended clinical support for novice nurses and introduce new knowledge more deliberately than do traditional orientation programs. Basic information and skill acquisition are the core features of these programs. This foundation builds on the knowledge and skills that these nurses previously acquired in their nursing school programs. Teaching usually is under the direction of a hospital educator and generally involves less senior staff as preceptors. Typically, the novice nurse starts with providing care to the least complex patients. The program establishes a foundation on which the novice can develop into a competent clinician.[25]

AACN has recently released the Essentials of Pediatric Critical Care Orientation program. This program provides a bridge for the knowledge gap between what nurses learn in their basic education program and what they need to develop clinical competence with critically ill pediatric patients. The program consists of an interactive eight-module course that provides case scenarios and practice activities that augment knowledge and lead to improved job satisfaction. This program provides flexibility because it is a self-paced didactic e-learning course that can be incorporated into a blended learning environment, combining traditional educational activities such as preceptorships, discussion groups, workshops, or simulation experiences.

In-Service Education

In-service education programs, which are the most frequent type of staff development activity, involve learning experiences that are provided in the workplace to assist staff in the performance of assigned functions and maintenance of competency.[27] These programs usually are informal and narrow in scope. They often are spontaneous sessions resulting from new situations on the unit in settings such as patient rounds or staff meetings. Examples of planned in-service sessions are demonstrations of new equipment, procedure reviews, and patient care conferences.

Continuing Education

Legislation, regulations, professional standards, and expectations of health care consumers help determine the need for continuing education. Continuing nursing education includes planned, organized learning experiences designed to expand knowledge and skills beyond the level of basic education.[27] The focus is on knowledge and skills that are not specific to one institution and that build upon previously acquired knowledge and skills. Examples of continuing education programs include formal conferences, seminars, workshops, and courses.

Certification in Pediatric Critical Care Nursing

In 1975, the AACN Certification Corporation was established to formally recognize the professional competence of critical care nurses. The mission of the AACN Certification Corporation is to certify and promote critical care nursing practice that optimally contributes to desired patient outcomes. The program establishes the body of knowledge necessary for Critical Care Registered Nurse (CCRN) certification, tests the common body of knowledge needed to function effectively within the critical care setting, recognizes professional competence by granting CCRN status to successful certification candidates, and assists and promotes the continual professional development of critical care nurses.

Before 1992, content and construct validity of the CCRN examination were established for critical care nurses who primarily care for adult patients. Pediatric critical care nurses who took the CCRN examination were tested on content that did not reflect their practice. In 1989, the AACN Certification Corporation conducted a new role delineation study. Major differences among neonatal, pediatric, and adult critical care nursing practice were identified in the types of patient care problems for which direct bedside care is provided and in the amount of time spent caring for patients with specific problems (Table 3-1). The results, for the first time, described the practice of pediatric critical care nursing and justified the need for separate pediatric, neonatal, and adult CCRN examinations.

In 1997, the unique competencies of pediatric, neonatal, and adult critical care nurses were rearticulated using the synergy model[1] as a conceptual framework. Recently, AACN published the new test plan (Table 3-2). To date 2610 pediatric critical care nurses hold CCRN–Pediatric certification (M. Herigstad, K. Harvery, C. Hartigan, personal communication, 2009).

Table 3–1 Percentage of Time Caring for Patients with Alterations in Body Systems

System Dysfunction	Pediatric Practice (%)	Neonatal Practice (%)	Adult Practice (%)
Pulmonary	18%	24%	18%
Cardiovascular	14%	10%	20%
Neurologic	14%	10%	12%
Multisystem	13%	10%	8%
Hematology/ immunology	5%	6%	2%
Renal	6%	5%	6%
Gastrointestinal	6%	6%	6%
Endocrine	3%	3%	5%
Behavioral/ psychosocial	3%	7%	4%

Effective for testing starting 2010, American Association of Critical-Care Nurses.

Summary

Pediatric critical care nursing has evolved into a specialty in its own right. Pediatric critical care nurses make significant and unique contributions to the health care of children. A pediatric critical care nurse requires knowledge and skills in both the art and science of nursing. A supportive, empowered environment and support for professional advancement are essential to the development of knowledge and skills.

Table 3–2 Pediatric CCRN Test Plan

I. Clinical judgment (80%)

A. Cardiovascular (14%)
1. Acute pulmonary edema
2. Cardiac surgery (e.g., Norwood, Blalock-Taussig shunt, tetralogy of Fallot repair, arterial switch)
3. Cardiogenic shock
4. Cardiomyopathies (e.g., hypertrophic, dilated, restrictive, idiopathic)
5. Dysrhythmias
6. Heart failure
7. Hypovolemic shock
8. Interventional cardiology (e.g., catheterization)
9. Myocardial conduction system defects
10. Structural heart defects (acquired and congenital, including valvular disease)

B. Pulmonary (18%)
1. Acute lung injury (e.g., acute respiratory distress syndrome)
2. Acute pulmonary embolus
3. Acute respiratory failure
4. Acute respiratory infections (e.g., acute pneumonia, croup, bronchiolitis)
5. Air leak syndromes (e.g., pneumothorax, pneumopericardium)
6. Aspiration (e.g., aspiration pneumonia, foreign body, meconium)
7. Asthma, chronic bronchitis
8. Bronchopulmonary dysplasia
9. Congenital anomalies (e.g., diaphragmatic hernia, tracheoesophageal fistula, choanal atresia, pulmonary hypoplasia, tracheal malacia, tracheal stenosis)
10. Pulmonary hypertension
11. Status asthmaticus
12. Thoracic surgery
13. Thoracic trauma (e.g., fractured ribs, lung contusions, tracheal perforation)

C. Endocrine (5%)
1. Acute hypoglycemia
2. Diabetes insipidus
3. Diabetic ketoacidosis
4. Inborn errors of metabolism
5. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

D. Hematology/immunology (3%)
1. Coagulopathies (e.g., idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, heparin-induced thrombocytopenia)
2. Oncologic complications

E. Neurology (14%)
1. Acute spinal cord injury
2. Brain death (irreversible cessation of whole brain function)
3. Congenital neurologic abnormalities (e.g., myelomeningocele, encephalocele, atrioventricular malformation)
4. Encephalopathy (e.g., anoxic, hypoxic-ischemic, metabolic, infectious)
5. Head trauma (e.g., blunt, penetrating, skull fractures)
6. Hydrocephalus
7. Intracranial hemorrhage/intraventricular hemorrhage (e.g., subarachnoid, epidural, subdural)
8. Neurologic infectious disease (e.g., congenital, viral, bacterial)
9. Neuromuscular disorders (e.g., muscular dystrophy, Guillain-Barré syndrome, myasthenia gravis)
10. Neurosurgery
11. Seizure disorders
12. Space-occupying lesions (e.g., brain tumors)
13. Spinal fusion
14. Stroke (e.g., ischemic, hemorrhagic)

F. Gastrointestinal (6%)
1. Acute abdominal trauma
2. Acute gastrointestinal hemorrhage
3. Bowel infarction/obstruction/perforation (e.g., necrotizing enterocolitis, mesenteric ischemia, adhesions)
4. Gastroesophageal reflux
5. Gastrointestinal abnormalities (e.g., omphalocele, gastrochisis, volvulus, Hirshsprung's disease, malrotation, intussusception)
6. Gastrointestinal surgeries
7. Hepatic failure/coma (e.g., portal hypertension, cirrhosis, esophageal varices, biliary atresia)
8. Malnutrition and malabsorption

G. Renal (6%)
1. Acute renal failure
2. Chronic renal failure
3. Life-threatening electrolyte imbalances

H. Multisystem (11%)
1. Asphyxia
2. Distributive shock (e.g., anaphylaxis)
3. Hemolytic uremic syndrome
4. Multiorgan dysfunction syndrome (MODS)
5. Multisystem trauma
6. Near drowning
7. Sepsis/septic shock
8. Systemic inflammatory response syndrome (SIRS)
9. Toxic ingestions/inhalations (e.g., drug/alcohol overdose)
10. Toxin/drug exposure

I. Behavioral/psychosocial (3%)
1. Abuse/neglect
2. Developmental delays
3. Failure to thrive

II. Professional caring and ethical practice (20%)

A. Advocacy/moral agency (3%)

B. Caring practices (4%)

C. Collaboration (4%)

D. Systems thinking (2%)

E. Response to diversity (2%)

F. Clinical inquiry (2%)

G. Facilitation of learning (3%)

Data from *Pediatric CCRN Test Plan,* Aliso Viejo, CA, 2009, American Association of Critical-Care Nurses.

References are available online at http://www.expertconsult.com.

Chapter 4

Research in Pediatric Critical Care

Randall C. Wetzel and Carol E. Nicholson

"A fool is a man who never tried an experiment in his life."
Erasmus Darwin, 1792

PEARLS

- Research is the right thing to do for critically ill children, their families, and our profession. Whether or not it is supported at your institution does not alter this fact, nor does it relieve you of your scholarly responsibilities as a physician.
- Make inquiry, comparison, and analysis a permanent part of your critical care practice. Keep a follow-up card as a lifelong habit in the practice of medicine. Go to postmortems, and keep looking through the microscope.
- Before you accept dogmatic teaching from anyone, make a habit of analyzing its basis. Keep a "reading" section on your follow-up card.

Among the factors that define a medical specialty is the recognition of a clearly defined body of knowledge that is intrinsic and unique to that specialty. This body of knowledge is determined by the disease processes that the specialists treat, comprehensive understanding of those disease processes, and, most importantly, the academic and intellectual constructs that allow the advancement of medical knowledge, not only narrowly in the specialty but also in general. Endeavors directed at increasing the specialty's knowledge base are the research interests of that specialty. Thus a recognized medical specialty has a clearly defined patient population, clearly defined disease processes, and clearly defined research interests. Medical specialties frequently have associated societies, professional organizations, and national institutes, all of which facilitate research funding, sharing of research information, and advancing knowledge in the specialty.

Because organ system classification of specialties is fairly obvious, it is a common basis for specialization. The specialists who treat diseases of the lungs are familiar with the wide spectrum of pulmonary diseases, their pathogenesis, and their treatment. There exists a large body of research-derived knowledge and a great deal of ongoing related research activity. This activity is presented at national meetings, such as the annual American Thoracic Society meeting. There is a network of extensive funding sources available to this specialty, such as the American Lung Association; the American Heart Association; and the National Heart, Lung, and Blood Institute (NHLBI). Taken together, these form the clearly defined specialty of pulmonary medicine. Not all specialties are organ specific; for example, infectious disease and immunology are specialties that are concerned with diseases that affect the entire patient. These specialties have managed to clearly define a body of knowledge that is both intrinsic and unique, as well as crucial, to the specialty.

How does critical care medicine measure up to this standard? Have we succeeded in defining disease processes, patient populations, and research efforts that are unique to critical care medicine? What are these areas? Is it necessary for intensivists to participate in some area other than critical care medicine for their academic and research involvement? Commonly, physicians whose clinical practice is critical care are involved in research integrated into multiple other specialty areas. To define critical care medicine as a medical specialty able to stand on its own, not only must the clinical practice and the pathophysiology of the unique disease entities be defined, but also critical care researchers must make a unique contribution to understanding and treating the pathophysiologic conditions that affect critically ill children. Without a body of research that is unique to critical care medicine, the certainty of the specialty's future will be in question.

Research Areas

There are clearly pathophysiologic processes that appear to be unique to critical care medicine. Probably the most clear-cut of these processes is acute respiratory distress syndrome (ARDS),[1,2] although this is only one manifestation of a systemic process. The syndrome appears to develop in critically ill patients whose initial injury arises from a wide variety of organ-specific insults. Although the lungs appear to be the primary target organ, all organs are affected by the same complex underlying pathophysiologic process. This process causes widespread endothelial injury involving many organ systems.[3] This results in tissue edema, decreased organ perfusion, ischemia, and multiple organ failure. This pansystemic disease is familiar to the intensivist and is one of the most extensive areas of unique research interest in critical care today. Understanding this systemic inflammatory response is central to understanding critical care.

Another major disease process that clearly interests critical care physicians is shock. Shock, whether it be hypovolemic, septic, or of some other etiology, by its very nature is a multisystem, non–organ-specific, acute, life-threatening process.[4,5] Another natural area for critical care research would

be specifically aimed at preventing and/or ameliorating the multisystem insults that occur because of the body-wide activation of potentially lethal mediators triggered by episodes of shock. The spectrum of research opportunities in this area ranges from molecular biologic to large-scale clinical trials and has grown exponentially in the past few years.[6]

Organ system interaction also provides an area of primary interest in critical care. In particular, cardiorespiratory interaction has immediate, everyday application in ventilatory management, cardiopulmonary resuscitation, and cardiac support. The physiology of how changes in the pleural pressure affect cardiac function during either spontaneous or positive pressure ventilation is an area of constant relevance to the intensivist.[7] In a broader sense, cardiorespiratory interaction extends beyond this arena. How changes in cardiac function alter ventilation, airway resistance, and lung compliance is an integral part of critical care. The pulmonary endothelial synthesis, release, and degradation of multiple mediators, ranging from myocardial depressant factors to systemic vasoactive substances, that alter cardiovascular function can be considered cardiorespiratory interaction and are of unique interest to the intensivist.[7] This area also encompasses a broad spectrum of possible approaches from molecular biology to cell physiology to integrated physiology. An area of research that is particularly important to critical care medicine is cell biology. All organ system failure can be described in terms of cellular failure. For example, the general effects of superoxide radicals produced by leukocytes on other cell functions are legion and clearly of interest to intensivists.[4,8] Extending the argument of cellular specialization is possible for other cell types. An argument could be made to consider the endothelium the specialty organ of intensivists.[9] All organs that fail in critically ill children contain large areas of biochemically active endothelium. This endothelium is important because it elaborates hormones and autacoids that have systemic and local effects. These effects include alteration of coagulation and blood viscosity, superoxide generation and tissue damage, smooth muscle regulation, metabolism of circulating vasoactive substances, and interaction with the immunologic system.[10,11] All generalized stressors (e.g., sepsis, hypoxia, hypovolemia) alter endothelial cell function. One way of looking at multiple organ system failure is to view it as an "endotheliopathy." This endotheliopathy gives rise to widespread organ-specific damage, such as renal failure, ARDS, myocardial depression, and alterations in the blood-brain barrier, with subsequent cerebral edema. Endothelial cell function changes over time as the child develops and may be specifically affected by disease processes particularly prevalent in children, such as the infectious vasculitides.[12] This sort of theoretical construct could serve as an organizational basis for research efforts in pediatric critical care and offer new insights into our understanding of critical illness in children.

Because of the astonishing success of the human genome project, the development of gene chips, and the increasingly realized potential of proteomics, understanding the genetic nature of critical illness no longer seems beyond our reach.[13] Understanding the genotype of individuals who physiotypically display fatal responses to meningococcal disease while their classmates remain asymptomatic, albeit colonized by the same serotype organism, holds the promise of prospectively tailoring therapy to each patient individually. The many genomic and proteomic projects developing within pediatric critical care will help our understanding of the genetic bases of critical illness and holds out hope for understanding systemic inflammatory response syndrome (SIRS) and sepsis.[13-15]

An area unique to pediatric critical care is that of caring for children and their families who must cope with acute critical and sometimes fatal illness. No other physicians deal with death and dying more frequently than intensivists. This role is especially important in the care of children. Supporting the family facing the acute, unexpected, critical illness and death of a child requires masterly physician interpersonal skills that may attenuate family problems long after the child's death. The psychosocial impact of critical illness and palliative care has been explored very little, and we need to know more. Such issues are intrinsic to critical care medicine, and it is imperative that intensivists become responsible for the research in this area. Potential avenues for the intensivist-investigator include epidemiologic study, such as family and sibling bereavement patterns, and randomized therapeutic interventions, such as the effect of frequent postmortem follow-up on the high incidence of divorce among couples who have lost a child.

Finally, and perhaps most importantly, the burgeoning area of medical informatics holds the promise of enabling us to understand complex, critical, but rare disease processes previously impossible to study.[16-19] Understanding knowledge discovery in databases and building national and international collaborative partnerships to understand the scope of pediatric critical care have come within our reach.[20] Informatics research with national funding may provide real-time guidance for management of the rarest critical illnesses. In addition participation in national databases to support quality improvement and multisite research studies provide a new and fertile area for critical care research.[21,22]

These examples indicate part of the wide spectrum of research opportunities in pediatric critical care medicine. There are many more, including the now well-established multicenter National Collaborative Pediatric Critical Care Research Network, now in its second 5-year epoch of funding by the National Institute of Child Health and Human Development (NICHD), one of the National Institutes of Health. Networked research is necessary in critical care and the Pediatric Lung Injury and Sepsis Investigators (PALISI; http://pedsccm.org/PALISI_network.php) is an important example of a national research network focused on pediatric critical care. Constant sensitivity to identifying the questions (incorrectly answered, unanswered, and unasked) is the character trait required in the academic intensivist if our specialty is to continue to grow. Identifying areas unique to critical care medicine provides the knowledge base for the specialty necessary for its growth and for our patients' well-being. Given the many unique areas of interest in critical care, how do we uncover them and encourage research in the subspecialty?

Wellsprings of Research

Collective Needs

Why must critical care collectively, as a specialty, support research in pediatric critical care? The arguments mentioned previously suggest that without the academic, intellectual, and scientific pursuit of areas that are specifically unique and relevant to critical care, we have no specialty. In this broad sense,

research establishes a collegial respect for physicians who practice critical care and engenders academic support for the specialty. If all we do is provide clinical care for desperately ill or dying children, and clinical care that other physicians do not understand by virtue of their not being dedicated to it, the challenge of "what do intensivists do?" should only in part be answered by "spend long hours with children who are critically ill and their families." This question addresses a deeper issue: Are intensivists contributing to the further understanding of critical illness? Are intensivists contributing to the intellectual advancement of medicine and the rich intellectual and academic milieu in the universities in which they find themselves? Are intensivists obtaining extramural funding for university-wide interactive and collaborative research efforts? Are intensivists training future generations of physician-scientists? Unless we can affirmatively answer these questions from a uniquely critical care point of view, it should not be surprising that physicians in other subspecialties do not understand or reliably value our labors. This justification—to ensure the viability and respectability of a specialty whose primary concern is treating the critically ill—is a major reason we must encourage and support research. Failure to do so is a failure to critically ill children.

A further reason for the commitment to research by the critical care medicine community is to allow young investigators ample introduction to research. They must be able to discover what research is, be provided with the tools to answer the outstanding questions in the field, and eventually make contributions both scientifically and educationally. These contributions will occur only if sufficient foresight is exercised to ensure that the facilities and resources are available. One of the chief rewards of developing this integrated structure will be the advancement of a specialty that truly is able to improve patient care. There are other rewards from this organized research endeavor and the education it provides. If the young investigator returns to clinical medicine, never to enter a basic science laboratory again or to organize even one clinical trial, this physician will at least be sensitive to the critical questions in patient care and be able to read and apply the literature with a better understanding. Many otherwise perfectly adequate young physicians are unable to critically evaluate the medical literature as a tool to improve management of their patients until they have been involved in contributing to it. Didactic methods are inadequate for teaching the rigorous effort required to write an article published in a first-class journal. It requires practical and challenging mentoring and arduous doing; however, once done, the emerging clinician is better able to understand and critically review the contributions of her/his colleagues and their relevance to critically ill children.

There is a further benefit from encouraging our fellows to research. The research effort provides excellent opportunities to observe how modulation of biochemistry, biology, and physiology alters the status of living beings. The practical knowledge gained in learning how to accurately measure the aortic/systemic and pulmonary artery pressures in animal models, determining the growth requirements of endothelial cells, maintaining sterile tissue cultures, and measuring pharmacokinetics provides insights into daily clinical practice unobtainable in any other way and practical for the care of every critically ill child. For this reason, it is nearly impossible to become a well-rounded clinician without having learned the basics involved in, and completed the exercise of, addressing a research question. The spinoffs of how to do cutdowns, insert catheters, start arterial lines, measure tidal volumes and pressures, manipulate ventilators, care for cultures, bioassay eicosanoids, perform chromatographic separation of bioactive lipids, and sequence the messenger RNA for endothelin immediately improve the bedside care of children, both intellectually and practically.

Individual Motivation

Beyond the learning relevant to clinical practice, individual motivation to answer questions and change the field is essential. Research is difficult, expensive, and time consuming. It removes the clinician from patient care, it is frequently thankless, often difficult to plan and organize, and hard to execute. Even when excellently done, it may be challenging to present and possibly not well received. Why then should any physician dedicated to the critical care of children be even slightly interested in becoming involved in research? Surely the desire to be promoted in the academic setting, see your name in prestigious journals, and impress your family, friends, and colleagues is insufficient motivation to contribute vast amounts of time, exhaust your intellectual and physical energy, and reduce your availability for patient care and family life. Although these may be some of the benefits of a research career, they are merely some of the lesser fruits of research. They are inadequate to provide the primary motivation for being involved in research. Personal motivations for research are many, and there are numerous rewards.

One of the most obvious is that being an attending physician in a pediatric intensive care unit 12 months of the year is not something that either can or should be done, no matter how much physical and emotional stamina one may have (or think he or she has). Diversion from clinical and administrative responsibilities and refreshment and renewal are obvious rewards of research. This benefit, prevention of burnout, is not achieved merely by avoiding clinical work. Rather, the invigoration that comes from involvement in, and a commitment to, improving patient care and advancing the specialty are the source of the benefits. Active involvement in research provides reciprocal inspiration from the daily questions in clinical work and the value of the research endeavor. It helps the clinician intensivist see the long hours of clinical care in a broader perspective. Of course, research can (and should) be fun. If it is not fun, if the investigator does not look forward to being involved in the understanding, development, design, execution, analysis, preparation, and presentation of the research, then it is not worthwhile for that individual investigator to remain involved. You must like what you are doing, or the dedication and commitment required for Edison's "99% perspiration for each 1% inspiration" will be lacking.

Personal motivation is the necessary starting point for research invovlement. No amount of external pressure can produce a successful researcher. Where does this personal motivation spring from? The noble goal of adding to the knowledge base of the field is excellent; however, it is unlikely that many clinicians wake up in the morning and say, "Aha! I will add to the knowledge base of critical care today." In the practice setting clinicians are continually challenged by questions that arise from providing critical care for children, by questions about patient management, and by uncertainties and confusion in providing patient care. It must be very rare

indeed for a young clinician not to wonder about, be curious about, or be interested in answering these questions. It is the role of all preceptors in critical care to make certain that the trainee is aware of these questions and that they are asked. To teach critical care as if it were dogma is destructive to these goals. To constantly point out and demonstrate where there are failures and conflicts in our understanding and where matters of style, rather than matters of substance, determine our clinical practice is to uncover fertile areas for research. Unless the young intensivist senses these exciting challenges, the personal enthusiasm toward research will not be discovered.

Another motivating factor is the simple desire to know what research is. The great shibboleth of research has been held up before medical students and pediatric residents for years. Nevertheless, most young physicians have no idea what research is. They may have seen a fragment of a clinical trial, but they likely did not participate in a basic research experience. All too frequently they have little understanding of the real application of the scientific method or statistical analysis. Curiosity for what research is should be recognized, fanned, and fed. The inquisitive clinician must not be lost because of a poor understanding of research or a feeling that it is an elitist club. For this reason, our fellowship programs must provide valid scientific research experiences guided by seasoned investigators. Not until junior physicians realize that they can acquire the skills to answer the questions that arise clinically, in a rigorous and scientific fashion, can we expect them to do so.

The previously mentioned personally motivating factors, which include personal aggrandizement such as fame, fortune, job security, avoidance of burnout, fun, ability, education, and training, still are not, however, sufficient. All of these possible motivations do not provide the major essential driving force. Individual curiosity, a tireless need to question, and the restless search for answers must be the source of the entire endeavor. Curiosity? Is this the crucial concept? Sir Peter Medawar calls it a "nursery word"—a motive too inadequate.[23] Everyone possesses curiosity, and yet not everyone makes a commitment to seek solutions, occasionally at great personal cost. So it must be more than mere curiosity. Medawar calls this driving compulsion the "exploratory impulsion"; Kant called it "restless endeavor."[23] It is not merely curiosity but a surrender to the urge, often sacrificially, to seek the answer that motivates the investigator. This urge must be strong because it will require a great deal of time and energy before the question that originally piqued the clinician's curiosity can be addressed. This innate, compelling motivation of the individual is the main driving force of medical investigation.

Where the collective needs of the specialty and the individual's needs come together is that both have a genuine, deep-rooted desire to understand better how to help critically ill patients. This symbiosis of specialty needs and individual motivation forms the essential chemistry of discovery. In a fascinating address to the American Society for Clinical Investigation, J.L. Goldstein[24] presented the formula:

Clinical stimulus + Basic scientific training = Fundamental discovery

The individual, when clinically stimulated, can make a fundamental contribution only with appropriate training. The specialty can meet the needs mentioned previously by providing that training. The collective combination of financial and intellectual resources and the individual's blood, sweat, and tears is critical. Resources will be provided only if the physicians involved in critical care are committed to providing, for individual intensivists who have the curiosity and desire, the means to find answers to their individual questions. No matter how well organized, the specialty organizations can encourage individuals to labor toward solutions only for the problems that interest them. Selection of these trainees is critical. Erasmus Darwin said in 1792, "A fool is a man who never tried an experiment in his life."

Let us not train too many fools. Constantly striving to recruit the seeker, doubter, questioner—and when they are recruited, to support them—is the responsibility of all physicians involved in critical care. Without them, critical care research will be nonexistent. Significant advances in our specialty can grow only from accepting this responsibility. Without this commitment to encourage and train, critical care medicine will lose promising young clinician-scientists to other specialty areas, because it will be only there that they will be able to seek answers to their questions. This crucial issue and its centrality to the growth of our specialty cannot be overemphasized. The training also must be thorough. This takes time, but without the commitment to train young investigators to think like basic scientists, they will be unable to apply the tools of basic science and will end up paralyzed and lost to the specialty of pediatric critical care.[24]

Doing Research

"Gentlemen, do not think! Try and be patient. Have you performed the experiment?"

John Hunter

Variations in study populations, techniques of data gathering, study designs, questions asked, answers required, types of analyses, and whether the question should be addressed clinically or by a basic science approach (and, if basic science, whether by molecular, cellular, physiologic, biochemical, or biophysical experiments) can be very confusing. Then there are statistics. To understand how to address a given question, familiarity with the basic process of research is necessary. For example, the simple question, "Should I give my septic, acidotic patients sodium bicarbonate?" could be addressed in many ways (and indeed has been!). The options range from experiments to discern the subcellular effect of changes in pH on mitochondrial function to prospective, randomized, double-blind, multicenter clinical trials to determine whether bicarbonate therapy improves survival in septic shock. All of these factors have a part in answering what may first appear to be a simple question. Many factors influence how the researcher goes about answering any question, not the least of which are the researcher's background and training. The availability of resources in the researcher's institution and previous research relevant to the question being asked are also important.

So, what is research? Research is scientific investigation. If the motivation to do research can be matched by the commitment of the specialty to support research, is that sufficient? How is the bedside problem answered? If a keen investigator with a good question has a willing pediatric intensive care unit director with money, or at least one who is willing to help find resources, what next? How is research done? What is the scientific process?

Over the past 200 years, the scientific method has been developed by learning how to test our guesses about the universe.[25,26] The key factors involved are the following:

- Observation
- Intuition
- Formulation of hypotheses
- Experimentation
- Development of scientific laws, theories, or axioms
- Testing these new theories

Sir Francis Bacon provided one of the first common-sense answers to the question, "How is research done?" The answer was "by observation and experimentation." Which observations and data should be collected may seem fairly obvious at first, but deciding what should be observed and recorded are the crucial research questions. Approaches that may be useful in determining whether bicarbonate helps a critically ill child include observing and recording every physiologic parameter and every biochemical response, as well as measuring every enzyme's activity and looking at urinary metabolic products. It is evident that these are not necessarily the best, most direct ways to answer the underlying question. Merely compiling a mountain of data without scientific reasons behind each observation (fishing) is risky, time-consuming, inefficient, and often futile. One of the main tasks of the investigator is to decide which observations in the whole set of possible observations are crucial. Lack of critical thinking may result in missing important observations and fruitless experimentation. Similarly, determination of what type of experiment should be performed is crucial.

What is an experiment? The original meaning of the term experiment was "a test made to demonstrate a known truth." It served as a means of proof for an already "known" truth. This sort of experiment was not designed to generate new knowledge. This Aristotelian concept of experimentation, involving classical deductive logic, has limited application in modern medicine, other than perhaps that of pedantry and teaching high school chemistry. The essential concept of experimentation that has a more contemporary meaning entails an uncertain or unknown outcome. To the present-day researcher, the purpose of performing an experiment is to discriminate between possibilities. How experiments are designed to discriminate between possibilities depends on the underlying assumptions. Understanding the logic that underlies how an experiment is performed is useful in avoiding multiple traps, not only in reviewing the data but also in applying experimental results to real patients. Bacon[27] noted: "If a man begins with certainties, he shall end in doubts, but if he will be content to begin with doubts, he shall end in certainties." Many experiments are still designed—contrived may be a better word—to demonstrate the validity of preconceived ideas (sometimes called an 'hypothesis'). This reasoning from preconceived ideas or premises to the specific situation is known as the process of deductive logic. Deductive logic is reasoning from the general to the specific. A clinical example of such deductive logic is the following syllogism:

Major premise: Penicillin is an effective treatment for pneumococcal pneumonia.
Minor premise: My patient has pneumococcal pneumonia.
Inference: I will treat my patient with penicillin.

The experiment performed in this case, treating a patient with penicillin, will have a certain outcome only inasmuch as the deductive logic is correct and the underlying primary assumption (major premise) and diagnostic result (minor premise) are true. In a general way, all specific conclusions that rest on authoritative statements of truth are deductive in origin. By their very nature, although they guide our clinical activity, they do not expand our medical knowledge. The hallmark of deductive logic is complete reliance on the certainty of known or revealed facts. Some 300 years after the modern scientific revolution and the birth of true scientific method, modern experimental medicine remains beset with this type of logic. Aristotelian experimentation is the process of clinical practice. We reason from general principles and accepted facts to specific interventions and treatments. The entire evidence-based practice movement is based on deducing therapy from sound premises.

The difficulty comes when the dogmatic assumptions that underlie our clinical practice, and deductively lead to our therapies, are incorrect. Aristotelian experimentation provides no way to approach outcomes in medicine that are exceptional, yet these are the very occurrences that may be enlightening. Charles Darwin has exhorted us never to allow these exceptions to go unnoticed.[28] Deductive logic is unable to assist in the discovery of new knowledge and therefore general principles. This was clearly noted by Bacon,[29] who stated in 1620:

"The syllogism consists of propositions, propositions consist of words, words are symbols of notions. Therefore if the notions themselves (which is the root of the matter) are confused and overhastily abstracted from the facts, there can be no firmness in the superstructure. Our only hope therefore lies in a true induction."

The great revolution in scientific and philosophic writing in the 1600s was typified by Bacon's absolute refutation of the concept that any new truths could be discovered merely by a deductive act of the mind[4]:

"The discoveries which have hitherto been made in the sciences are such as lie close to vulgar notions, scarcely beneath the surface. In order to penetrate into the inner and further recesses of nature, it is necessary that both notions and axioms be derived from things by a more sure and guarded way; and that a method of intellectual operation be introduced altogether better and more certain."

The Baconian revolution in scientific thought was dependent on observation and experimentation. The underlying premise was that the general could be determined, inferred, and understood from observing the specific. This led to the realization that by the use of thoughtful inductive logic, linked to observation and understanding, specific discovery of new generalized truths was possible.

A clinical example of this sort of contribution to modern medicine is the well-known example of vaccination. Jenner's recurrent observation of the specific immunity to smallpox of patients who had been infected by cowpox led to experimentation with observation and a series of inductive steps that ultimately led not only to the eradication of smallpox in the world but also to generalization of the concept of vaccination to other infectious processes and vast discoveries in the area of immunology. It is impossible to conceive how Aristotelian deductive logic could have led to these discoveries. Bacon's contribution was to realize that observations of the specifics in nature would lead, through application of the intellect,

through inductive logic, to the discovery of new truths. Bacon did realize that we were unable to rely on "the casual felicity of particular events"[23] to provide us with all the specific information required to discover scientific truths, even if we spent an entire lifetime observing nature. He thus realized the necessity to devise experiences and contrive occurrences to collect factual information by which we would understand the natural world. This is Baconian experimentation. However, this still was not experimentation as practiced in medicine today.

Current medical experimentation is more accurately described as Galilean experimentation.[23,28] The Galilean experiment discriminates between possibilities and, in so doing, confirms a preconceived notion by supplying facts that support the inductive process and lead to a sound conclusion. The essence of an experiment as proposed by Galileo was a true test, a trial, or an ordeal of an hypothesis. This constructive experimentation more accurately reflects what we think of today when we want to further our understanding of critical illness. As Stephen Hawking[26] put it in *A Brief History of Time*:

"Our present ideas about the motion of bodies date back to Galileo and Newton. Before them people believed Aristotle, who said that the natural state of a body was to be at rest and that it moved only if driven by a force or impulse. It followed that a heavy body should fall faster than a light one, because it would have a greater pull toward earth."

The Aristotelian tradition also held that you could work out all the laws governing the universe by pure thought: it was not necessary to check by observation. As incredible as it may seem, no one, until Galileo, bothered to see whether bodies of different weight did, in fact, fall at different speeds. Mythology reports that Galileo demonstrated that Aristotle's belief was false by dropping weights from the leaning tower of Pisa. The story almost certainly is untrue, but Galileo did do something equivalent: he rolled balls of different weights down a smooth slope. The situation is similar to that of heavy bodies falling vertically, but it is easier to observe because the speeds are smaller. Galileo's measurements indicated that each body increased its speed at the same rate, no matter what its weight. A scientific revolution ensued.

In Galileo's experiment, the hypothesis tested was that objects of different mass fall at different velocities. The "control" group could have been a group of spheres with mass = X. The experimental group (or groups) would have been X × 1 kg (or X × 1 kg, X × 2 kg, and so forth). Because the null hypothesis: that all objects (regardless of mass) fall at the same velocity could be falsified or disproven, the hypothesis could be tested. His data failed to support the hypothesis (supported the null hypothesis, failed to reject the null hypothesis), and the hypothesis was irrevocably disproved and destroyed, instantly. The old system was dead. The deductively logical syllogism of Aristotle's day was as follows:

Major: The velocity of a falling object is determined by the object's mass.
Minor: These two objects are of different mass.
Inference: They will fall at different rates.

This syllogism was disproved by a single observation. Therefore the conclusion was incorrect and therefore if the minor premise was true, the major premise had to be false. A new intellectual universe became possible. Every preconceived notion was testable by experiment. All that is required is a testable hypothesis. The routine function of medical experimentation, the purpose of all medical science and the major modus vivendi of all the national institutes, is the testing of hypotheses. Although gathering facts and cataloging their relationships as in Aristotelian and Baconian experimentation remains of some value, testing hypotheses is our strongest research tool. Galilean experimentation provided the capability of constantly revising our hypotheses and avoiding unnecessary persistence in theoretical structures based on hypothetical errors that lead to no more than a house of cards.The generation of scientific hypotheses that can be critically tested is the basis of scientific discovery. Discovery has its beginnings in imaginative preconception, which is the creative act of mind that gives rise to a hypothesis.[28] Asking the question or conceiving the question is only the beginning of the scientific process. Casting the question in the form of testable, verifiable, scientific hypotheses is where the creative work of research really begins. The brilliant guess, the eureka moment—these scientific insights are the sources of these hypotheses. The hypothesis is a mark to be attained, a suggestion of the probable, a provisional proposal of an underlying truth, or some specific facet of it. The hypothesis has but one purpose, to be tested. But this approach means that an hypothesis, no matter how interesting, can never be proven. Absolute proof of a hypothesis is not, by the very nature of inductive logic and Galilean experimentation, ever possible because all possibilities cannot possibly ever be tested. Again, according to Stephen Hawking[26]:

"Any physical theory is always provisional, in the sense that it is only a hypothesis: you can never prove it. No matter how many times the results of experiments agree with some theory, you can never be sure that the next time the result will not contradict the theory. On the other hand, you can disprove a theory by finding even a single observation that disagrees with the predictions of the theory. As philosopher of science Karl Popper has emphasized, a good theory is characterized by the fact that it makes a number of predictions that could in principle be disproved or falsified by observation. Each time new experiments are observed to agree with the predictions the theory survives, and our confidence in it is increased; but if ever a new observation is found to disagree, we have to abandon or modify the theory."

Whereas a theory is an organized system of knowledge used to analyze or explain nature or behavior, a hypothesis has no such value. Theories may be built up from facts learned by testing hypotheses and may even contain partially substantiated hypotheses that are useful in predicting events, but hypotheses are useful only insofar as their testing acts as a focus for the discovery of truths. Without a doubt, hypotheses are the most important instruments in research. Developing a hypothesis is the initial phase of research and scientific investigation. It generates the plan for the research. Nevertheless, it is "a means, not an end," as Thomas Huxley cautioned.[28] The ultimate goal of research is not to hunt blindly for unrelated facts but to test related hypotheses.

If we accept the fact that the purpose of experimentation is to test hypotheses, then it is clear that a necessity for research is to formulate appropriate hypotheses. The hypothesis must be focused, with a limited number of possible outcomes and limited number of implications that lead logically to further investigational steps. This minimizes futile activity.

A hypothesis that accommodates all possible phenomena or outcomes is totally uninformative. The more restrictive it is, the more focused it is, the more instructive it is. One final warning about hypotheses: although they are the driving force of research, they must be kept in their place. Accepting unproved hypotheses can clearly lead you down a rabbit hole, often a time-consuming, expensive, and disastrous one. Failure to give up unsubstantiated or disproven hypotheses can lead (and has led) to a futile cycle of experimentation. Although scientists require hypotheses, find them attractive, and may not be able to live without them, they must not fall in love with them.[23,28] The basic fact of science, that hypotheses are never proven and that they are only as good as the results they generate, must never be forgotten. Likewise, the physician-scientist as observer of nature must be encouraged to use quantitative and qualitative descriptive tools to develop the platform for meaningful hypothesis generation and testing.

The Null Hypothesis

Galileo's revolutionary experiment proved nothing! Rather, it disproved the accepted dogma by a single observation. When deductive logic is correctly performed and the major and minor premises are correct, the inference is absolutely, positively true. This is not true in the other direction. Reasoning from the inferences is unreliable. The arrival of two objects at the ground at different times does not assure us that the objects are of different mass or that objects of different mass fall at different rates. In the penicillin case, the fact that our patient improved with penicillin proves neither that he had pneumococcal infection nor that penicillin is effective against pneumococcus. He could have just had erysipelas. Then again, if the objects of different mass arrive simultaneously—that is, the inference is wrong—then something also is very wrong with one or both of the premises. If penicillin does not reliably, reproducibly treat pneumococcal pneumonia, then something is wrong with the diagnosis or with the efficacy of penicillin against pneumococcus. Yes, an astute clinician sees all sorts of problems in this statement, but the problems only emphasize the importance of rigid control of nuisance variables (discussed later). Nevertheless, the fact that inference is asymmetrical demonstrates that falsification—the disproving of a hypothesis—is logically a stronger, surer process than the so-called (and impossible) proving of a hypothesis. As Hawking explained, absolute proof is not possible. Instead, to support scientific hypothesis we generally attempt to disprove the opposite hypothesis, that is, we try to "refute the null hypothesis." For example, Galileo said: "All objects, irrespective of mass, fall at the same velocity." The null hypothesis would be that objects of different mass fall at different velocities or, as previously asserted, mass determines velocity. Galileo absolutely refuted this null hypothesis; thus his data were consistent with his own hypothesis. Even so, they did not prove it; he merely disproved the null hypothesis.

As a clinical example, if the hypothesis is "steroids improve morbidity in shock," then the null hypothesis is that they do not. To refute this null hypothesis, the investigator has to demonstrate a difference between steroid-treated and nontreated patients in an adequately randomized and powered trial. If so, the null hypothesis is rejected and the hypothesis survives this test—this time. Statistics are applied to determine the certainty of the rejection of the null hypothesis and actually are performed to demonstrate that the null hypothesis has been rejected with a degree of certainty. For example, if $P = .05$, then it is 95% certain that the null hypothesis is incorrect and that the results are consistent with the scientific hypothesis.

It is this asymmetry of inference that allows us to disprove major premises by demonstrating the untenability of the inference. This is how we support scientific hypotheses. This refutation of the null hypothesis is generally taken to affirm that the very opposite is true. This is done because falsification of the inference and/or minor premises proving the falseness of the major premise is such a potent tool. Proving the major premise true is, in fact, impossible. Thus the basic tool used to demonstrate that a hypothesis is true is that of proving that the null hypothesis is false. The scientist's experimental goal is to reject the null hypothesis rather than to prove the actual scientific hypothesis. Because refuting the null hypothesis is such a potent tool, good scientific hypotheses must be of such a nature that their null hypothesis (or, indeed, many of their null hypotheses, because several may stem from one hypothesis) can be tested. This test is virtually always a statistical one.

Medical Research

"It is incident to physicians, I am afraid, to mistake subsequence for consequence."

Samuel Johnson

The first great divide in medical research is between clinical and laboratory research. Many consider such a division arbitrary, and the bench to bedside to bench translational models that have enabled modern physician-scientists to bring breakthrough understanding to the care of critical illness mandate that effective pediatric critical care researchers have "feet" in both domains. Still, in this classical distinction, clinical research is carried out in patients. It is an extension of previous experience in patients or of results obtained from laboratory research. Clinical research can occur in any medical arena. Laboratory research clearly does not involve patients; rather, it relies on the results in animals or tissue-derived "subjects."

Clinical research can be either retrospective or prospective. Retrospectively, epidemiologic studies, demographic studies, and studies of disease processes and outcomes of management regimens can provide useful information in directing future therapy. Certainly the great wealth of data now available in patient records can continue to provide worthwhile insights to aid our patients. Unfortunately, retrospective trials cannot convincingly answer therapeutic questions; rather, their utility is in hypothesis generation. Their solution requires true Galilean experimentation. Baconian studies such as these prospective trials require as much planning as possible before the patient actually is observed for the results of a therapeutic intervention, but this has started to change. Learning from reliable observations is the basis of physical science, and applying these research principles to data obtained from human subjects is useful in reliably suggesting a general theory if large enough numbers of observations are collected and analyzed. In medical informatics, this is the basis for knowledge discovery in databases. Thus with a sufficient number of observations (controlled, defined, verified data) we may learn how to manage our patients by applying analytical techniques to retrospective events. The information revolution may be driving knowledge discovery once again toward some reliance on deductive logic.[18]

The principles that guide all medical research, including clinical trials, are in place to minimize the possibility of an incorrect conclusion. A major cause of error is bias, either by the observer or the subject. A further cause of incorrect conclusions results from inadequate study design that may prevent accurate statistical analysis of the information obtained.

The other overwhelming principle that guides clinical research is to preserve the rights, autonomy, and safety of the individual subject.[30-32] This is of particular importance in clinical research involving children. The issues of risk, informed consent, and the potential to benefit the patient are particularly finely focused in pediatrics. The spectrum of opinion runs from believing that research in children is not allowable to believing that child subjects should be treated exactly the same as adult experimental subjects. Any researcher who proposes doing clinical research in critically ill children must be familiar with all aspects of these arguments and realize the sensitivity of the issues involved in this area.[33,35]

Research Design

In the simplest of all experiments, two observable populations, the experimental and the control, are observed for discrete occurrences. The results of the experiment are that the two observable sets of data from these populations are or are not different. Performance of a critical Galilean experiment that is clearly designed and meticulously executed will unambiguously answer this question. Any experiment that does not contain a control is not truly Galilean. The control group contains subjects as identical as possible to the experimental group. The observations made are the same before and after the introduction of the independent variable.

Designing an experiment involves attention to three separate areas: independent variables, subject selection, and dependent variables. Essentially, an experiment involves controlling or altering independent variables while observing in the subject changes in dependent variables. In short, the scientific method can be reduced to "if I do A, then what happens to B?" An example in early pediatric experimentation is provided by the first demonstration of adrenaline. Sir Henry Dale injected ground-up cow adrenal gland (independent variable) into his small son (subject) and determined the effect on his son's blood pressure (dependent variable). The closer study designs are to this simple algorithm, the more likely they will yield clearly understandable, unambiguous, and true results. Unfortunately, this is rarely possible except in highly controlled settings.

The independent variable is that which is under the control of the experimenter. The dependent variable is that which reflects the effects associated with altering the independent variable.

Independent Variable

The selection of the independent variable in any experimental design is crucial. Not only can this be a treatment variable but also the level at which treatment is delivered (dose). The independent variable must be one that can be manipulated and rigidly controlled. For example, to determine the effect of light on bilirubin in jaundiced babies, the independent variable is light. This variable can be fluorescent, incandescent, or solar. The duration of exposure and the efficacy of various light wavelengths could be—and indeed have been—experimentally determined by changing the independent variable and measuring the effect on the dependent variable (bilirubin concentration). In most therapeutic trials, the independent variables are either treatment or no treatment. For example, you test the therapeutic efficacy of a drug or the comparison of two or more treatment interventions for a disease, such as acyclovir versus cyclosporine for treatment of herpes encephalitis. A recurrent trial design relevant to critical care is provided by multiple studies on the use of one of many steroids in septic shock. These include steroid versus no steroids as the independent variable or, alternatively, multiple dosing levels of steroids.

The definition of the independent variable must be as precise as possible. Independent variables can be qualitative or quantitative. From the phototherapy example, a qualitative independent variable applies to the type of radiation. The radiation could be solar or incandescent light, and there will be a difference in the response of the dependent variable. There are many different kinds of treatment. Quantitative differences in the independent variable, by contrast, result from the same treatment given at different levels. The simplest of these is comparison of zero (no therapy) to a known dose of therapy, for example, 0 mg of steroids versus 30 mg/kg steroids. In addition, multiple doses can be given for a comparison of dose ranges. The exact selection of the independent variable and the quantitative nature of it ideally should be dictated by the specific hypothesis being tested.

Dependent Variable

Both practical and theoretical considerations are necessary in determining which dependent variables to observe. Clearly, the dependent variables will be determined by the expected outcome, as indicated by the hypotheses. In large-scale clinical trials, the dependent variable can be as simple as mortality or as complex as altered hemodynamic function described by a broad spectrum of hemodynamic parameters. The potential for dependent variables is enormous; however, some rules guide selection.

Most statistical analyses limit themselves to assessment of one dependent variable at a time. Selection of the dependent variable is determined by its distribution within the population, how reliably it can be measured, how sensitive and specific it will be to the independent variable, and how practical it is to measure. Clearly, maximum sensitivity and reliability are preferable. The more sensitive and reliable the selected dependent variables, the more likely the time and effort invested, number of subjects required, and cost of investigating the hypothesis will be minimized. Variables may be either quantitative or categorical—nonnumeric and discontinuous. With regard to distribution, it is generally assumed that dependent quantitative variables in the study population will undergo a normal (gaussian, bell-shaped curve) distribution. When abnormal distribution occurs, it must be specifically addressed statistically. It also is possible, in some instances, to transform an abnormal distribution to a normal distribution for the purposes of analysis. Disease states are often not normally distributed and parameters may be skewed (asymmetric) or demonstrate kurtosis (distribution of values near the mean) both of which alter how the population variance relates to the mean and therefore the validity of statistical

inferences. Unfortunately, a single dependent variable rarely approximates the clinical situation, where a single independent variable intervention may have a series of effects on a host of dependent variables. Therefore it is frequently necessary to evaluate two or more dependent variables at any given time. This process requires advanced study design and analysis that takes requirement into account; for example, multivariant analysis may be required.

Nuisance Variables

Anyone who has ever attempted any form of scientific experimentation is familiar with nuisance variables. Nuisance variables are best defined as undesired causes of variation in the observed or dependent variable. These variables are of no interest to the investigator but may significantly alter the outcome of the experiment. For example, nuisance variables may include factors such as patient age, gender, disease process, previous therapy, socioeconomic background, nutritional status, and presence or absence of infectious disease processes. The list is long, even infinitely so, and this is a problem for scientists. Unless these nuisance variables are controlled, outcome is uncertain. For example, an epidemiologic experiment to determine whether fatality is more common in lower socioeconomic groups following road traffic accidents could miss the effects of underlying nutritional status, distance from the hospital, and previous disease process and thus arrive at an erroneous conclusion.

One way to control nuisance variables is to ensure that they are both constant and equivalent for all subjects for the entire duration of the experiment. For example, male sheep exactly 6 months old, weighing 30 pounds, and of a specific breed and diet would provide better control for nuisance variables than a population of sheep of any age, weight, gender, size, or breed. In clinical trials it is generally impossible to obtain ideally matched controls. It must be assumed that some nuisance variables will always escape control.

The second broad approach to controlling nuisance variables is to assign subjects to experimental groups *randomly*. The principle of randomization rests on the supposition that the study population contains normally distributed nuisance variables and that these nuisance variables will be equally and normally distributed in the experimental subgroups (discussed later). This assumption can be true only if the experimental groups are of sufficient size to assure normal distribution. This is one of the major factors determining sample size. Randomization is the most powerful and most commonly used tool for controlling nuisance variables.

A third method for eliminating the effect of nuisance variables is merely to include them in the experimental design and thus study their effect on dependent variables. A final, nonexperimental method of controlling nuisance variables is statistical control. Analysis of covariance is a method of statistical control that removes the effects of nuisance variables through the use of multiple regression analysis. This is a complex statistical manipulation that should be prospectively designed into any trial when eliminating anticipated (or even reveal unanticipated) effects of nuisance variables is necessary.

Both independent and nuisance variables can be caused by the subject's innate characteristics, such as gender, weight, age, and previous illness, or by external environmental influences. These environmental influences may include temperature, humidity, presence or absence of other caregivers, a variety of pharmacologic interventions, socioeconomic group, diet, and various other factors. Task-related variables also may affect the dependent variable. These factors may be inadvertently introduced into the experiment study design, and they must be rigorously sought and avoided. For example, the experimental design or the particular sequence of observations made may alter the dependent variable in such a fashion as to confound the effects of the independent variable.

Design Efficacy

The problem facing the investigator who wishes to address a medically related question is to design a study (or a series of experiments) that can answer the question as validly and efficiently as possible while taking into consideration the research situation available to the investigator. Efficiency of research design can be accounted for in several ways. Cost can be one of these determinants, and the cost per observation or the cost per experiment can be compared to the amount of information obtained. Alternatively, time can determine efficiency: the maximum useful data in the shortest period of time. In fact, careful stewardship of resources for biomedical research is an underappreciated principle. Every emerging researcher in pediatric critical care must commit herself/himself to incorporating such stewardship as an underlying value. These factors are inherently determined by the amount of variance in the dependent variable that can be attributed to extraneous or nuisance variables.

This situation gives rise to the concept of experimental error variance. A major source of this error is the variability inherent to subjects. A further cause is the lack of precise uniformity in experimental conduct. When comparing two groups it is important to ensure that observations are made at the point where differences between the groups are the greatest. It is possible that the effects of two drugs are equal at higher doses, but significant differences could exist at a lower dose range. Observations at the former point would yield negative results but at the latter point reveal a beneficial effect with less drug. Clearly, information about efficacy (dose response) is necessary before a comparison trial. Federer[27] formulated a method for evaluating the efficiency of experimental design that takes into account the number of subjects at each treatment level, the cost of collecting data per subject, the degrees of freedom, and an estimate of error variance per observation. These are factors the investigator must consider when designing any experiment.

The basic technique of experimental design is that of replication of observations in two or more subjects under identical experimental conditions. The number of replications or the sample size depends on the following five factors[36]:

1. Number of treatment levels
2. Minimum treatment effects to be detected
3. Error variance of the study population
4. Necessary power (probability of rejecting the null hypothesis)
5. Probability of making a type I error

There are two common ways of increasing the power of an experimental design. The first method is to design experiments that provide precise estimates of the desired treatment effects while minimizing error effects. The second method is to increase sample size.

Randomization

All statistical theory is based on the supposition that at some stage during the experiment, a process of random selection is performed. Conclusions based on these statistical studies are valid only inasmuch as the randomization process is understood and observed. A random procedure has at least two possible outcomes, and the probabilities of all possible outcomes are specified prior to the randomization procedure.[37] It is important to note the frequent errors practiced in the name of randomization. First among these is the naive belief that the number of subjects in an experiment is related to randomness. Although the principle of safety in numbers may be reassuring, it is unwarranted. Experiments usually are performed in only a small sample of a normally distributed population. If this sample is truly representative, then the size of the population sample does not matter. By contrast, if the sample of the population is not representative (e.g., it is drawn from patients at one end of the normal distribution), then no matter how large the sample, randomness will not be possible. For example, to determine the case fatality ratio in children with meningitis, it would be just as useless to study 10,000 as 10 autopsies.

It is important to note the difference between a random sample and a haphazard sample. A haphazard sample indicates the investigator has no idea of whether the sample is representative of the whole population and hence the value of the data. The more a given sample can be constructed wherein as many biases as possible are appreciated, the more likely the results will be truly randomized and known as opposed to haphazard. It is crucial to know that the investigator's ignorance of the characteristics of the sample population is not the same as randomization. Similarly, ignorance of associations within a sample population does not make the sample random and provides another serious source for potential bias. Simple inability to show any clear biases in selection does not assure randomization. Another error made in randomization is to confuse the source of bias by mixing populations of unknown bias. Finally, the absence of a clear plan for randomization does not ensure randomization; rather, haphazard sampling leads to haphazard results.

So how do we ensure that randomization takes place? Obviously, with an adequate sample of the best-designed and most homogenous population, randomization can be optimized. In any experiment requiring randomization, the study population must be as explicitly defined as possible before randomization occurs. This is relatively simple if all subjects are prospectively chosen (e.g., 10 patients with sickle cell disease). It is less clear when the subjects can be drawn from a large population (e.g., the next 10 children with ARDS). Second, the system for selection must be prospectively described. Steps should be taken to ensure equal numbers of, for example, boys and girls, age distribution, race, and operative procedure. Once the subjects have been defined and selected, a means of randomizing them, with a representation in the randomization procedure for each subject, must be made (e.g., even or odd numbers, a randomization table, or something as simple as drawing names out of a hat).[37] This process is only as useful as the prerandomization population is homogeneous. Of course, with human experimentation, subjects frequently differ. It also is necessary to describe the action to be taken following randomization; for example, all odd numbers get no therapy, and all even numbers get steroids or prostacyclin. Finally, the subjects are randomized, and nothing is allowed to alter the outcome. A large host of confounding factors in randomization will occur. Other randomizations, such as randomized block design and Latin square design, are potential approaches for solving these problems.[36]

Validity

Evaluating an experimental design requires taking into account those factors that ensure the validity of the results. First of all, the overall field of research must be known so that experimental observations can be made that provide the opportunity for comparison of findings with other investigators. In addition, accepted practices and procedures in the research area should be followed wherever possible. Next, it is necessary to decide if the data collection method produces reliable results and that the data obtained are accurate. It is also necessary that the design of the experiment permits the experimenter to determine which effects are caused by experimental error and which results are caused by manipulation of the independent variable. In addition, some attention is necessary to optimizing the efficiency of the experiment and understanding the experimental constraints. Finally, to justify doing any experiments at all, the design should be of sufficient power to be certain that an adequate test of the statistical hypothesis will result.[36]

It is essential to ensure that valid conclusions concerning the effects of the independent variable on the dependent variable can be drawn from the experiment.[38] In general, this is satisfied by statistical analysis. In addition, in the medical setting, generalizations of these results to populations and settings of medical interest are necessary. This requires probability theory.[37] It is important to realize that statistical theory and probability theory are not the same. The purpose of ensuring the validity of the statistical conclusion is to ensure that incorrect data resulting from errors in randomization and inappropriate statistical analyses are not made.[36] There are several threats to the validity of inference from the data.[38] Clearly, the statistical analysis must be correct, but in addition it is necessary to assess the internal validity of the experiment. "Internal validity" deals with the assumption that the relationship between observed variations in the dependent variable is resulting from variations in the independent variable. "Construct validity" of causes or effects deals with the potential that alterations in the independent variable and observations in the dependent variable result from and are construed in terms of other variables. Finally, "external validity" of the results indicates the extent to which the results of a particular experiment can be generalized to populations and subjects. This concerns comparison with existing results and the probability of extending the results of a given experiment to a wider population and ultimately to treatment decisions.[37]

Statistics: A Word

This section is not intended to be a primer on statistics or to serve as a catalog of how to do a *t* test or analysis of variance. Numerous textbooks and computer programs exist for those purposes. Rather, this section emphasizes the common—and most frequently violated—principles that

underlie the statistical analysis of experimental data. They are the source of rejection of articles and of grant applications and a great deal of wasted effort—not to mention the potential for misguided therapy. Every study, every paper, every grant, and ultimately the validity of every therapy rests on these principles. Statistical analysis of the data yields the likelihood of certainty from the experiment at hand.[36] Probability theory deals with the predictive statements based on the outcomes of an experiment.[37] In medicine, both diagnosis and prognosis rely heavily on probability theory. When analyzing experimental data, we generally think in statistical terms. Although statistical analysis of data frequently is used to apply results to the clinical situation, it really is valid only for testing hypotheses and estimating outcomes. Statistical approaches are concerned with the concept of a scientific hypothesis, not with medical treatment. Scientific experimentation is based on testing formulated hypotheses. Therefore a scientific hypothesis must be testable and requires, by its mere formulation, verification. Hypotheses should be reasonable, informed, and intelligent guesses about the phenomena observed in nature. They should be stated as far as possible in the "if A occurs, then B occurs" format. They should be testable. The common technique for assessing the plausibility of a scientific hypothesis is by constructing the hypothesis that manipulation of the independent variable (a treatment) has no effect. This is the so-called *null hypothesis* (as discussed previously). The objective of the experimental scientist is to demonstrate that the null hypothesis is untenable and therefore the hypothesis is supported by default (i.e., variation of the independent variable has some effect on the dependent variable).

For this purpose, the scientific hypothesis must be formulated as a statistical hypothesis by deductive inference, which then can be tested by random sampling and estimation from a population and subjected to a specific statistical test (Fig. 4-1). The statistical test will determine whether the null hypothesis is tenable or untenable, and this result, by inductive inference, will be applied to the scientific hypothesis under question. This sequence of demonstrating a scientific hypothesis is the basis of experimental medicine. One should not, however, infer that each scientific hypothesis has a specific and pertinent null hypothesis. Multiple null hypotheses may be compatible with the scientific hypothesis tested, and several may need to be tested to give a broad basis of acceptance to the scientific hypothesis. For example, if the scientific theory is "Mortality can be decreased by steroid use in septic shock," a potentially testable statistical hypothesis might be: "Steroids do not alter pH within 24 hours in patients in septic shock." Although the theory would be statistically difficult to demonstrate (and indeed has been) in a patient population by prospective controlled experiment with all other independent variables held constant, this particular null hypothesis could be tested. There are obviously assumptions between the relationship of pH and outcome. A more useful null hypothesis is that survival at 72 hours is not improved by steroids. This is a testable hypothesis, and with the appropriate study design and statistics it can be tested. Obviously, many other statistical hypotheses bearing on the scientific hypothesis can be designed. It is up to the investigator (and the evaluator of the investigation) to understand the relationship between the statistical hypothesis being presented and the scientific hypothesis being tested.

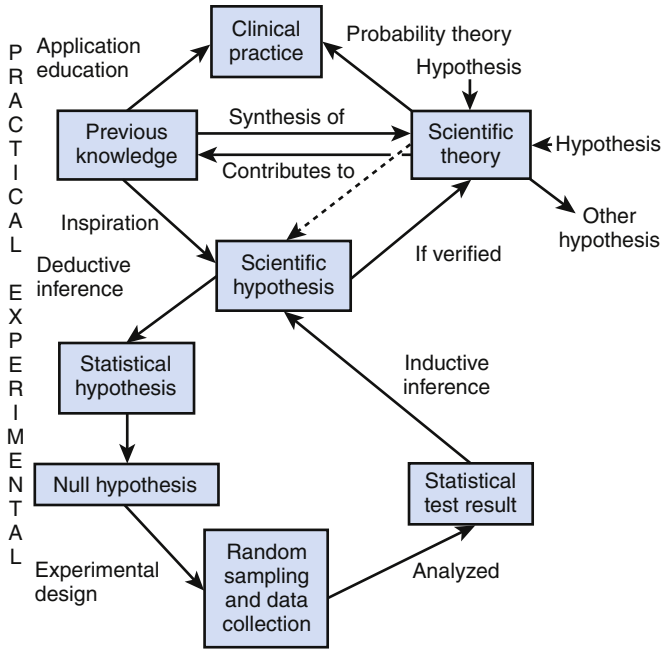

Figure 4–1. General schema of the relationship between clinical practice and medical research. Note the central position of the scientific hypothesis and the steps necessary for verifying it. Also note that the statistical analysis of experimental data does not apply to the application of medical scientific theory (built up of multiple hypotheses) to clinical practice.

Type I and Type II Errors

The aim of testing the null hypothesis is to either accept or reject it and thus to refute or support the hypothesis. This decision will be either correct or incorrect. An incorrect decision that leads to invalid conclusions can be made in two different ways. The first is rejection of a null hypothesis that is, in fact, true. This is a type I error. Second, a false null hypothesis may not be rejected when in fact it ought to be rejected. This is a type II error. The difference between these two arises, in part, from the asymmetry of proof described previously. Support for a null hypothesis does not necessarily disprove the hypothesis. There are also two choices of how a correct decision can be made. If there is a true null hypothesis and the experimenter does not reject it, this is correct acceptance of the null hypothesis. If there is a false null hypothesis that is rejected, then a correct rejection has also been made. These choices are summarized in Figure 4-2.

In general, the likelihood of making a type I error is determined when the level of significance is specified. The probability of making a type I error is .05, when α equals .05. This is the probability of rejecting a true null hypothesis. The determination of α also determines the likelihood of the correct acceptance of a true null hypothesis $(1 - \alpha)$.

The probability of making a type II error is symbolized by β. Thus the probability of correctly rejecting a false null hypothesis equals $1 - \beta$. Alternative terms for these errors are α errors (type I) and β errors (type II) for obvious reasons. β is determined by a number of factors, including sample size, standard deviation of the population in general, difference between the mean of the sample and the mean of the overall population, whether a one- or a two-tailed test is used, and level of significance selected. The power of a statistical test is defined as the probability of making a correct rejection $(1 - \beta)$. Because the

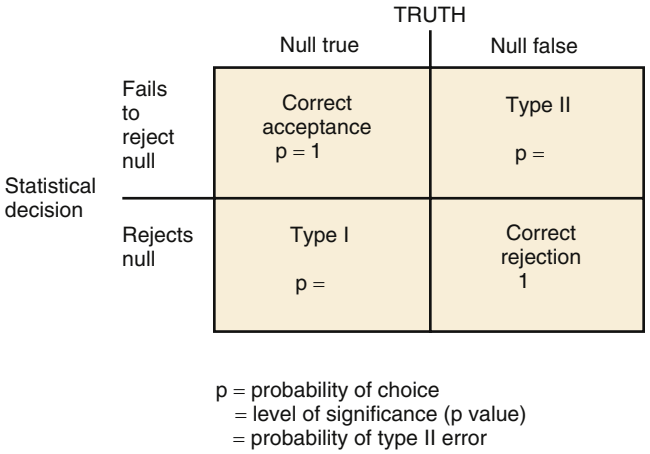

Figure 4–2. Difference between type I and type II errors in statistical analysis. Null refers to the null hypothesis derived from the scientific hypotheses. Note that the likelihood of a type I error, rejection of a true null hypothesis and therefore acceptance of the statistical/scientific hypothesis, is generally equal to the p value of the analysis. Thus when $P = .01$, there is only a 1% chance of a type I error. A type II error is more subtle and requires determination of β (see text) to understand the likelihood of falsely rejecting a true hypothesis.

mean of the overall population from which the study population is selected is generally unknown, an estimate of it must be made or a value selected that would be of interest. Statistical techniques are available that determine the sample size and population characteristics necessary for the experimental circumstances.[36]

The investigator must determine whether a type I or type II error is more costly. As an example, with regard to steroids and shock research, experiments are generally designed to test the null hypothesis that steroids are not effective as a therapy for shock. A type I error (rejection of the null hypothesis, when it is in fact true) could result in confirming the effectiveness of steroids and lead to their use. The consequences of this decision would be steroid therapy for septic shock. As long as this did not supplant another useful therapy or carry with it complications of its own, the consequences of this error would not be so severe. In contrast, falsely deciding that steroids were not effective, a type II error, would prevent the use of steroids in septic shock. However, further research might be stimulated that ultimately leads to an effective steroid regimen or alternate therapy. In this case, the long-term consequences of a type II error would be less than those of a type I error. A detailed understanding of the importance of accepting or rejecting the null hypothesis for each scientific hypothesis determines at what level type I and type II errors are acceptable. This is necessary information before designing an experiment. In general, making a type I error is more serious than making a type II error. For this reason, α frequently is set at .05 or .01. If a type I error could be very serious, then $P = .001$ may be necessary. Unfortunately, as α decreases, β tends to increase.

There are multiple threats to the statistical validity of experimental design. Some of the threats that increase the likelihood of type II errors are:

- Unreliability in measurement of the dependent variable that inflates the error variance
- Unreliable treatment, administration, and implementation
- Heterogeneity in the sample population because of idiosyncratic characteristics of subjects that inflates the estimate of error variance
- Presence of nuisance variables

To avoid making invalid conclusions or inferences from the data, one must realize that there are certain assumptions in statistical testing. For example, whenever multiple comparisons are made, there is the possibility of an error rate problem. That is, the likelihood of making an erroneous conclusion increases as the number of comparisons on the same set of data increases. To avoid these major errors in statistical design, multiple comparison tests and the definition of which tests are essential will determine which statistical tests are valid.

This introduction to statistical theory forms the essential basis of all experimental statistical testing. Although simple statistics and analysis of variance are by far the most commonly used statistical tests in medicine, the frequency with which they are inappropriately applied is staggering.[39] Study design must be simplified, and the statistical analysis that is to be used should be determined before the experiments are performed. Haphazardly searching for a statistical test to make the data significant is an all too common error that can be seriously misleading. Thus *a priori* decisions are necessary to ensure the validity of the inferences made from statistical tests. This point cannot be too strongly emphasized. It is the reason the experimental scientist must be familiar with statistics. Employing a mathematical statistician who does not understand the experimental and medical implications of the study to give some magical statistical analysis is inappropriate, especially if attempted *post hoc*. The more the statistician understands the medical setting of the experiment and the more the experimenter understands statistical theory, the more likely the results will be applicable to the children initially intended to benefit from the research.[40,41]

Neoempiricism, Data Mining, and Knowledge Discovery in Databases

The modern knowledge base of medicine has been vastly enhanced by inductive research (see above). The medical literature and the National Institutes of Health (NIH) depend on the hypothesis-driven research. The gold standard for medical therapy rests on hypothesis-driven, double-blind, randomized, rigidly controlled clinical trials analyzing specific data determined *a priori* by statistical means also determined *a priori*. In contrast, physicians practice empirically or perhaps rather, anecdotally, attempting to remember their experience and education, and hoping to apply it intuitively to the next patient. The persistence of anecdotal medical practice demonstrates our human comfort with this approach. The respected senior clinician who approaches a difficult patient with the words: "I once saw a patient like this…" is not lauded for his grasp of the literature but rather his clinical expertise built on experience and reason. This is empirical medical practice, almost the antithesis of evidence-based medicine. Or is it? The evidence of what the clinician remembers, what she has seen, experienced, the results of all of these natural experiments with thousands of patients and what the experienced clinician 'knows' to guide the next patient's therapy is based on personally gleaned evidence. Unfortunately, this depends on the

human grasp of the seven or so variables a mind can track at one time,[42] and the brilliance and frailty of human memory. We are all too familiar with errors in health care (from leeches to steroids) based on this sort of deductive reasoning (from known, 'true' generalities to specific facts).

But times have changed. Health care is an information business. We have vast quantities of data, which increasingly are becomingly digital in nature and thus available for sharing, analyzing, and learning and teaching from. This, at times overwhelming, amount of data, when managed by appropriate computational techniques, offers the opportunity to assist health care providers' memory and grasp of the data. Using computational techniques and modern data management as a cognitive prosthesis, it may be possible to support a new era of empirical research—a neoempiricism built on validated observations in thousands of patients detailing what has actually happened. We are in the situation now of having done the experiments but having failed to capture, keep, analyze, and learn from the data which could guide the therapy of the next patient.

Health care is now involved in collecting large amounts of data about patient care for purposes of quality improvement, oversight, and improving efficiency. There are also vast collections of clinical data potentially available for further analysis. VPS, LLC currently links over 85 hospitals' PICUs with data on over 300,000 patient admissions (https://portal.myvps.org/). It is possible to capture highly granular (detailed) data from electronic medical records capturing every blood pressure, heartbeat, and saturation plus much more from every critically ill child. This is a rich data source. Can all of these mountains of digital clinical observations be converted from mere data to information and knowledge to guide treating the next patient? Can we learn from what we have done, from the myriad experiments involving thousands of patients? To waste the potential knowledge available from managing these patients, or to continue to use it merely to inform clinicians one at a time, would be unethical. Failing to learn from each patient and share that knowledge is denial of the very ethos of medicine.[22] Fortunately, there are increasingly sophisticated techniques to do just that—learn from every single patient encounter, make the data and knowledge derived from it available and apply it to the next patient. To know how the last 300 children with asthma were treated in the last 6 months would paint a picture of the standard of care, provide real-life comparisons of approaches, and detail therapeutic responses. The summed experience of multiple practitioners would be available for the next child admitted with asthma—not relying on the clinician's memory but on valid data from hundreds of therapeutic trials. Learning from observations, i.e., data, is what science is about. In recent years, there has been tremendous growth in medical data mining—the process of analyzing data to discover patterns and associations. Associations, clusters, and linear sequences, often for the purposes of forecasting or predicting what may happen in the next patient.

Knowledge discovery in databases goes beyond data mining to extract unknown, implicit, and potentially new and useful information/knowledge. Using artificial intelligence methods such as machine learning, neural networks, and other sophisticated techniques to learn about and manage our next patient offers a challenging opportunity for bringing information to the bedside in near real time. There remain enormous challenges to make learning from clinical data possible. These challenges provide a valid research opportunity. How is medical data best mined, are routine business data-mining algorithms applicable to health care data? How can data validity be assured? What about the security and HIPAA issues involved with patient level data? The NIH, Agency for Healthcare Research and Quality (AHRQ), and the Department of Health and Human Services (DHHS) have recognized the importance of this field with related funding opportunity announcements.

Research Funding

Obtaining Financial Support

Research takes time and costs money. Investigators must have financial support for personnel and research materials. It is generally incumbent on the investigator with the idea and the enthusiasm for performing the research to acquire financial support, but senior investigators should provide advice and encouragement to less experienced scientists, and never convey the impression that their ideas are not of sufficient value to deserve consideration. It is necessary for any investigator with extramural funding to support the broader research effort, especially on behalf of young investigators. Without this commitment, the resources necessary for research will never be available. All investigators are aware of the difficulty of obtaining—and the increased competitiveness for—extramural research support. Despite the prophecies of doom and gloom, myriad funding sources remain available.

Since World War II, the prosperity of the United States has enabled the NIH to become preeminent as a resource supplier for medical research by conscious governmental effort. Although this system has funded the tremendous surge in medical research that contributed to the growth of medical schools, university faculties, and hospitals and a research effort second to none in the world, it also has rendered this establishment dependent on federal dollars. This dependence has made the politicization of medical research difficult to avoid.[43] Some in the research community may express the opinion that these national funding programs have become less supportive of the ideas of individual investigators and more directive of national medical research priorities. Nevertheless, approximately 80% of overall NIH funding still supports investigator-initiated research. The experienced or emerging investigator needs to become familiar with diverse sources of funding and how to access them, and the experienced investigator has a responsibility to help.

Sources of Research Funding

From the perspective of the investigator, sources of research funding can be broadly divided into intramural and extramural sources. Intramural funding is that available from within the investigator's institution. The source of funds for this research is private endowments, grants, donations and gifts to the university, and clinical funds directed to research support via individual clinical departments. In addition, universities may receive training grants from federal organizations or other granting agencies to facilitate training, education, and research endeavors by their faculty, fellows, and staff.

Box 4–1 Funding Resources

Many of these resources can be found online or in university offices for sponsored research or research administrators, deans' offices, or medical school and university libraries.

Annual Register of Grant Support

Catalog of Federal Domestic Assistance

Commerce Business Daily

Federal Register

Foundation Directory

Foundation Grant Index

NIH Extramural Programs

NIH Guide to Grants and Contracts: Weekly publication of funding initiatives http://grants1.nih.gov/grants/guide/index.html

National Science Foundation Guide to Programs

Research Awards Index

Small Business Innovation Research and Technology Transfer (SBIR/STTR) Programs http://grants.nih.gov/grants/funding/sbir.htm

CDC research funding opportunities: http://www.cdc.gov/od/pgo/funding/grants/grantmain.shtm)

SAMHSA: http://www.samhsa.gov/Grants/index.aspx

FDA: http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm

AHRQ

HRSA

American Association for the Advancement of Science (AAAS) Science Web site: http://www.sciencemag.org/

The Grant Doctor (e-mail: grantdoctor@aaas.org)

Funding sources search engine: http://www.grantsnet.org.

Government contracts

Industrial/pharmaceutical research support

Box 4–2 Guidelines for Grant Writing

- Read and study the instructions.
- Present a well-organized, precise, lucid explanation of all points.
- Never assume the reviewers will know what you mean.
- Explicitly and clearly, state the rationale of the proposed investigation.
- Refer thoroughly to, and demonstrate thoughtful familiarity with, the literature.
- Use well-designed tables and figures; a picture is worth a thousand words.

Intramural Funding

The first line of funding for the junior investigator generally is intramural funding; however, securing it should not delay the investigator's exploration of extramural funding possibilities. Scientific productivity is the first concern for the new investigator, but being productive financially is always an asset. Intramural funds are developed and administered by individual research directors, division and department chiefs, institutions, and dean's offices. Donations from patients, private individuals, and corporations, and funds generated by the clinical activity of individual faculty members support innovative entrepreneurial "start-up" research projects that serve as pilot and preliminary studies to ultimately obtain extramural funding. Junior faculty should not hesitate to seek such support from hospital auxiliaries, private foundations, or individual donors.

Providing access to funds for junior investigators is the responsibility of senior physicians with long-term commitments to critical care medicine. Frequently, the fundraising foundations of hospitals or the research offices can help the investigator find resources from these sources. Without this "seed" money, new ideas may never get far enough to generate extramural funding and bear the fruit of complete investigation and experimentation. A commitment to research as a vital part of clinical practice, as well as seeking and dispersing gifts and donations, is crucial to ensure vital funding for the research endeavor in critical care medicine. The percentage of research funded from clinical resources, external donations, and extramural research funding varies widely. Young investigators should understand that this seed money usually is for a limited time. Once they have been given an opportunity to initiate their work, most institutions expect them to find extramural funding, so that other young investigators can be supported.

Extramural Funding

Extramural funding comes from numerous private and public sources to which the investigator can apply either independently or through the sponsorship and direction of the institution. Federal funding accounts for a large proportion of available extramural support in U.S. universities performing biomedical research. Much of this funding comes from the NIH, and valuable insight into the agency and the process of obtaining funding can be obtained from the NIH Web site http://www.nih.gov/. In this section, we discuss some of the funding opportunities available through the NIH. A subsequent section discusses the NIH structure and operation as a major part of the "research landscape" in the United States.

Extramural support sources include private philanthropy, industrial/pharmaceutical research support, private grants and contracts, and government grants and contracts. Exhaustive lists of granting organizations should be available in the deans' offices and offices of sponsored research and research administration at any academic instituton (Box 4-1). The staffs in these offices may be an underutilized resource at many institutions, and critical care investigators should identify and contact them. Another obvious source of funding opportunities comes from within the specialty's collegial network. Conversations with colleagues within the university, professional organizations such as the Society for Critical Care Medicine and the American Academy of Pediatrics, and personal research contacts frequently provide useful information on the current funding available from various sources. In addition, numerous research publications in this field may be found in the medical school or university library or at the dean's office (Box 4-2).

These publications provide a useful, but not exhaustive, list of potential resources for research allocation and an excellent starting point. Additionally, most universities have career development awards and institutional granting organizations that can provide interim, emergency, and seed support for

research projects with the promise of obtaining extramural funding. Again, reference to the local university offices is suggested.

Between 1994 and 2006 the NIH budget was aggressively increased by Congress, but such increases have not continued and this has led to significant tightening of funds. The largest segment of the NIH budget still goes to funding extramural (that is, the research is conducted outside the NIH campus) investigator-initiated projects, as summarized in Figure 4-3. Because of the more competitive budget situation, it is crucial that those with ongoing research interests maintain a detailed understanding of the NIH, our federal government's principal agency for supporting biomedical research.

Although obtaining funding through the NIH can seem daunting, it is best to begin any such endeavor by understanding some of the basic funding mechanisms because this may ultimately assure successful choices. Funding may take several forms. The most common form is direct grants, which are reasonably unrestrictive and awarded to institutions in response to specific applications by investigators. These grants provide the major basis of federal funding. Under most circumstances, institutions receive substantial indirect funds from NIH-funded research: an additional 50% to 70% is added to the grant amount, supplying the institution with substantial support for facilities and administration (also known as "F and A" or indirect costs). There are many types of NIH grants: the investigator should peruse all of them on the Internet (http://grants1.nih.gov/grants/index.cfm). The following brief discussion of a few of these mechanisms is introductory only.

- **Research Project Grants (R01s)** are awarded to an institution on behalf of a principal investigator who has requested support for a specific research project in an area in which he/she is competent and interested. This funding mechanism is widely considered to be the vehicle for successful scientific support and the goal of the investigator with serious research aspirations.
- Most NIH funding goes to investigator-initiated proposals, and the R01 is the most commonly used mechanism. The research plan focuses on a specific set of research aims, and the plan to achieve these aims typically is hypothesis-driven. The level of support varies; the budget (direct costs) of an R01 typically is $250,000 to $350,000 per year, with 3 to 5 years of support requested. The award is renewable, in a competitive renewal process. The specific policies and scope of the R01 can be reviewed on the NIH Web site, http://grants.nih.gov/grants/guide/pa-files/PA-10-067.html.
- **Small Grants and Exploratory/Developmental Grants:** The R03 is a small grant mechanism that offers up to $50,000 (direct costs) as a level of support for 2 years. Although not all institutes offer this funding mechanism, it is often used as a first independent funding mechanism by new or emerging investigators. It may be especially useful for obtaining pilot data to answer scientific questions or provide direction for future larger studies. The R21 or exploratory/developmental grant provides 2 years of support for planning research or for exploration of scientific questions, particularly innovative approaches. This mechanism provides up to $275,000 direct costs during the 2 years. These two funding mechanisms are significantly less difficult to obtain for newer investigators than the R01, because requirements for substantial pilot data are less.

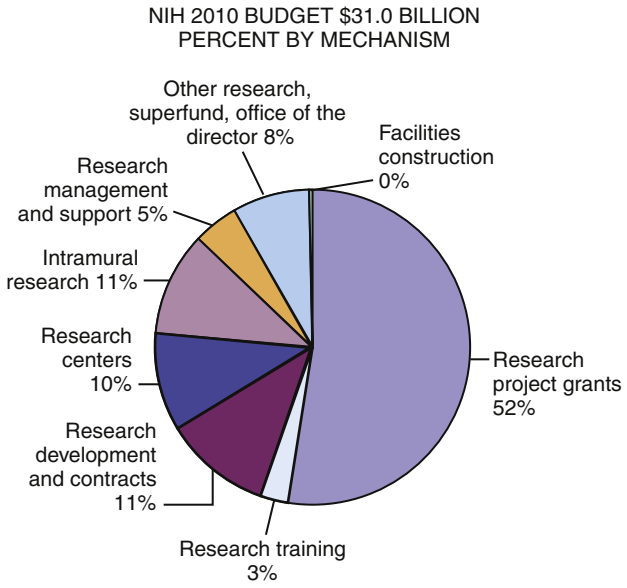

Figure 4–3. National Institutes of Health (NIH) budget for fiscal year 2010. Approximately 75% to 80% of NIH funds support investigator-initiated science outside of the NIH.

- **Program Project Grants** are awarded to the institution and are provided to support broad-based, long-term research programs involving multiple investigators, multiple projects, and a common objective. Often, the objective is announced in a scientific initiative, such as a Request for Applications (RFA), or a Program Announcement, published by one of the government agencies or one of the NIH institutes.
- **Research Career Development (K series) and Training Grant Awards (F and T series)** are given to institutions to develop the research capabilities of emerging investigators (F and T series) and to develop research careers with mentoring (K series). In our emerging specialty, these merit further discussion (see below). The NIH Web site provides an overview of the commitment to early stage investigators (http://grants.nih.gov/grants/new_investigators/index.htm). At the junior faculty level, career development awards are available for those wishing to enhance their early research careers through work with an experienced mentor. Every junior faculty member with research as a substantial interest should consider the K mechanism. These are salary support grants that provide mentored research time for individual emerging investigators. Typically, 75% salary support is provided. This NIH award series has been expanded in recent years. Some of the specific career development and fellowship awards of significance to critical care investigators are listed below.
- **The K series** (K01, K08, K23, and several others) provide mentored investigator funding opportunities from the NIH and are often used as a first funding mechanism. Choice of mentors is crucial, and this choice should be made with the nascent investigator's interests foremost. It is nearly essential that the mentor have established extramural funding from the NIH; mentors should not be young investigators with their own K awards. An exciting recent development for emerging scientists in pediatric critical care (at the junior faculty level) is the Pediatric Critical Care Scientist

Development Program established in 2004. This program had 15 Scholars in its first 4 years, and the application deadline is October 1 of each fall. Information can be obtained from http://www.pccsdp.org/, or interested applicants may contact the program director, who will provide assistance to applicants in the strategy of obtaining funding, and who has a list of potential mentors.

- **Institutional Training Grants (T32):** These awards are made to institutions for support of graduate research training, postdoctoral research training, and research fellowships in clinical and basic science investigation.
- **Cooperative agreements ("U series" funding mechanisms)** are becoming increasingly important, especially in research networks. The government agency enters into an agreement with the investigator(s) to manage the project cooperatively, for example, the National Collaborative Pediatric Critical Care Research Network (CPCCRN) established in 2005. These awards are made after application for specific funding opportunities published by the NIH. The specific collaborative terms are spelled out between the investigator and the funding organization. Industry is providing a greater portion of research resources.

In 1980, 30% of health research was funded by industry compared with 59% by the federal government. By 1990, industry was funding 45% of U.S. biomedical research efforts. Economic fluctuations make it difficult to predict future trends, but such support will likely continue. Industry supports research in two ways: first, by funding foundations that support research, and second, by contracting with researchers to perform specific, directed product development, such as drug trials, clinical studies, and product evaluation. Information about these programs is available from the sources listed earlier and from the Food and Drug Administration (FDA).

Contracts provide another funding source. These formal agreements are made either with the federal government (often the NIH but many other federal agencies also issue research contracts), industry, or with private foundations for specific research projects designed by the grantor of the contract. Research contracts can be divided broadly into contracts that provide reimbursement for the cost of investigations and experiments, and fixed-price contracts that basically are awarded to achieve a specific goal at a fixed cost to the grantor of the research contract.

Awareness that industry (pharmaceutical agencies, insurance companies, medical equipment companies) has the money to fund its research priorities and wants to carry out such studies should motivate all in pediatric critical care to explore contact possibilities and increase awareness of these opportunities. In addition to direct business contacts, the critical care investigator should become familiar with the Small Business Innovation Research and Technology Transfer (SBIR/STTR) Programs, which are an important source of research funding. Companies seeking professional research consulting are listed on the SBIR/STTR website.

Foundations may be merely philanthropic (funding good ideas) or they may be directive (addressing issues of specific interest to the foundation).[44] They can bring investigators together, fund research, and disseminate ideas. Foundations are a source of research "venture capital" and as such often take greater risks than federal funding agencies.[44] Accepting research support from industry (whether through a foundation or more direct corporate source) has ethical implications.[45] Research and clinical decisions should be guided by data, not funding sources. Private funding for research, especially if lavish, may raise questions regarding the integrity of the researcher; for this reason, prospective ethical guidelines are essential. Clear declaration of all potential conflicts of interest must be made, including those that may have only the appearance of conflict.[46] Although absolute ethical integrity is the cornerstone of research (see below), it is nowhere more critical or more readily corrupted than when dealing with profit-motivated industry.

National Institutes of Health

The NIH is an agency of the DHHS. The DHHS has overall responsibility for many other agencies, including the Centers for Disease Control and Prevention (CDC), FDA, Substance Abuse and Mental Health Services Administration (SAMHSA), Health Resources and Services Administration (HRSA), and the AHRQ. Many of these agencies (and other federal agencies) have research funding programs in addition to that of the NIH.

The NIH is made up of 27 institutes and centers. Its structure is summarized in Figure 4-4.

Most of these individual NIH institutes (called "ICs" at the NIH) and centers have programs that provide both intramural (internal to the NIH) and extramural (outside the NIH) funding support for research. The institutes with only extramural funding programs are shown in black in Figure 4-4. Some of the NIH institutes that may be supportive of critical care research and therefore are most familiar to intensivists are:

- National Institute of Child Health and Human Development
- National Heart, Lung, and Blood Institute
- National Cancer Institute
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute of General Medical Sciences

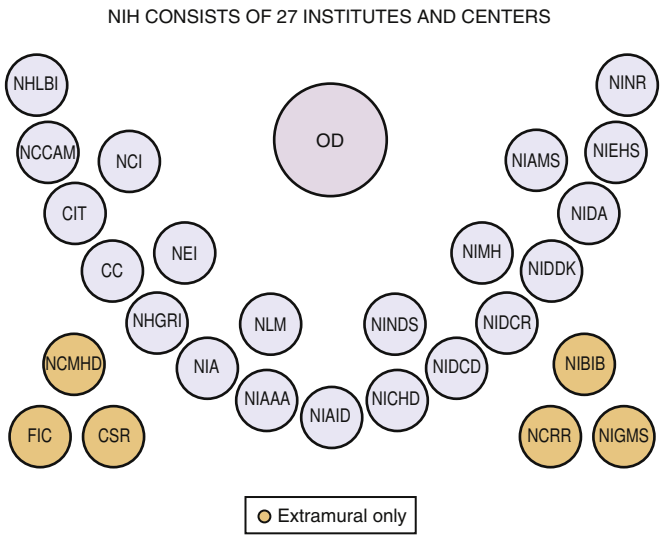

Figure 4–4. The 27 institutes and centers at the National Institutes of Health (NIH). Those shown in white support both intramural (at the NIH) and extramural science. Those with gray backgrounds support only extramural science.

Each NIH institute is accessible through the NIH Web site at: http://www.nih.gov/. By visiting the Web site of the specific IC, one can review the funding priorities and programs, and find scientific contact personnel who are of great assistance to investigators. Both NICHD and NIGMS have formal programs that are specifically supportive of critical care research. Both institutes offer career development, institutional and individual training awards, and investigator-initiated awards. Program staff generally make themselves available for questions and guidance.

The NIH extramural programs are divided into grants, contracts, and cooperative agreements. The role of the NIH in each of these programs is, respectively: patron, as granting agency (grants), to provide assistance and encouragement; purchaser (contracts), to provide procurement of necessary resources; and partner (cooperative agreements), an assistance mechanism (rather than an "acquisition" mechanism) in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during performance of the activity. The NIH publishes the weekly NIH Guide for Grants and Contracts, which announces NIH scientific initiatives and provides NIH policy and administrative information. The guide publishes notices, program announcements (PAs), requests for applications (RFAs), and requests for proposals (RFPs). It is important for investigators to understand the basic differences in these scientific initiatives. Checking the guide weekly (subscribe at http://grants1.nih.gov/grants/guide/listserv.htm) provides access to the latest funding initiatives at the NIH as soon as they are published. PAs have no specific funds set aside but indicate broad areas of ongoing research interest within the NIH. FOAs (funding opportunity announcements) are formal announcements describing an institute's initiative in a specified scientific area. Requests for Applications are announcements that indicate that funds have been set aside to make awards in the area requested. They serve as invitations to investigators in the field to submit research grant applications for a one-time competitive assessment.

The following is a general scheme of how an NIH grant application is processed. This scheme serves as the model for grant applications discussed in the following section (Figure 4-5). The investigator initiates a research idea and, in conjunction with the school or other research center, electronically submits an application to the NIH. Applications initially go to the NIH Office of the Center for Scientific Review (CSR), where the application is assigned to the appropriate study section and institute.

The study section, as the peer review groups are widely known, evaluates the study for scientific and technical merit and assigns a priority score. The grant application is evaluated for programmatic relevance by the NIH staff of the individual institutes and submitted to the Advisory Council, which officially recommends funding action to the director of the NIH institute. The responsibility of each component of this review system for grant applications is outlined in Figure 4-6. The first-level peer review provides the initial scientific review of grant applications for scientific merit and assigns them a competitive score, using published criteria available on the NIH Web sites. The instructions to reviewers are reproduced here for investigator convenience but can be downloaded from the Center for Scientific Review Web site (http://cms.csr.nih.gov/PeerReviewMeetings/ReviewerGuidelines/). It is important to be aware that different funding mechanisms may have different review criteria. As well, the review process and reviewer selection process are explained at the CSR home page (http://cms.csr.nih.gov/). The criteria for each funding mechanism are available online at http://www.csr.nih.gov/guidelines/guidelines.htm.

This first-level review, known as peer review (study section is often used to describe the first-level review group), does not set program priorities or make funding decisions. Study sections elect not to discuss noncompetitive applications (those proposals in the bottom 50% of those being reviewed at a given session) submissions.[47] Nevertheless a complete review is done and a written critique provided to the investigator. Scoring is provided by section of the grant, but an overall

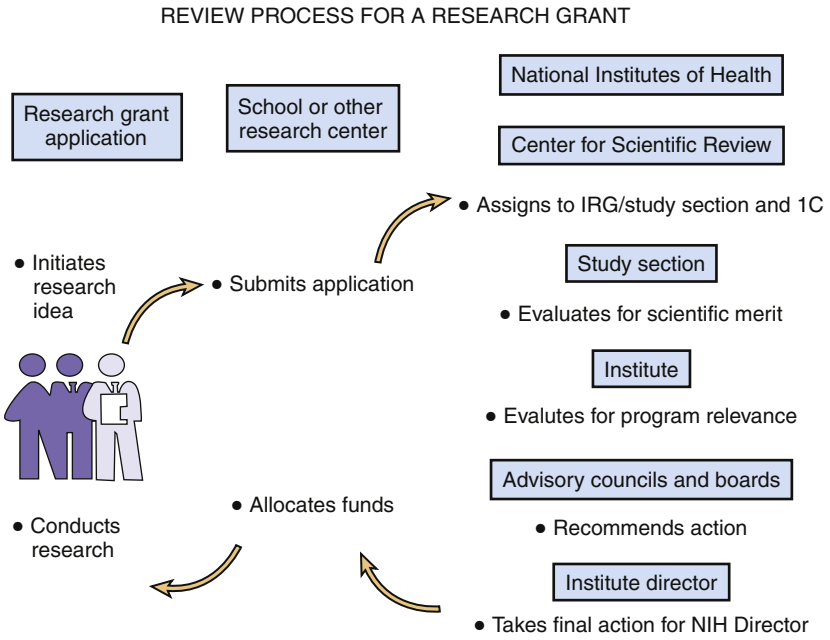

Figure 4–5. Schematic representation of the course a National Institutes of Health grant application follows in the review process. *(Courtesy the Office of Extramural Research, Office of the Director, National Institutes of Health, Bethesda, MD.)*

score is not provided. The reasoning is that these proposals are not presently fundable, and what is really needed is a thorough critique that conveys to the applicant-investigator the level of overall enthusiasm among the reviewers for the proposed research and specific, helpful feedback to the investigators. Sometimes, specific actions required to make the proposal more competitive are suggested. All proposals, scored and unscored, receive this feedback.

After scientific merit review in the study section, the scored proposals go to the second level of review, which is the Advisory Council. The Advisory Council is a national-level group composed of distinguished scientists and community members who advise the director of the institute on policy and funding decisions. Here, the quality of the study review group's assessment of the grant application is evaluated, and the council makes recommendations for funding to the institute's director after considering the recommendations of program staff of the institute. At this second level of review, the council evaluates program priorities and relevance by recommending funding and advises on policy. The institute's director takes final action to allocate funds. When funds are allocated, the individual researcher conducts the research using the allocated funds granted to the investigator's institution. This dual level of review is summarized in Figure 4-6.

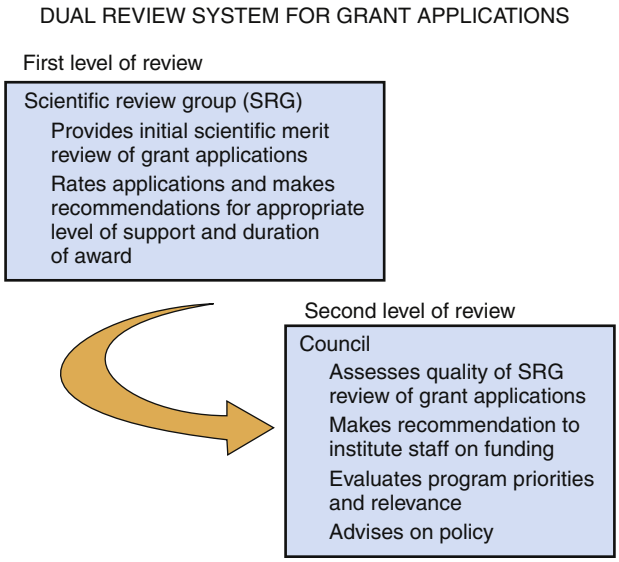

Figure 4–6. All National Institutes of Health grant applications undergo two levels of review. Of note is that the study group does not make funding decisions. It can, however, review and advise on the appropriateness of the proposal budget. *(Courtesy the Office of Extramural Research, Office of the Director, National Institutes of Health, Bethesda, MD.)*

Writing the Grant Application

In making grant applications, particular attention should be paid to the due dates and instructions for application, as well as page number limitations. Although the following guidelines are specifically intended for NIH grant applications, they serve as general guidelines for any granting organization. It seems superfluous to say that no matter how brilliant the idea, it must be presented to the granting organization in a readily accessible, understandable, clear, and concise fashion. Proposals that are clear and concise, with a precise approach and research plan are more likely to gain reviewer enthusiasm.

In general, investigators reviewing the grants are at the top of the scientific community pyramid (Figure 4-7). They are active and productive researchers who have been through the process themselves. They are both sympathetic and critical. There are no guarantees that they are interested in the individual investigator's area of expertise, that they are uniformly knowledgeable about it, or that they are committed to funding it. As a matter of fact, NIH reviewers are specifically admonished to make no evaluation or recommendation about funding. Rather, the reviewers' judgment of scientific merit is to be precise and thorough. Most reviewers want to act as advocates for individual research proposals; it is the investigator's

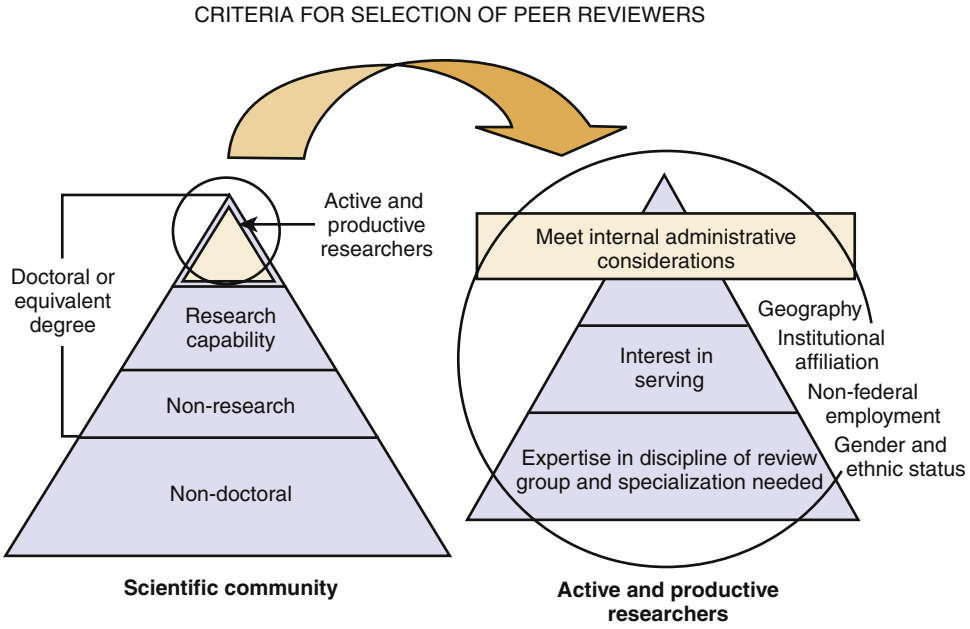

Figure 4–7. Reviewers are chosen from the peak of the scientific community's active researchers. *(Courtesy the Office of Extramural Research, Office of the Director, National Institutes of Health, Bethesda, MD.)*

responsibility to provide the reviewer with the ammunition necessary to support the research proposal accurately and effectively to the study section as a whole.

When writing a grant, it is essential that the same care and consideration, if not more, for the development of ideas and presentation of concepts be used as in the final publication of the research. The review process of a research grant application will be every bit as critical and rigorous as the review for publication of articles. To allow an ongoing contribution to the research effort in the field, success with grant applications is always a necessary step. The following section serves only as a quick overview of how successful grants are written. Basic concepts that underlie all successful grant applications are that they present a good idea backed up with good science and presented in a well-written format. The applicant should be particularly attentive to the detailed instructions that are provided for each mechanism. Periodically there are significant changes to the format and length of NIH grants, but the general outline remains similar. Four questions must be approached:

1. What do the investigators intend to do? (specific aims)
2. Why is it important? (significance)
3. What has already been done? (preliminary studies, other investigations)
4. How are the aims to be accomplished? (experimental plan)

Writing a grant proposal can be intimidating and confusing; however, lucidly presenting these simple points not only makes a grant easier to present but also easier to award. All investigators must realize that they are assessed on the quality of the grant and not just on their track record[46]:

"If you are a beginning investigator submitting your first application and worried because you do not have a professional reputation, remember that you will have already impressed the reviewers in the literature section by your familiarity with the field, and your capability for keen and wise discrimination between the significant and the banal, the valid and the presumed…"

The research grant application provides numerous opportunities to demonstrate qualifications and scholarly attributes; however, it also readily reveals faulty thinking, hasty preparation, superficiality, and inexperience.

Hypothesis-Driven Research-Specific Aims

This section is restricted to a single page, and forms the "good idea" portion of the application in which the investigator should document the creative, valuable, and exciting research questions that need to be answered. It justifies the rest of the proposal. There should be two to three specific aims, generally with individual statements of hypothesis. In general, the hypothesis should be aimed at delineating, explaining, understanding, or defining mechanisms of action. This is in distinction to those where the goals are merely observational, empirical, or data-gathering exercises. Frequently this is a matter of correctly stating the research endeavor. For example, an investigation to determine whether there are gender differences in hypoxic pulmonary vasoreactivity (HPV) could be justified on a descriptive basis, or it could be justified as the means of examining a hypothesized, specific research question delineating using the differences between male and female responses to injury in an animal model, with the specific aim of reaching a significant conclusion about how gender and/or the presence of estrogen modulates endothelial prostacyclin release, and providing a mechanistic answer.[9,49,50]

The research proposal should have specific, achievable, well-defined goals that are neither overly ambitious nor superficial. During development of NIH proposals, these research aims should be conveyed, via e-mail, to the program staff of the institute that is the contemplated recipient of the proposals. These program staff are committed to assisting potential grant applicants to improve their applications and help them be competitive. Criticism, tightening, and delineation of hypotheses should be completed and reconveyed to the investigator. Then, biostatistical assistance, including power analysis, can be obtained and a detailed research plan generated.

It is emphasized that the Specific Aims page may be the most important page in the entire grant proposal. Reviewers are very busy individuals, and this page forms the "bait" to make the reviewer excited about reading the remainder of the proposal with a positive attitude. Experienced grant writers indicate that they spend up to 75% of their entire writing effort on this single page.

Although the specific proposal should have specific aims, it also is important to present how these research aims fit the broader picture. This is accomplished by relating the research aims and hypotheses of the grant to long-term scientific objectives and integrating them into the overall field relevant to the proposal. The summary paragraph at the end of this page should help the reviewer understand the importance of the project in the broad picture. All of the problems in an area of research cannot be solved by one research proposal.[51,52]

Significance

Although the literature supports the significance of the proposed study, the grant applicant should present a thorough familiarity with the literature, its deficiencies, contradictions, and pitfalls. It should be clear to the reviewer how the hypothesis (or data mining or descriptive project) was generated from the current field of knowledge and exactly how the present proposal fits into that area readily and concisely. A thorough review of all available literature on the subject must be carried out on a continuous basis. Investigators should search the NIH Reporter *system (http://projectreporter.nih.gov/reporter.cfm)*—this system has replaced the older CRISP database of federally funded studies—so that they can present their own work as innovative and an important new development of the science in the field. This site is also particularly useful for trying to identify potential mentors and collaborators.

Preliminary Studies

Pilot studies with preliminary results should be included to demonstrate that the hypothesis is testable and supportable, or the descriptive project practicable, and that the investigator has the capabilities of pursuing the research goals. Reference to abstracts and papers previously published by the investigator and preliminary studies with data presentation should provide a complete overview of the capabilities of the investigators. The investigator's scientific capabilities must be evident in the presentation of the proposal.[46,51]

Experimental Plan

The methodology should be appropriate, available, well worked out, and well supported. In addition, it should be specifically targeted and precisely capable of addressing the questions raised in the specific aims. Methodology must be described so that the reviewers can be assured that valid results will be achieved. If new methodology is being proposed, detail is necessary to assure the reviewers of the applicability of new methodology, as is inclusion of preliminary results demonstrating the likelihood of success of the experiments.[48,51,52]

As clear a statement as possible of the underlying assumptions and their validity and of the limitations and applicability of the proposed research plan should be presented. Investigators applying for career development awards (K awards) should be aware that although the science they propose will be reviewed, the most rigorous analysis will be applied by the reviewers to the career development plan as outlined. The mentor's commitment to the emerging investigator must be specific, and the mentor must be well qualified for the task. Specific discussion must be provided as to how the requested support will result in the development of the scientist who is capable of achieving the aims of the proposal. Formal course work and specifically mentored laboratory work are two crucial elements in this plan.

Specific attention must be paid to how the data will be evaluated, analyzed, and statistically approached. An expert statistician's input before submission of the proposal is essential, and the analytic plan (including power analysis) must be included. At the end of reading the method section of the proposal, the reviewer should be confident that the investigator understands and intends to use good scientific method to address specific aims in a logical, clear, focused, and precise manner.

Presentation

The final necessity for a research proposal is that it be well presented. Overall, the number of grant applications at the NIH has increased, and the competition for support has become greater. Visually attractive, well-presented, easy-to-follow, clearly delineated research proposals will clearly stand out from the herd. Although showmanship will not make up for poor substance, sloppy applications may obscure good science. The first rule is strict adherence to the guidelines in the research application with regard to page number, layout, content, and other details. A clear, simple, lucid, grammatically correct, and typographically perfect presentation is essential; leave nothing to assumption and guesswork. Seeking help from many sources with different skills and perspectives is tremendously valuable. Senior department members, deans, review offices, research administrations, English teachers, spouses, lay people, and other investigators all may have valuable contributions to make to the clarity of a research proposal. Frequently, it is worthwhile to have a grant proposal read by an outside, independent, unbiased assessor before it is submitted to the NIH. Review by a successful investigator who is neither familiar with nor involved in the specific research area can be invaluable.

Familiarity with and commitment to the guidelines and recommendations for both human and animal experimentation is essential. Obtaining institutional review board (IRB) approval of research proposals before submission to the NIH is not mandatory. Be aware, however, that the proposal will not be funded until this clearance is officially verified. The internal review process of the institution may be of benefit in establishing and clarifying research proposals. Finally, budget preparation must be meticulous. As a general rule, everything should be justified briefly and concisely.

Although excessive financial support should not be sought, the investigator must request sufficient resources to achieve the specific aims. Availability of other resources, such as capital equipment, research space, and collaborative resources, to complete the work should be demonstrated. Frequently, preparation of the budget for the proposal is a very time-consuming process. The investigator should not be intimidated by this process but should not underestimate its importance. The investigator should first determine precisely what is needed to perform the experiments and what the technical and personnel needs are, and then, in conjunction with the university, determine fair costs for these items, supported with documentation where necessary. Reviewers are most concerned with completeness of budgetary considerations. A grant that has insufficient resources to achieve its goals is a waste of time, money, and effort for both of the NIH and the investigator.

Page Limitations

New, stringent, page limitations add an additional challenge to successful application. Writing must be concise, yet not obscure the excitement and clarity of the science. The critical importance of the Specific Aims page is increased by the shortening of the remainder of the application. Material that relates to the investigator's particular skills relating to the grant are now included in the NIH Biosketch, and should not be in the main scientific narrative. The resources section of the grant should include institutional support, equipment, and commitment to young investigators. These topics are important components of K applications. Perhaps most important, the smaller grant format should allow the writer more time to polish and enhance the grant, using feedback from colleagues. This will, of course, occur at competitor institutions as well. Thus, the shorter format both enhances the opportunity and importance of writing a tight, concise, and exciting proposal. A "seven steps" guide presented in Appendix 4B (available online at http://www.expertconsult.com) has been helpful to many applicants.

Your Chances: Money

Anyone who is in the remotest way connected with the biomedical research effort in the United States is aware that there is never sufficient money to fund all of the worthy ideas.[52] Regardless of whether this money crunch arises from the ambitious, laudable scientific goals, budget deficits, or shifting priorities, a competitive system will be necessary for the foreseeable future. The concern for the continued existence of medical research has led to some fairly horrific statements. It is simply not true that "… nothing is getting funded these days…" —the NIH budget is more than double its budget in 1994. More dollars go to research than at any previous time, and more awards are made. However, the recent leveling of funds has resulted in a shortage of funding compared to the number of applications being received, since the first years of the new millennium. This results in a lower percentage of grants receiving funding. What is certain is this: *You will not receive funding from an NIH grant if you do not apply.*

With all of the available resources for American pediatric critical care researchers, we all wonder "how we can look so rich and feel so poor?" Up through 2002 the NIH budget was doubled. Such expansions are unlikely in the foreseeable future. Nevertheless, Congress has made its intentions quite clear: the desire is for an expanded, rather than contracted, biomedical research effort. More people are submitting grants; that is, the competition is getting tougher. In 1993, 4121 of 19,072 R01s (22%) were funded. From 1999 through 2001, the percent funded increased to 32%, but has declined since then, and in 2009 was down to 22% again. The total number of applications increased to a peak of 29,097 applications in 2006, and has decreased since, perhaps reflecting discouraged investigators, but was still 26,675 in 2009. Of these 5924 were funded, an increase in numbers of over 40%. The percentage of applications funded varies by institute, budgetary availability, and national priorities. Research project grants also undergo a substantial budget cut after award. About 17% to 20% is not uncommon. All of these factors have sustained major changes in recent times, and it is likely that considerable variation will continue over time.

Despite the challenges, more people are involved in medical research now than at any previous time in our history, and more funding is going toward it. Priorities for biomedical research shift with national priorities, economic change, technologic and business developments, and political interest. Total reliance on funding from the federal government is unjustified and risky. We need to be aware of other available sources of extramural funding and encourage industrial and private support for research endeavors in pediatric critical care, as well as provide evidence of our own commitment to the research endeavor by continuing to contribute support from clinical income. Since the previous edition of this textbook, the number of pediatric critical care physicians with NIH funding has dramatically increased; this is due to focused efforts by leaders in the field and at the NIH to encourage young investigators to apply for funding. The perception of "tight funding" should not discourage pursuing the data upon which future grant applications will depend and from which future improvements in pediatric critical care will come. The future of our young patients is dependent on continuing our efforts to secure funding for research in our field.[53]

Your Chances: Cultures in Conflict

By training, philosophy, motivation, and research style, doctors and scientists might as well be from different phyla.

***New York Times,* April 24, 1992**

The competition is not merely other pediatric intensivists. Researchers in pediatric critical care must be involved with, collaborate with, and be familiar with the work of investigators from other areas of medicine who may not be clinical researchers at all,but rather basic and translational scientists.

A *Journal of the American Medical Association* editorial titled "The Two Cultures of Biomedicine: Can There Be a Consensus?" crystallizes the problem.[54] A researcher-developer stated, "For medicine to advance, you have to be willing to have your patient die on the operating table," whereas a typical clinician said, "The more important thing when you are starting, is to finish with a live patient." These two approaches must be made compatible, and both are essential for our patients' well-being. The practical, patient-concerned physician must apply the results of biomedical science and work in close collaboration with the basic researcher to maintain the appropriate focus. Pure scientists are concerned with studying the underlying mechanisms of diseases, which, to them, may be abstract entities. That is, they seek to describe pathways and phenomena without a direct link to human health and disease.[55] They need to understand the clinical and human significance and impact of the questions asked and results obtained. This difference is expressed in the *New York Times* by a research director: "I go through medically-oriented publications and see they don't have enough controls and they ignore relevant interpretations of their data. You can get the idea that doctors are too free and easy with science."[55]

The fact that two cultures in biomedical research exist is clear. This is recognized not only by teaching hospitals, where they tend to exist side by side, but also by the community and, clearly, by the NIH. This division cannot be allowed to develop as a polarized dichotomy. The two sides need each other. Physician-researchers are classically viewed as the pinnacle of academic success, but only inasmuch as they are true researchers who understand patients' needs. The fact that they are so well-respected supports the notion that they also are quite rare. Cooperation between these two cultures of biomedical research is the only hope for clinical and basic biomedical science, and neither can exist without the other, contrary to what either may wish. As Tom Stossel, director of the Translational Medicine Division at the Brigham and Women's Hospital in Boston, said[56]:

"Modern medicine is an increasingly complex and troubled profession, but most will agree that science is at its heart. People know this and demand technical and scientific excellence as well as caring from their physicians. Consumers' wishes aside, the constant evaluation and reevaluation of the knowledge base in medicine—pathogenesis, diagnosis and therapy—is a medical categorical imperative. Physical, biologic, and behavioral sciences underpin medicine, but the science that is unique to medicine is clinical investigation."

Competition for limited resources will remain intense. There should, however, be no competition over turf. There need be no competition over areas of interest, and indeed there can be no competition from nonphysicians in the unique science of medicine/clinical investigation. Allocation of resources will be in the direction where collaboration, cooperation, and cross-fertilization between the two cultures of biomedical science are the most fertile. There is no need for competition for ideas. As Stossel concluded: "All kinds of research are needed. The fund of medical knowledge seems vast indeed, but the reservoir of ignorance is even greater."[56]

Research Ethics

"There is no vice that doth so cover a man with shame as to be found false and perfidious."[57]

Francis Bacon, 1578

A comprehensive presentation of the ethical issues for investigators is beyond the scope of this chapter. Each clinical investigator must be thoroughly aware of the ethics of human

investigation before committing children to the necessary uncertainties of research.[56] Issues of information, understanding and consent, risk to patient and investigator, privacy concerns, and the welfare of patients participating in research have been thoroughly discussed in many publications. All of these issues require the investigator's attention. There is, however, more. It cannot be too strongly stressed that intrinsic to these issues is the necessity for well-designed studies that are likely to yield useful results and to be of future benefit either to the patients enrolled in a given trial or to future patients. As Nelson[59] has stated:

"The prospective, randomized, double-blind, controlled, multicenter clinical trial requires a pre-contract among investigator, physician and informed patient that the rigorous rules of statistical mathematics will be enforced."

Performing shoddy or slipshod science is among the most unethical actions possible for any investigator, experienced or naive, to commit. For those investigators involved in animal research, rigid adherence to standards of ethical animal treatment is necessary.[60,61] These standards should be as stringently maintained as in human trials. The sacrifice of animals in poorly designed studies that yield useless results is unacceptable. Such experiments lend credence to the animal rightist's bumper sticker: "Animal research = Scientific fraud." All investigators should adhere to the rules and procedures of their local institution, their state governments, and the NIH when dealing with animals in a humane fashion.[62] Constantly reviewing how subjects—whether animals or children—are treated and the value of any trial or experiment is a mandatory part of professional scientific practice.

Nothing is more important in the practice of medical investigation than absolutely rigid, scrupulous adherence to the truth. The goal of research is to discover true results upon which to base sound conclusions. This goal is threatened in two major ways. The first is poor science, sloppy techniques, and "honest errors." The second is fraud. Both must be avoided. As CP Snow[63] has said:

"The only ethical principle which has made science possible is that the truth shall be told all the time. If we do not penalize false statements made in error, we open up the way, don't you see, for false statements by intention. And, of course, a false statement of fact, made deliberately, is the most serious crime a scientist can commit."

False statements made intentionally or in error cannot be tolerated. This is important not only during the final summation and reporting of results but also at every step along the way. The least suggestion of fudging or poor study design, the least bit of misrepresentation of results at any stage, is merely the first step on the slippery slope that ultimately leads to out-and-out fraud. Advice given by Samuel Johnson[64] in 1778 is valuable for all of us who are concerned with scientific observation and reporting, whether supervising or performing research at any level:

"Accustom your children constantly to this: If a thing happened at one window and they, when relating it, say that it happened in another window, do not let it pass, but instantly check them; you do not know where deviation from the truth will end."

Several threats to the truth occur during the course of medical research. As in all things, recognizing the potential errors is the first step in preventing them. From the very conceptualization of the hypothesis, when there is a risk for plagiarism, through the indifference of senior investigators, to the final analysis of data, the truth is challenged. Charles Babbage, the nineteenth-century mathematical genius remembered as the prophet of the electronic computer, gave us three interesting definitions of data misrepresentation nearly 150 years ago[65]:

"Trimming: the smoothing of irregularities to make the data look extremely accurate and precise.

Cooking: analyzing only those results that fit the theory and disregarding others.

Forging: inventing some or all the research data reported, or reporting experiments to obtain those data which were not performed."

Every investigator at every level must incessantly resist these temptations. Meticulously resisting overzealous curve fitting, data smoothing, data elimination, and data insertion is necessary. All forms of unacceptable behavior stem from one or more of these three cases, or from carelessness or plagiarism. Although we may not be certain where the slightest "deviation from the truth will end,"[64] we can be certain that, in time, these deviations will be discovered. As Shakespeare said[66]:

"Time's glory is to calm contending kings,
To unmask falsehood and bring truth to light."

Scientific fraud will be discovered in the long run. An interesting, if extreme, example is that involving the Nobel prize-winning physicist Robert A. Millikan. Not until 1978 was research he published in 1913 discovered to be based on cooked data.[67] Millikan represented his results as being from an unselected, consecutive group of drops, which he examined for electrical charge. As it turns out, the group was highly selected. Although 65 years elapsed before the truth emerged, the certainty of Shakespeare's dictum was supported. Generally, the discovery of fraud is not so protracted. This is a good thing; otherwise, the errors resulting from subsequent work based on false data could be quite serious. Adding fraudulent bricks to the edifice of medical knowledge undermines the entire structure and may add to suffering of critically ill children and their families.

In addition to the certainty of discovery aspect of Millikan's error, another lesson is evident. This particular case demonstrates that even the great are not immune to the temptations of dishonestly interfering with results. Perhaps our conviction and love for our hypotheses, which may lead to "honest errors," also occasionally lead to serious and unacceptable overenthusiasm. A.J. Balfour,[68] in a letter to a friend in 1918, was well aware of this risk of enthusiasm: "It is unfortunate considering that enthusiasm moves the world, that so few enthusiasts can be trusted to tell the truth."

Perhaps this particular skepticism is what we all must have, most importantly for our own work and not only for the work of others. Although tremendous energy and enthusiasm are necessary to do research, skepticism is necessary to

present it. Biased enthusiasm leading to nondeliberate alterations of results and frank dishonesty clutters the history of science.[69] Such alterations not only lead to the dishonor of individuals involved but also contribute to a lack of faith in the entire enterprise, no matter how well intentioned. Perhaps even worse than this, fraud in medical science misleads one's colleague and can lead to years of fruitless investigation and dangerous therapies.[14] Straightforward honesty is the basis of honor in science.

It's unfortunate to need to focus on this topic so strongly; however, it has become increasingly clear that we cannot be too cautious.[69,70] Anything less opens the door for the sort of embarrassment that Braunwald and American medicine suffered at the hands of Darsee and continue to suffer by finding research based upon that fraudulent data.[70] Science is a cooperative enterprise. Continual questioning of oneself and each colleague and continuous sifting and analysis are necessary. This provides the excellence referred to in an editorial in *Nature*[71]:

"A research laboratory jealous of its reputation has to develop less formal, more intimate ways of forming a corporate judgment of the work its people do. The best laboratories in university departments are well known for their searching, mutual questioning."

Scrupulous attention to honesty is crucially important because of an inherent characteristic of the scientific method. As discussed earlier, we can support theories only by disproving the null hypotheses. We can never absolutely prove them. Because we can never prove a theory, science is inherently based on uncertainties. The risk of basing our knowledge on uncertainties is obvious. When uncertainties become dishonesties, the entire structure and process of scientific thought are distorted.[71] Fraudulent data, as in the cases described above, or "in service" to controversial theories serves only to inflame passions and obscure the needed answers to pressing issues. Examples that have affected broad swaths of society include the impact of the fake "Piltdown man" on the discussion of evolution and that of the questionable data from the University of East Anglia on the climate change debate (see below).

Add to our communal necessity for rigorous truthfulness and accuracy the fact that many of us are unable to thoroughly and completely understand data generated in areas even closely related to our own, and the situation is even more concerning. We frequently are asked to accept on faith the statistics, results, research techniques, and conclusions based on theories and hypotheses with which we are unfamiliar and certainly unable to test ourselves. In addition, ideas spring into our minds; whether the sources are a paper recently refereed, a research grant recently reviewed, or an idea that occurred to us from our own data is sometimes difficult to ascertain. The potential for chaos and error is great.[71] In this milieu, the presence of police officers, watchdogs, and whistle blowers is too rare and, for the sake of productive research, somewhat undesirable. Journal reviewers should determine whether the results are of sufficient importance to justify publication. Reviewers cannot reliably "police the data." The best source of check and countercheck is at the bench level, where researchers work together.[71,72] The price to be paid by failure and/or fraud at this personal level is far too great. The words of Jacob Bronowski[73] in *Science and Human Values* again demonstrate the overwhelming imperative of honesty:

"All our knowledge has been built communally; there would be no astrophysics, there would be no history, there would not even be language, if man were a solitary animal. What follows? It follows that we must be able to rely on other people; we must be able to trust their word. That is, it follows that there is a principle, which binds society together because without it the individual would be helpless to tell the truth from the false. This principle is truthfulness."

Perhaps no story is more illustrative of the consequences of unethical scientific behaviour than the recent revelation of massive, repeated, pervasive fraud committed by climate researchers at the University of East Anglia's Climate Research Unit.[74-76] Not only does it appear that every form of data manipulation and outright falsification, including data destruction, cooking, fudging, cherry-picking, trimming, and forging has occurred, but also that there was blatant subversion of the peer review and funding processes. Investigators at the top of the climate research world, by bullying other investigators, blocking publication of conflicting studies, and refusing to release and even destroying data have cast doubt on all of climate research and the validity of global warming.

If true, global warming has consequences for the survival of life on Earth. Few scientific theories could be more important. To cast doubt on this potentially vital theory by shoddy research, fraud, and manipulation, is beyond despicable. If climate change is false, then the waste of huge financial resources for research, mitigation, and global economic impact to the tune of trillions of dollars, when they are necessary in other important areas is criminal. The politics of global warming, based on what may be false and fraudulent data present the huge possibility of global confusion over such a vitally important concern. Although this is disastrous enough, the devastation of 'climategate' goes beyond climate research. The entire edifice of scientific endeavor, largely funded by the public, with its promise of hope, has been seriously tarnished by the act of a few, careless at best and dishonest at worst, investigators in what has been called: "the greatest scientific scandal of our age."[77] Climategate undermines science, as stated in the *Wall Street Journal* article "Climategate: Science is Dying"[78]:

"Everyone working in science, no matter their politics, has a stake in cleaning up the mess revealed by the East Anglia emails. Science is on the credibility bubble. If it pops, centuries of what we understand to be the role of science go with it."

The authority of science is gravely damaged by this fraud and the public may conclude that science is merely another 'faction' – nothing but opinion. The consequences of this profound ethical breach for medicine are obvious.

Acknowledgment

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References are available online at http://www.expertconsult.com.

Chapter 5

Proving the Point: Evidence-Based Medicine in Pediatric Critical Care

R. Scott Watson, Mary E. Hartman, and Derek C. Angus

"Not all clinicians need to appraise evidence from scratch, but all need some skills."[1]

PEARLS

- All physicians have an ethical and clinical obligation to use the best available evidence whenever applicable.
- The evidence base for critical care is growing rapidly.
- Practicing evidence-based medicine is straightforward, and keeping up with relevant evidence is becoming easier and less time consuming.
- PubMed now includes research methodology filters (found under the "Clinical Queries" heading) that enhance the efficiency of searching the literature.
- Multiple evidence-based medicine–related resources also can be found on the Internet.

What is evidence-based medicine (EBM)? How is it different from what we have always done? EBM is simply the integration of the best available evidence with individual clinical expertise and patient preferences.[2] The definition is not complicated, and one could easily make the incorrect assumption that its practice is, and always has been, ubiquitous. However, proven interventions are often misapplied, and striking variations in clinical practice (not attributable to patient differences) occur even when high-quality evidence is available.[3-8] Practicing EBM in critical care in general and pediatric critical care in particular poses unique challenges. Decisions that can have profound implications for a child and his or her family must be made quickly and, until recently, with little good external evidence. However, pediatric critical care and EBM both have matured to the point that EBM is an indispensable and realistic component of optimal practice.

Despite decades of international support and growth, the practice of EBM continues to be hindered by misconceptions. It is not "cookbook medicine" that suppresses the individual freedom of practitioners.[9] (To the contrary, EBM relies on individual clinicians to accurately identify clinical situations to which external evidence can be applied.) It is not a cost-cutting tool. Treatments found to be effective may be more expensive than the previous standard of care. It is not unrealistic to think that physicians in the "real world" can practice it. Criticisms that EBM is too difficult and time consuming may have been valid in the past, but advances in literature search engines and the increasing availability of EBM resources make it accessible and applicable for busy clinicians.

This chapter provides an overview of the steps in practicing EBM, including a summary of common study types, information about many excellent EBM-related resources, and definitions of selected terms used in EBM (Appendix 5A, available online at http://www.expertconsult.com). EBM is here to stay, and the field of critical care is in the midst of a groundswell of outstanding clinical research that is improving the outcome of critically ill patients. Our goal is to demystify the process of EBM so that pediatric intensivists can keep up with these changes, understand EBM, and incorporate it as a fundamental element in their practice.

The Evidence-Based Medicine Process

The steps in the EBM process are straightforward: (1) define the problem, (2) search for relevant evidence, (3) evaluate the evidence, and (4) apply the evidence.

1. Define the problem

   EBM starts with a well-built clinical question that is constructed to facilitate an efficient literature search (see http://www.cebm.net).[10] The question needs to clearly state the patient population; the intervention(s), event(s), or exposure(s); and the outcome of interest. These steps were codified by Doig and Simpson[10] in the simple mnemonic PICO: ***p***opulation, ***i***ntervention, ***c***omparison, and ***o***utcome. Focusing the question is key because it enables identification of relevant search terms (described below).

2. Search for relevant evidence

   Keeping up with the basic pediatric literature alone would require reading at least five articles per day, 365 days per year.[11] The objective of searching the literature is to find the answer to the clinical question as quickly and efficiently as possible amidst the 20,000 medical journals and more than 2 million articles published annually.[12] To hone in on relevant articles, a search strategy should take advantage of Medical Subject Headings (MeSH) and incorporate new and useful filters that have been developed. Taking advantage of specific combinations of MeSH terms has been found to increase the speed and effectiveness of searches.[13]

MeSH are descriptive terms assigned to each bibliographic reference in Medline by the National Library of Medicine. There are 25,186 terms organized into a hierarchical structure (http://www.nlm.nih.gov/mesh/meshhome.html). At the most general level are very broad headings such as "Diseases" or "Organisms." More specific headings are found at more narrow levels of the 11-level hierarchy, such as "Sepsis" and "*Neisseria meningitidis*." Thousands of cross-references also exist that assist in finding the most appropriate MeSH (e.g., "MODS, see Multiple Organ Failure").

So that clinicians need not memorize complicated combinations of search terms, search engines have incorporated many of these terms into easy-to-use research methodology filters for clinicians. These filters are combinations of search terms that can increase searching efficiency. PubMed, for example, allows searchers to select filters for studies of etiology, diagnosis, therapy, and prognosis. Similar filters can be found in Ovid Technologies' search engine, in addition to filters on clinical prediction guides, qualitative studies, costs, and economics. In both, the choices are presented under the "Clinical Queries" heading. Searchers can choose among highly sensitive searches to produce comprehensive retrievals (particularly useful for subjects in which little work has been done), highly specific searches to retrieve only the most rigorous studies and little nonrelevant material (for subjects in which much work has been published), or optimized searches to maximize the tradeoff between sensitivity and specificity.

In addition to Medline, multiple other specialized databases and Internet-based resources are available that can yield relevant results quickly. Table 5-1 lists a sample of these resources. One of the best known is the Cochrane Library, which contains a large collection of peer-reviewed systematic reviews on a wide variety of health care interventions.[14] It is thoroughly indexed and easily searched. ACP (American College of Physicians) Journal Club and Evidence-Based Medicine are EBM-related journals that are linked for searching through Evidence-Based Medicine Reviews (EBMR) from Ovid Technologies. The British Medical Journal publishes *Clinical Evidence*, an annual compilation in book and CD-ROM format of the best available evidence on the effects of common medical interventions. In addition, the PedsCCM Evidence-Based Journal Club posts critical reviews of studies related to pediatric critical care.

3. Evaluate the evidence

After a search yields potentially useful evidence, the clinician must evaluate the evidence and determine its scientific validity and clinical utility. For a piece of evidence to be useful, it must be valid, have clinically important findings, and be applicable to the particular patient. Guides for assessment of validity, such as those shown in Box 5-1, exist for different types of studies. Worksheets to determine whether a study is valid are available from a number of sources, including the Centre for Evidence-Based Medicine and a number of the Web sites listed in Table 5-1.

Study Types

The type of clinical question determines what kinds of studies are most relevant. For example, questions about therapy usually are best answered with a randomized controlled trial (RCT) or systematic review. On the other hand, to determine the prevalence of a disease or risk factors for its development, observational studies are needed.

Interventional Studies

Interventional studies are clinical experiments, the strongest of which is the RCT. RCTs are the gold standard in the assessment of the efficacy of an intervention.[15,16] Randomization minimizes the risk of an unequal distribution of known and unknown factors (confounders) that may influence patient outcome. The presence of a control group helps distinguish changes in outcome that result from the therapy in question from changes that otherwise would have occurred. Because of their high cost, RCTs usually are designed to maximize the likelihood of finding a positive effect. Therefore they tend to be efficacy studies, with highly selected patient populations treated by experienced providers. The effectiveness of a therapy as used in general practice often requires additional study, usually through subsequent observational studies.[17] In addition, many questions cannot be answered, either ethically or practically, by an RCT, such as the effect of intensivists on patient outcomes.

Observational Studies

The principal alternative to interventional studies involves observation rather than experimentation. Observational studies are powerful tools for addressing many questions that RCTs cannot and for generating hypotheses that can be tested in interventional trials. For example, they can elucidate epidemiologic characteristics and prognosis of diseases or effects of organizational characteristics on outcome. They can provide information on a treatment's effectiveness (as opposed to efficacy) and determine cost effectiveness. They have become increasingly sophisticated in design and execution, but, as with all study types, they have limitations. Confounding may be difficult to control, and even if known confounders are well controlled, unknown or unmeasured confounders may influence study results. Selection of an appropriate control group is crucial but can be difficult. If conducted retrospectively, observational studies are subject to recall and selection bias.

Different kinds of observational studies are designed to address different types of questions. These kinds of studies include case-control studies, cross-sectional surveys, and cohort studies. In case-control studies, researchers compare subjects with a particular outcome (the cases) to subjects who do not have the outcome (control subjects). Ideally, the case subjects and control subjects are identical except for (1) the outcome of interest and (2) the risk factor or exposure that leads to the outcome of interest. With such a study, risk factors or exposures that are responsible for the outcome (e.g., smoking as a risk factor for lung cancer) can be identified. Of course, finding groups of patients that are so nearly identical is impossible. However, well-done case-control studies that include rigorously selected case subjects and control subjects can be extremely informative. They often are the only feasible study method for uncommon outcomes or when the lag time between an exposure and outcome is very long.

Cross-sectional studies provide a snapshot of a population at one point in time. They can identify the prevalence, or frequency, of a condition, such as the frequency of sepsis among patients in an intensive care unit. They are relatively inexpensive and can be conducted in a short time. Cross-sectional studies usually establish only association, not causality.

Table 5–1 Partial List of EBM Resources on the Internet

Resource	Web Site
EBM WEB SITES	
Centre for EBM, Oxford	www.cebm.net
Centre for Evidence-Based Child Health	http://www.ich.ucl.ac.uk/ich/academicunits/Centre_for_evidence_based_child_health/Homepage
EBM Toolkit, University of Alberta	http://www.ebm.med.ualberta.ca/
User's Guide to Evidence-Based Practice, Centre for Health Evidence	http://www.cche.net/usersguides/main.asp
University of Washington EBM Internet resources	http://healthlinks.washington.edu/ebp
Netting the Evidence: Database of EBM Web sites	http://www.sheffield.ac.uk/~scharr/ir/netting/
Health Information Research Unit, McMaster University	http://hiru.mcmaster.ca
MEDLINE SEARCHES	
PubMed	www.pubmed.org
SYSTEMATIC REVIEWS	
Cochrane Collaboration	http://www.cochrane.org/
AHRQ Evidence-Based Practice	http://www.ahrq.gov/clinic/epcix.htm
National Guideline Clearinghouse (AHRQ)	http://www.guidelines.gov/
Clinical Evidence (from the *British Medical Journal)*	http://www.clinicalevidence.com/ceweb/conditions/index.jsp
Best Evidence Topics	http://www.bestbets.org
Centre for Reviews and Dissemination, University of York	http://www.york.ac.uk/inst/crd
CRITICAL CARE JOURNAL CLUBS	
Critical Care Journal Club, Critical Care Forum	http://ccforum.com/articles/browse.asp?sort=Journal%20club%20critique
PedsCCM Evidence-Based Journal Club	http://pedsccm.org/EBJournal_Club_intro.php
American Thoracic Society, Evidence-Based Critical Care	http://www.thoracic.org/sections/clinical-information/critical-care/evidence-based-critical-care/index.html
ONLINE EBM JOURNALS	
ACP Journal Club	http://www.acpjc.org/
Bandolier	http://www.medicine.ox.ac.uk/bandolier/
Evidence-Based Medicine	http://ebm.bmjjournals.com/
JOURNALS	
Pediatric Critical Care Medicine	http://www.pccmjournal.com
Critical Care Medicine	http://www.ccmjournal.com
Critical Care Forum	http://ccforum.com/
Pediatrics	http://pediatrics.aappublications.org/
Journal of Pediatrics	http://www.jpeds.com/
Archives of Pediatrics and Adolescent Medicine	http://archpedi.ama-assn.org/
JAMA	http://www.jama.com
New England Journal of Medicine	http://www.nejm.com
British Medical Journal	http://www.bmj.com
The Lancet	http://www.thelancet.com

In cohort studies, researchers follow a group of subjects through time, recording exposures and outcomes. Cohort studies have a number of strengths, including the ability to establish the timing and sequence of events and provide population-based results. The best cohort studies measure exposures and outcomes in a blinded, objective manner, have long and complete follow-up, and identify known confounders. One of the most famous and successful cohort studies in the United States is the Framingham Heart Study, which fashioned the current medical view of atherosclerotic disease.

Case reports may be the only available information in support of a therapeutic strategy, especially for extremely rare or fatal conditions. In addition, some therapies evolved into the standard of care based on case reports and anecdotes prior to

Box 5–1 Critical Appraisal of a Study of Therapy

Are the results of the study valid?

- Were patients effectively randomized?
- Were all the patients accounted for?
- Was follow-up complete?
- Were patients analyzed according to how they were randomized (i.e., intention to treat)?
- Were all people involved in the study blinded?
- Were the groups similar at the start?
- Were the groups treated equally apart from the experimental intervention?

Are the results clinically useful?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?
- Are the patients similar to the "norm"?
- Were all clinically important outcomes considered?
- Was a cost-to-benefit analysis performed?

Adapted from Sackett DL, Straus SE, Richardson WS, et al: *Evidence-based medicine: how to practice and teach EBM*, ed 2, London, 2000, Harcourt.

the use of randomized trials. The difficulty generalizing from case reports makes them among the weakest forms of clinical evidence.

Research Summaries

Research summaries that provide a standardized, thorough critique of studies are particularly valuable for busy clinicians. Formal summaries of research are becoming increasingly well done and common. Single studies can be presented in a format called a *critically appraised topic*, which addresses issues of validity and clinical utility in a standardized manner.[18]

Multiple studies of a single topic can be summarized in several different ways. Narrative reviews include traditional review articles and textbooks. A knowledgeable author reviews the literature, formulates an opinion, and disseminates this opinion along with references to support it. Narrative reviews provide a detailed qualitative discussion that usually is easy to comprehend. Unfortunately, the literature is rarely searched and evaluated in an organized, reproducible manner. Textbooks are well organized and synthesize tremendous amounts of information. However, because of the inherent lag in publishing times, they can be an unreliable source of current information. There is no way to ensure that the evidence is complete or that it receives an unbiased critique. For example, in 1988, pooled data from nearly 9000 patients in 15 studies on the use of prophylactic lidocaine in patients with acute myocardial infarction showed that the practice was useless at best. Nonetheless, in 1990, narrative review articles and textbooks still contained more recommendations for the use of prophylactic lidocaine than against it.[19]

A systematic review combines the results of multiple studies through the systematic search, assembly, and appraisal of primary research. Systematic reviews are an exhaustive effort to find all related information in a given area. Criteria for reviews to be systematic, as opposed to narrative, are explicit. Search criteria, including the inclusion and exclusion criteria for individual studies, are predefined. The methods section provides search terms and key words to establish reproducibility. They can provide an excellent summary of the literature up to the date of the review. The main disadvantage of systematic reviews is that they are only as good as the studies they include. However, even when the studies are weak, systematic reviews can be an important means by which to identify gaps in evidence and thus outline a research agenda.

In a meta-analysis, data are combined from multiple studies to yield a quantitative summary. If the combined studies use similar methodology and are of high quality, meta-analyses can increase the power to find an effect. However, difficulties in interpretation of summary statistics arise when meta-analyses combine studies that vary in quality, population, or intervention.

Levels of Evidence

One of the most widely used taxonomies for classifying evidence and clinical recommendations comes from the Oxford Centre for Evidence-Based Medicine (Appendix 5B, available online at http://www.expertconsult.com). Each study can be assigned a level of evidence based on its design and quality. For a given topic, the quality of the entire body of evidence forms the basis for the strength (or grade) of a clinical recommendation. The best studies are level 1a evidence (systematic reviews of studies using similar methods), and the worst studies are level 5 evidence (expert opinion). Clinical recommendations then are graded from A (consistent level 1 evidence) to D (level 5 evidence or troublingly inconsistent or inconclusive studies).

Apply the Evidence

The strongest evidence is useless unless it is effectively applied. Bedside decision making has been the traditional focus of EBM. Clinicians must use their knowledge and experience to understand how the results of studies can be applied to individual patients. With evidence in hand, a clinician practicing EBM will place it in the context of the specific clinical circumstances and the patient's (or guardian's) preferences.[20] Patient characteristics or preferences may be sufficiently unique to render even good evidence inapplicable.

EBM can be implemented on a larger scale through clinical practice guidelines and clinical pathways, which can disseminate and promote best practice at institutional, regional, or national levels. They are especially useful for common illnesses and procedures, and they allow implementation of EBM even when individual physicians are unable to incorporate evidence by themselves because of a lack of either time or expertise. The most compelling guidelines contain a summary of the evidence both for and against the guideline and how to apply the recommendations to specific clinical situations.[18] Recently, the Centers for Medicare and Medicaid Services have begun to link reimbursement for the treatment of some conditions with the provision of elements of care thought to be essential based on extensive bodies of evidence (such as the timely administration of antibiotics for pneumonia).

Challenges to Evidence-Based Medicine

It is impossible to practice EBM without evidence. Until recently, a paucity of strong evidence existed in support of particular care paradigms in the critically ill, with even less evidence related to critically ill children. A growing number of studies now offer guidance on a wide set of critical

care problems.[21] However, much of our care remains largely empiric. A basic tenet of EBM is that a lack of evidence that an intervention is effective is not proof that an intervention is ineffective (i.e., "Absence of evidence is not evidence of absence"). This issue is particularly relevant to pediatric critical care, in which numerous therapies are used without proven efficacy, and the evidence base for many other therapies is from studies of adults. Whether unproven therapies should be used depends on (1) whether proven alternatives are available, (2) the likelihood and magnitude of potential harm from the therapy, (3) the natural history of the disease or condition being treated, (4) in the case of prophylaxis, the risk of developing disease, and (5) the cost of treatment (as well as the cost of not treating the patient).

Even for therapies proven to be effective, clinicians must weigh the potential risks and benefits for a given patient. Evidence-based guidelines can be useful in helping clinicians and patients make these decisions, but they cannot take the place of clinical judgment. Treatments that are proven to be useless or harmful should be avoided, of course. However, restrictions on existing therapy solely on the grounds that the therapy is unproven are generally inappropriate.

In the absence of practice guidelines and clinical pathways, EBM relies on individual clinician skill and initiative. Unfortunately, each step of EBM practice can be challenging, particularly for clinicians with little EBM experience. Generating specific, patient-centered questions is difficult. Because of the relative paucity of available evidence, searching for the right article can be akin to searching for a needle in a haystack. Fortunately, electronic databases are increasingly user friendly and efficient. The culture of medicine and the methodology of EBM are changing to put applicable, understandable evidence at the fingertips of clinicians.

Conclusion

The practice of critical care is changing constantly, but studies documenting remarkable practice variation suggest that the change is much too inconsistent. Intensivists tend to be resourceful, creative, efficient, and comfortable with applying clinical skills to desperate circumstances amidst a paucity of evidence. Although critical care physicians often have both the predilection and facility for making important decisions quickly and independently, that same temperament may impede the acquisition and application of a growing body of evidence related to critical illness and critical care.

All physicians have an ethical responsibility to apply EBM. Meticulously designed and executed clinical research is expensive and difficult to perform. Society expends scarce resources on it. Subjects in clinical trials face significant personal risks in hopes of a better outcome and for the advancement of knowledge. Our responsibility extends beyond individual patients, for whom the benefits of using the best available treatment usually are clear. We owe it to subjects of prior trials, researchers who carried out the trials, and the society that supported them to use and build on the knowledge gained. The unique vulnerability of critically ill patients, with their significant risk of death or long-term morbidity, creates perhaps a stronger ethical imperative for intensivists to use evidence whenever it is available. When evidence is inadequate, we are left to do our best with our clinical expertise for our current patient and to generate the evidence needed for future patients.

References are available online at http://www.expertconsult.com.

Chapter 6

Outcomes in Pediatric Critical Care Medicine: Implications for Health Services Research and Patient Care

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PEARLS

- Quality improvement seeks to improve care while health services research seeks to advance knowledge and identify best practices.
- Ensuring quality is an important aspect of delivering critical care services to children, and clinical outcomes are an important measure of the quality, safety, and effectiveness of care.
- A framework that integrates pediatric intensive care into "Systems of Care" is helpful for organizing and improving the delivery of services to patients and assuring that they receive the best possible care.

Quality in health care has received increasing attention over the last several decades. This focus has been particularly apparent over the last 10 to 15 years and has captured the attention of clinicians, managers, executives, insurers, and policy makers.[1,2] Unfortunately, much of the discourse has been vague, and clinicians, in particular, may not fully understand how quality is defined, what it means to their patients, and how it can be incorporated into their daily practice.

Pediatric critical care medicine (PCCM) has experienced challenges similar to those of other disciplines in attempting to quantify clinical outcomes. As physicians, we are biased in our assessments by our knowledge and experience. Physicians rarely have sufficient objective and quantifiable data to make decisions about outcomes, except perhaps at the extremes of illness severity. Often, there is insufficient time for understanding how clinical decisions are made, how care is delivered, and how to evaluate the achieved outcomes. Without the evaluative step, we fall short in identifying opportunities to improve our care. While physicians certainly do influence the ultimate outcomes of the critically ill child, the system of care includes important contributions by other clinical team members and non-human factors that can also influence quality and outcomes.[3]

This chapter provides a framework for understanding outcomes from critical illness for the acutely ill or injured child and considers mechanisms for contributing to new knowledge through health services research (HSR) methods.

What Is Health Services Research?

Health services research (HSR) is a field of inquiry that is concerned with the creation of new knowledge related to the organization and delivery of health care services and their outcomes.[4,5] A number of formal definitions have been provided by leading organizations over the last several decades and demonstrate how the conceptualization of HSR has evolved with time and become more comprehensive (Table 6-1).[6-8]

The discipline of HSR has relevance for social science fields like health policy and economics as well as for clinical disciplines like PCCM. This section will focus on how pediatric critical care is organized and how bedside care can be used to explore differences in treatments and outcomes within and across pediatric intensive care units (PICUs), hospitals, regions, and populations, so that new knowledge is generated, shared with colleagues, and applied. The results of HSR can also inform policy decisions that can influence the organization, financing, and structure of health care delivery for critically ill children.[4]

A System of Care

An organized and methodical system of care is necessary to ensure that critically ill children receive care that is of the highest quality.[9] This begins prior to the time when the services are actually needed and relies upon a primary care structure that ensures children can benefit from preventive strategies designed to keep them healthy. There are important strategies that are necessary for assuring childhood health including adequate nutrition, appropriate vaccinations, and easy access to clinicians for acute minor illnesses and injuries,

necessary medications, and follow-up care for chronic conditions. Unfortunately, in some settings, the capacity to manage pediatric health prior to acute illness is lacking. The result is that timely delivery of services cannot be ensured and an unnecessary burden is placed upon emergency department (ED) services.[10]

The provision of health care is complex and requires appropriate organization. The study and evaluation of the organization of care, as is accomplished using HSR methods, provides some of the most fertile ground for generating new knowledge and identifying opportunities to improve outcomes for critically ill children.[4,5] Some believe that this organization, particularly for high-end pediatric clinical services like pediatric critical care, should be highly regionalized (Figure 6-1). There are a number of good reasons to favor regionalizing care, including the need to reduce unnecessary variation and improve outcomes and resource use, both from a structural (e.g., ICUs, bed numbers) and a human perspective (e.g., manpower issues). However the term 'regionalization' does not convey one of the most important aspects of PICU care related to outcomes—integration of care. Regionalizing care will prove to be insufficient for generating good outcomes if care from the child's immediate environment to the tertiary or quaternary hospital is not integrated, and if there is not shared accountability for outcomes at the population level.

Most states have coordinated systems for supporting the care of the acutely ill or injured patient on a regional basis.[11] This is good news, but unless the regional care structures are integrated into a hierarchically arranged system of care based upon increasing patient complexity, outcomes may fall short. In an integrated model, children with acute illness can gain access to the health care system through a number of different access points and be cared for by appropriately trained personnel at each level of care.[10] For those children whose condition deteriorates or whose care needs become more complex with time, the system's integrated components can assure that the child's and family's needs are met in a timely and seamless manner by progression through the integrated system with established measures of performance.[12] The investigation of how the health care system is organized, how the system's components operate, how it is funded, and what alternatives may work better are fundamental HSR analyses.

Organizing Health Systems

Systems represent a concept of an "integrated whole" that is dependent upon components and the relationships of those components to one another both inside and outside of the system for the successful delivery of outputs (or outcomes if the system under investigation is health care).[13-15] Systems have structure, and this structure provides a framework to organize the components into a hierarchical arrangement, known as *microsystems* and *macrosystems*, that helps to provide an understanding of the components' relationships to one another.[13-15]

While these terms might imply two different levels of functioning, there are multiple levels of embedded hierarchy that can be described between the microsystem and macrosystem levels.[13-15] This approach is useful for describing the complex care required by the critically ill child in the PICU; it provides important opportunities to consider, study, and improve care more broadly for pediatric patient populations, as would be performed in HSR.[4-5] To succeed with this approach, the interdependent components of systems need to be considered and criteria-based quality measurement and improvement need to be operationalized within and between the levels of the system's hierarchy.[16] These relationships among and between the system's components have important implications for addressing both the quality of care and HSR questions.

Microsystems and Macrosystems

Microsystems

A system's hierarchy can be collapsed to the frame of reference of a single critically ill child and the respective system components that affect that child (Figures 6-2, *A* and *B*). The system components are termed 'microsystems' and, when integrated and functioning appropriately, provide for consistent performance.[13,15] At the unit level, there is a nursing microsystem; a physician microsystem, often with attendings, residents,

Table 6–1 Contemporary Definitions of Health Services Research

Source	Year	Definition
Agency for Healthcare Research and Quality	2002	Health services research examines how people get access to health care, how much care costs, and what happens to patients as a result of this care. The main goals of health services research are to identify the most effective ways to organize, manage, finance, and deliver high quality care; reduce medical errors; and improve patient safety.
Academy for Health Services Research and Health Policy	2000	Health services research is the multidisciplinary field of scientific investigation that studies how social factors, financing systems, organizational structures and processes, health technologies, and personal behaviors affect access to health care, the quality and cost of health care, and ultimately our health and well-being. Its research domains are individuals, families, organizations, institutions, communities, and populations.
Institute of Medicine	1995	Health services research is a multidisciplinary field of inquiry, both basic and applied, that examines the use, costs, quality, accessibility, delivery, organization, financing, and outcomes of health care services to increase knowledge and understanding of the structure, processes, and effects of health services for individuals and populations.
Institute of Medicine	1979	Health services research is inquiry to produce knowledge about the structure, processes, or effects of personal health services. A study is classified as health services research if it satisfies two criteria: it deals with some features of the structure, processes, or effects of personal health services. At least one of the features is related to a conceptual framework other than that of contemporary applied biomedical science.

and fellows; and microsystems for providing respiratory care, social work, radiology, and laboratory services.[13,15] Each of these microsystems operates within a broader framework for providing care across hospital units, or even across hospitals or the population (Figure 6-2, *A* to *C*). When components within these systems fail, the child and family may experience adverse events, safety problems, errors, excessively long lengths of stay (LOS), or even unnecessary death, and the family's perception of the experience is suboptimal.[17,18] Normally, these systems function quite well, given their complexity and interdependence; the child achieves a good outcome, and the family is satisfied.

Macrosystems

Variability in performance within microsystems creates problems with performance at the macrosystem level, as care across the different dimensions of quality is aggregated.[18] An analytic approach that capitalizes on the contextual elements of individual microsystems while addressing the broader concerns of the macrosystem's performance is important for understanding and improving the care for the population (Figure 6-2, *B* and *C*).[13-15] Hierarchical modeling and cluster analysis are some of the available analytic tools to improve our understanding of the interaction of system elements that are parallel or at multiple levels of hierarchy.[19] For example, to achieve appropriate estimates of ICU care at the state level (macrosystem), analytic approaches that account for similarities in practice patterns at multiple ICUs within a given hospital (microsystem #1) or within a given city (microsystem #2) because of geographic proximity need to be used. These methods are globally termed hierarchical or multilevel models, because they help to account for biases at multiple levels of the macrosytem.

The six dimensions of quality as described by the Institute of Medicine are operative at both the macrosystem and microsystem levels (Table 6-2).[1-2] While the prior section was focused on improving the clinicians' understanding of how new knowledge can be generated through HSR methods, the intent of the following section is to provide an improved understanding of important patient level outcomes in PCCM for quality improvement. The distinction is a bit artificial in that the study of outcomes in the PICU can also be used to generate new knowledge about delivering care at the bedside.

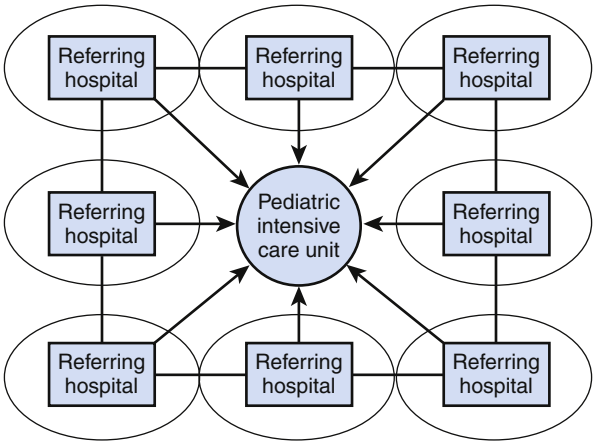

Figure 6–1. Hub and spoke model for regionalizing pediatric critical care services that assures integration for children within and across communities served by local hospitals.

The Macrosystem: Pediatric Critical Care

The three major focus areas of interest for considering pediatric critical care at the macrosystem level are access, quality, and cost. These areas also provide an important framework for considering the organization and delivery of care for the critically ill child at the macrosystem level. Figure 6-3 provides a schematic overview of how the critically ill or injured child

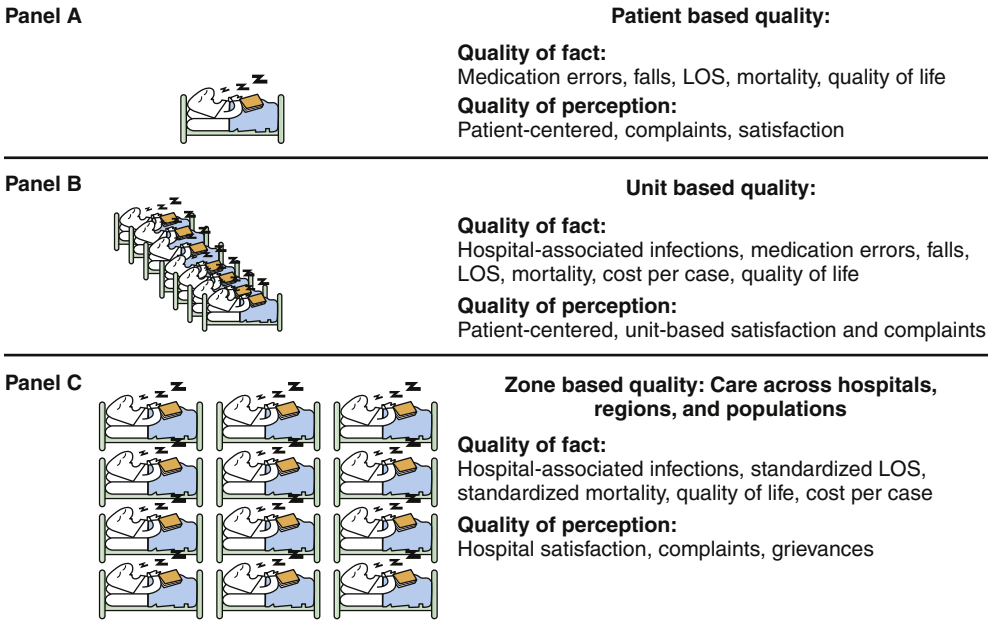

Figure 6–2. A depiction of three levels of organizing care at the microsystem level for pediatric critical care, and examples of outcomes in fact and perception associated with each level. A represents the outcomes focused on the patient level. B represents the outcomes focused on the unit level. C represents the outcomes beyond the intensive care unit.

experiences the health care system. While this figure represents a somewhat linear depiction of these care experiences, the reader is reminded that there is considerable overlap and interaction between the different elements of the system.

Access

Access represents the entry point into the health care system for those seeking care. For children, access represents the availability of appropriate services and financing to ensure that children are able to see providers with the knowledge, skills, and abilities to deliver care appropriately.[4] Care needs for children are different from those of adults and require specific considerations for the acutely ill or injured child.

Access to pediatric expertise for anticipatory care and acute care is important. At the policy level, access depends on an adequate number of pediatric providers distributed in a way that assures appropriate primary care. The medical home is one model that attempts to anchor children with primary care providers who act on behalf of the child to organize and coordinate their care.[20-22] With this model, age-appropriate anticipatory guidance for health concerns is provided, and vulnerabilities such as underimmunization, obesity, and risk-taking behaviors can be addressed proactively. When a child becomes ill, it is important to have access to providers and services for timely intervention and referral without the need to use other system structures (e.g., EDs). This ensures that care be provided at the most appropriate entry level, thereby saving higher-level resources for those most likely to benefit. This has important implications for the critically ill child.

Acutely ill children can decompensate quickly. Resources to care for these children also must be organized in a way that allows the child to receive lifesaving and resuscitative care immediately (see Figure 6-3). Considerable improvements in prehospital emergency care of children have been undertaken over the last several decades.[11] These improvements have been aimed at assuring that community-based prehospital providers have the pediatric training and equipment to deliver appropriate care and safely deliver the child to appropriate ED resources.[11]

While access points like EDs are readily available in many communities, they may not be staffed or equipped to provide specialty care for acutely ill or injured children.[10] Emergency care for children is an example of one 'specialized care area' that is notable for considerable variation in ED readiness and provider training for pediatric emergencies.[10] Of the more than 30 million pediatric ED encounters annually in the US, only 18% are provided at pediatric EDs.[10] Children have important differences in their anatomy, metabolic demands, and disease processes that make the expertise and equipment for their diagnosis and treatment different than those for adults. Unfortunately, only 6% of all EDs nationally had the necessary supplies for pediatric emergencies.[10] In addition, there are unique emotional and developmental considerations that need to be accounted for when caring for acutely

Table 6–2 The Institute of Medicine's Aims of Quality

Quality Aim	Definition
Safety	To limit the unintentional harm associated with the delivery of health care
Effectiveness	To use evidence-based practices, the best scientific evidence, clinical expertise, and patient values to achieve the best outcomes for patients
Efficiency	To provide care that is done well and with limited waste
Equity	To provide care that is free from bias related to personal demographics like gender, race, ethnicity, insurance status, or income
Timeliness	To provide care without unnecessary wait and to assure that patients have access to the care they need
Patient-centeredness	To provide care that reflects a focus on the patient's needs, including empathy, compassion, and respect

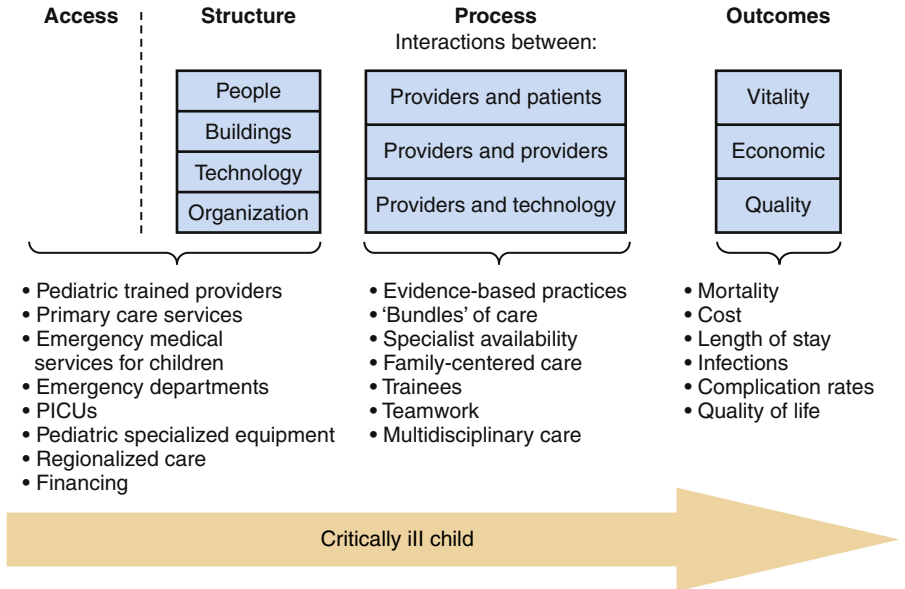

Figure 6–3. The macrosystem of care for the critically ill child, demonstrating the major components of access, structure, process, and outcome.

ill children and their families in the ED, and this expertise may not be present in all EDs. Hence, when confronted with acute, severe, complex, and infrequently encountered pediatric emergencies, long delays may be experienced before definitive critical care services and expertise are available and provided to the child. Given a child's limited ability to compensate during a physiologic crisis, these delays in care lead can potentially lead to worse outcomes.

Quality

Quality is defined as the degree to which health care services for individuals and populations increase the likelihood of desired outcomes and are consistent with current professional knowledge. Donabedian's seminal work described three major components of quality structure, which were first applied to health care in the mid 1970s and continue to provide a useful framework for quality improvement and health services research.[23-24]

Structure

Structure represents the organization of health care services, including the "bricks and mortar," personnel, and technology required to deliver care (Figure 6-3).[23] The modern PICU is staffed with a multidisciplinary team of providers with the availability of specialized expertise and technology to care for the critically ill child. The organization of pediatric critical care services is important to consider, given how they function as access points to personnel with the expertise to use advanced lifesaving technologies for critically ill children. There are several examples from our colleagues in other disciplines where systems of care have emerged and been organized at the macrosystem level for the benefit of patients, with improved outcomes. Specialized cancer centers and trauma centers are two notable examples, but even within the discipline of critical care medicine, pediatric critical care and neonatal critical care have operated, almost since their inception, with an organized and systematic approach.

A similar system of hierarchically arranging critical care for the pediatric patient, based upon increasing complexity and documented guidelines for critical care services and personnel at each level of care, can be envisioned at the macrosystem level. The provision of multidisciplinary critical care has improved the safety, quality, and efficiency of care in the ICU. However, despite these efforts, several challenges remain. First, in-house critical care attending physicians at regional centers improve the quality of care and patient and physician satisfaction in ways that are simply unavailable at smaller facilities. However, there is a disparity between the number of ICU beds and the supply of qualified intensivists, which is likely to become even more apparent as hospitals attempt to meet staffing recommendations of groups such as Leapfrog.[25] Second, critical illness represents a spectrum of disease severity that by its nature introduces variability at both the provider and institution levels. What is really needed to overcome the problems of a fragmented system is a solution that is designed and integrated in a way that allows national standards of care to get to the bedside at the local level in the near future. A system that is structured to provide highly integrated, well-coordinated care, of the highest quality based upon current scientific knowledge, and the most cost effective, should be the goal of any macrosystem.

While PICUs are neither distributed uniformly nor provide the same level of care, one approach for expanding the scope of services to communities without PICUs, while maintaining a central core of specialized expertise is the "hub and spoke" model (see Figure 6-1). This model depends upon a regional referral base that has the appropriate structures, including appropriately trained personnel, equipment, and knowledge, to identify, resuscitate, stabilize, and perhaps even care for, moderate degrees of pediatric illness. When the child's care needs outstrip the capabilities of these referring institutions, organized interhospital transportation services are available from a central hub to provide immediate access to care for those children who need it. This approach accomplishes several things. First, it improves access to specialized care for moderate-severity pediatric conditions for children in the communities in which they live. Second, it provides an organized and readily accessible access point for children who may become severely ill and require services and technologies unavailable on a widespread basis because of the cost of maintaining them. Third, this approach ensures the expertise of the core PICU because large volumes of patients with severe illness are needed to maintain specialized expertise. Finally, system level efficiencies allow the appropriate care to be delivered in a cost-effective manner in locations that are equipped to deal with them (see Figure 6-1).

Process

Donabedian described processes of care as the interactions between providers and patients that effectuate the delivery of care (see Figure 6-3).[23-24] Of importance, PCCM is highly dependent both on personnel and technology, but neither one of these structural components alone will assure the delivery of appropriate care. Only when trained personnel are provided with technology that is working appropriately and in adequate supply can quality be ensured.[18] For example, the most highly trained intensive care team including an intensivist, nurses, pharmacists, respiratory therapists, and social workers will be unable to sufficiently care for a critically ill child with respiratory failure if they do not have access to appropriate ventilators. Similarly, a ventilator, without appropriately trained personnel will also be insufficient for delivering care.

While Donabedian was primarily interested in the care processes that involved provider-patient interactions, with the evolution of PCCM there is now recognition that the provider-technology processes and the provider-provider processes represented by teamwork are also essential elements of this care delivery.

Pediatric critical care services are heavily dependent upon technologies for the delivery of care. A large component of critical care training is focused on the ability to assess, diagnose, and treat the critically ill or injured child. The training consists of significant experience in using life-sustaining technologies that are aimed at supporting the child's failed organ systems until they are once again able to compensate on their own. Critical care clinicians need to know how to initiate and discontinue these supports for the benefit of their patients as well as investigate problems that occur during their use.[18] The interactions between the clinician and the equipment are important to understand if there is to be success in achieving desired outcomes. For example, a clinician caring for a critically ill child with respiratory failure who is unable to troubleshoot the alarms or address malfunctions in the equipment

will be providing a substandard approach to care. Even simple devices like intravenous infusion pumps require the clinician to be trained and educated to more fully understand the opportunities for error.

The multidisciplinary clinical team that integrates with the family in shared decision making is essential to ensure quality for the child.[18] A team consists of two or more individuals with specialized knowledge and skills who are assigned to interdependent roles and tasks allowing them to accomplish a specific goal. When functioning well, teams can improve safety, and compensate for faulty system design and process failures. The care of a critically ill patient depends heavily on the assurance of good system design, knowledge, skills, and teamwork. In the ICU setting, Pronovost and colleagues identified teamwork and communication between nurses and doctors as critical 'nontechnical skills' for preventing harm to ICU patients.[26] However, there are limited data regarding teamwork and its effect on safety in the pediatric intensive care unit.

The PICU has historically been a place where the necessary knowledge and skills to care for critically ill children are present. Improvements in PICU design have fostered safer and more family-centered care. However, empirical evidence regarding the importance of teamwork and communication on patient care in the PICU is limited. Some foundational work that seeks to understand the attitudes of pediatric critical care providers towards teamwork have been performed.[27] In addition, there are some important examples that highlight how team performance can help to compensate for inadequacies in clinical performance in the care of pediatric patients, particularly in those team members that are less familiar in caring for children.[28]

Outcomes

The end result of the health care experience is reflected by health outcomes, which are usually considered in three major categories: vitality outcomes, economic outcomes, and quality outcomes (see Figure 6-3). Regardless of the category, outcomes should be objective and clearly defined. Quantitative estimates of clinical status must be used to assist with the evaluation of outcomes across different patient populations or ICUs. For critical care, this has been accomplished through the use of scoring systems that account for variability in patient case mix.

Survival and death have been the primary vitality outcome measures used in neonatal, pediatric, and adult ICUs. They occur with sufficient frequency in ICU settings, are well-defined, and are clearly important. Physiology-based estimates of mortality exist for each of these three ICU patient populations.

Neonatal Intensive Care Unit Mortality Scores. The Clinical Risk Index for Babies (CRIB) and the Score for Neonatal Acute Physiology (SNAP)[29] are two physiology-based mortality scores for neonates. CRIB was developed in the United Kingdom, before the widespread use of antenatal steroids and surfactant, for infants weighing less than 1500 g.[30,31] Six commonly measured variables, some of which are subject to physician practices, are collected within the first 12 hours of birth. SNAP II is a physiology-based score for neonatal severity of illness developed from large samples from United States and Canada. SNAP II has also been modified for use as a mortality prediction model (SNAPPE II) by the addition of variables including birth weight, small-for-gestational-age, and low Apgar scores.[32]

Pediatric Intensive Care Unit Mortality Scores. The two most commonly used severity-of-illness scores in pediatrics are PRISM and the Pediatric Index of Mortality (PIM). PRISM is now a third-generation score (PRISM III) developed from more than 11,000 patients in 32 PICUs, with the most recent recalibration being performed on more than 19,000 patients.[33,34] Mortality predictions can be made using the first 12 hours (PRISM III-12) or 24 hours (PRISM III-24) of physiologic variables and laboratory and diagnostic data. It is unique in that it can predict both mortality and LOS.[35]

PIM was developed on 5695 patients from Australian PICUs and one British PICU. It was developed using physiologic and laboratory data available upon patient presentation.[36] This was intended to eliminate the theoretical concern of lead-time bias, the concept that therapies initiated prior to the stabilization of the patient would alter a severity score that used physiologic measures obtained within the first 12 or 24 hours.[37] Thus models such as PRISM III that use data collected over the first 12 or 24 hours after admission might be affected by the quality of the initial pre-PICU management and thus affect the predicted mortality. The PIM score uses data collected from the time the ICU team first contacts the patient (e.g., in the ED or in transport) and through the first hours of PICU care. PIM includes mechanical ventilation as a predictor variable and as a result introduces the biases associated with the use of mechanical ventilation throughout the health care system, including the prehospital and emergency department settings into the prediction models. Although PRISM has been externally validated by other national and international PICUs, PIM has not been extensively tested in the United States.

There has been concern by many that the focus on death may miss other important outcome measures, such as disability. Measurement of serious disability has been a difficult problem in pediatrics because it is difficult to define, and there is wide variability in physician estimates of disability. The Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores are global assessments that can quantify overall morbidity and cognitive impairment specifically for children.[38-40] Differences between baseline and discharge POPC and PCPC scores have been associated with morbidity, length of PICU stay, total hospital charges, discharge care needs, and summary measures of severity of illness. These scores do correlate with neuropsychological tests at hospital discharge, the Stanford-Binet Intelligence Scale IV, and the Vineland Adaptive Behavior Scales at 1 and 6 months postdischarge follow-up. Unfortunately, these scores depend upon the providers' estimates of the disability, which is typically not a core competency of PICU staff, and try to assess children for functional status at a time when the child is heavily dependent on others for their care. Finally, these tests (POPC and PCPC) are not sufficiently precise for use in individual patients. Individuals with the same neuropsychological measure might fall into very different POPC and PCPC groups based on the qualitative assessment of the caregiver's assessment of functioning. However, it appears that other outcomes, such as morbidity and disability, correlate well with the changes that affect mortality.

A new outcome measure, the Functional Status Scale (FSS), was recently developed and validated.[41] This scale is intended for use in large outcome studies of patients across the pediatric age spectrum, from term newborn to adolescents, in a wide range of inpatient environments. It comprises six domains, including mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status, and correlates with adaptive behavior scales that require more time and specific expertise. Scoring in the FSS does not require expertise outside the realm of ICU physicians or nurses, is not subjective, and can be done rapidly. It is likely that this scale will enhance ICU outcome studies, providing significantly richer data related to morbidity and disability.

Economic outcome indicators are increasingly available and useful when evaluating expensive or resource intensive therapies. Several resource outcomes are commonly measured including length of stay, costs, and the use of critical care therapies, such as mechanical ventilation or vasoactive infusions.

Outcomes that relate to the performance or process of care are referred to as quality outcomes. These outcomes include adverse events such as nosocomial infection, surgical complications, and outcomes regarding functionality and health status, including disability as described above.[30]

The Microsystem: Pediatric Intensive Care Unit

The PICU can be considered as either a macrosystem or a microsystem depending upon the components of the system under study, the context, and the questions under consideration. Quality efforts are directed at improving care and outcomes.

Patient Level

An understanding of the fundamental work involved with caring for the acutely ill or injured child is important for advancing a discussion on clinical outcomes at the patient level. Figure 6-4 portrays the direct interactions between the expanded care team and the child and family needing PCCM services prior to and after their arrival in the PICU. A systematic model of outreach that allows appropriate care to be delivered to children where and when it is needed is an important part of this approach. For many locales, this is organized as a "hub and spoke" model (see Figure 6-1) where a PICU supports and integrates the care from a number of regional referring hospitals, assuring timely and efficient access to tertiary or quaternary pediatric services when the child's needs dictate.

Mechanisms for assuring outreach include information for referral hospitals, so that they will know what is available in their region to assist with caring for the child and family. Many hospitals use critical care transportation systems to bring needed services to the child in the community with skilled and experienced guidance from the region's PICU. Patient care dialogues and relationships are fostered in these episodes of care. The result is that referring centers gain valuable backup and expertise, tertiary PICUs are supported through these outreach efforts by an important referral base, and important services are provided to the children, families, and communities being served.

Once the child and family gain access to the PICU, they need to be welcomed, assessed, and triaged to an appropriate level of care (see Figure 6-4). Conditions can change during transport and the child may appear better or worse than the initial reports. The child and family then enter an important series of steps that include introductions to the care team, an assessment and plan of care, the establishment of whether advanced technologies are required, and the planning and delivery of treatment by members of the PICU team (see Figure 6-4). These steps are second nature to many who work in the PICU because they are performed repetitively. However, identifying each of the process steps not only provides an important framework describing the work of bedside care, it also represents the first step in understanding outcomes from critical illness.

At the bedside, the individual child or family experiences these steps in a way that is up close and personal. What may be a rote process for providers is an emotionally charged experience for the child and family. Figure 6-2, *A*, provides an important framework for understanding outcomes at the patient level. Each care episode can be evaluated using a standard quality improvement methodology that allows the care

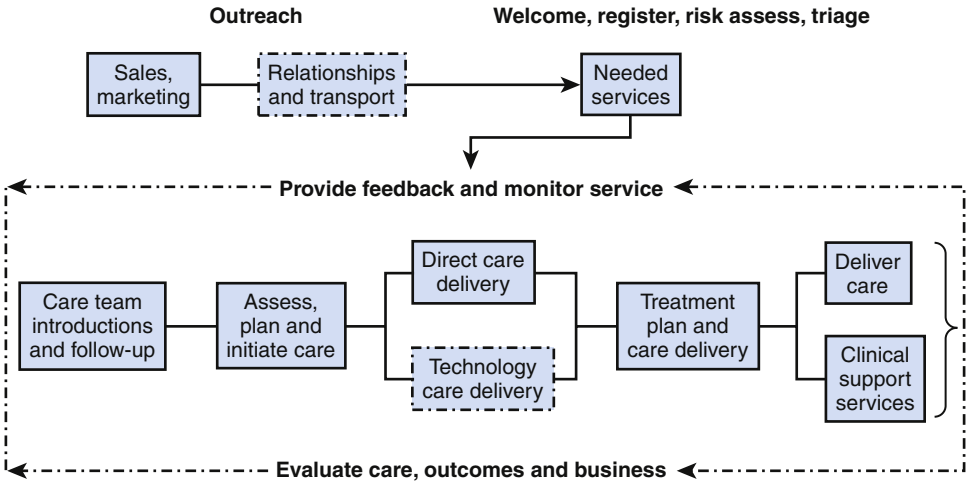

Figure 6–4. The microsystem of care for the critically ill child, demonstrating the major components of outreach, assessing, triaging, delivering, and monitoring care along with the evaluative components of outcomes.

to be measured and improved so that the care experience for the next family might be better.

There are two specific categories of care that can be evaluated at this time (Figure 6-2, *A*). The first category is referred to as *Quality of Perception* and allows the providers to have an improved understanding of how the family experienced the care. Taking the time to elicit feedback about the steps that were difficult, scary, or burdensome is an important opportunity for the family to provide feedback to members of the team. The second category is concerned with Quality of Fact, which is an evaluation of whether or not the child and family's clinical care needs were met. Reflecting on the care and its outcome are important for the team's learning. Did the child die? If so, why? If the child lived, is he or she left with disabilities or chronic conditions affecting quality of life that might have been averted? Were procedures performed appropriately and when needed? Was the referral timely? If yes, did the transport team arrive in a timely manner and provide the necessary services? If not, how can referral hospitals be assisted in knowing when to call for transport? While clinicians tend to be concerned with evaluating the elements of the clinical work, there are important operational components that can affect the delivery of clinical care and which also need to be addressed, including how long the child waited, whether the records and diagnostic studies were immediately available, and how long it took for clinical interventions to occur.

Because the patient is the focal point of these experiences, the measurement tools that are used include straightforward counting statistics. A medication error, a central line infection, a fall, or a complaint can be numerically tallied to provide the team with an understanding of their performance. Considerable practice-based learning can take place in these "n of 1" cycles that allow clinicians to see how their work succeeded or where it perhaps can be improved. The use of both factual and experiential aspects of care is the first step in understanding outcomes at the patient level.

Intensive Care Unit Level

While individual providers and managers are certainly interested in individual outcomes occurring one patient and one bed-space at a time, managers and directors can add value by assisting their teams in understanding aggregate outcomes across individual patients in the same PICU. Figure 6-2, *B* demonstrates how the individual outcomes can be incorporated at the unit or macrosystem level. Both Quality of Perception and Quality of Fact are also operative at the unit level. However, rather than using "counting" statistics to understand performance, "percentage statistics" are used. At the unit level, rates and proportions are used to monitor care over time. For example, medication errors per 1000 doses dispensed, ventilator-associated pneumonias (VAP) per 1000 ventilator days, and the percentage of families rating the care as "excellent" are all commonly used measures to monitor the care in the PICU.

Management and leadership can make a difference in improving PICU care, and the use of data is fundamental to being able to demonstrate improvements over time within a given PICU or in comparison to other PICUs. Whatever outcome measures are considered, they should be objective, clearly defined, reproducible, and account for differences in case mix and severity. While managers may evolve a level of comfort with percentage statistics and macrosystem thinking, individual clinicians may not. One reason for this is that individuals can have difficulty processing these complex rates and understanding how rates can lead to changes in their behavior that improves outcomes. Hence, it becomes important for managers to provide appropriate context for their staff. If the ventilator-associated pneumonia rate is 10 per 1000 vent days and this year's goal is to reduce it to 5 per 1000 vent days, the manager can convert the rate into the number of patients affected. Bedside clinicians can more easily remember the personal connection they had with the child or family who experienced a VAP under their care and are more likely to work to prevent the occurrence of VAP than if the numbers are represented as percentage statistics.

Beyond the Pediatric Intensive Care Unit

Figure 6-2, *C,* provides the next level of comparison for understanding outcomes. Whether the macrosystem analysis is focused at the hospital level, the regional level, or the population level makes little difference, the fundamental constructs of Quality of Fact and Quality of Perception are still operative. The strategy for measurement includes both counting and percentage statistics, as well as a few additional advanced epidemiologic and statistical tools to assist with understanding the delivery of health care across broader geographic regions, populations, or conditions. The use of these statistical tools does little to assist with distinguishing between quality improvement and research. Rather it is the intention of the analyses that helps to distinguish between the two types of work.

Conclusion

Understanding the organization of health care services has important implications for generating new knowledge through the use of HSR methods and actually improving care for critically ill pediatric patients. The quantitative and qualitative approaches used in research and quality improvement are complementary between the two disciplines. However, the clinician needs to have a clear understanding of the intent of the analytic approach and what he or she will do with the findings.

References are available online at http://www.expertconsult.com

Chapter 7

Safety and Quality Assessment in the Pediatric Intensive Care Unit

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PEARLS

- The six domains of quality in the pediatric intensive care unit are safety, effectiveness, patient centeredness, timeliness, efficiency, and equity.
- Research demonstrates that errors in health care are often caused by poorly designed systems of care.
- Three essential activities of a patient safety program include risk identification, risk analysis, and risk reduction.

Since the last edition of this book, the importance of quality improvement (QI) and patient safety to pediatric intensive care units (PICUs) has increased. At the same time, the science supporting improvements in QI and patient safety has evolved. Unfortunately, both QI and patient safety draw on knowledge and concepts that are neither part of traditional medical education nor are intuitive. Using real-world examples, this chapter explores important concepts of safety and quality, with an emphasis on pediatric critical care.

A Brief Consideration of the Relationship Between Safety and Quality

Many similarities exist between safety and QI. As a result, there is potential confusion between the two domains. Are they the same? Is safety really applied QI? The Institute of Medicine weighed in on this discussion by identifying safety as a component of quality in the report Crossing the Quality Chasm.[1] Based on this report, safety is a prerequisite to achieving quality. That is, it is impossible to achieve true quality without improving safety. Others who argue that attention to other aspects of quality beyond safety is critical have confirmed this observation.[2] For the pediatric critical care provider, the important point is that safety is a necessary prerequisite for quality, but improving safety is insufficient to achieve quality.

State of Safety and Quality in Pediatric Intensive Care Units

The Institute of Medicine's report, *To Err is Human,* was the first widely recognized publication to identify the scope of preventable medical harm.[3] In response, patient safety and quality was placed on the radar screen of consumers, policy makers, and providers. Perhaps the most visible response from these groups is the focus on measurement as an attempt to drive improvement. Inherent to this is the recognition that adoption and public reporting of performance measures is a necessary (though not sufficient) step to achieving a high-quality health care system.

In PICUs, the increased focus on safety and improvement is evident in three major developments. First, the National Quality Forum endorsed the adoption of and public reporting of six PICU-specific performance measures in May 2008 (Table 7-1).[4] These measures were created based on the recognition that performance measures designed for adult populations may not be appropriate for application to the pediatric populations and settings.[5,6] For many PICUs, measurement and reporting of these endorsed measures is voluntary. However, formal endorsement by the National Quality Forum makes these measures "fair game" for evaluation by payers and accrediting bodies such as The Joint Commission.

A second development illustrating the importance of QI and patient safety to PICUs is the national catheter-associated bloodstream infection (CA-BSI) team collaborative.[7] This national initiative is focused on applying bundle tools to reduce cather-associated bloodstream infections. Based on data from 29 teams, applying the bundle recommended by the collaborative prevents 22 CA-BSI infections and saves two lives and $750,000 each month.

A third manifestation of the increased importance of QI and patient safety in PICUs is the American Board of Pediatric's requirements for Maintenance of Certification. Intensivists interested in maintaining their credentialing must now demonstrate that they meet four conditions: professional standing, lifelong learning, cognitive expertise, and performance in practice.[8] A component of meeting these conditions is the active participation in an improvement project. Of note, active participation in the previously mentioned CA-BSI project will meet this condition.

Consistent with each of these three developments, multiple authors have concluded that physician leadership and participation are crucial to the success of QI and patient safety efforts.[9,10] Unfortunately, a 2003 survey among U.S. physicians showed that they infrequently participate in improvement efforts, they don't routinely use data for assessment of their performance, and are reluctant to share those data.[11]

Table 7–1 Endorsed Pediatric Intensive Care Unit Measures

Measure	Description
PICU standardized mortality ratio	The ratio of actual deaths over predicted deaths for PICU patients, adjusted using an accepted risk of mortality tool.
PICU severity-adjusted length of stay	The number of days between PICU admission and PICU discharge for PICU patients, adjusted using an accepted risk of mortality tool.
PICU rate of unplanned readmissions within 24 hours of PICU discharge	The total number of patients requiring unscheduled readmission to the ICU within 24 hours of discharge or transfer, over the number of discharges and transfers.
Review of PICU unplanned readmissions within 24 hours of PICU discharge	Periodic clinical review of unplanned readmissions to the PICU that occurred within 24 hours of discharge or transfer from the PICU.
PICU pain assessment on admission	Percentage of PICU patients receiving pain assessment on admission.
PICU periodic pain assessment	Percentage of PICU patients receiving periodic pain assessment while in the PICU.

Specific to the PICU environment, a more recent survey of pediatric critical care providers demonstrated that responders had poor knowledge of national quality and safety initiatives and similarly poor compliance with these national initiatives.[12] These data suggest that significant gaps in knowledge and practice of safety and quality activities by physicians caring for critically ill children persist.

Fundamentals of Quality Improvement and Patient Safety: Systems Thinking

To understand patient safety and quality in health care, one first must recognize the importance of systems to the way care is delivered. The Institute of Medicine, drawing from James Reason's studies of errors, defines a system as "a set of interdependent elements interacting to achieve a common aim." One model of systems in health care consists of five interaction components: people (1) use tools and technologies (2) to perform tasks (3) within an enviroment (4) in the context of an organization (5).[13] Each of these five components interacts with the others to yield the emergent properties (greater than the sum of the parts) of safety and quality.

Several essential implications follow from this model. First, no matter how safe any component is (ie, an intensivist who never makes mistakes), it is the five components and their interactions that determine if care is safe and of high quality. Second, if you change any of these components, it will have impact on the other components and their interactions. This is illustrated through the routine practice of cannulation for extracorporeal membrane oxygenation (ECMO) in the PICU. Merely changing the environment from the PICU to the hospital parking lot would have dramatic implications for the people, their tasks, the tools, and the organization's culture and liability. A third implication of this model is that changes to one or more of the five components will inevitably impact their emergent properties of safety and quality. This is illustrated by the growing literature that suggests that "safety technologies" may actually cause errors and harm.[14-19] Thus for critical care providers, understanding the role of systems in the work done in an intensive care unit (ICU) is crucial to improving quality or reducing harm.

Additional characteristics of systems that are important to intensivists are their complex adaptive nature[20] and the concept of tight coupling.[21] A complex adaptive system is one with several characteristics. First, complex adaptive systems have multiple similar agents that are autonomous entities that observe and act on their environment (such as PICU providers). More important, these multiple agents are adaptive, allowing for a high degree of resilience to system changes. The complex adaptive nature of the PICU is illustrated by sudden, unpredicted events such as codes, an unplanned extubation, or even multiple simultaneous admissions. In each of these scenarios, the future was unpredictable, the response was adaptive, and order is emergent rather than predetermined.

A tightly coupled system has events that must occur sequentially; it does not tolerate variation in supplies or inputs without creating delays and may tolerate failures less well than systems with slack designed into them. An example of tight coupling in the PICU is the common challenge of patient flow. An unplanned admission from the operating room (OR) requires a PICU bed postoperatively. The OR team is under pressure to transfer the patient to the PICU as soon as possible to free up the OR room and prevent delays in the surgical schedule. However, the patient who could leave the PICU can not be transferred because there is no floor bed. There are no floor beds because there is a delay in paper work and the need for a parent to drive the floor patient home. In this process, failure at any step leads to delay, the steps allow for little variation in process, and the majority of steps must occur sequentially. These features of complex, tightly coupled systems are endemic in health care settings.

Quality Improvement and Value

Quality has been defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[22] This definition, which comes from the Institute of Medicine, draws from the work of Donabedian.[23] In his work, quality was defined in the context of structure, process, and outcomes. In other words, to measure quality, you should consider the structure or capacities of health care, the process or interactions between patients and care providers, and the outcomes or evidence of changes in a patient's health condition. Ideally, considerations of quality should consider all three components.

The Institute of Medicine has identified six essential domains for achieving health care quality.[1] These areas include safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity. Based on these and Donabedian's components of quality, efforts to improve quality should consider improvement of process, structure, and/or outcome focused on one of the six areas identified by the Institute of Medicine. The first of these domains, safety, is discussed in depth later in this chapter. These initiatives are intended to identify, analyze, and reduce risks that contribute to medical errors and

injuries.[24] The CA-BSI bundle project discussed previously is an example of QI leading to improved safety.[25]

The second domain, effectiveness, implies providing services based on the best available scientific knowledge in order to achieve the best outcome. Publication and implementation of clinical practice guidelines seek to decrease unwarranted variability in care resulting in improved outcomes. A practical example of the latter is the 2002 American College of Critical Care Medicine guidelines for hemodynamic support of pediatric and neonatal patients in septic shock. Studies have provided evidence that these guidelines are useful and effective, though evidence that clinical guidelines are often violated [26,27] indicates that promoting their use will remain an additional challenge.

Patient-centeredness describes the provision of care in a manner that is respectful of and responsive to individual patient preferences, needs, and values. In the PICU, many children may be unable to express their desires. Therefore, the experience of their parents is recognized as being fundamental to defining this aspect of quality. Applying this perspective, the principle of family-centered care mandates incorporation of parents in daily aspects of care. Measuring patient and family satisfaction may be invaluable to improving this aspect of PICU quality. One strategy shown to have a positive impact on satisfaction is the presence and involvement of parents on rounds.[28]

Timeliness, the fourth domain of health care quality, involves the reduction of waiting and potentially harmful delays for both those who give and receive care. The PICU provides multiple opportunities for improvement in this domain including but not limited to the timely administration of antibiotics, timely and goal-directed fluid resuscitation, and timely communication of significant radiology and critical laboratory findings.

Efficiency in the PICU could be measured by the ability to achieve adequate outcomes while keeping resource utilization appropriate, thus minimizing cost. Length of stay (LOS) is a common meaure of resource utilization in the PICU, and reduction is one potential method of reducing cost and improving efficiency. In adult ICUs, consistent identification of daily rounding goals during multidisciplinary patient care rounds leads to reduced LOS with improved staff understanding of what is needed to perform care.[29] It is important to note that improvement efforts targeted solely at efficiency may have unintended but foreseeable adverse effects on safety and satisfaction. This could be seen if efforts to reduce LOS lead to premature discharge with subsequent readmission. Thus, improvement efforts may need to view how they influence all six of the domains.

The final domain of quality is equity. Essentially, the quality of care provided in the PICU should be independent of characteristics such as gender, ethnicity, geographic location, and socioeconomic status.[30] Studies have documented disparities in the allocation of resources to critically ill adults related to race and insurance status.[31] In one multicenter study of three PICUs, the authors concluded that risk-adjusted mortality and resource utilization for critically ill children did not differ according to race, gender, or insurance status. However, uninsured children had significantly greater physiologic derangement at time of PICU admission.[32] More research into the issue of equity in pediatric critical care may be necessary before the community concludes there is no room for improvement. Even if admission criteria are free of inequity, are there comparable resources available for effective long-term care?

A discussion of the definition of quality should include potential shifts in thinking. Of note, there is literature suggesting that beyond quality, the issue of value is important to health care. In this context, value is defined as a measure of quality per unit cost.[33] This can be illustrated by considering what automobile the reader drives. Whether an entry-level compact car or a "loaded" luxury vehicle, for each consumer there is some determination of both the quality of the vehicle and whether that quality is worth the cost. Although robust measures of quality and true costs remain elusive in health care, critical care providers could improve value to patients by improving quality, reducing cost, or both.

Quality Improvement Methods

QI seeks to improve the quality of care. To improve care, you must first define the process of care that needs improvement. Ideally, a goal is set to define what is desired in terms of the outputs of the process. Then data are obtained to understand the process, and finally interventions are made with follow-up measurement to assess the change, positive or negative.[34]

Several important components are included in the last paragraph. First, you must define and understand a specific process or system. This is critical to making improvement feasible. For example, a hospital may identify that its LOS for patients with diabetic ketoacidosis is prolonged compared with peer organizations. However, efforts to improve all the elements involved in the hospital course simultaneously likely will fail because of the magnitude of the efforts. Instead, by identifying the components included in the hospitalization and contributing to the LOS, it may be possible to focus on manageable segments of the care process and make incremental change.

A second important concept is understanding variation in the data and the value of data over time (see the section on variation and display of data over time). As data are understood, goals can be set and interventions made. Continuing data acquisition allow assessment of the impact of the interventions. The establishment of goals provides a target for interventions and a context for measurement of data. To paraphrase a QI cliche, changing a process through an intervention is not the same as improving a process. Instead, measurement of data and comparison to set goals allow for assessment of improvement.

Ideally, these changes and reevaluations are done in an iterative manner. This method has been labeled as the "PDSA (Plan, Do, Study, Act) Cycle."[34] The Institute for Healthcare Improvement (www.IHI.org) has advocated use of a PDSA method over a short period to create what it calls "rapid cycle improvement." With either model, changes often are introduced quickly and sometimes multiple changes are introduced simultaneously. This method has evoked pushback from some physicians because of an apparent lack of scientific and statistical rigor. From a QI standpoint, many improvements are achieved without the need for meeting a given P value. Ironically, the resistance to QI methodology because of lack of statistical rigor is inconsistent with much clinical practice in the PICU. There does not exist a standard of care that every intervention performed in resuscitating a patient be accompanied by evaluation for statistical significance. In fact, resuscitations may involve multiple interventions

(endotracheal intubation, chest compressions, administration of medications) in a rapidly sequential or simultaneous manner. With a successful resuscitation, an intensivist may be unable to identify which of numerous interventions was responsible for the improvement. Arguably, if improvement occurred, neither the patient nor the family necessarily cares which intervention resulted in the positive change. Such is the QI mindset. If a given intervention can be identified and causation established for a specific improvement, this information may be applied to different settings. However, the goal is improvement, and improvement without clear identification of the causative factor remains an improvement.

Variation and Display of Data over Time

If an intensivist watches a physiologic monitor for any length of time, it is normal to view variability in heart rate and other vital signs. This reflects the dynamic nature of physiologic systems and processes. Similarly, health care processes vary within certain ranges under normal circumstances. Reacting to changes within normal variation may lead to interventions that increase variation rather than reducing it.[35] However, the range within which the variation is occurring may be outside the desired goal. Thus improvement may address the amount of variation associated with an existing system and/or fundamental redesign of the system.

Again, understanding the normal variation in a process is critical. The PICU provides physiologic illustrations of this concept. A patient who is doing reasonably well in the PICU has a normal range of heart rate variability, and loss of heart rate variability has been associated with increased risk of death in certain populations.[36] Similarly, a relatively well patient in the PICU who acutely develops either tachycardia or bradycardia merits evaluation for new or worsened pathology. In this case, the heart rate variation that normally occurs does so within certain parameters. This variation is called common cause variation in the QI literature. When the variation crosses either the upper parameter (tachycardia) or lower parameter (bradycardia), then something is amiss. The same holds true for processes and systems within health care. Variation that crosses certain thresholds or is an abnormal outlier is called special cause variation.

Plotting data over time allows for an understanding of this variation, normal or abnormal, in data. When data points (eg, LOS) are placed on a chart with time (eg, in days) plotted on the ordinate, this is called a run chart. Control charts, or statistical process control charts, also plot data over time. However, control limits are added that help define the limits of normal variation. Control limits, first described by Walter Shewart in the 1920s, are calculated in a variety of statistical manners, in part depending on the type of control chart. The type and distribution of data determine the choice of control charts[37]; methods for choosing a control chart are beyond the scope of this chapter. At the most basic limit, control levels are set at three times the standard deviation of the data, around the line of central tendency.

In general, when data exist within the control limits, a process is said to be in control. Data that either extend beyond the control limits or demonstrate one of several patterns suggest either an unstable process or a process that is responding to a change. This change may be an intentional effort to alter a process or may represent the effect of an unknown cause. Returning to the heart rate analogy, a patient who becomes bradycardic from hypoxia would demonstrate deviation of the normal heart rate variation in response to the special cause (hypoxia). Correction of the hypoxia ideally returns the heart rate (process) to its normal range of variation. An example of a control chart is displayed in Figure 7-1. Another example of process variation over time in the PICU is rates of CA-BSIs. For years, CA-BSIs were viewed as an unpreventable cost of PICU and adult ICU care. However, the systematic introduction of central line insertion bundles has resulted in transformative improvement in rates of CA-BSIs. With the addition of central line maintenance bundles, ICUs have reached sustained CA-BSI rates of zero. Analagous to the rate of codes outside an ICU with the introduction of a rapid respose team (see Figure 7-1), plots of CA-BSI rates over time in control charts similarly allow intensivists to understand the relationship between improvement efforts and infection rates.

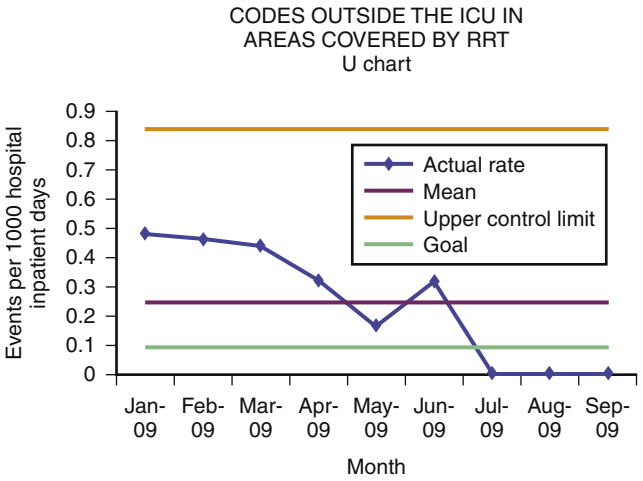

Figure 7–1. Control chart demonstrating codes outside the pediatric intensive care unit in areas covered by a rapid response team.

Other Quality Improvement Tools

Interested readers are directed to one of the numerous QI primers available for a thorough discussion of tools used in QI. However, several of these tools bear at least some mention. A Pareto chart is simply a histogram used to identify the major contributors to a problem or variation. For example, if PICU LOS is of concern, it may be beneficial to identify which, if any, diagnosis categories contribute to the prolonged LOS. By plotting LOS in days on the abscissa against diagnosis on the ordinate, those diagnoses that contribute to the greatest portion of the length of hospitalization might be identified.

Root cause analysis (RCA) is another tool used to attempt to identify the root cause for an event or problem. In its simplest form, RCA is performed by asking the question "why?" five times. Often used in conjunction with a cause-and-effect or Ishikawa diagram, the process of root cause investigation seeks to identify what caused a failure in a process (safety related or quality related) by defining the contributing factors (Figure 7-2). From each of the five categorical branches, smaller branches are added that answer the question "why?,"

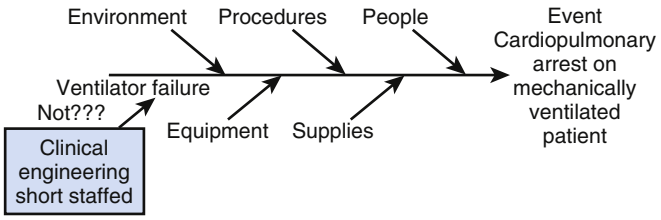

Figure 7–2. Sample cause-and-effect diagram with partial completion to demonstrate structure.

and in turn the same question of "why?" is asked again. The resultant diagram often is described as a fishbone, explaining the third name for this diagram: a fishbone diagram.

By asking the question "why?" repeatedly, the belief is that the root cause of a problem can be identified. This leads to three limitations of RCA. First, there is great danger of introducing hindsight bias. The investigators' beliefs of what happened may lead them to identify only those things on the cause-and-effect diagram.[38,39] A second, related limitation is that RCAs may restrict problem solving and brainstorming to only those factors that are known. Because you only know what you know and, similarly, you don't know what you don't know, there is the potential for missing important factors.[40] Finally, the most important limitation of RCA as a tool is the suggestion that there is a single root cause. This is a dangerous belief. Usually there are multiple causes of events. To limit thinking to one or two causes oversimplifies the situation and may preclude meaningful improvement. Use of RCA should be tempered with the knowledge of these limitations and the potential for drawing incorrect conclusions.

Fundamentals of Patient Safety

Patient safety is the freedom from preventable injury, an adaptation of the definition used by the Institute of Medicine.[3] For the sake of completeness, we offer two accepted defintions of error. The first definition of error draws from the work of James Reason,[39] who defines human error as consisting of two possible types of failure. First is an error of execution, in which a correct plan of action is not carried out correctly. An example is ordering intravenous morphine for a patient in pain, with the patient inadvertently receiving a tenfold overdose. A second failure is an error of planning. In this case, the action taken is incorrect. An example might be treating a patient with respiratory distress with beta-agonists when he or she has a pneumothorax. The execution of the action would have been correct, had the patient's problem been reactive airway disease.

The second definition of medical error considers an error any overuse, misuse, or underuse of medical care. In this setting, overusing radiographic imaging such as head computed tomography for every seizure in a known seizure patient, misuse of analgesics when sedatives are indicated, and underutilization of immunizations all are considered medical errors.

In addition to errors, there are adverse events. An adverse event is an undesired outcome of medical care. Adverse events, by definition, are unwanted. However, they are not necessarily the result of an error. Idiosyncratic drug reactions are an example of an undesirable event that is both unpredictable and unpreventable.

Errors, Injuries, Systems, and Risks

A central goal of all health care is to provide care without causing harm. Unfortunately, the identified harm in health care is often incorrectly attributed to a problem with errors, instead of understanding that both errors and harm are the result of poorly designed systems of care that either promote errors or allow harm to occur in the face of errors. This is manifested through such statements as: "We wouldn't have this safety problem if we could stop people from making so many errors." This, in turn, suggests that to achieve safety, we simply need to urge people to follow policies and be careful. However, people make errors; as long as there are people in PICUs, there will be errors. To that end, there are numerous safety improvement efforts that focus on people that can be seen by the following "solutions:" warning labels, signs and posters exhorting staff to "be careful" and to "do this" or "do not do that," repeated educational campaigns, and reliance on policies and procedures. None of these activities is bad per se, and in fact, they can be part of an effective safety effort. However, they are not sufficient to provide safety. In each of those "solutions," the goal is to error-proof the people, despite the inherent property of people to err. No amount of rules, education, or warnings will prevent errors from occurring.

In contrast, the science of Human Factors Engineering (HFE) supports the belief that efforts to improve patient safety that depend on requiring people to be infallible are misguided, wasteful, and potentially harmful. The previous section on systems thinking clearly identified patient safety and quality as emergent properties of systems. Not suprisingly, there is research that demonstrates that errors often are caused by poorly designed systems or "design-induced" errors.[41] Therefore, if an error occurs, one should not ask "why did the person make the mistake" but rather "what caused the mistake to occur?"

A clinical example that is relevant to PICU care is the restriction of the availability of high-risk medications. Sources of medication errors include the storage of look-alike vials or medications of the same name but differing concentrations in the same area for use in the PICU. An incorrect look-alike medication can be given in error, potentially resulting in harm. A safety program focused on "people" would solve this problem through educating staff to pay more attention to look-alike vials and to make the labels on the medications appear more distinct. In contrast, an HFE or system-based approach would involve removing the high-risk medications to another area, making it impossible to confuse medications or concentrations. In others words, by redesigning the systems for medication storage and access, the opportunity for error (and harm) decreases or even ceases. Central to this solution is the characteristic of using system redesign to reduce the risk of errors and harm. Consistent with epidemiological and public health models that attempt to identify, understand and reduce risk factors for disease or injury, the risk-reduction approach described here is a standard HFE and safety science approach.[42-44]

Improvement in the Pediatric Intensive Care Unit

The thought of improving safety in the PICU is daunting. The number and complexity of care processes seem overwhelming, and it is reasonable to wonder how to even begin. Building on the concepts of systems and risk reduction, a simple approach

to improving patient safety in the PICU involves three steps: risk identification, risk analysis, and risk reduction.[45]

The process of risk identification is relelatively straightforward. Drawing on reported events, chart reviews, concerns identified by staff, patients, and families, as well as issues identified in other units in a hospital, one can compile a list of potential risks that may be relevant to the patients cared for in the PICU. Of note, both errors and injuries inform the identification of risks. However, rather than focusing exclusively on trying to reconstruct prior events, the idea is to use past events to guide proactive improvement efforts to prevent future risks.

As the list of identified potential risks is generated, the next step is to systematically analyze the risks. This analysis involves three major steps. First, ask: "Is our PICU at risk for this happening?" If the identified risk was related to a published report of ECMO pump failure and ECMO is not performed in your PICU, then you can safely conclude that this risk does not apply. In contrast, if your PICU does perform ECMO, then the second step involves gathering more information to inform the risk assessment. This step might involve understanding what brand or type of pump was failing and whether this pump is in your center. Finally, after all available data are gathered (or perhaps new data are collected), the final step in risk analysis is to provide clinical interpretation by clinical experts familiar with the process. In the case of the ECMO pump scenario, a group of surgeons, intensivists, nurses, and perfusionists would weigh available data to determine the extent of risk for their PICU population.

The last step of improving safety would be performing risk reduction, which would involve pulling together a team to brainstorm improvements and the potential unintended consequences of each potential improvement. The latter portion of this step is critical. A simple but potentially hazardous solution to the ECMO scenario would be electing to cease all new ECMO support. Although this solution would surely prevent adverse events from ECMO pump failure, it might also result in preventable harm to patients who could be saved by ECMO. Similar to the step of risk analysis, risk reduction requires people knowledgeable about the processes to help guide improvements and prevent introducing unintended new risks.

Understandably, not every risk identified in the PICU is amenable to reduction by the PICU team alone. For risks that cross multiple units or may require significant resource investment, the identified and analyzed risks should be communicated to hospital leaders who then can weigh these risks with all others identified in the organization. However, this proactive and evidence-based approach can provide a standard framework for safety improvement. Additionally, this risk-based safety improvement approach lends itself readily to risk-based safety metrics.

Culture

As attention is shifted from individuals to systems, inevitably the issue of accountability is raised. Commonly expressed concerns center on whether focusing on systems rather than individuals somehow absolves health care providers from responsibility. In part, this concern arises from a well-intended (but misguided) effort to move from a punitive culture in health care to a "blame-free" environment. The intention was not to create systems deplete of individual accountability, but to avoid blaming individuals for situations beyond their control or that resulted from human error to which anyone would be vulnerable.

One solution that represents a system focus has been described as a "just culture."[46] Under this model, systems problems and human error are considered. The model promotes efforts to learn from errors without punishing individuals involved. Systems problems that create situations in which individuals are "set up" to make errors also are treated as learning opportunities. When individuals violate policies, often because of "normalization of deviance," the response again is not punitive but instead focused on making it easier to do the right thing. In the PICU, this can be seen when workload constraints make performing required double checks on pump programming unrealistic. The failure to perform double checks may occur daily by many staff members without event, and no action is taken to stop the behavior. When a neglected double check leads to an error or harm, the traditional mindset is to punish the involved parties, despite a systematic acceptance of this behavior. In a just culture model, rather than punish the individual, efforts are made to again make it easier or more desirable to "do the right thing."

Systems thinking and a just culture are consistent with punishment. This may occur in the face of willful or reckless behaviors that place patients at risk. A physician who provides patient care while intoxicated is an example of reckless behavior that would be unacceptable in a just culture. When behaviors show a pattern of violations that individually may not represent reckless behavior but collectively demonstrate a high-risk pattern, the just culture model proposes two considerations.[46] First, the person may work in a high-risk situation where such patterns are inevitable. Alternatively, the person involved may have individual characteristics, such as marital stress or deteriorating physical abilities, which would require removing the person from that situation in a nonpunitive manner. It should be noted that, on rare occasions, individuals may be viewed as "out of control" because of mental health problems, substance abuse, or even patterns of behavior. As mentioned previously, a just culture would require prompt intervention to help or remove these individuals to prevent harm to patients and other providers.

Teams and Teamwork

The need for improved teamwork is a recurring theme in patient safety. This is certainly true in the PICU environment. However, there are important differences in how critical care physicians and nurses perceive what is meant by teamwork and how well their team performs.[47] One conclusion by the authors is that these differences might be due to training, gender, or role-related culture. Another potential explanation may be poor understanding of the sciences of teams and team performance.[48-53]

In PICUs, there is a variety of teams. There is the patient's care team comprising the nurses, respiratory therapists, pharmacists, attending physicians, and perhaps trainees such as residents and fellows. There are also the within-discipline clinical teams, such as the nursing or physician team that cares for a given patient over shifts, days, and weeks. A nurse and his or her nursing assistant might also be a team, as might all of the nurses on a given shift in a given ICU. However, despite that fact that we might call each of these "teams," that does not mean that they identify themselves or perform as teams.

Teams are "two or more individuals with specialized roles and responsibilities who must interact dynamically and interdependently and are organized hierarchically to achieve common goals and objectives."[54] But more than that, according to HFE evidence, high-performing teams are those that have been trained to have, and have demonstrated proficiency in, specialized knowledge, skills, and attitudes that support teamwork.[55] For example, in high-performing teams, all team members have the following knowledge: they share the same mental model of what needs to get done, they all know the team mission, and they all know each others' roles and expectations. Similarly, in high-performing teams all team members have been trained and have demonstrated proficiency in the following skills: back-up behavior, team leadership, conflict resolution, and closed-loop communication, among others. However, few health care organizations train their staff to have that knowledge or those skills. Until that happens, HFE research suggests that there will not be high-functioning teams in health care (including PICUs).[56]

Technology

PICUs are full of technology. Not surprisingly, there is a perception that additional technologies may enhance safety. Specific technologies attributed with improving safety include electronic health records, clinical decision support, computer provider order entry (CPOE), bar-coded medication administration, and "smart" infusion pumps. These technologies have been linked to reduction in errors, even though little evidence exists that they reduce harm to patients. There is also evidence that these technologies can introduce new types of errors, violations, and harm.[57-62]

That technologies intended to improve safety may create added errors, rule violations, and risks may seem counterintuitive. However, the systems model described previously helps explain this seeming paradox. For instance, CPOE does not exist in a vacuum within the ICU. Instead, people (physicians, nurses, pharmacists) must use the CPOE system to perform tasks (ordering, modifying, and managing medications) within a busy and often distracting ICU environment. Independent of whether the CPOE system works as intended, the interactions between technology and people, tasks and environment, not to mention how the technology was implemented and supported, will ultimately determine whether the CPOE improves or sometimes worsens medication safety.[63] Health information technologies intended to improve safety may have usability problems[64-70] that increase the likelihood of user errors, provide misleading feedback, lead to high rates of false alarms, or difficulties interpreting data. Examples of usability problems include CPOE systems that preselect a patient, increasing the likelihood of entering orders on the incorrect patient, as well as defibrillators that have unclear displays resulting in failed attempts to cardiovert a patient. If such usability problems exist, it can lead to the previously mentioned "design-induced" errors.[41]

As with team training, there is a rich body of non-health care literature and a growing body of health care-specific literature that can guide the design, selection, and implementation of technologies to yield the best results.[63,70-74] Without leveraging this knowledge, PICU providers risk the unintended but foreseeable consequences of suboptimal technology adoption and potential harm to their patients.

Patient Safety in the Pediatric Intensive Care Unit: Past, Present, and Future

The body of health care safety science has grown dramatically since the last edition of this text.

Now, patient safety is the subject of its own textbooks, with numerous national and international meetings devoted to expanding knowledge and improving solutions (Table 7-2). With this in mind, it is impossible to provide a complete discussion of all topics for the PICU audience. It is important to know that there are many important topics worthy of additional consideration. These include fatigue and performance in the PICU, the potential for simulation, and the importance of leadership and culture of safety in the PICU.

There is an evolution in the approach to patient safety within a clinical environment, including the PICU. The most basic approach that still exists in health care is one of denial (ie the belief that a PICU has no safety issues). However, in the absence of concrete evidence that harm such as CA-BSIs or decubitus ulcers do not occur in that unit, this approach resembles that of the flat Earth society: unfounded disbelief.

Beyond denial is the reactive approach, characterized by error counting, blame finding, and people-based "solutions." Unfortunately, this approach may be well intended but harmful because of the impact on care providers and the culture of safety. Next is a proactive approach in which PICU teams seek to identify, understand, and reduce risks in their environment. However, nothing about this approach assures that variation will not undermine safety improvement efforts.

The desire to eliminate unwanted and harmful variation is central to the standardization-based approach to safety. In

Table 7–2 Sampling of Major Patient Safety Meetings and References

Meeting or Text Title	Annotation
National Patient Safety Foundation Annual Patient Safety Congress	Annual national conference focused on patient safety improvement
Agency for Research and Quality Annual Conference	Annual national conference focused on the science of patient safety
Institute for Healthcare Improvement's Annual National Forum on Quality Improvement in Health Care	Annual national meeting focused on quality with some emphasis on safety
National Initiative for Child Healthcare Quality's Annual Forum on Improving Children's Healthcare and Childhood Obesity Congress	Annual national meeting focused on pediatric quality with limited emphasis on safety
To Err is Human: Building a Safer Health System	Seminal publication addressing the patient safety problem in the United States
Handbook of Human Factors and Ergonomics in Health Care and Patient Safety	Authoratative text providing the "basic science" of patient safety
Internal Bleeding: The Truth Behind America's Terrifying Epidemic of Medical Mistakes	Despite sensational title, an excellent introduction to patient safety issues

these aspiring "high reliability organizations," there is a focus on standardization of processes in the care environment. For processes such as preparing and dispensing a medication, handoff communications, or placing a central venous line, standardization will reduce unwanted variation and potentially reduce waste while improving quality and safety. At the same time, the practice of standardization can be overused. Standardizing the ordering, dispensing, and administration processes of aminoglycosides in septic PICU patients would be beneficial; standardizing to a single dose of aminoglycosides regardless of patient age, weight, or renal function would be potentially dangerous.

If standardization of a process will support the needs of ICU providers in all or nearly all cases, HFE supports its use, allowing exceptions for the few cases where a standard process does not apply. If, on the other hand, standardization will only support the needs of the providers some of the time, then standardization may be problematic. After all, if a standardized process does not fit many typical situations, then standardizing will simply create more "violators."

The potential goal of safety programs both in and out of the PICU is resilience. "Resilience is the ability of systems to mount a robust response to unforeseen, unpredicted, and unexpected demands and to resume or even continue normal operations."[75] Any PICU faced with a mass casualty or even simultaneous cardiac arrests in patients understands the challenge of unanticipated demands on the system of care delivery. What is less clear is whether the PICU team can rise to meet these demands while still providing care to the other patients in the PICU. Safety science has revealed that it is the people in the complex systems that provide resilience[76,77] or the ability of the system to function safely despite the inherent complexity and the risks. Thus, when PICUs are provided resources and designed such that they can meet these demands while providing care to the other patients and assure safe and high-quality outcomes, then the goal of resilience is met.

Conclusions

The issues of patient safety and quality have proven themselves to be more than a fad. Continued and better recognized harm to patients is drawing greater attention from patients, their families, payers, regulatory bodies, and a growing number of health care professionals. As is true with any complex system, there are no easy answers to improvement, and those improvements targeted at "fixing people" are destined to fail. Instead, by learning and applying quality and safety science, there is the opportunity to enhance the historically good outcomes achieved in the PICU.

References are available online at http://www.expertconsult.com.

Chapter 8

Information Technology in Critical Care

Steven Pon, Barry Markovitz, Carl Weigle, and Brian Jacobs

PEARLS

- Information technology promises many benefits but is not without limitations and pitfalls. Physicians must learn about these technologies to develop realistic expectations, maximize their benefit, ensure patient safety, and avoid potentially catastrophic perils.
- In most institutions, administrators and nurses drive the advancement of various information technologies. Physicians, especially intensivists, must become involved in the selection and development of these technologies if their needs and concerns are to be adequately addressed.
- Organizations must ensure the security and confidentiality of personally identifiable protected health information. They must understand the legislated privacy rules and safeguard the security and confidentiality of patient data.
- All computer users should understand the threats to security and privacy for themselves, their computer, and their network. Users should make informed decisions about the measures required to safeguard security and privacy that are commensurate with the task at hand.

By one analysis, medicine is an information service. Its practitioners tirelessly gather and assimilate information while sometimes adding to the collective body of knowledge. Clinical information is meticulously compiled and interpreted for each patient, the disorders that afflict them, and the therapies to treat them. Efforts to automate medicine do not place patients on conveyor belts to be serially and automatically poked and prodded. Automation efforts are directed at managing the flow of information. Medical information is wielded to protect life and to shepherd death. Compassion, judgment, and technical skill may distinguish excellence in the discipline, but information defines medicine.

The volume of medical information, expanding at fantastic rates, threatens to drown even the most conscientious practitioner who devotes every waking hour of every day to collecting, cataloguing, and assimilating it. Advances in information technology (IT) can both fuel the information explosion and contain it. Computers connected to one another and to large data repositories give practitioners immediate access to vast knowledge and data while streamlining the tedious chores of searching and collating that information. IT has changed the way we practice.

Demonstrations of the potential of IT typically inspire awe and admiration. However, when the technology migrates from demonstration to actual use, awe and admiration sometimes give way to disappointment and disgust. The novel features that users think they need are either impossible to achieve or require significant reengineering of the original product. The lure of the idealized technology suffers from its real limitations. Knowing the limitations helps users to avoid falling victim to them. This understanding can help the clinician focus on what can be accomplished readily while awaiting "the next upgrade."

The Electronic Health Record

The computer-based patient record (CPR) or electronic health record (EHR) is defined as a comprehensive database of personal, health-related information that is accessed and updated across a health care network.[1] Its potential and real benefits include the following:

- Improved quality of care through more timely, more complete, and better organized information delivery to the health care provider, with decision support and clinical pathways
- Cost savings through elimination of duplicate testing, shorter lengths of stay, and more efficient data collection and review
- Higher productivity by structuring patient care tasks to improve continuity of care and reduce practice variation by facilitating the creation of more consistent and more comprehensive content, and by making the medical records more readily accessible to more users simultaneously
- Facilitate research, education, quality improvement, outcomes assessment, and strategic planning.

The three principal functions of such a database, like any database, are data acquisition, data access, and data storage.

Data Acquisition

The complete EHR acquires data from a variety of sources, including hospital registration, nursing and physician input, laboratory services, radiology and other test interpretations,

therapist and nutrition services, monitoring devices, and physicians' orders. The most important system that feeds the database is the "enterprise-wide master patient index," which ensures that each patient is identified properly and uniquely. All other systems must have the correct identifier in order to deliver their data to the correct patient record. A multimedia database can include images such as radiographs, electrocardiograms, fetal monitoring, sonography, magnetic resonance images, computerized tomograms, and even paper-based documents such as consent forms, questionnaires, and, sometimes, handwritten notes and hand-drawn diagrams. Data acquisition is organized in a manner that minimizes duplicative effort and maximizes data consistency.[2]

One of the significant challenges to any implementation of an EHR is engineering the various interfaces between it and the host of systems that feed it data. Some of the feeder systems, such as laboratory services, have their own established validation protocols that are applied before transmission to the EHR.

Data originating from bedside devices such as cardiopulmonary monitors, pulse oximeters, ventilators, and intravenous infusion pumps represent critical elements of the patient care record. Manual capture and entry of these data into the EHR by nurses and other healthcare practitioners is associated with inefficiency and transcription errors. Technology is currently available to connect devices to the EHR through bedside medical device interfaces (BMDI). BMDI allows properly formatted data from a medical device to flow into and update the patient's EHR. One of the challenges in BMDI relates to the diversity of medical devices and EHRs, which makes it impractical for most vendors to directly connect. Often, biomedical device integration systems are required to extract, read, interpret, and forward data to the EHR in order for it to be useful. Basic physiologic data including heart rate, blood pressure, and respiratory rate are generally the first to be targeted for EHR integration. Other types of monitoring data that can be integrated with the EHR include temperature, pulse oximetry, end-tidal CO_2, and cardiac output measurements. Other types of devices that can be utilized for BMDI connectivity include intravenous infusion pumps, ventilators, dialysis, hemofiltration systems, cerebral oxygenation monitors, and extracorporeal membrane oxygenation systems.

One of the clear benefits associated with BMDI is the improved efficiency associated with not having to manually retrieve and record the data. The increased efficiency therefore allows the nurse to spend more time at the patient's bedside or in other important activities. Though this time saving is minimal for any one piece of patient data, when the aggregated data for each patient and for the entire facility is considered, the opportunity for cost saving likely exceeds the cost of the initial investment. Another potential benefit concerns the completeness and accuracy of the data in the EHR. BMDI increases data-sampling frequency possibilities, which is particularly important in a dynamic patient situation where data may be changing rapidly. Caretakers may request higher data sampling frequencies without impacting the need for additional patient care resources. In addition, reading and manually recording data into an EHR is often associated with transcription errors. BMDI reduces the likelihood of these transcription errors.

Considering that a data element passes from one of several feeder systems through different computers, with possible transformations of that data element along the way, and considering the possibilities of lost transmissions, computer down-times, and network interruptions, consistent error-free data feeding would seem a virtual miracle. In a high-volume environment, a centralized interface engine that routes and converts transaction messages from disparate feeder systems can solve many of the interface issues efficiently and in a timely fashion.

The capture of textual information, such as progress notes, nursing assessments, or even radiology reports, presents particular challenges for several reasons. For the most part, text is entered via a keyboard, but alternatives include voice recognition, handwriting recognition, or handheld and wireless devices. Many other technologies have failed in practice to date. Semiautomated text entry with menu systems feeding structured and unstructured forms have met with some success. Although these solutions do not have the same expressivity of free text, they lend themselves to the capture of text as data. Collecting data better allows for future analysis, but despite this significant advantage over collecting bland text, it tends to be rigid, can make documenting the unusual impossible, generally requires more time to collect, and may be a significant source of frustration for the clinician. An as-yet-untested strategy is to allow free text entries but to apply natural language processing to extract data from it for analysis. The decision to pursue data rather than text requires an institutional commitment to the philosophy that data are more valuable and are worth the difficulties they can present.

Data Access

The computerized patient record serves as the focal point for most health care professionals. It might be accessed at inpatient sites, but also in emergency departments, nursing facilities, continuing care centers, physician offices, clinics, laboratory facilities, treatment centers, and, in the case of home health services, the patient's home. An ideal computerized patient record should be available when and where it is needed. However, databases with sensitive information must be controlled to prevent unauthorized use or alteration. These systems must satisfy five requirements:

1. Access control: Only authorized persons are allowed access for authorized uses.
2. Authentication: Some confirmation that a person granted access is, in fact, who he or she purports to be.
3. Confidentiality: No unauthorized disclosure of information is allowed.
4. Integrity: Information content is unalterable except under authorized circumstances.
5. Attribution/nonrepudiation: Actions taken (access, data entry, and data modification) are reliably traceable.

The interface through which most health care providers interact with the EHR should be user-friendly and intuitive. Most clinicians have little time or patience to sit through tedious training sessions, and, once trained, few clinicians will recall more than a minimum required to complete their immediate, routine tasks.

The system should be capable of providing a full, seamless view of the patient over time and across points of care. Views should be configurable so that a given user's information needs and workflow can be accommodated. Both detailed and summary views that juxtapose relevant data allow the clinician

to acquire the information required to optimize expedient decision making. Displays should be configured to highlight key information while suppressing clutter but making all pertinent data readily accessible. Dynamic linkages should exist between the computerized patient record and supporting functions such as expert systems, clinical pathways, protocols, policies, reference material, and the medical literature.

Response times must be sufficiently speedy and workstations should be conveniently accessible to the point of care. Mobile connections are a bonus. Access to patient data via wireless connections with portable devices is an attractive alternative for users but must overcome usability and security hurdles before it can be fully implemented (see section on Security & Privacy: Wireless Networks).

The patient database also supports many areas of research, education, decision support, and external reporting. Thus, data in aggregate can be accessed by administration, finance, quality assurance, and research areas.

Data Storage

The multimedia data of the comprehensive EHR are stored on media that allow for long-term storage while allowing searches and rapid retrieval of enormous volumes of data. The database must be updated in a way that ensures that it is current, complete, and consistent. Data, once entered, should be modifiable only in accordance with strict rules that assure data integrity.

The architecture of the database can be centralized or distributed, replicated or not. A centralized database is stored at a single site, whereas a distributed database is a single logical database with segments that are spread across multiple locations connected by a network. A replicated database has the advantage over a nonreplicated database by having at least one copy of all records in case the primary copy is inaccessible because of computer or network failure. The challenge of replication is maintaining consistency among all the copies, requiring timely, automatic synchronization of the original database and its replicas.

Even replicated databases must be backed up periodically to ensure against data loss. It is essential for an EHR to have a strategy for doing so as seamlessly as possible and for establishing a clear and workable recovery.

Once stored, the data should have a time stamp. Although the data can be modified, both the original and the revised versions should be maintained with appropriate time stamping. Appropriate safeguards must ensure database integrity so that its pieces do not lose their links and that the data are not subject to unauthorized modification. Supplanting the paper record with the EHR as the official medical record requires thoughtful consideration of the limitations of paper copies to reflect accurately the electronic record. Sanctioned hard copies of the patient record will be necessary for sharing with other health care institutions or with the legal system.

Whereas a clinical data repository is a database optimized to retrieve data on individual patients, a data warehouse is a database designed to support data analysis across individuals. This function can be distinguished from a simple archival function. The warehouse structure is designed to support a variety of analyses, including elaborate queries on large amounts of data. The data are generally static and updated intermittently in batches rather than continuously.

Hospitals can use data warehouses to perform financial analyses or quality assessments. With decision support tools, they can be useful in negotiating managed care contracts or distributing resources to clinical or ancillary services. Subsets of a data warehouse that are structured to support a single department or function are "data marts." These subsets are designed to perform periodic analyses or to produce standard reports run repeatedly, such as monthly financial statements or quality measures. Online analytical processing (OLAP) is decision support on databases that are partially digested for analysis and thus are more rapidly accessed. In finance and administration, they can assist in strategic planning by predicting the impact of decisions before they are made. In medicine, it can take the form of a clinical database to support evidence-based decisions. Data mining applications can sift through mountains of data in the warehouse and run complex algorithms to find obscure patterns. However, as with any database, the questions must be defined as precisely as possible and the database designed accordingly if meaningful results are to be expected.

Clinical Decision Support

Decision support systems are an integrated set of programs and databases that provide users with the ability to interrogate those databases and analyze information, retrieving data from external sources, if necessary, to assist in decision making.[3]

Most medical decision support systems are designed to improve the process and the outcome of clinical decision making. They can yield most of the benefit of clinical information systems; for example, they can shorten inpatient length of stay, decrease adverse drug interactions, improve the consistency and content of medical records, improve continuity of care and follow-up, and reduce practice variation.

Retrospective decision support tools can be applied to aggregate patient data to find historical patterns. Real-time decision support systems can be passive or active. Passive systems are activated when clinicians request help. Such assistance can come as reference material, automated calculations, or data review. Active systems include alerts and reminders that are triggered by preprogrammed rules governing specific circumstances. For example, an order for penicillin in a patient who is allergic to it can cause a warning to display.

An effective decision support system must have accurate data, a user-friendly interface, a reliable knowledge base, and a good inferencing mechanism. The knowledge base can include information regarding risks, costs, disease states, clinical and laboratory findings, and clinical guidelines. The inference engine determines how and when to apply the appropriate knowledge while carefully minimizing disruptions of workflow.[4,5]

Patient Safety

Patient safety concerns remain paramount in any hospital system, including clinical information systems.[6,7]

To the extent possible, redundant systems should be in place to minimize the effect of the failure of a single component. Robust down-time contingency plans must be developed should the clinical information systems cease normal function in either planned or unplanned situations. These contingency plans must account for continued data acquisition

and retrieval and provide for mechanisms for communication among health care providers and services. Users should be informed about recovery procedures and what they mean to the clinical database. Do backlogged data generated during the down time ever enter the system? How are they timed? Or is there a gap in the clinical information that the clinicians must fill in for themselves if they want the whole picture?

Many anomalous circumstances related to the EHR can threaten patient safety. Data, such as a laboratory value or a physician order, can be entered into the wrong patient record and prompt the clinician to respond appropriately but on the wrong patient. Similarly, data can be displayed in ways that are so confusing that they are interpreted incorrectly.

Default behaviors of portions of the computerized patient record should be designed carefully, because busy or distracted clinicians may accept the default without understanding what they are accepting or without considering the consequences.

Automated Adverse Event Detection

Children are at significant risk for adverse drug events, and recent studies have begun to describe the frequency and epidemiology of medication errors and adverse events in pediatric inpatients.[8-10] In 2006, The Institute of Medicine released guidelines urging improved surveillance systems to detect adverse events.[11] Traditional methods used to detect adverse events in children included manual chart review and voluntary incident reporting. These detection systems are inefficient and significantly underestimate the number and prevalence of adverse events.[12,13]

Another manual detection strategy relies on trigger methodology where an occurrence, found on manual chart review, triggers further investigation to determine the presence of an adverse event.[11,14] For example, the administration of flumazenil may trigger the detection of benzodiazepine-induced respiratory depression. Automated adverse-event detection relies on the generation of a trigger report from the EHR, which indicates the possibility that an adverse event has occurred requiring further investigation. This methodology has been proven an efficient and cost effective way to detect adverse events.[15-19]

Promises and Limitations

Information technology in the form of an EHR promises improved patient care.[20,21] Potential benefits of information technology include providing rapid access to integrated clinical data and extant medical knowledge, eliminating illegibility, improving communication, and issuing applicable reminders and checks for appropriate medical actions.[22]

A number of studies show that information technology can provide various benefits, including increasing adherence to guidelines (particularly in the outpatient arena) and decreasing some medication errors.[23,24] However, the majority of these studies come from a very small number of institutions with homegrown clinical information systems that were developed by devoted groups of clinicians.[25] Very few studies show that the commercially available systems confer similar benefits, and even if they do, it is unclear that their success can be migrated from one implementation to another.[26-28] In fact, any benefit may be outweighed by new problems introduced by the systems themselves. In effect, one set of problems may be traded for another.[29,30]

Despite considerable progress, the sentiment expressed by G. Octo Barnett in 1966 is often echoed today, "It is frustrating to meet with repeated disappointments when the objectives are superficially so simple."[31] The medical information space is vastly more complicated than it seems at first. EHR software programs are enormously complex, are built by large teams of programmers with input by numerous clinicians, demand high-speed processors and high-bandwidth networks, and rely on often fragile interfaces with other hospital systems. Implementation currently requires tremendous effort by both clinicians and technical specialists to configure these systems according to the specific needs of an institution and in ways that will enhance care rather than impede it. An often unappreciated complicating factor is that the technology does not simply replace paper; it also reengineers care—deliberately or not. (See Unfavorable Alteration of Workflow.)

Errors can and do occur in programming or configuration. Many programming deficiencies can be detected and corrected with thorough testing, preferably in a development environment that does not affect real patients; however, some of these problems will only become apparent under unique circumstances that are presented by patient care. Indefatigable vigilance for these errors is essential.

Numerous other unintended consequences result from implementing an EHR, including the creation of new kinds of errors, an increase in work for clinicians, an untoward alteration of workflow and change in communication patterns, an increase in system demands, a continuation of the persistence of paper use, and the fostering of potential overdependence on the technology.[32-34]

New Kinds of Errors

While some errors can be avoided by using an EHR with computerized physician order entry (CPOE), other errors may be created or propagated.[35,36] Many "new" errors are a result of poorly designed interfaces. For example, clinicians can easily make "juxtaposition errors," intending to select one item but selecting another close to it on a long, dense pick list in a small font. A similar kind of error is mistaking an open chart of one patient to be that belonging to another or picking the wrong patient from a long list of patients.

Interfaces between electronic systems are particularly vulnerable and can cause various new kinds of errors. Patients who have been physically transferred but remain, disembodied, in their previous electronic location may have all of their care suspended pending completion of the electronic transfer. Worse, should electronic transfers be delayed, medications may be delivered to a patient's former room and administered to a different patient admitted to that room. Allergies may be entered in the bedside system, but interface problems can prevent that information from reaching the pharmacy or nutrition systems. Occasionally, laboratory results can be inserted into the wrong medical record because of interface issues.

Rigid interpretation of policies and procedures can be configured into the EHR but may lead to difficulties in clinical practice when dealing with ambiguous circumstances and exceptions. Sometimes the process of care is incompletely understood and codification can be disastrous. Policies at most institutions include automatic stop orders that require rewriting medication orders in a specified time frame. Compliance to this rule can be forced with programming, but

implementing this rule without safeguards could lead to automatic discontinuation of medications and missed doses.

The benefit of legibility in electronically written notes can be outweighed by novel problems. Overuse of copy-paste functions can result in repetitive, monotonous, and loquacious notes punctuated by the sin of propagating erroneous text verbatim. Automatic transcription of data such as laboratory results or vital signs often bypasses cognition, something that does not happen when data are transcribed by hand.

Increased Work for Clinicians

While transcription errors can be eliminated by computerized order entry, it often falls to clinicians to shoulder the added burden of what might otherwise be considered clerical functions. Documentation in a structured format rather than as free text can enhance completeness and facilitate later data retrieval; however, it can also increase work by forcing the clinician to find ways to fit round pegs into square holes. Similarly, rigidly structured order input can force clinicians to waste time trying different ways to order nonstandard tests or therapies—with little guarantee that these orders will actually be executed if they are routed to electronic limbo.

Clinical alerts can help clinicians make decisions, e.g., when penicillin is mistakenly ordered for an allergic patient, but persistent interruptions of work by alerts can increase the workload of the clinician who must decipher their meaning and assess the risk in each specific circumstance. The frequency of these alerts can become intolerable when they are not delivered to the right clinician with the right information and at the right time and place. When these alerts become too frequent and too predictable, clinicians often adapt by "response chaining": dismissing the alerts with rote keystrokes much as a pianist plays a familiar tune. Alerts that evoke this response cannot be effective and may be counterproductive.[37]

Poorly integrated clinical information systems cause clinicians to access many different sources for information to solve a clinical problem, thereby increasing work. Similarly, users should not be required to input the same bit of data in multiple locations in different systems.

Another time-consuming feature of the EHR, and perhaps the most exasperating, is the loss of data, particularly when busy clinicians lose long notes they have just meticulously written. Workstation or interface crashes, network collisions, inopportune time-outs, or system failures of other types can be the culprit. System delays from a wide variety of causes also waste valuable time, as does having to hunt for an available workstation because those installed are insufficient in number or inconveniently placed.

Unfavorable Alteration of Workflow

The introduction of an EHR system significantly alters the sociotechnological milieu. Previously well-functioning medical practices may become entirely dysfunctional. Implementation of an EHR requires modeling of work processes but can sometimes result in ossifying those processes into something too inflexible for efficient and effective patient care.

Patients expected to be emergently admitted to the pediatric intensive care unit (PICU) but still in transit often have medications and urgent therapies ordered and prepared before arrival. A CPOE system may prohibit ordering or dispensing medications for patients who have not yet been admitted. In a paper environment, nurses frequently arrange dosing schedules based on the ordered frequency, the frequency of other ordered medications, and the availability of intravenous access. However, in many CPOE systems, medication orders go direct to the pharmacy and bypass the bedside nurse. Physicians are then saddled with picking the specific times of administration, only to have that schedule revised later by the nurse.

Sometimes, well-defined manual processes can be implemented in more than one way electronically. Without clear delineation of an institutionally sanctioned method, confusion and catastrophe can result. Transferring patients from one unit to another or to the operating room typically requires the discontinuation and reinitiation of all orders, including medications. With implementation of CPOE, clinicians without proper direction could suspend rather than discontinue the old orders. Reactivation of suspended orders could result in duplication and double dosing of medications ordered on transfer.

Redundant orders are sometimes facilitated by CPOE. The gate-keeping function of clerical personnel processing orders for routine radiographs or laboratories is bypassed. Remote access by multiple physicians acting on the same bit of new information can also generate duplicate orders.

Untoward Changes in Communication Patterns

Many care providers blame clinical information systems for unsatisfactory reductions in face-to-face communication. Some users complain that the EHR creates an "illusion of communication,"[38] where users believe that information entered into the system will be somehow communicated to the relevant personnel. This assumption can result in missed or delayed execution of orders or failure to appreciate the recommendations of a consultant. Users may erroneously assume that allergies entered into the system will adequately protect patients from receiving offending food or drugs.

Because of the time-consuming nature of CPOE and because workstations are not always available at the bedside, orders are often written after work rounds. In teaching hospitals, order writing is often delegated to the least experienced individual, such as the first-year resident. Residents may not readily appreciate the nuances of an order until they are confronted with an order screen that demands input he or she had not previously considered. By that time, the other members of the care team have disbanded, and clarification of the order requires tracking down and reconsulting the relevant personnel.

High System Demands and Frequent Changes

No installed EHR can remain static for long. Maintenance, revisions, and upgrades of both software and hardware contribute to constant flux. Consequences should be expected with every change, and many changes require testing that can become onerous. While minor changes can occur without supplemental training of personnel, failure to provide training for some changes can cause significant user frustration and errors. Some configuration changes requested by one group may also adversely affect other users in unexpected ways. Mechanisms must be developed to resolve conflicts of this nature. As clinicians become increasingly dependent on the system, pressure to keep the system operational mounts, requiring around-the-clock technical support. One analogy likened system maintenance to "repairing a jet engine in flight."[38]

Persistence of Paper

Anecdotally, installation of an EHR is associated with an increase in consumption of paper towels: clinicians often jot vital signs and other data on any scrap of paper to be entered into the EHR at a later, more convenient time. While "going paperless" is an often-stated goal, the total elimination of this most versatile recording device is unlikely. An EHR changes the pattern of paper consumption: a higher proportion of pulp is sent to the shredder rather than to medical records. Reports are printed in the process of caring for patients and are often discarded at the end of a shift. Some institutions also regularly print worksheets as backup in the event that the system experiences unscheduled downtime.

A more insidious problem of persisting paper can arise when the patient chart is divided between paper and an electronic version, particularly when one medical service writes notes in one medium and another service uses the other. Splitting physician documentation can result in breakdowns in communication, with serious consequences. Delineation of the exact constituents of the legal medical record is also a necessary exercise, one that must be repeated as the systems change.

Overdependence on Technology

As the EHR becomes more integrated into clinical practice, downtime becomes more onerous on the users. Prolonged failures can even cripple an organization by causing delays, diminishing capacity, and limiting capabilities. Although backup systems can never quite replace the fully functioning system, contingencies for downtime must be developed, and users must be adequately trained to execute these plans efficiently.

Clinical decision-support systems (DSS) can enhance the educational value of interactions with the EHR. They can also increase reliance on the information presented, without providing significant learning, thereby precipitating uncertainty and paralysis of practitioners who encounter situations in which decision support is not available. The danger also exists that clinicians will accept advice rendered by clinical DSS in circumstances when they should not. Furthermore, the clinician who expects to be protected by a system of alerts may be less vigilant than he or she would have been in the absence of alerts and can ultimately be betrayed by an inconsistent system.

Human Factors Engineering

Cognitive science, computer science, and human factors engineering are among many disciplines that can facilitate development of a successful EHR system. Human factors engineering investigates human capabilities and limitations and applies that knowledge in the design of systems, software, environments, training, and personnel management. Application of human factors considerations in developing an EHR, particularly regarding CPOE, can maximize successful design and implementation of these systems. Some human factors principles may seem self-evident but can be overlooked when not approached systematically. Developers must understand the users, undertake detailed task analyses, and assess computer-supported cooperative work—the study of how people work within organizations and how technology affects them and their work. Three principles that may improve clinical information systems are accounting for incentive structures, understanding workflow, and promoting awareness of the activities of other group members. Institutional and personal incentives for using an EHR differ, but only the latter will effectively influence use. Awareness of the roles played by other team members enhances collaboration. Improving collaboration may decrease the incidence of medical errors.[39,40]

Another important area of human factors engineering relates to interface design. Interfaces should be simple and consistent, with important data highlighted, such as the patient name or weight. "Progressive disclosure" means that commonly used and important functions should be presented first and in a logical order, whereas infrequently used functions should be hidden but available. Minimizing "human memory load" can be accomplished by displaying all relevant information together on one screen rather than relying on the user to remember critical bits of data from different parts of the chart. Potential user errors should be anticipated, and easy error recovery should be designed into the system. Error messages should be informative and could include advice about error recovery. Other feedback should be provided to acknowledge user actions, particularly when the system appears frozen. Given the chaotic healthcare environment, the interface should also be designed to forgive interruptions, allowing work to be saved and facilitating task resumption.

User satisfaction is an important predictor of system success. Satisfaction is enhanced when the systems are designed with the users' needs and preferences in mind. Peers who serve as advocates for their groups during development and subsequently teach other users generally increase acceptance of the systems. Ease of use, rapid response times, flexibility and customizability, mobile workstations, implementation of effective decision support tools, access to reference information, and adequate training and support are all important factors in enhancing both user satisfaction and system success.[41]

Continued Promise

The Institute of Medicine, in its report, "Crossing the quality chasm: a new health system for the 21st century,"[2] stated that health care should be safe, effective, patient-centered, timely, efficient, and equitable. The Institute further noted that these goals could be more easily reached through judicious application of IT. Automated order entry systems can improve safety. The use of automated reminders based on clinical practice guidelines, computer-assisted diagnosis or management, and evidence-based medicine (EBM) can improve the effectiveness of medical care. IT can enhance patient-centered care that is respectful of and responsive to patient preferences, needs, and values by recording them and appropriately reminding the health care professional. It can facilitate access to clinical knowledge through web sites and online support groups. Clinical decision-support systems can be used to tailor information and disease management messages based on the patient's individual needs. Timeliness can be improved by e-mail, telemedicine, and direct and immediate access to diagnostic test results and other clinical information. IT can improve efficiency by using clinical decision-support systems to reduce redundant and unnecessary tests and procedures, by improving communication among multiple providers of care to individual patients, and by supplying data for performance and outcome measures. Enhancing equity among patients and across socioeconomic, geographic, race, and ethnic lines can be achieved if IT can improve access to clinicians and clinical

knowledge, although it would depend upon equitable access to the technology infrastructure. IT is playing the starring role in the drive to improve the quality of health care today, and the Institute called for a national commitment to build the information infrastructure to support health care.

Design and Implementation

Implementation of an EHR system requires an investment of additional staff, hardware, software, and an expanded communications infrastructure or network. For large hospital networks, the costs can be exorbitant.[42]

Developing an EHR requires careful planning and phased implementation. The specific needs of the institution must be examined, particularly with regard to the existing technology and practices. The process should be viewed as an opportunity to enhance care, rather than simply to replace the paper, and requires reassessment of existing practices and re-engineering of healthcare delivery. As each incremental phase of implementation is approached, the focus should be on overcoming specific barriers to care rather than on the nebulous goal of "creating a paperless process."[43]

The first phase generally provides a patient-centric repository of clinical test results, including laboratory, radiology, pathology, and other textual data. A subsequent phase can include capture of paper document images, radiology images, and other nontextual data. A key phase is the capture of clinical data at the point of care, including vital signs, intake and output, nursing documentation, and physician notes. Implementation of a physician order-entry system is another key phase that requires careful coordination among services and interdigitating systems.[44-46]

Ensuring that the EHR satisfies every need involves considerable planning, designing, and testing. Even well-designed, off-the-shelf EHR systems can satisfy only 80% of the complex requirements of any multipractitioner organization. The remainder must be either adapted from other content or created from scratch. Substantial "expert" direction from teams of physicians, nurses, other allied healthcare providers, and medical records and financial staff is required to assist in developing the design and implementation of all EHRs.[47] If clinicians abdicate their responsibility in participating in this tedious process, they are virtually ensuring that the resulting system will fail to satisfy their needs. Physician acceptance and participation can be enhanced by acknowledging the importance of physicians in the process, training them early and often, frequently and routinely eliciting their feedback, and demonstrating responsiveness to their needs and concerns.

Clinical information technology specialists generally interpret the requests from clinicians for configuration. A dedicated technical staff must also ensure instantaneous access to, and constant availability of, patient information. As the size and variety of information systems increase, enterprises will find it necessary to implement a "help desk" service.

Health Information Exchange

The electronic exchange of clinical data among applications internally within single organizations has a relatively long and successful history, in contrast with such exchange externally among multiple organizations. Both are essential for the best possible practice of critical care medicine.

Data Exchange Within a Single Health Care Organization

Norman Maclean might have been describing clinical data in the PICU when he wrote: "It is hard to know what to do with all the detail that rises out of a fire. It rises out of a fire as thick as smoke and threatens to blot out everything—some of it is true but doesn't make any difference, some of it is just plain wrong, and some doesn't even exist, except in your mind, as you slowly discover long afterwards. Some of it, though, is true—and makes all the difference."[48] The detail that rises out of critically ill children reaches their physician's mind in part directly through the five senses, as it has for millennia; and in part through a series of transfers and transformations in various computer applications. Done well, those transfers and transformations clear the smoke, reveal the truth, and make a difference.

The initial transformation typically involves transduction of physical information (pressure, temperature, absorption of electromagnetic radiation, etc.) into an analog electrical signal. That transduced signal is then, in a bedside monitor, amplified and converted from analog to digital form. In that form, the information can be displayed as a real-time wave form, or converted to a snapshot or moving average for numeric display, or stored in a series of snapshots for display of trends. These functions are supported and enhanced by a network of monitors, central servers, and displays. Confined by the boundaries of the monitoring network, the information is, by definition, of limited value.

Those limits are lifted when the information moves across an interface into subsequent information systems. In the good old days, that interface was a nurse, who transcribed information from the monitor onto a paper flow sheet the size of a small tablecloth. Now the interface is mostly electronic, and the "tablecloth" is an electronic database allowing a flexible re-display of the information. The electronic interface is possible because monitor vendors and EHR vendors employ a standard method for data exchange in the form of "messages" sent from system to system. That messaging standard has been developed since the late 1980s by the standards development organization named Health Level Seven (HL7).

HL7 messages convey information among a variety of clinical information systems in a typical children's hospital—demographics, laboratory test results, transcribed documents, radiology test results, medication doses, vital signs, and so forth. The number of HL7 message interfaces in a given institution is in inverse relation to the degree of integration of the core EHR, and the degree of end-user adoption of that EHR. An institution with physicians, nurses, and pharmacists using a single integrated EHR for all medication management, documentation, and order entry will need far fewer interfaces than one with a separate system for each function, or with multiple documentation systems.

Data Exchange Among Multiple Health Care Organizations

Compared with the 20 successful years of intraorganizational data exchange, the interorganizational exchange of data has a history more brief, and successes that are less widespread. In the early 1990s, Community Health Information Networks (CHINs) (e.g. the Wisconsin Health Information Network, http://www.whin.net/clinical) had limited local successes in

sharing clinical data using a central repository subscription model. In the 2000s, Regional Health Information Organizations (RHIOs) began to form. By 2009, 57 of 193 identified RHIOs were found to be actively exchanging data.[49]

With the establishment of the Office of the National Coordinator for Health Information Technology (ONC) in 2004, attention was directed to the need for a national health information network (NHIN). The ONC and the importance of health information exchange (HIE) were given a boost by the Health Information Technology for Economic and Clinical Health Act (HITECH Act) of 2009, a part of the American Recovery and Reinvestment Act (ARRA) of 2009. In the HITECH Act, economic stimulus funds for provider organizations were tied to meaningful use of certified health care information technology (HIT). While the specific mechanics of determining "meaningful use" are yet to be finalized, it is clear that HIE will be an essential element.

The importance of HIE to critical care may be found in handoffs in care between organizations (i.e., interfacility transport) and in multicenter patient registries, such as Virtual PICU Systems. In the former case, the HL7 standard Continuity of Care Document (CCD), which is based on the HL7 Clinical Document Architecture (CDA) standard,[50] provides structure that EHR vendors can use to pass patient-specific summary data between disparate EHR systems. In the latter case, the Quality Reporting Document Architecture (QRDA) is an HL7 Draft Standard for Trial Use (DSTU) developed to support the exchange of quality data from clinical rather than administrative systems.[51] For ICUs with fully implemented EHRs, the QRDA offers the promise of automated data uploads for registries and for mandated regulatory reporting, without the need for costly and fallible manual transcription, and without the dubious relevance of administrative data.

Protected Health Information

Ensuring the privacy of personal health information has always been a concern, but the availability of this information in electronic form raises new concerns because securing it is not a simple matter of putting it under lock and key. In legislating the Health Insurance Portability and Accountability Act (HIPAA) to protect health insurance coverage for workers and their families when they change or lose their jobs, Congress also sought to alleviate some of the administrative burdens on health care providers by mandating standards for electronic data interchange (EDI). Because electronic transactions between providers and insurers would become easier, and more personal health information would become available in electronic form, privacy and security rules were incorporated into the legislation. These rules apply specifically to protected health information (PHI), which is any health information that can be linked to an individual (Box 8-1).

The Privacy Rule applies to protected health information whether it is stored in electronic form or not. The Rule limits the nonconsensual use or release of protected health information, gives patients new rights to access their medical records and to know who accessed them, restricts most disclosures of health information to the minimum needed for the intended purpose, establishes penalties for improper use or disclosure, and establishes new requirements for access to records by researchers and others. The impact of HIPAA on research relates to consent paperwork that safeguards the privacy of patients participating in research, simplified guidelines regarding the limited circumstances where patient health information can be used for research purposes without authorization by the research subject, and clarifying methods by which protected patient health information can be de-identified so that such information can be disclosed freely.[52]

The Security Rule attempts to provide a uniform level of protection of all protected health information that is housed or transmitted electronically. These standards mandate safeguards for physical storage and maintenance of equipment that contains patient data. Network closets and servers should be locked up and data must be backed up. The displays of computers in public areas should be turned away from open view, and screens installed to limit the viewing angle. Storing protected health information on computers in unlocked offices, on laptops, or on removable media such as flash drives is prohibited unless the data are encrypted. Users should log out of applications that access PHI when those applications are no longer needed. Access to data must be limited to authorized personnel on an as-needed basis with clear administrative policies for granting and revoking those privileges. There must also be technical safeguards to prevent unauthorized intrusion into networks or interception of transmissions over open networks. Firewalls should protect hospital networks, particularly if there are wireless access points. PHI should never be sent by email without encryption because standard email is inherently insecure.

The implementation of the Security and Privacy Rules varies with the circumstances of each organization. Regardless of the specifics, institutional policies must be established and followed. In the past, violations of such policies, including

Box 8–1 Elements Considered Protected Health Information

- Names
- All elements of dates (except year) for dates directly related to an individual, including:
  - Birth date
  - Admission date
  - Date of procedure
  - Discharge date
  - Date of death
- Telephone numbers, fax numbers
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers
- Device identifiers and serial numbers
- Web URLs
- IP address numbers
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images
- All geographic subdivisions smaller than a state, including:
  - Street address
  - City
  - County
  - Zip code, and their equivalent geocodes
- Any other unique identifying number, characteristic, or code

sharing personal passwords or accessing information to which employees had no right to access, were punishable by official reprimand or, at worst, dismissal. With the new rules, violators may face criminal or civil penalties as well.

Clinical Tools

Information technology has clearly changed our world. The typewriter has disappeared from the office milieu, conspicuously replaced by computers with word processors. Presentation programs and digital light projectors have supplanted slides and overhead projectors in the lecture room. Appointment books and Rolodexes have given way to personal portable electronics. Computationally intensive activities such as statistical analysis no longer reside in the realm of mainframes and punch cards.

In clinical areas, ritualized calculations have become easier and less prone to error with the development of computer applications developed for a variety of platforms from cellphones to networked computers. Some of these programs now can be found in a variety of devices not traditionally considered computers but which operate on integrated circuit computer chips, such as intravenous infusion pumps.

Smart Infusion Pumps

Errors related to intravenous infusions are often associated with significant harm in the PICU. A 2001 study involving pediatric inpatients noted that intravenous infusions were associated with 54% of potential adverse drug events (ADEs).[8] Furthermore, ADEs associated with intravenous infusion devices generally result from incorrect programming. Smart infusion pumps represent a new generation of intravenous infusion pumps and have been associated with a reduction in medication administration errors.[53]

Most intravenous infusion pumps in use today have the flexibility and capacity to deliver a wide range of infusion rates and volumes. In an effort to standardize pump systems throughout an organization, the same device may be used to deliver medications to an infant or an adolescent. Therefore significant dosing errors can be easily programmed by a bedside provider if there are no double checks or electronic decision-support systems in place. Smart infusion pumps contain sophisticated software that allows for programming medication safety libraries within each pump. In addition, these devices may be queried to allow aggregation and analysis of data regarding infusion practices for quality improvement purposes. Furthermore, some pump vendors offer the ability to connect the device via a wireless network to allow bidirectional flow of information to and from the pumps.

Smart infusion pump medication libraries include drug name, usual concentrations, and dose range checking to avoid high or low dosing for both infusion and bolus dosing. Generally these libraries are created for a given patient care unit, patient population, or provider group. Providers who attempt to program the pump beyond the limits set in the library will encounter an alert that may either be overridden (soft alert) or not overridden (hard alert). The impact of smart infusion pump technology on patient safety is not completely clear at this time. Rothschild et al. noted no measurable impact on the serious medication error rate using this technology in a controlled trial in the ICU.[54] These devices must be paired with optimal design and process change in order to achieve meaningful outcomes.

Bar Coding in Health Care

In 2004, the FDA published a "Bar Code Rule" mandating manufacturers and repackagers to have a bar code of the National Drug Code on the immediate drug containers label by April 2006.[55] An integrated system that includes bar coding of medications focuses on preventing errors in drug administration, which may represent up to 38% of medication errors.[56] The essential components for safe medication administration utilizing bar code technology revolve around the "five rights": the right patient, right drug, right dose, right route, and right time. In bar code medication administration, the nurse uses a bedside scanning device to scan the medication, the patient's wristband, and the nurse's identification. A query is then sent to the EHR to the patient's medication orders. A match on the five rights then signals the nurse that the medication may be administered. Though bar code medication administration systems have been associated with error prevention, they have also been associated with new errors.[57] Proper implementation is key to achieving value with these systems.

Virtual Care and Telemedicine

Telemedicine typically refers to remote patient care for diagnosis, treatment, or consultation using some form of information transfer technology. Primary and subspecialty care can be brought to underserved areas of the world, from rural regions to prisons.[58]

Pediatric subspecialties, including critical care, have experimented in telemedicine for decades, and evidence suggests that such care is both effective and cost-effective. While many technical, legal (licensing and credentialing), and financial hurdles remain, telemedicine is emerging as a viable and valuable care delivery model for critical care, either as a consultation service or as a remote "e-ICU."[59,60]

Creative twists on traditional telemedicine in the PICU are also being explored. A recent pilot PICU telemedicine project created individualized, password-protected web sites for PICU patients—their beds equipped with webcams—allowing families remote access to their children's clinical status, complete with nursing notes and patient images. In addition, each child's web site had a messaging area, where nurses and family members could exchange comments and questions. Preconfigured laptop computers were even available for loan to families in need. A separate web site for each child with physician notes and radiographic images was made available to the patients' community physicians. Clearly, there is merit to keeping the referring physician informed of his or her patient's progress. However, the promise of information technology may be greatest as a means of empowering children and their families during their hospitalization.[61]

Medical Knowledge Bases

The vast amount of medical information that clinicians need to practice evidence-based medicine can only reasonably be managed today by networked, searchable, and linked medical knowledge bases. Online search engines, accessible with

Box 8–2 Top-Ten List of Web Sites Relevant to Pediatric Critical Care Medicine

1. PedsCCM: Pediatric Critical Care Medicine web site (PedsCCM.org)
   Still the number one "hit" on Google when entering "Pediatric Critical Care Medicine," this is the headquarters for pediatric critical care medicine on the web. It represents a multidisciplinary educational and practical resource, with announcements, reports, opportunities (including fellowship listings and physician and nursing jobs databases), organized links to original educational material and research reports, and the PedsCCM Evidence-based Journal Club.
2. American Academy of Pediatrics (www.aap.org)
   The Section on Critical Care of the American Academy of Pediatrics (AAP) is very active in promoting the interests of critically ill children and pediatric intensivists within the Academy. The Academy is the prime advocate for children's health care in the United States. For AAP members, the Members Only channel contains timely announcements relevant to all pediatricians. The AAP Policy Statements and Practice Guidelines are available on this site. In addition, the AAP publishes a monthly review of pediatric critical care in its PREP series; PREP ICU is a Critical Care Subspecialty Self-Assessment Program, approved for use as part of the American Board of Pediatrics' Maintenance of Certification for pediatric intensivists.
3. Society of Critical Care Medicine (www.sccm.org)
   As a prime supporter of the intensivist-directed multidisciplinary critical care team, the Society of Critical Care Medicine (SCCM) plays an important role in education and advocacy. The SCCM's educational and research programs, including the American College of Critical Care's guidelines and practice parameters, are on this site. The organization has launched an online "digital community workplace" with chat rooms, threaded discussion groups, file sharing, and calendar functions. There are designated "e-rooms" for every section, chapter, and committee of the SCCM.
4. Diagnostic Decision Support
   Isabel (www.isabelhealthcare.com) Although now only available via subscription, the natural language decision support reminder system, Isabel, was developed by a pediatric intensivist.
5. Journals:
   Pediatric Critical Care Medicine (www.pccmjournal.org)
   Critical Care Medicine (www.ccmjournal.com)
   Intensive Care Medicine (www.springer.com/medicine/journal/134)
   American Journal of Respiratory and Critical Care Medicine (ajrccm.atsjournals.org/)
   Chest (chestjournal.chestpubs.org/)
   These are the major journals in our specialty, all available online.
6. General Medical References
   UpToDate (www.uptodate.com)
   This resource is probably the preeminent regularly updated and reliable reference source online.
7. Calculators on the web and downloadable applications
   Cornell's Dr. Steve Pon maintains multifunction medical calculators (http://cornellpicu.org/). ICU scoring systems are available for the Société Française d'Anesthésie et de Réanimation (http://www.safer.org/article/315/scores). PICUTools is a downloadable suite of such tools for your Palm OS PDA (Dr. Michael Verive at www. mverive.com). Medical "apps" for the Apple iPhone probably number in the hundreds as of this writing via the iTunes Store (www.iTunes.com/Downloads). Finally, the revered Harriet Lane Handbook is now available in multiple handheld formats (www.skyscape.com).
8. Networking
   The Virtual PICU (www.picu.net) joins nearly 100 PICUs learning how to track outcomes, measure quality, and engage in benchmarking. The VPS (VPICU Performance System) is available through the VPICU, as is information on distance learning, pediatric critical care telemedicine, and more. The VPICU also hosts our specialty's premier discussion forum (email and/or web-based), the PICU list.
9. Drug References
   Few resources benefit more from the rapid accessibility and searching capability than drug databases and references. Many exist, from the venerable Physicians Drug Reference (www.pdr.net) to the well-established Drug Information Handbook from Lexi-Comp (www.lexi.com/). Versions of several drug databases for handheld devices also are available and are rapidly becoming indispensable to junior and experienced clinicians.
10. World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS)
    An organization of member societies of pediatric intensive and critical care from around the globe.

natural language queries unfettered by complex rule-based search terminology requirements, have revolutionized access to multiple types of medical knowledge bases (Box 8-2).

Nearly anyone who has used a web browser is familiar with the power of natural language queries posed to a highly intelligent search engine. Indeed, the power of one such engine has turned searching the web with this tool into a verb: to Google. Google and Google Scholar (searches limited to scholarly databases), have become quite useful even for professional medical knowledge searches. Some clinicians have even taken to searching Google with a list of signs and symptoms as a diagnostic decision-support tool.

Resources available for free access online include classical original medical literature citations, such as via the National Library of Medicine's PubMed site (http://www.ncbi.nlm.nih.gov/pubmed). Powerful and focused results are now possible without understanding the difference between MeSH (Medical Subject Heading) terms and keywords. Abstracts are presented, and if the full-text paper is online anywhere, PubMed provides a direct link. More and more publishers and journals are opening (at least) their archived editions older than 6 to12 months to free access on the Internet. PubMed itself is a large repository of freely available manuscripts from a wide range of journals.

Also online are pharmaceutical databases, medical calculators, textbooks, image libraries, evidence-based reviews and guidelines, though not all are necessarily freely available. For physicians in academic medical centers, however, contractual arrangements between universities or hospitals and publishing cooperatives can enable apparently free access to the end user if the resource is accessed from within the institution's

network. Many publishers also allow free access to users in developing countries, potentially revolutionizing education and communication even in remote corners of the world.

The accompanying CD for this chapter includes several computer-generated animations, demonstrating a unique teaching capability of technology. Pediatric critical care medicine is in the forefront of using this technology for teaching purposes, as Tegtmeyer et al. published the *New England Journal of Medicine*'s first computerized instructional video on arterial catheter insertion.[62,63]

The Internet and the Patient

Though beyond the scope of this text, health care providers should be aware of the extent to which Internet access is empowering patients and families. Consumers are becoming increasingly savvy in their ability to access reliable medical information from the web, including the same research papers and guidelines that providers rely upon. In addition to access to medical information, the Internet provides patients and families access to each other. Social networking sites, some disease-specific, enable virtual support groups to share experiences worldwide. So we should not be surprised if a parent enters the PICU and asks why, given the evidence and recommendations, is their child's head of the bed not elevated 30 degrees as a preventative strategy for ventilator-associated pneumonia. Another family may relate how different the treatment for their child's condition is elsewhere, or ask why they can't be enrolled in a clinical trial they located on Clinicaltrials.gov.

Research Databases

There are few areas of clinical or laboratory research that do not generate volumes of information that require analysis. All but the simplest studies involve entry of data into an electronic database. Perhaps the most common types of databases involve single flat tables of variables and measured values. In fact, many researchers use spreadsheet programs, not database programs, to perform most of their analyses. As data are acquired and complex relationships among the data are built into the data models, their structure becomes more intricate and better suited to true database programs. Most of these are relational database programs that run on personal computers or on mainframes. Both the characteristics of the data and the nature of the desired output affect the design of the data models and database structure.

There are areas of research where the sheer volume of information can overwhelm any single program or computer system. The solution to which more researchers are turning has met enormous success in fields such as astronomy, astrophysics, and genetics. That solution is "internetworking."

Integrating data from multiple, disparate databases to form public repositories open for new discovery is a difficult problem. The separate databases could be consolidated into one large database, but both the data and the data model can easily become asynchronous with the contributing databases. The other approach is federation, where the original databases exist on their own but are linked together and bound by data standards. These include standard, regulated vocabularies, and a standard syntax to govern the form of the data. Rather than adopting a particular platform (Unix or Windows) and a particular program, eXtensible Markup Language (XML) has emerged as the standard syntax because of its flexibility. It also allows these databases to be freely available on the Internet and open to query by researchers worldwide. Specialized data that require further characterization are governed by additional specifications such as Biopolymer Markup Language (BIOML) and MicroArray Markup Language (MAML) for microarray data.

The field of bioinformatics occupies the intersection between biogenetics and IT.[64] The volume of biologic data being collected cannot be digested without some way of processing it. The data include not only DNA sequencing, but also polymorphisms, cross-species comparisons, levels of mRNA expression, protein-protein interactions and enzyme kinetics, location of gene products within the cell, and the three-dimensional structure of the macromolecular gene products and their ligands. The Human Genome Project owes a great portion of its success to advances in bioinformatics. Linking these databases with clinical databases represents additional challenges, but ones that are being met. The Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim) database of inherited human disorders is a successful example. Linking genetic variation and clinical response to drugs with the goal of adjusting therapeutic regimens according to genetic profiles represents the challenge of pharmacogenomics.[65]

Given the direction of this evolving technology, it is conceivable that clinical data from multiple institutions could be linked in similar ways. Detailed analysis for patterns in large volumes of clinical data can serve as a springboard to novel clinical studies. This kind of analysis is known as data mining in some disciplines but is referred derogatorily as data torturing by some. The true value of this approach cannot yet be predicted, but there can be no argument that the limitation of most studies in pediatric critical care is currently the paucity of data from individual institutions. In aggregate, who knows what we may learn?

Ethics and patient privacy and confidentiality represent key issues for some of these research efforts. Simply removing patient identifiers is not adequate because it is still possible to bring together information from a variety of sources to reconstruct, either exactly or probabilistically, the identity of patients. Fortunately, there are means for adequately protecting confidentiality, including mediation and scrubbing. Mediation programs on a database limit the kinds of queries and responses based on specified rules and requester privilege. Scrubbing blurs the data by decreasing precision or reporting ranks rather than actual values. It also limits queries to those resulting in more than a specified "bin" size. Queries that violate preset rules would not yield results. Although the privacy and confidentiality issues may be soluble with judicious application of technology, the ethical issues may be more intractable and will require careful study and action.

Virtual Pediatric Intensive Care Unit Systems

In collaboration with the National Association of Children's Hospitals and Related Institutions (NACHRI), and the National Outcomes Center located at Milwaukee Children's Hospital and Medical System, the Virtual PICU (funded by the Childrens Hospital Los Angeles and the L.K. Whittier Foundation) developed a data collection tool specifically designed to understand pediatric critical care, the distribution of demographics, diagnoses, and outcomes, and to form a basis for clinical research, quality improvement and, ultimately,

comparative data analysis. Over the years, there was significant "scope creep" and the minimal database evolved in to a comprehensive tool for understanding pediatric critical care and exploring outcomes in a comparative fashion.

As of 2009, there are 85 PICUs participating in the Virtual PICU Systems (VPS), which includes over 250,000 patient admissions in the database and is growing at a rate of over 70,000 cases per year. Participating institutions participate in an advisory committee, a users' group organization with annual meetings, and a research committee, and receive periodic comparative quality reports detailing the performance of their ICUs along multiple axes, modeled on the Institute of Medicine's "Six Dimensions of Quality."

The VPS database has been used extensively to inform pediatric critical care research. Merely providing demographics and descriptions and diagnostic patterns in critical care has aided the design of multiple national research projects and National Institutes of Health funded projects. However, the core purpose of the prospective data collection is quality improvement, allowing comparative data reporting against comparable but unidentified institutions. These reports enable intensivists to objectively demonstrate the quality of the care they provide.[66]

Security

The security of a networked system involves at least three components: physical security, prevention of unauthorized access, and protection from malicious software.

Physical access to sensitive portions of the system must be secure. Servers should be in locked rooms with controlled access. Networking closets with wiring and hubs should be locked. Sensitive equipment must be protected from extreme temperatures, fire, and water damage. Backup power sources are required. Workstations, wherever possible, should be in open areas where their use can be monitored, but not so open that unauthorized persons can peer over a user's shoulder to steal a user name and password or to see sensitive information. Physical security also involves ensuring that the data are backed up and readily accessible whenever they are needed.

Preventing unauthorized electronic access involves blocking attacks from the outside and authenticating legitimate users before allowing them access. Wireless networks must be configured to minimize the risk of intruders tapping into the system. Systems can be attacked by malicious software, loosely labeled as viruses. Securing systems from these threats is becoming increasingly challenging.

Firewalls

Any computer or network with connections to the outside world, such as the Internet, is vulnerable to attack. These attacks can come in the form of a hacker gaining access to confidential data or another causing data loss or corruption. The first measure of security against such threats is a firewall. In the parlance of architects and builders, a firewall prevents fire from spreading across sections of a building while allowing traffic through specially constructed doors. A network firewall protects the resources of a network from unauthorized access while allowing its users access to external resources such as the Internet. Personal firewalls can protect an individual computer from certain kinds of network traffic.

The simplest firewalls are packet filters. Information is sent across a network in packets wrapped in layers of protocols with a header that includes IP addresses and port numbers. Packet filters examine the headers and, based on a set of rules configured into them, allow or deny passage of each packet. Routers can be configured as packet filters, becoming screening routers. However, not all packets are what they appear to be, and packet filters do not examine their contents. Readily available hacking tools can create normal-appearing packets that can take advantage of well-known security flaws in network applications.

Proxy servers provide the next level of firewall protection. They intercept requests for data from network users and forward them using the proxy address (hiding the requester's internal network address). The reply from the Internet returns to the proxy server, which evaluates it to ensure that the contents contain an expected response. If the commands or data are suspicious, the packet is discarded. Legitimate packets are forwarded to the requester but only after they are repacked in a new packet. No packets ever cross directly from the network to the Internet or from the Internet to the network. The proxy server is always between them, evaluating each packet trying to make its way through.

Software on the user's computer or on a computer that serves as a gateway to other networks can function as a firewall. In fact, home computers constantly connected to the Internet via a broadband connection (e.g., cable modem, digital subscriber line [DSL], or integrated services digital network [ISDN]) should have personal firewall software to protect them from attack. A "firewall appliance," a hardware device dedicated to this task can also do the job.

Even with a firewall to protect the perimeter of a networked environment, much vulnerability remains. For example, any computer on the network connected via modem to any outside system effectively bypasses network firewalls. This security flaw can be plugged with properly configured firewall software. Effective security solutions include network and Internet gateway monitoring, intrusion detection, firewall software for vulnerable nodes, antivirus software, and periodic penetration testing. Firewalls are only one bulwark against attack.

Wireless Networks

Wireless networking allows freedom from the tether of network wiring. In a large intensive care unit with multiple patient rooms and shifting isolation precautions, an untethered workstation allows efficient access to information systems during rounds, making it an integral part of the information exchange.

Most hospital networks do not provide for wireless technology, citing the security risk. In fact, many wireless implementations allow the equivalent of leaving the wiring closet completely open for intruders to enter and plug directly into the network. The Institute of Electrical and Electronics Engineers (IEEE) 802.11 standard on which these networks are based includes a provision for encryption called wired equivalent privacy (WEP) that was eventually superceded by the more secure Wi-Fi Protected Access (WPA or WPA2). Surprisingly, most implementations of wireless networks do not use any encryption method. Many network administrators do not even bother changing the factory default security settings, including passwords.

It is possible to sufficiently secure wireless technology, even for the most sensitive applications. WPA2 and all other security features must be configured appropriately. The access points can be positioned to minimize inadvertent transmission beyond the desired boundaries of the building. The connections can also be limited in number and by media access control (MAC) address, which identifies each node on a network. The most effective strategy is to place the wireless access points behind a firewall and have wireless users gain access to the network by using a virtual private network (VPN).

Virtual Private Network

A VPN is a private network set up within a larger public network. It can provide a secure private connection from a home or remote office, over the Internet or other unsecured network (e.g., wireless), to the hospital's local area network for access to the clinical information system and other sensitive applications. With a combination of secure authentication, encryption, and "tunneling," the remote user can have access to the same applications as if he or she were on site. Authentication ensures that only authorized persons gain access to the VPN. Encryption prevents the data from being read if intercepted. Tunneling allows the data to traverse the Internet and get past the firewalls and gain access to the network (Figure 8-1).

Remote access to patient data is one of the major issues where physicians and IT administrators clash. Physicians demand it, but the administrators are reluctant to implement it, especially in view of the HIPAA security regulations. The security of a VPN is a function of how tightly authentication, encryption, and access controls are connected. A VPN with a desktop firewall solution and appropriate audit trails is a compromise that is workable in many institutions.

Authentication

Authentication is the process of establishing the identity of a user to a computer or system with some degree of certainty. Most often, it is used to grant access. The most common method of authentication uses passwords. "Smart cards" with magnetic strips or barcodes are another method of authentication. Their problems relate to loss or theft, if not duplication or forgery. Biometrics identifies individuals by fingerprints, faces, voices, irises, retinas, signatures, or other physical attributes using some combination of hardware and software. Although the specifics vary, the general process includes collection of the biometric information by a scanner (fingerprints), a camera (face), a microphone (voice), or some other modality. This information is converted by some algorithm to a mathematical template that can be compared with a database of authorized users. The data often are encrypted to prevent intercepted information from being used as keys. Biometric devices are not bulletproof and can be fooled or bypassed. However, as the technology matures, the problems may diminish.

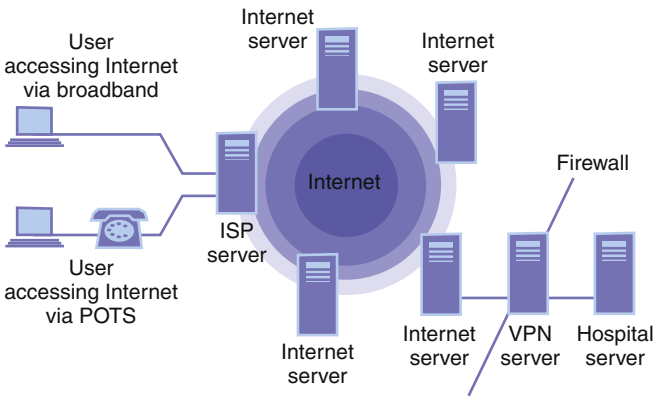

Figure 8–1. Virtual private network connection. The user gains access to the Internet through any means, usually an Internet service provider (ISP), while running VPN software. Data are directed at the hospital VPN Server by "tunneling" through the public Internet by encryption and special packaging. Once the data stream reaches the hospital's VPN server, it is unencrypted and sent through the firewall to the hospital server that receives the data, the latter oblivious to the fact that the data came from outside the hospital network. The reply to the user follows the same path through the VPN server that encrypts and packages it to traverse the public Internet.

Most security experts agree that the best way to effectively protect any computer system is to layer complementary technologies, hence the adage, "Something you know. Something you carry. Something you are." Items known to the user include passwords and other personal information. Items carried by the user can include keys or identification cards with barcodes or magnetic strips designed to make forgery difficult. Authentication based on an individual's physical characteristics using biometrics composes the last category. A multilayered approach may be necessary to protect super-secret government agencies, but the requirements for most medical information are less stringent. Although some zealous individuals may equate patient privacy with national security, multilayered security systems may be difficult to implement, particularly in an environment where slow or unreliable access may compromise a patient's well-being.

The authentication system widely used remains the combination of user ID and password. These systems are only as secure as the least compliant user. Although there are recommendations regarding choosing and maintaining passwords (Box 8-3), many users ignore these guidelines, making the entire system vulnerable to unauthorized access.

Poorly designed passwords are vulnerable to cracking by any of a number of commercial software programs or by any enterprising programmer. In general, passwords should not be single words. They should be some combination of small

Box 8–3 Guidelines for Creating Passwords

1. Passwords should be at least six to eight characters in length, the longer the better.
2. Passwords should include uppercase letters, lowercase letters, and numbers. Non-alphanumeric symbols (e.g., #, @, !, &) can often be used, depending on the system.
3. Passwords should be easy to remember and easy to type.
4. Do not use any readily accessible information as any part of a password. This includes your user name, full name, address, birth date, or Social Security number.
5. Do not use single words or simple word combinations. Dictionary attacks can test millions of words or word combinations per second, including foreign words.
6. Do not record passwords on any unsecured medium, such as notes beside the computer, on an identification badge, or in a book.
7. Change your password every 4 to 6 weeks.
8. Do not recycle old passwords or use the same password for several different applications.

words and numbers, and they should be changed with some frequency. They should never be written down, let alone posted on the side of the monitor. Passwords should never be shared. Most hospitals have policies that forbid sharing or borrowing user names and passwords. Dismissal is generally the penalty for such infractions.

Users should always log out of all systems before stepping away from a workstation to prevent giving others unauthorized access on their login. Because users do not always remember to do so, there should be a mechanism for automatic logout or lockdown if there is no activity over a specified period. Workstations that have "timed out" should still be available for use after the user has been reauthenticated or when another user is authenticated.

Viruses or Malware

Malicious software, or "malware," is designed to damage or infiltrate computer systems of unsuspecting users. Knowing how malware works is an important step in preventing an attack. The taxonomy of malware includes viruses, worms, Trojan horses, and "blended threats" that have features of more than one type.

Computer viruses are malicious programs attached to executable files or programs. They technically require human intervention to spread from machine to machine, as when users share files on transportable media, across a network, or via e-mail. Once on a system, the damage occurs only when the file is opened and the program executed by the user. Worms differ from viruses by the method they are transmitted from system to system. No longer limited by human intervention, worms can replicate and spread wildly within a system and across networks, sometimes by hijacking an e-mail program and using the stored email addresses to distribute themselves. The damage occurs when the program is executed by the user, initiating unchecked replication and using up the computer's resources. Trojan horse programs are disguised as, or are embedded in, programs that appear legitimate but perform some illicit activity when they are run. They typically do not replicate themselves or infect other files. Some Trojans are written to cause the loss or theft of data such as password information. Others make the system vulnerable to takeover by another computer. Still others simply destroy programs or data on the hard disk. The increasingly common and dangerous blended threats combine features of different kinds of traditional malware while attempting to exploit multiple vulnerabilities on both single-user computers and network servers. By using several different techniques targeting different weaknesses, blended threats can spread rapidly and cause widespread damage before they can be detected and neutralized. Combating blended threats requires an integrated solution at all levels of a network, including web servers, e-mail servers, and client computers, to protect every vulnerability.

At one time, document files were considered safe because they did not contain any executable programming. Modern word processors, spreadsheet programs, and other applications can create document files that contain macros. Macros are programs that allow a certain degree of automation in the creation or modification of that document and are embedded in the document file. Although these macros allow for additional functionality, they can be co-opted for malicious purposes. Obviously, not all macros are viruses, but if a file contains a macro, it would be wise to consult the author as to its legitimacy and whether it can be disabled without compromising the document. Other types of document files, including Joint Photographic Experts Group (JPG) graphic files, have been shown in laboratories to be capable of carrying viruses, but none have yet surfaced "in the wild."

Early web documents contained only textual information, graphics, and rudimentary formatting. The wish for enhanced functionality to augment the modern web experience led to the creation of new programming languages. ActiveX and Java programs embedded in a web page can generate eye-popping special effects and can greatly increase the interactive nature of web encounters, but they also can be used as means to attack computer systems. Web browsers configured with "high" security settings prevent ActiveX and Java programs from executing. Unfortunately, this configuration can significantly degrade the web experience, and it is a difficult task to selectively block malicious programs while allowing others to run.

Hoaxes or phantom viruses, although not technically malware, prey on the naïveté of most computer users. Although they generally amount to no more than an e-mail chain letter, they sometimes advise users to delete a needed file, adding that the "virus" cannot be detected by any antivirus software. Most of these false warnings urge users to "forward this to everyone you know" in an effort to perpetuate the hoax. If there is ever any question regarding a legitimate threat or a hoax, users should consult the web pages of any of the antivirus program distributors or perform a simple web search.

Safe computing practices should be used at all times and by all users within a system (Box 8-4). Antivirus software programs should be installed on every computer and the virus definitions should be kept up to date. The virus definitions are strings of bits that uniquely identify each virus from any other file, much like a DNA fingerprint. Out-of-date definitions cannot protect users from the most recently identified threats. Although some viruses can be intercepted by network administrators who protect their mail servers with antivirus software, there are other means by which malware can infiltrate a system. Sharing files through instant messaging or downloading files via web sites, newsgroups, or file transfers (file transfer protocol [FTP]) are among the many sources of security breaches. Carelessly and indiscriminately running received executable programs, opening received documents, or allowing ActiveX or Java programs from questionable web sites to run are high-risk behaviors.

Some experts view the current reactive paradigm of malware protection insufficient to secure legitimate users from the threat of increasingly sophisticated, malicious, and destructive attacks we likely will see in the future. Some security developers are turning to more proactive approaches to detect and neutralize yet unknown threats. One approach has distributed attack sensors on servers throughout the Internet to provide early warning. Another approach is heuristic analysis, where abnormal behaviors propagated by files identify and isolate potential threats.

User Privacy

The Privacy and Security Rules outlined by HIPAA regulate access to patient information. However, the privacy of the computer user, whether related to patient information or not, is vulnerable on many other fronts.

Box 8–4 Safe Computing Practices

- **Back up your data.** Safe computing practices can decrease the risk to your data but cannot eliminate it altogether.
- **Use antivirus software.** Use real-time virus protection at all times. Scan all files obtained across network or Internet connections, including from e-mail, web sites, instant messaging, or other sources. Scan all flash drives, CDs, or other removable media that are given to you. Scan all software before you install it. (There are verified reports of brand-new, shrink-wrapped retail software that contained viruses.) Periodically scan all hard drives on your computer. Maintain the most up-to-date virus definitions.
- **Beware of e-mail attachments.** Be suspicious of all e-mails, but especially those that are unexpected or out of character. Do not leave infected e-mail attachments or any unwanted attachments on your system. Do not set the e-mail program to automatically open attachments. If the e-mail program can render HTML messages, set it to disallow all executables (ActiveX, Java, and JavaScript).
- **Do not share.** File sharing and printer sharing should be disabled if these functions are not needed. If they are needed, limit access to your network. Never allow anonymous sharing of your system. Turn off unneeded services, such as hypertext transfer protocol (HTTP), FTP, Telnet, and personal web servers. Be wary of any files given to you, particularly those with the file extensions .exe, .com, .bat, .pif, and .vbs.
- **Use a firewall**. Use a hardware or software firewall. Files attempting access to the Internet or Internet servers attempting to access your computer should be investigated before they are granted access in the firewall configuration. Know the range of IP addresses used in your network so that intruders can be more easily detected.
- **Protect passwords**. Follow accepted guidelines for creating strong passwords. Do not record passwords in any unsecure documents. Disable password management in the web browser.
- **Keep security updated**. Obtain and install all software security updates, particularly for operating systems, e-mail clients, and web browsers.
- **Keep browser security updated**. Consider setting the browser security setting on "high" to prevent ActiveX or Java programs from running. This configuration may degrade your web experience, depending on the web sites that are frequented. Consider obtaining and using software to manage cookies and to warn you of web bugs.
- **Use macro virus protection**. Offered by some programs, notably Microsoft Office, macro virus protection identifies files that contain any macro before they are opened. It cannot determine whether these macros are viruses or legitimate macros.

The amount of personal information disclosed over the web intentionally or inadvertently can be disturbing to persons concerned about privacy, but every web surfer can take certain precautions. Primarily, users should not disclose any information they do not want to share. If personal information is required, as in a financial transaction, make sure the information is transmitted over a secure connection. Avoid answering questions such as your annual income, your mother's maiden name, or your Social Security number. If some information is "required," you should feel free to make up an answer. In addition, unless you are fond of junk e-mail, you should opt out of getting "special offers."

Your web browser can reveal volumes about you, including your computer's IP address, the web sites recently visited, and the contents of your browser memory cache. Users should routinely purge their browser cache, their browsing history, and the location bar memory. Cookies should be reviewed periodically with one of the available utilities. Those that contain sensitive information or belong to undesirable sites should be deleted. Some advertising networks allow users to opt out of their systems by going to the http://www.networkadvertising.org web site. Special applications or services can be used to block web bugs or to surf anonymously through a web proxy server.

For many of the threats to security and privacy in the electronic world there are software solutions with varying degrees of effectiveness. Some e-mail services can make the sender anonymous; others provide secure, encrypted mail, saving only one copy to be retrieved by the user. Other software can filter out spam—unsolicited e-mail advertisements—although many standard e-mail agents can perform similar filter functions. Several antispam software packages include antivirus scanning of all incoming mail and some firewall capabilities. It is possible to prevent your IP address from being discovered, even by web bugs, and to encrypt all web page requests. Still other products can block, sort, or clean up cookies. Advertisements can be blocked, as can any site with potentially objectionable material.

It takes a fair amount of effort to protect your privacy. Cookie sorting can take as much as a half-hour per week, but even sporadic use of online commerce requires cookies. Constructing an impervious wall of privacy is not a practical goal. There will be tradeoffs between the services provided by web sites and the personal information you are willing to surrender, but there are abundant wares available that can help keep your business your own.

Spyware

Various technologies to spy on computer users exist, and new classes continue to be developed. Spying software can log every keystroke, raise flags when key phrases are typed, capture and store periodic screen shots, record e-mail and chat sessions, and report suspicious activities by e-mail. Use of this kind of software in the workplace is becoming more commonplace as employers seek to recoup lost productivity from their workers engaging in non–work-related activities. Some computer viruses or other malicious software (see Viruses or Malware) include spyware that can snoop on and even commandeer the victim's computer. Other spyware attempts to capture passwords or credit card information and forward them via e-mail or Internet relay chat.

Hardware key loggers are inconspicuous devices that can capture every keystroke typed on a keyboard en route to the computer. Hidden in the keyboard or the computer case and completely undetectable by software, they can capture more than a year's worth of typing.

Network sniffers can effectively perform a wiretap on a network or over the Internet by intercepting and recording packets of raw data to and from the victim's computer. Most of the data, particularly e-mail, that traverses networks is not encrypted and therefore is highly vulnerable. Wireless networks (802.11 protocol) are even more accessible (see section on wireless networks).

A computer stores a wide range of backup data and cache information to speed performance and help recovery in the event of system crashes. Even files that you thought you had deleted may continue to exist on your hard drive and may be recoverable by forensic software. Web browsers also store a history, cookies, and cache that usually enhance a user's experience on the web, but can also be a font of information to an investigator. Furthermore, as some White House staffers discovered to their dismay, e-mail deleted from their own computers was not necessarily removed from their e-mail host server.

Countermeasures require that users be aware of the potential threats. Installing and frequently updating antivirus software is only the beginning. Spying software can take up significant disk space, cause unexpected disk activity, or produce unusual network traffic. Personal firewall software can warn the user that his or her computer is sending information without authorization.

Cookies

Web pages are considered "stateless," that is, they have no way to know what items are in the electronic shopping cart or to even remember anything about the user or where on the web site the user had been. In order to improve the experience, cookies were developed. Cookies are data created by a web server, stored on the user's computer, and later read by the originating web server. A cookie includes the address of the web site that sent it. Web browsers will allow a web site to read only those cookies originating from that site and no others. Cookies also include a date after which that cookie is set to expire and to be removed from the user's computer. They can track where on the site the user has been and how often. They can remember user IDs and passwords, and they can remember user preferences so that content can be tailored to the user's interests. Although they can "improve your experience," they also can offer a wealth of information for marketers and others.

Cookies are stored in a file on the hard disk. The web browser can be set to accept all cookies, reject all cookies, or notify you if a cookie is being set. The ubiquity and importance of cookies make the latter two choices virtually untenable; however, newer versions of popular browsers provide some ability to selectively reject cookies and to allow editing of cookies to eliminate any information you would not want sent back to web sites on future visits. Most reputable web sites mention the use of cookies in their privacy policies. These policies often go unread, they are not binding and often are subject to change without notice.

Web Bugs

Information about web traffic and about the persons who visit certain web sites is extremely valuable to commercial web sites, advertisers, and others. Web bugs exploit the way browsers handle web pages to surreptitiously collect limited but important information. These "bugs" (as in clandestine listening devices, not insects or programming errors) also are known by euphemisms such as "web beacons," "clear GIFs," "1-by-1 GIFs," "invisible GIFs," and "beacon GIFs."

A web bug is a graphic on a web page designed to feed information back to the owner. The size of these images typically is 1×1 pixel; some are not just small but also are invisible. They often are in the graphical interchange format (GIF) file format (Figure 8-2).

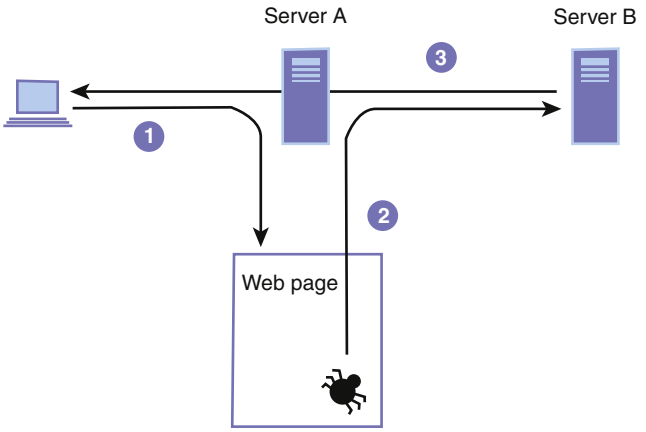

Figure 8–2. Web bugs. (1) A user requests a web page from Server A. (2) A web bug on the requested page points to an image on Server B. That server can record the information that is relayed to it, including the IP address of the requesting computer and the URL of the web page containing the web bug. (3) Server B can send a cookie directly to the requesting computer. If the user visits another site with a Server B web bug, that cookie will tell it where else this user had been.

The information that can be sent back to the server includes the IP address of the user's computer, the URL of the web page, the URL of the web bug image, the time the web bug was viewed, the kind of web browser used, and any cookies previously set for that server. It can provide an independent accounting of the number of persons visiting a particular web site or the popularity of a particular web browser. Furthermore, anything entered on a web page, whether a zip code, birth date, or even search strings, can be shared among web sites. Advertising networks can generate a detailed personal profile by piecing together all these data and other publicly available data. This profile can be used to specify the banner ads displayed, and the web bugs can correlate the display frequency of a particular banner ad with what was purchased.

Software is available that serves as bug repellant, but its use can make it difficult to navigate certain sites without a barrage of warnings. Most web sites make their privacy policies available. The reputable sites mention the use of web bugs, although they often use one of the euphemisms listed.

Profiles and Privacy Policies

Reading privacy policies posted on Internet sites can be fairly revealing and can precipitate significant paranoia. These disclosures often admit to using a variety of methods of tracking user patterns, although they are nonbinding and subject to change without notification. The methods of user tracking are not limited to those outlined here. For example, one popular drug-information personal device software company admits to tracking the number of times a drug is looked up and the screens viewed. These data are sent back during synchronization and are stored in aggregate and as personally identifiable information. Furthermore, the profiles are supplemented by public information about users from sources such as the American Medical Association.

Although much of these data are collected to "improve customer satisfaction," we should not assume that the intentions

of all collectors are to benefit the users. Some may have nefarious intent. Regardless of their intent, creators of certain software or web sites leave few alternatives to these invasions of privacy besides total abstinence.

Electronic Mail

E-mail has been likened to sending a postcard written in pencil. Just like a postcard that passes through many hands between writer and reader, e-mail can be read by anyone who can view the message as it passes by their electronic eyes either on a mail transfer agent (MTA) or on the network. Not only can the message be read, but it also can be "revised."

E-mail originally was developed to deliver only plain text (American Standard Code for Information Interchange [ASCII]). Sending anything other than plain text required that the data be "attached" to an e-mail message. Attaching files requires that they be coded for transmission and decoded once received. The most common method in use today is multipurpose Internet mail extensions (MIME). Sending files as attachments to e-mail allows users to share documents, photographs, and computer programs, but also viruses.

Although standard e-mail messages are pure text, some e-mail software can view messages that are composed like a web page in hypertext markup language (HTML). This web browsing feature requests images and other components to be downloaded and renders the HTML with fancy text, tables, images, and hyperlinks. Although this capability improves the user experience, it also opens new vulnerabilities, particularly the web bug method (see section on web bugs). The most readily accessible information by this method is the user's IP address. Reading this kind of e-mail can synchronize the IP address to an e-mail address, a threat to anonymity that exposes users to an explosion of junk e-mail.

HTML mail opens additional vulnerabilities through exploits of programming languages such as ActiveX, Java, and JavaScript. Users should configure their e-mail client software to disallow the execution of these programs.

The bane of most e-mail users is "spam" or unsolicited advertisements. They are the junk mail and the telemarketers of the Internet. The authors of spam usually purchase your name and e-mail address from a marketing agency or directly from web sites you visited. Other than limiting yourself to web sites that do not collect your e-mail address and refusing to disclose your e-mail address altogether, there are some things you can do to reduce spam. Some spammers offer opportunities for users to "unsubscribe" from their mailing list. Although these offers sometimes are legitimate, a response often only serves to identify the user's e-mail address as "live" or valid. Addresses that are known to be valid often are subjected to more vigorous spam campaigns. Some users prefer to maintain more than one e-mail address, reserving one for work, one for personal use, and yet another for use in public areas such as web sites that require an e-mail address. Most e-mail software programs offer methods of filtering messages and applying a variety of automatic actions. Users can create filters to automatically delete messages from senders of spam. These messages should be deleted from both the user's computer and the mail server.

If these measures fail to adequately control spam, some software packages are designed specifically for this purpose. This software filters content for common phrases used by spammers. Content filtering can be expanded to eliminate other inappropriate messages, such as sexually explicit language or racial epithets. Many corporations use content filtering on their mail servers, blocking or tracking inappropriate language, corporate secrets, and even viruses.

Conclusion

Medicine is an information service and critical care is perhaps the most information-intensive medical subspecialty. It is no accident that many intensivists have a particular interest in IT, but every practitioner will be more effective if he or she obtains the skills to better manage the flow of information. Furthermore, as physician leaders focusing on IT, intensivists can lead the way in creating a safer environment for all patients. Understanding the limitations and pitfalls of the technology and exercising caution as it is implemented is of paramount importance for success.

As everyday users of IT, all users should understand the threats to privacy and security, not only for our patients but also for ourselves. Networked systems are as vulnerable as their weakest link. Sustained vigilance and safe computing practices are essential to avoid calamitous data loss or exposure to exploitation.

With these caveats, IT greatly enhances our lives and our work. It profoundly augments what we know and the speed with which we know it. We and our patients are both better because of it.

References are available online at http://www.expertconsult.com.

Chapter 9

Family-Centered Care in the Pediatric Intensive Care Unit

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PEARLS

- Using family-centered care principles to establish the parents as partners with the health care team encourages trust and cooperation, reduces fear and anxiety in both the patient and family, and creates an environment of mutual respect.
- Access to their critically ill child is reported by parents to be a high priority. Benefits have been clearly demonstrated when pediatric intensive care unit policies support parent presence in the unit at all times, including periods that traditionally have been closed to them, such as change of shift, during admissions, and during emergencies.
- Access to information provides parents with tools to better collaborate with the health care team. Participation in rounds, access to their child's medical chart, and daily communication with a care provider result in more accurate exchange of data and fewer errors in communication and improves the patient's and family's experience.
- Pediatric intensive care unit staff can facilitate parents' participation in the daily care of their child, thereby supporting the parental role, preserving the parent-child bond, and reducing the impact of traumatic events, such as procedures and resuscitation, on both the patient and family.

Admission to the pediatric intensive care unit (PICU) constitutes a crisis for both the patient and family. This crisis is amplified by the stress felt by the parents in the ICU environment. (In this chapter, the term "parents" is used for the primary caregivers of the child, whether they are biologic, adoptive, legal, or other.) The main contributors to the stress are the child's uncertain outcome as well as the disruption of the parents' role and their separation from the child. In addition, the environment, appearance of the child, procedures performed on the child, and staff interactions all contribute to stress.[1-9] A crisis is an emotionally destabilizing change that occurs when a person's normal and usual methods of coping and problem solving are not effective.[10] Reestablishing the parental role in partnership with health care providers as early as possible mitigates the fear and frustration experienced by most families. Establishing this partnership is the core of the family-centered care philosophy, and it requires respectful attention at every level.

Caring and Compassion

In 2009 the Institute of Medicine[11] reported on its model for improvement, which included six quality aims: safety, effectiveness, equity, timeliness, efficiency, and patient-centeredness.

The Institute of Healthcare Improvement[12] adapted these into their "Idealized Design of the ICU." PICU leaders,[13] in collaboration with Agency for Health Care Research and Quality, took this model and adapted it to the PICU setting. Patient-centeredness is weighted as having importance equal to the other core components of the model, including safety and effectiveness. Core components of patient-centeredness were defined as empathy, compassion, and respect. This patient-centeredness should be extended to the parents. In many cases, the admission of a child to an ICU may be the most stressful, frightening event a parent has ever experienced. Providing empathy and compassion to patients is central to the work of critical care providers, but this care must be extended to the parents and is just as important as providing exceptional clinical care. Actions that can demonstrate care for parents include skilled communication, education, emotional support, and promotion of family participation in care.[13]

Humanitarianism and Defining the Family

Care teams can spend a great deal of time determining who is "the family" or "the immediate family." Traditionally, parameters pertaining to visiting and involvement in care have been defined and limited by the preferences of the health care team. Extended family and important friends often have been excluded. For many years the definition of *family* used by health care teams was based on the 1950s model of two biologic parents being the primary care givers and the main support being the grandparents.[9,14,15] These assumptions are no longer valid. The team should ask the parents to define their family so that caregivers are clear on who can receive information, be present, and be integrated into the care team. It is important to understand both the legal and informal arrangements of the family so that information is communicated to the appropriate members and requirements pertaining to consent and other legal issues are maintained.

Although these logistical arrangements are necessary, humanitarianism should be demonstrated toward the entire

family. One must recall that individual members of the family may have different fears, dreams, and expectations for their child. Providers are providing care not only for the child and parents, but for siblings, relatives, and an extended network of friends, teachers, and classmates. As noted by Kissoon,[16] "Whatever the composition of the family, the humanistic leader recognize[s that] paternalistic physician-patient/family interactions are outdated and should be replaced by partnership." Listening to parents and supporting them is respectful and fosters a collaborative relationship.

Family-Centered Care Core Concepts

Family-centered care is based on the assumption that the family is a child's primary source of strength and support. Family-centered care is characterized by four principles:

- **Dignity and respect.** Health care practitioners listen to and honor patient and family perspectives and choices. Patient and family knowledge, values, beliefs, and cultural backgrounds are incorporated into the planning and delivery of care.
- **Information sharing.** Health care practitioners communicate and share complete and unbiased information with patients and families in ways that are affirming and useful. Patients and families receive timely, complete, and accurate information in order to effectively participate in care and decision making.
- **Participation.** Patients and families are encouraged and supported in the decision to participate in care and decision making at the level they choose.
- **Collaboration.** Patients and families also are included on an institution-wide basis. Health care leaders collaborate with patients and families in policy and program development, implementation, evaluation, health care facility design, professional education, and delivery of care.[17]

Some general considerations described by the Institute for Family-Centered Care include a shift in attitudes and the development of new language. Some themes to be considered when developing guidelines around principles of family-centered care should include these concepts (Table 9-1).[17-23]

Challenges for the Team and Family

For families, critical care means fear, imbalance, turmoil, crisis, and a host of other sudden, deep emotions.[24] Both physical and psychological demands are placed on the family.[25]

Although the majority of families are able to adjust during this crisis, some are overwhelmed to the point of dysfunction. Like any other traumatic situation, for a small percentage of families, the crisis is sufficient to collapse an already overloaded family system.[9] Family functioning, adaptability, and resilience are affected by many factors, including the family's baseline functioning before their child's critical illness.[25] The family that lacks the financial, physical, emotional, or psychological resources to cope with the crisis of a hospitalized child deserves special consideration. All available resources should be directed to the family to assist them in their ability to support their ill child. A multidisciplinary team, including a social worker, child life specialist, pastoral care provider, and psychiatric care provider, when appropriate, may assist the family in resolving the concerns distracting them and enhance their coping skills, allowing them to focus on their child. It is helpful to designate one health care provider as the spokesperson with whom the family can speak daily for medical updates, which reduces the opportunity for confusion or contradiction among caregivers. If the family is still unable to provide a calm, nurturing atmosphere for their child after provision of these additional practical, psychological, and spiritual supports, it may become necessary to structure or limit the family's participation.

Culturally Sensitive Care

Culture is a pattern of learned beliefs, shared values, and behavior that includes language, styles of communication, practices, customs, and views on roles and relationships. It goes beyond race, ethnic background, and country of origin.[26]

Because individual clinicians cannot be knowledgeable about all cultures or even the major groups of organized religions, the unit should develop principles of cultural competency.[27-29] Many hospitals are creating Centers of Diversity and Health Equity to assist in developing and implementing policies that create and maintain a culturally competent environment. Providers can be trained in interpersonal interpretation—that is, to look beneath the surface when communicating with someone from another culture, to listen actively, and to seek out the real meaning underlying a family member's statement.[26] Many hospitals are creating Patient Navigator Programs to build trust with families in their own language and ensure that families understand the care that is being provided. Patient navigators are trained, culturally sensitive health care workers who provide support and help families navigate through the various components of the health care system. Additionally, patient navigators help providers understand families' particular needs.

Taking into account the diversity and uniqueness of each patient and family is important if one is to provide respectful care and services that are responsive to their language, race, gender, culture, spiritual values, family configuration, education, and other attributes. One of the most effective ways to understand the needs of an individual family is to ask. Often the spokesperson for the family can provide the team with the necessary information that will assist in the care of the critically ill child.

Professional Boundaries

Although family-centered care principles require a shift in professional practices and a change of culture within the hospital, professional roles still must be clearly defined and respectfully maintained. When entering the child's room, clinicians should introduce themselves to the family and explain their role on the care team. Respect toward other members of the health care team should be demonstrated at all times. It is crucial to maintain good working relationships when caring for a critically ill child whose clinical condition may change quickly and whose outcome may depend on continuous collaboration between persons of many disciplines.[16] Stable, trusting relationships between a patient, family members, and providers is critical in treating and managing a patient's illness. However, developing and maintaining stable, trusting relationships in the PICU can be challenging. Developing a

Table 9–1 Family-Centered Care Concepts

Traditional	Contemporary	Concepts
Deficit	Strength	Highly involved parents who require detailed information and continual presence with their child have often been considered a distraction to the delivery of care because of the time and energy required by the health care team to attend to these parents. Sometimes, the parents have been thought of as a nuisance. The paternalistic model of desiring parents to be passive observers of care is now called into question. A family-centered care approach considers involved parents to be a strength to the child and multidisciplinary team. Appropriately incorporated into the delivery of care to the child, the parents can be an important asset.
Control	Collaboration	Traditionally, the health care team has controlled the degree of involvement parents had in their child's care. This control has included all aspects of care, including access to the child, information, and even the care being delivered. The contemporary approach of collaboration incorporates the parents in all aspects of care and supports the parents as an equal team member for the optimal delivery of care to their ill child.[59]
Expert	Partnership	In the oldest and outdated model of critical care, the delivery of care was driven by the medical physician without input from other disciplines. As critical care has become more complex and progressed over the years, most intensivists value the contributions of a number of experts from a variety of disciplines, such as nursing, respiratory care, social work, and pharmacy. Partnerships have been established with a variety of experts to deliver comprehensive critical care. Partnering with parents places value on what the parents bring to the team, such as continuity, history, and how the child responds to illness and treatment.
Information gatekeeper	Information sharing	Health care team members and institutions have desired to control information. This control of information has been considered to be related to the parents' lack of ability to understand medical concepts and/or health care providers' fears of litigation. Information sharing actually decreases the risk of litigation and gives parents the necessary tools to make complex, informed decisions.
Rules	Guidelines	Historically, administrators and managers have set rules for how family members should behave while in the hospital. The connotation of the word "rule" is considered harsh and not congruent with the approaches of family-centered care. The use of *guidelines* for behavior is more respectful and demonstrates an attitude of flexibility and collegiality.
Visitors	Parents	In some of the older models of critical care, parents had strict restrictions on how much time they were permitted to stay with their child. For example, in some settings, only weekly visits were allowed. More recently, visitation has been liberalized, but some units still limit visitors to certain hours of the day or specific time increments. Parents should be exempt from most rules of visitation. Parents should be considered an extension of the child and should have full access. The most respectful language is not to call the parents visitors at all but to reserve that term for casual acquaintances of the child or family, such as a school friend or teacher.
Rigid	Flexible	Some units still approach unit standards by rigid rules, setting policy in the strictest sense. In this traditional model of strict adherence to policy, the individual needs of the patient and family are not respected. Some units set policy based on experience with the worst circumstances. Families ask that policies be created to meet most families' needs with room for flexibility and regard for the needs of the child.

clear understanding of the concept of boundaries and therapeutic relationships and a skill set in these areas is crucial.[30] A therapeutic relationship is defined as "an interactive relationship with a patient and family that is caring, clear, boundaried, positive, and professional."[30] Therapeutic relationships involve ensuring that patients' and families' needs are met while maintaining personal and professional boundaries. Providing services beyond the scope of your professional role undermines the health care team partnership, no matter how well intended your actions. It is the professional's responsibility to maintain boundaries and help parents and families maintain theirs.

Personalizing Care

The environment of care has a growing impact on families.[26] Creating an opportunity for the individual characteristics of the child to be expressed when the child is unconscious promotes humanitarianism in the PICU setting. Individualizing the environment to include photos, favorite toys and blankets, music, and audio recordings of siblings and family members is an effective technique. The creation of a collage or poster about the child and family is an activity that often is well received by families and clinicians alike and can be therapeutic for the family. Mementos from home draw providers to the bedside and promote conversations that provide a glimpse of the child when he or she was well,[30] assist the care team in getting to know the family, and help the team see child and family as people, not just diagnoses.

Communication

The highly technical nature of the PICU environment and its multiple caregivers, paired with parental stress, creates a complex situation with a great potential for miscommunication. It is important to establish clear lines of communication both among the various members of the health care team and between the team and the family.[26] Because the stressed family is less able to take in, comprehend, and retain information,[21,31-33] explanations must be clear, concise, and repeated.

Special attention must be focused on avoiding medical jargon and abbreviations. Routine care conferences should be held because they are an important avenue to provide information, share opinions, and reach consensus. These care conferences may be held to provide medical updates or make treatment decisions.[26] It may be helpful to advise parents to maintain a bedside journal or log in which they can note information given and list questions to be addressed later. Placing a board in the child's room that lists the names of the care providers, the daily plan, and goals and that is updated daily is helpful to families. Collaborative care planning will help reduce stress for all persons involved in the care of the patient and may resolve or defuse conflicts between the family and the medical team or within the team itself.[26]

Daily Communication

To reduce confusion or contradiction among the caregivers' messages, it is helpful to designate one health care provider as a spokesperson with whom the family can speak daily. Ideally, this person should be the attending physician.[27,34] The content of the communication should include the status of the child, the results of any tests, procedures, or consultations, and the plan of care. Different families prefer different communication styles; the best practice is to ask them how they like to give and receive information. One helpful mnemonic that has been shown to improve communication in the ICU is VALUE (***v***alue, ***a***cknowledge, ***l***isten, ***u***nderstand, and ***e***licit).[35]

Daily contact should allow sufficient time for questions and support and should occur in a quiet environment. The decision to talk at the bedside versus at a remote space depends upon the level of consciousness and developmental level of the child, the type of information to be communicated, and the desires of the family. Generally, in the case of a conscious adolescent or an older, mature school-aged child, it may be most appropriate and respectful to include the patient in the conversations rather than exclude him or her. Alternatively, initial conversations may be conducted away from the bedside and then duplicated at the bedside of the awake, more mature child. Ideally the health care provider should sit down with the family and allow the conversation to include a period of silence to ensure that the family has ample time to voice questions and concerns. Listening is one of the most highly rated traits of health care providers by family members and leads to greater family satisfaction with care.[36]

Consultants should communicate directly with the attending physician who is coordinating the care before talking with the family. Parents can become confused and overwhelmed when they receive different portions of information from a variety of providers. If care is complicated or if the ICU stay extends beyond a week, arranging a family care conference that can include more family members and all important members of the care team is strongly encouraged. Care conferences can provide the opportunity for more in-depth discussion and more time for family questions and comments and should be considered a critical aspect of ICU family-centered care.

Respectful Language

All written and verbal communication should be respectful in tone and content; it also should be concise and consistent. Effective and understandable communication between parents and the medical team benefits the child, decreases parental stress and anxiety levels, and is the basis for trust.[37] It is helpful to communicate information in a variety of formats.[4] Information should include an explanation for why some restrictions are necessary (e.g., safety, a sterile environment, and isolation) and why some behaviors are prohibited (e.g., consumption of food in the patient's room and cell phone use). Table 9-2 provides examples of ways to communicate ICU restrictions without being perceived as being unnecessarily controlling or demeaning. Most families respond positively to guidelines that protect their child, especially when the guidelines are presented with a rationale. Staff should be reminded that most parents have never had experience in an ICU and do not arrive understanding expected behaviors. Questions should be answered honestly in terms families can understand.[26] Patients and parents need to be treated as equal partners as much as possible and be allowed dignity and control to the extent that is practical.[16] Respectful language between staff members is important, especially in the presence of family members. Family members who are sleep deprived and stressed may misunderstand conversations that are not respectful. This situation may lead to increased worry or lack of trust in their care providers' ability to work together as a team or even in their overall competency. Additionally, family members, who often seek information, may listen for inconsistencies by observing disagreements. Its important for the entire team to understand how conversations and language that is not collaborative can be misunderstood.[38] Table 9-3 provides examples of ways that problems may be communicated among staff that are less likely to add to patient and family distress.

Table 9–2 Examples of Traditional and Respectful Language Used with Visitors

Traditional Language	Respectful Language
SIGNAGE	
Parents only after 8 PM	Visitors are welcome from 10 AM to 8 PM. Parents are always welcome.
No smoking	A site for smoking is provided on the first floor outside the entrance.
SPOKEN	
You are not allowed to eat here.	Let me show you where you can eat.
You need to clean your hands.	Let me place that gel where you can reach it.
You can't use your cell phone here.	Let me show you where you can use your cell phone.

When English Is not the Primary Family Language

Families who do not speak the primary language of the medical team have considerable additional stress. Expecting them to be able to conduct conversations without a professional interpreter for either in-depth discussions or short updates or questions during the day is an unreasonable expectation. Even families who speak "pretty good English" will have more

Table 9–3 Communication Among Staff Promoting Patient and Family Trust

	Not Respectful (Does not Promote Trust of Parents)	Respectful (Demonstrates Collaboration)
RN to MD	You ordered that test wrong.	I was notified that we need to change how the test was ordered; I can show you how.
RN to MD	You ordered a 10 times overdose of morphine.	Can you please change this order? Our typical dose of morphine would be 1 mg for a patient of this size.
RN to MD	You just contaminated your gloves.	Let me grab you a new pair of gloves.
RN to resident	You'd better not wake up that baby; he just got to sleep.	He just fell asleep—would it be possible to examine him later? I can call you.
RN to resident	Why don't you know how to order this medication?	Do you want to grab your fellow to help you order this medication?
MD to RN	Why didn't you call me with this result last night?	Please feel free to call me anytime; I would appreciate hearing these results, even if it is in the middle of the night.
MD to RN	Why did you give him so much sedation? He is too sleepy.	How much sedation has he had?
MD to RN	Why did you lose that arterial line?	What happened to the arterial line?
RN to RT	You did not clean your hands before touching the patient.	Let me grab you some hand gel.
MD to family	The nurses should have called me about this; how long has this been going on?	Can you tell me how long this has been going on?

MD, Physician; *RN,* registered nurse; *RT,* respiratory therapist.

difficulty than native English speakers in processing new information during this time of crisis. Interpreters are essential in situations in which a language barrier exists.

Care should be taken in choosing an interpreter. The complex medical issues that arise in the PICU require a trained interpreter for effective communication to occur.[26] Using another family member as an interpreter is not advisable because it puts undue pressure on that person. In addition, the interpersonal dynamics of their relationships can influence communication and compromise the patient's confidentiality or may even lead to inaccuracies.[26,39] When an interpreter is not readily available onsite, use of interpretation services by telephone is preferable to use of a family member. It should be the standard of care to provide professional in-person interpreter services at least daily.

Access to Information

Second only to their need to be with their child, parents need easy access to information.[32,40-44] In addition to conversations with the health care team, parents should be supported with regard to access to their child's medical record. Access to the same information available to the other health care team members in the same format encourages trust and cooperation. Having a health care professional available for clarification as needed may be helpful but is not mandatory. Requiring parents to go through administrative or legal protocols to gain access to this information is destructive to the partnership of care. In that environment, ultimately, no matter how conscientiously it is delivered, the care of the child suffers.[45]

Technology

As the public becomes more technologically sophisticated, they expect the same sophistication in the ICU, including Internet access at the bedside. Traditionally, families may have been discouraged from using the Internet to obtain information, but most care providers realize that a large portion of the public uses the Internet as their first source of information. Providers must find a way to partner with parents and, rather than discouraging use of the Internet, work with them to explain what they are finding and provide appropriate sites that include accurate information and are sanctioned by the hospital and/or subspeciality.

In addition, as the public has become more e-mail savvy, they expect rapid communication and a timely response to their questions, regardless of whether an individual provider is present. Some units could allow families to e-mail the attending physician, with time allocated for the physician to respond daily. Furthermore, a growing number of ambulatory care centers provide patients with access to their electronic medical record. This same system could be used for critically ill patients. Although one can imagine challenges that might occur with any given system, providing access to laboratory results, diagnostic studies, and even surgical reports could facilitate knowledge and understanding of particular conditions.[25,46]

Rounds

Family-centered care can be effectively enhanced by inviting parents to attend and participate in daily multidisciplinary rounds. To ask parents to leave when the multidisciplinary team is focused on their child fosters mistrust and decreases efficiency. Traditionally, parents have been intentionally excluded from rounds, or they have been allowed to stay but not encouraged to contribute. Clinicians have feared that parents may misinterpret information, become concerned about staff competence, delay rounds by asking too many questions, or unintentionally inhibit necessary open and honest communication between health care providers about the patient's care. Contrary to these concerns, parents' participation in

rounds works well, improving parental satisfaction, patient care, and teamwork.[47]

Family participation in rounds provides an opportunity for open communication for families, patients, and the entire health care team. All team members should be encouraged to contribute information and ask questions. Parents often are excellent historians and keen observers of their child. Parents should be recognized as their child's expert, having a unique perspective on how their child responds to illness and treatment. Parents also can provide needed continuity with large and constantly changing care teams.[32] It is important to orient the parents to the purpose and system for rounds upon admission to the hospital. If rounds are to be the primary contact with health care providers for the day, the parents need to be informed of this so they are prepared to ask questions and to ensure they understand the care being delivered. The team should provide adequate time to conduct rounds if this is the model that is developed. If the model does not provide time for questions from parents, this situation should be communicated to the parents early on so they understand their role and do not become disappointed or frustrated by incomplete communication during rounds. In this case, the attending physician needs to ensure that he or she has time later in the day to meet with the parents.

Shift Report

Traditionally, parents have been asked to leave when nurses make their shift report. The same concerns and benefits related to rounds are applicable here. When concerns about confidentiality or legal issues exist, staff can accommodate the parents by making their report elsewhere. Other than factors relating to legal issues of abuse or neglect, parents have a right to know the details of their child's care, so information communicated through the report should already be available to the parents, including unplanned events.[9]

Depending on the unit design, concerns may exist about privacy and confidentiality of information when patients are in a shared space (e.g., double rooms and wards). Providers should be sensitive to issues of confidentiality but also should be reminded that parents, who often are present continuously through the day, may be very knowledgeable about the condition of their child's roommate, just by virtue of being present and overhearing routine conversations of care. Parents also are responsible for protecting the privacy of all patients and for being respectful. Most hospital brochures and parent handbooks speak to this point.

Disclosing Medical Errors

Disclosing errors or unplanned events demonstrates the principle of communicating complete and unbiased information in ways that are affirming and useful. As Levinson[48] comments, "Building a relationship in which the patient (and family) feels respected, supported, and trusting is critical to patient and family satisfaction and malpractice risk reduction." The person delivering these messages needs to follow the same principles that one does when conveying any other difficult news: Tell the parents as soon as feasible in a private setting. Communicate without blame how the error occurred, let them know what to expect, and help them to understand the implication of the error and its effect on their child. Elicit and acknowledge their responses. Parents should be reassured that everything will be done to prevent the incident from recurring. Clearly communicate any plans for follow-up, which includes identifying a contact person. All medical errors, even those that have minor or no effects on the child, should be reported.

Multidisciplinary Team

A variety of disciplines are needed in the care of any critically ill child. The components of the team are dependent on the needs of the child, although a physician and nurse are always included. The assignment of a consistent physician and nurse has been shown to decrease parental stress.[33] This assignment may be difficult to accomplish, particularly during an extended ICU stay; however, every effort should be made to ensure health care provider continuity. In the course of a child's stay in the PICU, the family will meet many team members. It is important for everyone to understand that any of these team members can become the family's primary source of support. In complex situations, the multidisciplinary team may become quite large and may contribute to family stress. The family should be encouraged to keep a written record of health care providers for clarity. In certain complex situations, establishing a continuity attending physician may be helpful. Regular care conferences also may be helpful in these circumstances.

Social Worker

Social workers are integral members of the health care team, and all parents should have access to a social worker.[28] This individual may be a member of the PICU team or part of a continuity team based on a specialty, such as cardiology, oncology, or organ transplantation. Often PICU admission, critical illness, and trauma are not anticipated and parents are unprepared for the turmoil they are thrown into. Having a social worker available who can provide crisis intervention and assist families in understanding the implications and complexities of the medical situation and the PICU is extremely important. Feelings of helplessness and an overall feeling of being out of control are common among parents,[49] and the social worker's ongoing supportive care, grief/bereavement counseling, and provision of concrete needs are critical in alleviating some of their stress. The social worker can be available consistently, can educate the family regarding how the PICU works, and often serves an important role as a liaison between families and the medical team. Social workers can be advocates for parents as they help them address the special needs of their child and family with the team.

The social worker's initial and ongoing psychosocial assessment of the family can help the medical team provide culturally appropriate and family-centered care. The social worker also provides a liaison with community resources, child protective agencies, and law enforcement when necessary.

Chaplain/Spiritual Care

The chaplaincy service carries an important role in providing respectful spiritual care and emotional support to patients, families and staff. This may take place through conversation and listening, rituals, prayer, help in ethical decision making, and bereavement support. They can offer Interfaith opportunities for worship, celebration, reflection, and spiritual exploration. They can also provide assistance with contacting a local

or hometown faith community or minister, priest, rabbi, or other spiritual leader.

Child Life Specialist

A child life specialist (CLS) should be available to all critically ill children.[28] Factors associated with the highest stress for parents include disruption of normal interactions with their child, changes in their child's behavior or emotions, parents' inability to comfort their child, and having a child undergo painful procedures.[26] The CLSs are members of the health care team who work directly with patients and families to help reduce anxiety and adjust to the hospital experience. A CLS can provide support and create a coping plan with patients to use during a medical test or procedure. They utilize therapeutic and medical play to help patients understand medical procedures and provide ways to express feelings and help maintain a sense of control. A CLS can teach coping techniques, such as distraction, guided imagery, and story telling, as a means to reduce pain and anxiety.[50] Bedside activities can be provided to support a child's need to play. A CLS can work with community resources, schools, and in-home care personnel to assist with the child's transition after discharge from the hospital.

Pet Therapist

Pets are considered by many persons to be part of the family. They provide emotional support for many people, particularly in times of stress or illness. There is growing support of animal-assisted therapy in many areas of health care, including critical care, as a complementary therapy.[51] Benefits for patients include an increase in positive outlook, stress reduction, normalization of the hospital environment, and overall feelings of comfort and happiness.

In general, there are two main approaches to pet therapy in the ICU. The first incorporates the family pet, and the second makes use of a professional or therapy dog. Incorporating the family pet into the child's hospital stay meshes well with the concept of family-centered care. Pets have a significant effect on humans by lowering stress, stabilizing the heart rate, and improving mood. Pets have been shown to prevent depression.[52-55] Many cases have been reported of critically ill patients responding to pets in a positive way, such as by becoming more interactive and willing to participate in their own care and recovery.

It may not always be feasible for a child's pet to visit because of distance, the animal's temperament, or other logistical realities. An alternative to having the patient's own pet visit is the presence of a professional or therapeutic animal. Although the emotional tie to the therapeutic animal will not be present, benefits similar to those seen with the patient's personal pet can be observed.

Parent Advisory Council/Family as Consultant

One of the principles of family-centered care is the collaboration of providers with patients and families.[17] As expert "consumers," families bring an experiential perspective and creative solutions that help advance the best possible care.[22,56] Many hospitals have created Family Advisory Councils composed of parents who have had a wide variety of health care experiences. They advise the hospital on how it can more effectively meet the needs of children and their families. Additionally, they can provide recommendations and feedback on policy, programs, and organizational changes that affect the family experience. Family "consultants" can be used at the unit level for a variety of activities (Box 9-1).

Box 9–1 Family Consultant Activities

- Teacher/orienter of new nursing or medical staff by sharing stories and answering questions about the experience as a parent in the PICU
- Author and analyst of satisfaction surveys
- Member of focus groups that are considering changes in service delivery
- Co-leader of a parent support group
- Consultant on orientation materials for families
- Consultant for PICU remodel or redesign team
- Committee member for relevant topics, such as ethics or quality improvement

Parent Support Group

While their child is in the PICU, parents naturally seek the understanding of other parents in similar circumstances. Availability of parent support groups can meet this need.[20,57,58] These groups may be led by a trained parent volunteer and/or a professional. Participation can help to normalize the hospital experience by providing an opportunity to share stories in a supportive environment. Other more structured parent support groups and sibling groups meet regularly and usually are convened around a specific population, such as organ transplant, cancer, or bereavement.

Volunteers

Volunteers play an important role in providing normal activities for ill children. They can engage in distraction and quiet play, such as reading or watching a movie, or more active play, such as games and crafts.[31] Volunteers also can be trained to perform more advanced tasks. For example, volunteers who receive training in crisis intervention can staff the waiting room. Another example of the use of volunteers can be found at Children's Hospital in Seattle, Washington, where volunteers in an "Aunties/Uncles" program develop and maintain an emotional, nurturing bond with a specific hospitalized infant or child when the parents are unable to provide that time at the bedside. These specialized volunteers commit to spending 5 to 6 days per week at the hospital for a minimum of 6 months. Parents give their permission for this surrogate to be with their child.

Financial Services

Although paying the bill usually is not the concern of the health care team, it may be a serious stressor for a parent in the PICU. This added stress can affect the parent's ability to make careful decisions. In some cases, parents may worry that their child will not receive the best care because of their limited financial resources. Recognition of socioeconomic constraints such as the inability to pay for care or to be away from work and trying to alleviate these hardships are important aspects of family-centered care.[16] Providing a financial counselor who can coordinate care with insurance carriers and identify alternative sources for payment can greatly reduce the anxiety of the parents.

Ethicist

Ethical dilemmas are inherent in modern medical practice and are frequently identified in the PICU. That said, a large proportion of what appear to be ethical dilemmas are frequently

failures in communication, both between staff and between staff and the family. Improving communication at all levels and at all times will greatly help to prevent and reduce disagreement and the need for ethical intervention. For true ethical dilemmas, training staff in ethical principles and having an ethicist as part of the core multidisciplinary team can foster open discussion and resolution of difficult issues for the entire team, which includes the family.[59] Whenever possible, it is most beneficial to have an ethicist present on a regular basis rather than only during a crisis. Because ethical concerns are recurrent, having a familiar person with whom to consult is a way to be supportive of staff and families.

Palliative Care

Pediatric palliative care services complement other health care goals and should be widely available in the PICU. Palliative care teams care for a wide variety of patients and ideally become involved at the time of a life-threatening diagnosis.[33,60] Palliative care resources are not limited to end-of-life issues and hospice care. In fact, palliative care complements cure-directed therapies. Because of the misconception that palliative care is limited to end-of-life issues, many pediatric palliative care teams around the country are changing their names to Pediatric Advanced Care Teams. The trained palliative care expert can facilitate discussions between the medical team and the family that takes into consideration the preferences and values of the family, medical indications (benefits and risks), quality of life, and contextual issues such as cultural, spiritual, and community supports. This discussion is coordinated with health providers and family members, resulting in the completion of a comprehensive decision-making tool. This tool sets the care plan, which follows the patient through his or her illness to the return home.[61] This document, which is revised as needed, allows for earlier coordination in the hospital and within the community, resulting in more consistent and compassionate care on all levels. In complex situations, the palliative care team member can provide excellent continuity of care, both within the PICU and beyond.

Access Concepts

Access to their child is probably the single most important issue for a family with a hospitalized child.[1,3,5,9,32,41,62] For the child, the family provides a reassuring constant in the unfamiliar PICU environment. To mitigate the anxiety experienced by families in crisis and the displacement of parental roles, access should be supported 24 hours per day, with clear communication related to the importance of parental involvement. Parents should be viewed as partners in care rather than visitors. Additionally, to the extent possible within the constraints of the medical care, parents should be given every opportunity and encouragement to have physical contact with their child. Parents can be leery of medical technology, and staff should help them overcome this uneasiness.

Admission Process

The admission process can be frightening for the parents and child, especially in cases of emergent or unplanned admissions.[63] Every effort should be extended to help the parents acclimate to the new environment with compassion, courtesy, and time. Parents report a loss of control, which can be unbearable when they are separated from their ill child. To support the child and the parents, caregivers should invite the parents to be part of the admission process and support them in their desire to remain with their child.[1,21,32,63-65]

If parents cannot be directly at the child's bedside because of space limitations or caregiving tasks, a space should be provided for the parents where they can see their child. They usually understand the need to be away from the bedside in this instance and, upon being given a brief explanation and a dedicated space near their child, they usually are tolerant of the separation. As soon as feasible, a caregiver should provide the parents with some initial brief information. Because anxiety greatly affects short-term memory, it often is difficult for stressed parents to take in detailed information early on. Once the child is stabilized and caregivers have more time to devote to the parents, caregivers can sit down with the parent, either at the bedside or in another confidential space, to provide more information.

The initial information given to parents should include the condition of the child, what has been done so far, and the plan of care. Parents often request a prognosis as well. When done well, this discussion is a predictor of later comprehension of what is communicated by the health care team.[27] Once the child is stabilized and the parents have spoken with the physician, cues can be taken as to when the parents are ready for a general orientation to the unit (Box 9-2). For a scheduled stay in the PICU, this orientation can most effectively be done prior to the admission.[66]

Sibling Participation

Siblings are an important but often overlooked part of the process of adjustment for patients and families to hospitalization. Sibling presence at the bedside should be supported based on the needs of the patient, parents, and sibling.[9,67-71] Siblings have not always been welcome in the PICU, although the concern that young siblings pose a greater infectious risk to the patient than do adults was disproved in the 1980s. Some persons fear that siblings will become frightened by what they see. However, siblings often appear to accept the environment better than do some adults. Often the sibling's imagination about the condition of an ill brother or sister is much worse than the reality. During an initial visit by siblings, time should be spent preparing them, the parents, and the patient for the hospital experience.[67] Any trained team member can prepare

Box 9–2 General Orientation to the Unit

- Access to the unit
- Communications within the unit (telephone, pager, computer)[56,81]
- Bedside accommodation of family members
- Handwashing protocols
- Isolation protocols
- Sibling visitation guidelines
- Sleep accommodations
- Eating/drinking possibilities at the bedside and within the hospital
- Clinical team member identification and roles
- Multidisciplinary rounds orientation
- Registration paperwork

the family, but the preparation might be most effectively done by a social worker or CLS. The patient's condition should be explained to the sibling so the interpretation is not left up to the child's imagination. It often is helpful to show the siblings a photo of the patient and the room and discuss what will be seen. This step helps prepare siblings for what they will see. Siblings should be allowed and prepared to visit, but they always should be asked if they want to change their mind, and their decision to decline a face-to-face contact should be respected. During the visit, a clinician should be available to support the siblings and answer questions. Following a visit, a short debriefing is helpful to answer additional questions and support siblings in expressing their feelings. Providing materials for the child to prepare a memento, such as a card or drawing, to be left at the bedside can be therapeutic for the entire family.

Family Space

Family-centered care principles can be demonstrated by the physical setting.[33,43,72,73] The patient's bedside should include dedicated space for families. The space should include an area where parents can sleep so they can stay overnight if they wish, storage, individualized lighting, and a phone with voice mail and computer access. Additional support space can include sleeping facilities in close proximity to the PICU. Parents should have access to shower and laundry facilities, a cafeteria, and transportation.[20]

Participation in Care

Parents are better able to cope when their role as caregiver is maintained.[1,6,7,21,43,64,69,74,75] Staff are accustomed to providing all the care for their patients, and they often feel that parents expect this care. Yet for many parents, the provision of such care can be alienating because they may feel incompetent to care for their own child. Staff can help parents provide care for their child, thus promoting the parent-child bond and improving the self-esteem of the stressed parent.[7] Staff, especially nurses, can collaborate with parents in defining the kind of care both parents and caregivers are comfortable in providing. Parents may feel frightened by their child's appearance or overwhelmed by the technology, and they require assistance in developing their new role as parents of a critically ill child. Part of routine care in the PICU should include the education of parents on the technology attached to their child, such as monitors. Traditionally, some nurses have encouraged parents to ignore the monitor or not pay attention to it, trying to get the parent to focus on their child and not be concerned about every beep and alarm. It is very difficult for parents to disregard these devices that are attached to their children, and not educating families has been shown to increase their stress level.[76] The clinician can be most effective by clearly communicating safe and appropriate care for the individual patient and modeling the behavior. This modeling may be as simple as holding the child's hand and helping the parent to do the same. Parents can participate more actively as well. They can be given options, such as assisting with bathing, positioning, or massage.

Procedures

Clinicians may have concerns about parents' presence during procedures, but a growing body of evidence demonstrates that parents want to be present, and this approach generally works well.[77-85] In academic hospitals where junior staff are learning how to perform procedures on patients, clinicians may feel uncomfortable with parents observing. Because the teaching process will occur whether or not the parents are present, it is honest to support the parents' presence if that is their preference.[9,82] As with any event, the parents should be prepared for what to expect. In addition, parents should be told who will be performing the procedure, any teaching that will take place, how the parent can support the child, and where in the room they can safely remain.

When the parents choose not to stay or cannot be present, they should be provided a comfortable place to wait that is close to the PICU. There should be a plan for communicating with the parents during the procedure and at its conclusion. If the child will be sedated for the procedure, the parents should be allowed to stay with the child until he or she has been sedated and then brought back to the bedside at the conclusion of the intervention.

Resuscitation

Clinicians have expressed a number of concerns related to parental presence during their child's resuscitation (Box 9-3). However, increasing evidence and a wealth of clinical experience supports the parents' presence.[14,82-95] Parents may wish to be present even during resuscitation. Preparing them for what they will see is an important aspect of supporting them so they can be at the bedside. One of the primary benefits is that the parents can see that every effort was made to save their child. Often when parents are not allowed to be present, their imagination of what is happening behind closed doors is worse than the reality. They may come to mistrust the team and begin to question what really happened in their absence. Additionally, parents may believe their presence gives their child strength and that it is important that they be with them spiritually. Parents come to trust the health care team more because they witness the team working together in a common effort to save their child. Even in cases in which resuscitation fails, the partnership developed between the parents and health care providers previous to and during the resuscitation can be helpful for the parent's acceptance of the child's death.[96,97]

It is important that parents be given a choice of whether to be present. In all cases, a staff member should be assigned to the parents to explain the care being given to their child. Ideally the parents should be familiar with this caregiver, but this scenario may not be possible, nor is it essential. The caregiver should give brief explanations of what is occurring, answer questions, and act as a liaison between the resuscitation team and the parents. This individual should be focused on the parents and not

Box 9–3 Clinicians' Cited Concerns/Fears Regarding Parents' Presence During Resuscitations

- Interference with the resuscitation
- Misinterpretation of the team's performance
- Liability risk
- Team competence questions
- Familial emotional injury
- Staff uncomfortable with grieving family members present
- Distraction, lack of concentration by medical team

be directly involved in the resuscitation. Because most units have preassigned roles for resuscitations, one should be designated for parental support. Finally, families should be offered the opportunity to be alone should they feel the need.

In some units, the parents of other patients are asked to leave the area when a resuscitation is occurring. This practice should not be routine unless space is extremely limited and the parents would interfere with the ability of the team to deliver the care. Parents should stay with their own child so that they can comfort them in the midst of what is happening around them. It can be frightening when a child is separated from a parent and is left behind, unsupported, during a crisis. Parents can be helpful by staying with their child if staff are pulled to another bedside to assist with an emergency. Parents also can share in the experience with their child and provide ongoing and future support related to the event.

Transferring out of the Pediatric Intensive Care Unit

Transfer from the PICU can be a time of anxiety and uncertainty. Families experience loss when they leave caregivers with whom they have developed relationships during crises. Among the fears reported by patients and families is not knowing what to expect from unknown caregivers. Additionally, they report anxiety related to the higher patient-to-nurse ratios and leaving an area where every patient physiologic event is closely monitored. The family can benefit from a variety of approaches to allay their anxiety, all geared toward providing encouragement, information, and inclusion in the process.[98-101]

If the child has been in the PICU for an extended period or the parents are particularly anxious, a care conference can be arranged with staff from the receiving unit to delineate who will be caring for the child when the child is transferred, discuss the goals of care, and answer any questions the parents may have. PICU staff should be careful to speak positively about staff in other areas of the hospital and reassure families about their competence in handling emergencies.[100] Written information about the transfer has been shown to significantly reduce parental anxiety about imminent transfer from the PICU.[98] Other potential interventions for improving the transition for families, especially those with long ICU stays, are noted in Box 9-4.

Compassion Fatigue

The very nature of the work in the PICU puts care providers at increased risk of burnout and compassion fatigue (also known as *vicarious traumatization*). These two syndromes can affect the care provider's mental and physical health, contribute to impaired job performance and lower team moral, and even lead to suboptimal quality of care, medical errors, and lower patient and family satisfaction.[102] To cope with the difficult nature of this work, many care providers distance themselves emotionally from their work. Care providers can develop detached responses to families and their experiences and suffering because of the perception that detachment protects against burnout and compassion fatigue.[103] Contrary to this belief, a recent study found that a practice called *exquisite empathy*, described as "highly present, sensitively attuned, well-boundaried, heartfelt empathic engagement,"[104] actually was protective against burnout and compassion fatigue.[102] To provide optimal family-centered care in the PICU, it is imperative to learn about these syndromes, educate staff, employ organizational changes, and encourage staff self-care practices to mitigate symptoms.

Box 9–4 Activities to Prepare for Transfer

- Initiate transfer process early
- Remove monitor well before transfer if the patient will be off a monitor in the receiving unit
- Identify a primary nurse prior to transfer who will meet with the family to help them plan their involvement in the patient's care
- Conduct a tour of the receiving unit
- Provide written information prior to transfer, including descriptions about the receiving unit and its staff
- Assign a PICU liaison check-in with the family after the transfer

References are available online at http://www.expertconsult.com.

Chapter 10

Ethics in Pediatric Intensive Care

Joel E. Frader and Kelly Michelson

PEARLS

Major Principles of Medical Ethics

- Beneficence: Provide care that benefits patients
- Nonmaleficence: Avoid harming patients
- Autonomy: Individuals should decide what constitutes their own best interests
- Justice: Provide service fairly, without bias from factors irrelevant to the medical situation

Informed Consent

- Patients or surrogates must have adequate decision-making capacity (competency, in legal terms)
- Patients or surrogates must have the ability to understand and communicate about the medical situation
- Patients or surrogates must have the ability to manipulate information and deliberate about the nature and consequences of alternatives
- Patients or surrogates must have the ability to make a choice among alternatives based on relevant values
- Decision makers should have adequate, comprehensible information
- Professionals should assess the decision maker's understanding of the situation and alternatives
- Valid choices require freedom from undue pressure

Decision Standards

- Substituted judgment: Surrogates decide based on knowledge of the patient's views of the situation or, if that knowledge is unavailable, on the patient's general beliefs and lifestyle
- Best interests: Surrogates decide based on information about the patient's situation, alternatives, and overall judgment about which course best serves the patient

Intensivists struggle with value questions all the time, regardless of whether they explicitly label the process "ethical decision making." This chapter addresses some of the common and more important moral questions arising in pediatric intensive care units (PICUs). It aims to clarify how the values of patients, families, health care professionals, and those of the wider society do and should influence the practice of pediatric intensive care. Although the goal of the chapter—helping intensivists to help patients and families better—is practical, it is best served if the reader appreciates a small amount of the theory that supports much of contemporary medical ethics.

Moral Theory

Medical ethics does not constitute a completely independent field. Most persons think of medical ethics as an applied discipline of the wider branch of philosophy that is ethics. Like most other intellectual pursuits, ethics has developed according to several theoretical traditions. In Western ethics, two particular ways of thinking have dominated for some time. Because these approaches may yield rather different perspectives on some questions, they deserve mention.

Consequentialism

One tradition, known as *consequentialism,* examines the correctness of an action according to what effects the act will likely have on the real world. Good actions produce the most favorable ratio of happiness, pleasure, or some similar value to unhappiness or a similarly disvalued result. The utilitarian philosophers Bentham and Mill enjoined us to seek the greatest happiness for the greatest number of individuals possible. These theories emphasize the social nature of human moral action, requiring calculation of the consequences of an act. Only after determining the impact of an action for those directly and remotely involved can a person pronounce ethical judgment.

Deontology

The other main approach to moral theory proceeds from different premises. Deontology (from the Greek word for duty) holds that some actions have intrinsic moral worth. Many religious moral rules conform to this view. Hence the Ten Commandments pronounce that we should not kill. Other approaches, such as Kant's categorical imperative, also proclaim universal truths and rules that persons should honor irrespective of the consequences.

A consequentialist might claim that removal of organs from persons in a persistent vegetative state does not harm the individuals because they can no longer experience meaningful life, or even hunger or thirst. The consequentialist also might assert that harvesting the organs best serves the class of patients in a persistent vegetative state because, overall, transplantation fosters the well-being (and by implication, happiness) of humans who can actually benefit from continued treatment. Some deontologists, however, surely would argue that the killing that necessarily results from the removal of vital organs, no matter what the intent, undermines human dignity and is morally impermissible.

Prevailing Principles

Despite the "opposing" traditions of ethics, most persons in medical ethics agree on a small number of important principles that should guide medical behavior. The reader should note, however, that narrow adherence to these notions encourages an oversimplified approach. Medical ethics neither begins with nor ends with the principles named here. A more nuanced view includes many more considerations and a clear sense of how different ideas interact, especially how some moral duties conflict with others. Nevertheless, a few guideposts may help intensivists understand that medical ethics, like clinical medicine, uses formal logic and has a recognizable structure.

Beneficence

The first principle, beneficence, demands that physicians provide care that benefits the patient. This principle may seem self-evident until you remember that many potential conflicts of interest can influence medical decisions. For example, parents of children may face tragic choices about the support of a sick child whose survival could endanger the economic or psychological integrity of the rest of their family. Other conflicts may involve doctors, especially those in a fee-for-service system, who benefit financially from providing services that promise only marginal, if any, additional benefit.

Nonmaleficence

Beneficence contrasts with nonmaleficence. According to this notion, doctors have a duty to avoid harming patients. Again, the idea may seem obvious, but the practical application involves considerable complexity. For example, when deciding whether to use extracorporeal membrane oxygenation for a desperately ill infant with a diaphragmatic hernia, you must consider the possibility that the technology will extend the life of the baby only by several days but may cause discomfort to implement and maintain; that is, no long-term benefit will accrue to balance the burden of the procedure. Similar reasoning might apply to cases of malignancy for which chemotherapy and other treatments have no or little likelihood of producing a cure or substantial life prolongation, whereas the treatments impose burdens, such as nausea, itching, extreme fatigue, and high risk of infection. The principle of nonmaleficence reminds us to take potential pain and suffering seriously before recommending no-holds-barred medical intervention.

Autonomy

When considering which medical treatments will best help a patient and what harms to avoid, a natural question arises: whose perspective should we use? The principle of autonomy suggests that we must respect individual human differences. To the extent possible, persons should decide for themselves what is in their own best interests. In pediatrics, respecting autonomy can present difficult questions about when children develop the capacity and independence to accept or refuse recommended treatment. The autonomy principle reminds us that individuals or their families often have different values and goals from those of their physicians. Medical decisions usually should be in accordance with the patient's or family's perspective.

Justice

The fourth principle, justice, provides some of the most pressing and challenging dilemmas for modern medical care. Put simply, this principle exhorts us to use our services fairly, that is, to avoid decisions that accept or reject candidates for treatment based on factors that are irrelevant to their medical situation, such as poverty. The application of the justice principle runs into two major obstacles today. First, members of our society seem to have a great deal of difficulty agreeing on what constitutes just or fair allocation of medical resources. Second, we have not yet decided exactly how considerations of justice should affect the medical care system.

Medical goods can be distributed, assuming not everyone can have everything, according to a number of different schemes: based on the likelihood of success; by some definition of need (urgency, desperation); as a reward (for past achievement, for waiting the longest, for future contribution); by equal shares; by random assignment until the goods run out; or, as we often do in our society, by ability to pay. Different philosophical and political traditions support each of these approaches, and we seem far from agreeing on which is best.

With respect to the second issue, some persons urge physicians to ignore financial constraints to do everything "medically indicated" for patients, regardless of the economic consequences.[1] The argument is that, at least for decisions about individual patients, physicians discharge their fiduciary responsibility only by advocating the best, even if most expensive, care. Macroeconomic concerns, regional and institutional issues, and microeconomics challenge this view.

From a macroeconomic perspective, our society resists increasing medical spending as an ever-increasing proportion of total social expenditure (such as percent of gross domestic product). Most Western industrial countries spend on average 9% of gross domestic product on health care. Does the United States get incrementally better outcomes for its 15% or larger outlay?[2] By many measures of public health (e.g., infant mortality and longevity), the well-being of the U.S. population does not reflect our high medical expenses.[2] Similarly, does the way we spend our health care dollar make the most sense? Should we spend great sums of money on expensive intensive care at the end of life for patients with little likelihood of benefit? In pediatrics, we have reason to believe that preventive measures (e.g., immunization and accident prevention) reduce morbidity and mortality rates[3-5] and, in some cases, save money.[3,4]

Regional and institutional economic questions involve matters such as consolidation of care to increase economic efficiency and medical efficacy. However, political and psychosocial factors often lead to duplication of services and diffusion of experience. Certain programs may even create conflicts of interest. For instance, a hospital could offer a particularly scarce and expensive service (e.g., extracorporeal membrane oxygenation or pediatric organ transplantation). The costs of the service might be so high that just a few patients treated "free," that is, without charge to the family, might threaten the economic stability of the enterprise. Such fiscal concerns surely help shape what services institutions offer and the way those services become available (are "marketed") to those in need.

With respect to microallocation, intensivists frequently engage in decisions about the distribution of specific services

to particular patients, sometimes with clear awareness that competition exists under conditions of scarcity. With a nearly full ICU and a large demand for postoperative care for the cases on the next day's operating room schedule, intensivists often must negotiate and juggle, trying to meet varying claims about who should occupy scarce beds and receive nursing attention. Even the decision to use one vasoactive drug or antibiotic instead of a far more or less expensive agent requires an attempt to balance expected benefit against drains on resources. It seems inappropriate to demand that physicians ignore such actual conflicts. Intensivists, like other practitioners, rarely enjoy the luxury of having a single duty to a single patient with an unlimited ability to pay for services. Although doctors might prefer to leave economic considerations to policymakers and the marketplace, justice issues do find their way into ICU routines.

The challenge for the pediatric intensivist involves applying the various ethical principles and perspectives to individual cases and to policies that affect how the unit operates. The following sections focus on a few topics where ethical concerns arise frequently.

Health Care Decision Making: Consent

A major shift in doctor–patient–family relations occurred in the last half of the twentieth century. Doctors now have less freedom to make paternalistic decisions about how to treat patients according to their own beliefs and feelings than they did in the 1950s. With a wider range of technical options, social trends emphasizing individual liberty and consumer preferences, and the weakening of traditional authority and trust in professionals, legal and moral arguments at the beginning of the twenty-first century emphasize patient/personal choice in directing medical decisions.

These trends have become embodied in the doctrine of informed consent. Backed by philosophical arguments concerning the importance of individual and family autonomy, ethicists, legal scholars, and judges have advanced the notion that patients or their valid surrogates have the right to or should, if they wish, determine which of the available medical alternatives to follow.

In most circumstances, minors are legally incompetent; that is, state statutes determine the age at which children become legally entitled to make binding decisions, including those about medical care. In general, children have limited legal rights to make medical decisions for themselves until age 18 years. As a consequence, like other legally incompetent patients, surrogates must authorize medical treatment for children. Usually, parents serve as the valid surrogates for their children. Moreover, informed consent, per se, has limited direct application in pediatrics. Valid consent requires adequate information and understanding, involves judgments about a proposed intervention, and reflects personal values bearing on the situation; thus consent can only be given by a patient with decisional capacity.[6] Strictly speaking, parents or guardians give informed permission, a concept supported by the American Academy of Pediatrics.[7]

When parents or another surrogate provide informed permission for older children and adolescents, clinicians should seek the child's assent when possible. By obtaining the child's assent, clinicians empower children to the extent of their capacity and foster trust in and improve patient-physician relationships. According to the American Academy of Pediatrics, assent should include: "(1) Helping the patient achieve a developmentally appropriate awareness of the nature of his or her conditions; (2) telling the patient what he or she can expect with tests and treatment(s); (3) making a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding (including whether there is inappropriate pressure to accept testing or therapy); and (4) soliciting an expression of the patient's willingness to accept the proposed care."[7] In certain situations, U.S. federal regulations require respecting the child's wishes, such as in proposed participation of a minor in research that provides no substantive potential for individual benefit. In the clinical arena, when treatment refusal is not life-threatening, physicians should make an effort to understand the patient's reasons for refusal and help him or her understand the consequences of such a decision.[6]

Certain legal and ethical exceptions exist where a "child" has decision-making authority for himself or herself. Almost all states have statutory provisions for children to obtain treatment for sexually transmitted diseases without parental or other surrogate consent. In many states, similar laws apply to children seeking contraception, care for pregnancy-related matters (sometimes including abortion), and mental health care, including care for substance abuse. Children may achieve legal status to make their own medical decisions when emancipated. Depending on the jurisdiction, emancipation may mean graduation from high school, joining the armed forces, living separately from and economically independent of parents, or being pregnant or being a parent. Thus under some circumstances a critically ill minor may be legally entitled to consent to or refuse treatment, even over and against parental wishes.

In addition to specific legislative rights for some children to consent for themselves, another legal notion may apply. Courts have used the theory of the "mature minor" in judging whether a child has the capacity and maturity to decide what is best for herself or himself. Such cases typically involve chronic or long-standing medical conditions where the minor has had an opportunity to observe the implications of the disorder; to experience the effects of the disease; and to reflect on the religious, moral, and factual matters relevant to medical decisions. Examples of such situations include adolescents with cystic fibrosis, end-stage renal disease, and muscular dystrophies. The mature minor doctrine allows that, in selected cases, the child may accept or decline life-sustaining treatment, such as dialysis, mechanical ventilation, and transplantation, with or without agreement from the family. Other situations might include those where long-standing and well-thought-out beliefs, such as those held by adolescent Jehovah's Witnesses, would lead the child to refuse blood transfusions that otherwise might be essential for appropriate medical care. These cases require careful individual determinations about the actual capacities of the patient and the issues involved, and prudence may suggest judicial review. (This discussion does not imply that legal entitlement equals the best moral solution to dilemmas or disputes. However, the law recognizes that some children have legitimate independent claims regarding their medical care that may differ from the expressed wishes of their parents or guardians. This legal recognition suggests that, at times, professionals should support admittedly divisive stances that minor patients take.)

The right, in the law, of a "reasonable person" to accept or refuse offered medical treatment, however, involves some important qualifications. The legal reasonable person standard assumes a competent patient or surrogate. To make a valid choice, the patient or surrogate needs comprehensible information about the medical situation so that any choice reflects the range of alternatives and their consequences. Simply having the information does not suffice; the decision maker must actually exhibit an understanding of what he or she has learned. Finally, choices of individuals or surrogates should occur voluntarily, that is, free of any undue pressure, especially from health care providers.

Competency

Legal entitlement does not mean the proposed decision maker actually is competent, whether referring to the child, a parent, or other guardian. More accurately, we should regard competency as a legal determination, and physicians must assess the decision-making capacity of the patient or surrogate. This capacity has several features and elements. First, capacity to make medical decisions involves specific determinations for each "significant" decision. A patient or surrogate may have appropriate capacity to accept, in general, medical efforts to prevent death from fulminant hepatic failure. However, the patient's agreement to accept intensive care does not provide a warrant for the doctors to proceed directly to liver transplantation. The proposal of the latter treatment should trigger a separate exploration of the decision-maker's capacity to agree to transplant surgery. Similarly, decisional capacity refers to specific kinds of decisions. If a parent cannot balance his or her checkbook or pay medical bills on time (because of a lack of understanding of what is involved, rather than a lack of funds), it does not follow that such a parent cannot rationally refuse mechanical ventilation for a son or daughter with a degenerative neuromuscular disease. Further, disagreement with a medical opinion does not, in and of itself, constitute grounds for declaring a patient or surrogate incapable of making sound choices. Rejection of medical recommendations may trigger concern about mental abilities, but such disagreement does not establish the case that the decision maker lacks decision-making capacity.

Although not everyone agrees on how to define medical decisional capacity, most persons accept the notion that it involves (1) an ability to understand and communicate about the medical situation at hand, (2) an ability to manipulate information about the situation and deliberate about the nature and consequences of alternatives, and (3) an ability to make a choice among the alternatives, preferably based on relevant values.

Information

Assuming a patient or surrogate has appropriate decision-making capacity, the decision-maker needs information about the patient's condition, prognosis, and alternative treatments. Clinicians should provide details without jargon and abbreviations. Frightened and dependent patients or surrogates may nod or respond as if they understand, but some empirical evidence and common sense suggest otherwise.[8,9] Ethical and legal considerations require that the information be understandable to the decision-maker.

In addition to the actual content of any information provided, doctors must consider the timing of decisions and the state of mind of the decision-maker. Even the best prepared patients or surrogates may need complex material presented repeatedly (hence the value of written or audiovisual aids) and may need time to absorb and reflect on what he or she has learned. A common problem is the assumption by health care professionals that consent (or refusal) occurs at some magic instant in time, usually associated with a signature on a form. Lidz, Appelbaum, and Meisel[8] suggested a superior conception of consent as a process that occurs over time in the context of a relationship among doctors, patients, and surrogates. Although intensivists may object that the nature of their patients' problems and the hectic critical care environment make evolving, deliberative, and relational consent unrealistic, truly emergent treatment decisions remain relatively rare and, in any case, are exempt from legal consent requirements. Most important decisions can occur with adequate time for reflection and with time for relationships to develop. Also, physicians should not consider decisions immutable. Just as medical situations change and require reconsideration, so may the goals of treatment and the acceptable means of reaching those ends remain fluid. The concept of "time-limited trials" may help health care professionals and patients or surrogates remember the value of periodically reassessing courses of action.[10,11]

Understanding

For the capacitated decision-maker who has received sufficient understandable information, the clinician can and should determine if the decider actually comprehends the facts and issues. Experts disagree on what criteria to use in assessing understanding. Some persons accept having the decision-makers repeat a summary of the facts and concerns (which demonstrates recall rather than understanding), whereas others have health care providers ask detailed questions in which they probe the matter. Still others permit the assumption of understanding in the absence of questions from the decision maker. Clearly, a "yes" answer to the question "Do you understand what I have just said to you?" demonstrates very little. Research suggests that physicians routinely overestimate what patients and family members understand.[9] Some persons might say that life-and-death treatment in the ICU is so complicated that parents cannot possibly understand it anyway. Although we should perhaps seriously consider this challenge to the value and importance of informed consent and patient or surrogate autonomy, these concepts remain the legal standard of care and deserve attention on that account.

Voluntariness

The final aspect of informed consent that requires discussion involves whether the patient or surrogate has given permission for treatment or diagnostic tests freely or voluntarily. Permission obtained under duress generally cannot be considered valid consent. Here, as with other aspects of consent, we may encounter difficulty agreeing on how to determine what constitutes freely given acceptance of medical plans or recommendations.

The usual model of informed consent applies most directly to situations in which all parties have considerable time to

reflect on the available options. Although in some cases we need not invoke the notion of emergency, patients or parents may not have many hours or days to consider alternatives. Do time limitations themselves constitute so coercive an influence as to invalidate full consent? Surely the nature of the patient's situation can prevent ideal, deliberative decision making. Having to make decisions that may affect life and death may leave parents feeling, "If we don't accept this doctor's plan, we may be harming our child." Undoubtedly, telling parents faced with a life-and-death matter that they must accept their doctor's favored approach when several valid medical alternatives exist cannot be tolerated.

Shared Decision Making

Although the shift in decision making has been toward patient autonomy, the general approach to medical decision making is also changing. The emerging interest in shared decision making focuses on the process and places less emphasis on the specific endpoint chosen. The concept of shared decision making was first introduced by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research in 1982. In that report, shared decision making was described as a process based on mutual respect and partnership between the patient and clinician.[12,13] Although a variety of definitions for shared decision making exist, a literature review describes common characteristics, including deliberation/negotiation; flexibility/individualized approach; information exchange; multiple individuals; compromise; mutual respect; partnership; and patient education and participation.[14] Shared decision making involves a process of clinicians, patients, and, where appropriate, loved ones considering together all options, accounting for patient values or best interests, and finally arriving at an appropriate choice for the patient in the particular situation. Shared decision making allows physicians to take an active role in decision making; indeed, in some circumstances patients may ask the physician to assume the entire decision-making responsibility.[14]

Surrogate Decision Making: Parental Rights and Obligations

Theorists and courts have agreed that autonomous individuals can accept or reject medical treatment for almost any reason.[15] Doctors have had to defer to adult patients' whims, isolated false beliefs, and strongly held opinions about medical matters to satisfy society's insistence on respecting individual liberty. (The need, in the end, to accept reluctantly that what a person believes to be an inappropriate course of action does not relieve the physician from the burden of trying to dissuade the patient from his or her view.) Parents and others with responsibility for surrogate decision making, however, must adhere to different standards. In the cases of individuals who have had an opportunity to express beliefs about desired or unwanted medical care, surrogates usually must use a standard known as "substituted judgment." In these situations, surrogates attempt to decide what the particular patient would want under the specific circumstances based on their knowledge of the patient's views. Written documents (such as "living wills"), oral discussions of particulars (such as the patient's feelings about long-term mechanical ventilation after severe head injury), or a general understanding of the patient's preferences and lifestyle all may form the basis of legally valid surrogate decisions.[16] To the degree that young patients with sufficient decision-making capacity, such as adolescents with sickle cell disease at risk for cerebral vascular accident or those with muscular dystrophy at risk for cardiac or respiratory failure, have expressed views about possible treatments before becoming unable to express their wishes, the notion of substituted judgment also should prevail in pediatrics.

Far more commonly, however, substituted judgment makes no sense in pediatrics. It only can be a flight of the most fanciful imagination: just how might a toddler with a high spinal cord transection from a motor vehicle accident "think" about what he or she would want (death or a life on a ventilator)? Accordingly, most scholars in ethics and most courts have attempted to apply a different standard for making decisions for children, that of "best interests." The standard enjoins the surrogate to take into account all relevant information about the patient's condition and the alternative treatments (including, presumably, the resources available to obtain and maintain care) and decide, all things considered, on what course to follow.[17]

One term used by many persons, "quality of life," has received considerable attention in these decisions. The phrase has been used to convey two substantially different concepts. Some persons reject quality-of-life considerations because they believe that parents, doctors, or others use it to make judgments about the social worth of the patient; that is, for some persons, quality of life implies something about the potential of the patient to contribute to the general social welfare (e.g., hold a job, pay taxes, or simply consume resources). Those who fear that social worth will equal quality of life strongly oppose taking quality-of-life evaluations into account in surrogate decisions. Most commentators mean something different. For them, quality-of-life considerations involve overall prognosis, including pain and/or suffering associated with the patient's condition(s) and treatment(s); the practical likelihood of overcoming barriers to effective treatment, including the financial, social, and psychological resources available to the patient and family; and other nontechnical matters.

Aside from confusion about what meaning to assign to the phrase "quality of life," it seems quite reasonable to weigh factors beyond simply what technical approaches can affect the child's medical condition(s). Although fears about inappropriate discrimination against the handicapped have a legitimate basis, history raises at least equivalent, if not overriding, concerns about excessive and inhumane treatment, whether in obeisance to the technologic imperative or in pursuit of a vitalist belief.[18] Examples include overzealous neonatal intensive life support in the face of increasing complications and parental objections, such as that detailed in *The Long Dying of Baby Andrew*,[19] or the use of artificial hydration and nutrition over surrogate objection, which took place in the highly publicized Terri Schiavo legal battle.

Arriving at an adequate, practically useful definition of "best interest" has eluded the efforts of many in the pediatrics, social work, legal, and ethics communities. Without a clear notion of what constitutes the best interests of the child, it has been difficult to establish readily applicable limits on surrogate decision making. A lively debate continues about the acceptability of including "third party" or parent/family considerations in decisions for or about children, especially life-and-death decisions.

The difficulty for the pediatric intensivist lies in knowing when parental or other surrogate decisions fall outside some socially or morally adequate range. These difficulties involve medical uncertainty about diagnosis and prognosis, varying community standards regarding many different practices (especially the existence of state laws on religious exemptions from child abuse and neglect laws), and changing social attitudes about lifestyle. Concrete examples of these problems illustrate the dilemmas.

Consider a critically ill child with intestinal failure. During the past few years, several treatments have been offered to children with short bowel syndrome and some severe motility disorders who approach exhaustion of their options for total parenteral nutrition. Controversy exists about the effectiveness of enteral feeding,[20,21] operations for improving intestinal function,[22] and small bowel transplantation.[23]

For each of these approaches, we know little about the long-term outcomes. No one has attempted a straight-on comparative trial of these radically divergent treatment methods, in part because of strong beliefs about which intervention works best. Unfortunately, these convictions have little or no basis in scientifically valid research. Some intensivists caring for a patient with short bowel syndrome believe that because neither the surgical approach nor intensive medical treatment has proven long-term benefit, parents should remain free to accept or reject each intervention and accept palliative/hospice care. Others believe it necessary to challenge parental refusal in court.

Resolving such a dilemma requires consideration of the general question of how much physicians need to know about any therapy, especially of the therapies they recommend, before justifiably attempting to impose treatment, through judicial means, on reluctant patients and families. A helpful question might be the following: what would the doctor choose for her or his own family? A study of neonatologists, pediatric cardiologists, and pediatric cardiac surgeons noted considerable discrepancy between what the physicians recommended to parents of newborns with hypoplastic left heart syndrome (HLHS) and what they would want for their own child. A significantly greater proportion of the physicians accepted nonsurgery—and the inevitability of death—for themselves compared with what they recommended to families.[24]

With regard to community standards of care, the majority of states have laws limiting the application of child abuse and neglect standards in cases in which parents invoked religious practices as the reason for delays in, or refusal of, medical care for their children. The manner in which religious exemption laws have been used, either in decisions not to intervene (i.e., order treatment or prosecute criminal cases when a child has been harmed) or as a primary defense in court, has varied greatly across jurisdictions. Most persons agree that parental religious beliefs should not prevent children from receiving clearly beneficial treatment that would permit the children to accept or reject their parents' faith when the children become more mature.[25] The difficulty comes in deciding what conditions warrant intervention and what treatments confer obvious benefits.

Criminal prosecutions in California, Massachusetts, Arizona, Florida, and elsewhere remind the pediatric community that certain religious convictions, in these cases Christian Science convictions, favor prayer over antibiotics for meningitis, surgery for bowel obstruction, and other standard medical treatments.[26] Assuming timely diagnosis and intervention, deaths of children could have been prevented, and the likely medical outcome would have been excellent. Yet in some cases that may involve pediatric intensive care, the need for treatment and its benefits leave room for doubt.

Some pediatric cardiothoracic surgeons have taken on the challenge of correcting congenital heart defects by using cardiopulmonary bypass without supplemental blood. At the request of families who are Jehovah's Witnesses, these surgeons agree to operate by using saline solution in the bypass circuitry. Documentation of their success has long been available in the peer-reviewed medical literature.[27] Witnesses believe that doctors can frequently provide adequate treatment without using the blood or blood products that their faith cannot accept. In other circumstances, pediatricians may request and receive court permission to treat sick children with blood transfusions when routine use of blood relies on tradition and not scientifically established need. For example, a child with an acute lung injury may receive packed red blood cells to maintain the hemoglobin above 10 mg/dL. Few data support a clear medical need for this intervention, and emerging data would refute the need for empiric transfusion.[28] In that and other circumstances involving the children of Jehovah's Witnesses, clinicians ought to think twice before seeking court orders to perform blood transfusions.

Although understandable, psychosocial factors that lead physicians, anxious to protect their patients, to assert professional control do not constitute an ethical justification for action. In light of the importance of religious freedom in the history and political system of the United States, intensive care professionals should consider giving great deference to personal beliefs, especially in medically marginal or uncertain circumstances.

If there is debate about the proper role of parental religious views in determining medical care for children, we have utter confusion about the role of so-called third-party considerations, such as the impact of a child's disease and treatment on the parents and other family members. Some authors have suggested that when substantial uncertainty exists about the benefits of treatment, when the burdens of treatment seem weighty (e.g., multiple operations, long-term hospitalization, or toxic drugs), or when the ability of the patient to experience human pleasures will be seriously compromised, parents can and should consider the impact of the child's treatment on the family as a whole.[29] Such concerns might include temporal, fiscal, and psychological resources that the sick child will consume and that might otherwise be available to siblings or other dependents.

These matters can become quite confusing, as the following case suggests. A 6-month-old child was referred to a distant center for consideration of organ transplantation. The message to the family at the referring hospital had been heard by the parents as ambivalent; that is, the parents believed the doctors in their hometown were not entirely convinced of the value or likelihood of the success of transplantation. The transplantation physicians believed the child was an excellent candidate for the procedure and had a favorable prognosis (65% or better 1-year survival, at the time). The parents hesitated to accept treatment, stating that transplantation would mean that the mother's recent reentry into her career would be derailed, that they did not want the (considerable) expense of chronic immunosuppressive medication, and that, all things

considered, transplantation seemed more of a burden to the family than they thought they could tolerate.

The situation caused considerable distress among the staff at the referral center. Had the parents said, "No, thank you, we'd rather take the money we'll have to spend on antirejection drugs and buy a sailboat," the staff would not have hesitated to challenge their decision-making authority. However, the parents stated coherent and serious concerns. Given the nontrivial risk of complications and the actual burdens of treatment (e.g., lifelong immunosuppression with possible serious infection, malignancy, and toxic injury from medications), their refusal of the "standard of care" (not experimental treatment) seemed difficult to accept but sufficient to prevent an attempt to obtain court intervention. No doubt some other centers would have reacted differently.

With regard to unorthodox parental preferences concerning treatment, courts have not always acted to support mainstream physicians. In one older but still important New York State case, the "Matter of Hofbauer," the courts supported the parents' choice of a licensed physician who agreed to treat the child's Hodgkin's disease with "nutritional or metabolic therapy, including injections of Laetrile."[30] The Court of Appeals of New York decided it could not and should not choose among treatments, each of which was supported by physicians legally practicing within the state. Following that view, parents only need to find a licensed practitioner to endorse their preferred approach to prevail in court. Doubtless the limits on parental or other surrogate decisions will continue to be debated by those concerned with pediatric ethics, laws, and medicine. For the time being, only a rough consensus exists that the best interests of the child should remain the guiding principle in most cases. When doctors and parents experience serious difficulty in defining or predicting what action will best serve the child's interests, other considerations become more important. Other legitimate concerns include the family's religious views or moral commitments, the family's resources, and the ordinary and reasonable plans and projects of family members.[31] Adherence only to narrow technical goals of treatment has little place in the provision of advanced pediatric intensive care.

Conscientious Objection to Participation in Proposed Interventions

The shift in medical authority from physicians to patients/family members has prompted some concern about loss of professionals' moral agency. Some physicians, nurses, and others have responded by claiming a "right" to refuse participation in some proposed or offered medical interventions, calling this "conscientious objection" based on religious or other strongly held personal beliefs. Curlin and colleagues[32] have articulated these concerns most clearly. Although many of the targeted practices concern reproduction, such as the provision of contraceptives or performing abortions, some interventions reach into the PICU, including offering nonsurgical palliative care for infants with hypoplastic left heart syndrome, procuring solid organs for transplantation after death declared by cardiac criteria, and use of palliative sedation at the end of life. In each of these situations some intensivists believe that participation violates their moral codes, and they invoke conscientious objection.

Some persons have pointed out problematic features of these claims of conscientious objection. Frader and Bosk[33] noted the historical development of professional codes and their link to social status and an ethic of dutiful subservience of the professional's personal well-being to that of the patient's best interests. In many contemporary claims of conscientious refusal to provide care, the professionals assert the importance of not participating in any aspect of the behavior they see as wrong, including discussing options with the patient or providing referrals to those who might engage in discussion or provide the service. Given the relative paucity of knowledge and skill patients possess, Frader and Bosk see this extended form of conscientious objection as abandoning the professionals' responsibility to fulfill the ethical and legal responsibilities encompassed by the doctrine of informed consent.[33]

May and Aulisio[34] note the importance of distinguishing between the formal complicity of acts, for example, taking the patient to die in the operating room to facilitate rapid removal of organs after death, and morally weaker material complicity in which one's behavior may lead to the undesirable outcome. May and Aulisio suggest that one cannot avoid material complicity in a world with social interaction and that material complicity, although real, is not strong enough to avoid the basic professional duty of telling the family of a dying patient about the possibility of organ donation after cardiac death.[34]

In controversial matters in which substantial numbers of professional colleagues and patients/family members consider a legally available option reasonable, such as nonoperative care of a child with HLHS, conscientious refusal appears to return to medical paternalism and may place undue burdens on patients and families to seek out professionals willing to talk about all the alternatives within the scope of standards of care.[35]

Pediatric Intensive Care and "Experimentation"

Experimentation has two rather common meanings. In the first sense of the term, experimentation refers to research; that is, the scholarly pursuit of generalizable knowledge. Many children receiving intensive care become "subjects" of research when their care follows protocols designed to assess the value of some element of the treatment. Sometimes the research element of the child's care is incidental, possibly even trivial, such as whether one brand of monitoring equipment speeds the jobs of the health care professionals more than another. To the extent that the research determines essential aspects of patient care and may affect outcome, however, doctors must approach such experimentation somewhat differently from their usual practice; that is, experimental treatments (or diagnostic procedures) require greater attention to parental authorization. As noted previously, children may receive treatment by court approval, over and against parental wishes, when the therapy constitutes the standard of care. By contrast, parents may, under regulations governing the use of federal research funds, refuse to enter children into research protocols and may withdraw their children from such projects at any time.[36]

The other meaning of experimentation concerns the "use" of the patient for the learning and practice of trainees. When and under what circumstances the subjection of critically ill children to additional risk or discomfort related to education

can be justified poses a number of difficult questions. First, the patients and their families represent a captive population. The majority of pediatric intensive care takes place in training institutions. Only rarely do parents have an opportunity to express a meaningful preference about which PICU should provide care for their child, given the relative scarcity of units, the relationship of any particular unit to other persons or facilities that parents have chosen (e.g., surgeon, oncologist, or hospital setting), and emergency situations in which legal, bureaucratic, triage, or other considerations leave little room for parental wishes. Unlike the wider "health care market," parents have few substantive choices about their child's ICU.

Second, training must occur. New generations of pediatricians, pediatric nurses, pediatric intensivists, and other specialists need to accrue experience so that they learn to care competently for subsequent critically ill children. Even with use of modern instructional aids, including realistic artificial models, animal laboratory experience, and intellectual preparation, the novice medical professional must perform her or his first intubation, central line placement, and other relatively risky procedures on actual patients.

The intensivist faces an uncomfortable dilemma: parental choice is severely constrained, yet the education must continue. Whether parental permission, even in the somewhat unlikely event of full disclosure and understanding, could be given freely can easily be questioned.

The institutions of medicine (i.e., the practitioners and the organizations that provide the care and the training) must do a better job of telling patients and surrogates that we continually need to teach people how to provide lifesaving care. Greater efforts at public education would at least help convince many persons of the long-term benefits of medical education. More importantly, the profession and the organizations need to promise and actually provide adequate supervision of trainee practice. It is one thing for a new ICU fellow to accomplish her or his first rapid sequence intubation in a trauma victim with a faculty mentor at her or his side, ready to advise or take over as needed, and quite another for the trainee to be thrown into the thick of the action with only telephone connection, if any, to an experienced consultant. The dual responsibilities of better education of patients and families and sufficient supervision need more attention from the intensive care community.

What should happen if parents know about and refuse involvement of trainees, despite realistic assurances of adequate supervision? Administrators may suggest holding fast to prevent the establishment of undesirable precedents. Although the worry is legitimate, one wonders if expending the time and energy involved in such a battle results in unreasonable delays in needed patient care, alienates the parties, and undermines the trust needed to facilitate treatment. Flexibility and interpersonal skill might accomplish more than rigid bureaucratic responses. Moreover, parental protest of this sort may reflect underlying anxiety about what is happening to their child or their role in whatever troubles have afflicted the patient. Direct inquiry regarding the parents' fears and guilt may provide greater benefit for all concerned than a confrontation over the educational mission of the unit.

Finally, the matter of practice on insensate or (newly) dead patients deserves mention, if not resolution. In these situations, doctors legitimately claim that the patient or former patient cannot "appreciate" any harm, and substantial benefit may derive from such "harmless" practice. Two problems arise, however. First, in our society we generally hold that dying patients, permanently unconscious individuals, or even dead bodies have interests. Religious and secular laws specify, often in great detail, what constitutes dignified treatment of bodies. In addition, formerly competent individuals have the legal right to specify how they wish to be treated should they become incompetent or die (e.g., via living wills, donor cards, and declarations about funeral arrangements, such as the desire to be buried or cremated). Thus how one construes harm to the body may vary, depending on perspective, and there is no guarantee that the patient or family will see things in the same way as do the doctors. The second problem derives from the first. Because most people hold that former persons and bodies have interests, one needs to determine those interests and obtain permission for the proposed action (assuming a coincidence of interests). Most doctors and other health care professionals do not want to ask permission to use bodies for practice. They fear a premorbid request will trigger unwarranted concern that the physicians will not do everything possible to prevent death and that a postmortem request will only add to family grief, not to mention the guilt and discomfort of the staff. Although this discussion may seem abstract or even absurd, picture a scene in which a resident is attempting a difficult intubation on a recently dead patient and a parent unknowingly slips into the room or through the closed curtain. Without proper prior authorization, it seems likely the discovery would produce an unwelcome response.

References are available online at http://www.expertconsult.com.

Chapter 11

Ethical Issues in Death and Dying

Norman Fost

PEARLS

- It is not only permissible to discontinue treatments that are not serving the patient's interest, it is obligatory.
- Claims of medical futility are rarely sufficient to justify unilaterally withholding or withdrawing life-sustaining treatment over the family's objection.
- The empiric fact is that, in the United States, it is difficult to find a case of physician liability for unilateral withholding or withdrawing of life-sustaining tretament unless the conduct was "outrageous."
- The Baby Doe regulations do not regulate physicians or hospitals. They regulate state health departments, all of which have been found to be in compliance.

Critical care, perhaps more than any other medical specialty, is devoted to saving lives. The intensive care unit (ICU) epitomizes the successes of medical technology in averting or delaying death. But it also is the focal point of claims that sometimes technology goes too far and that we should not always do all that we can do. This chapter summarizes the ethical and legal issues involved in death and dying in the pediatric intensive care unit (PICU) and identifies areas of consensus.

Withholding and Withdrawing Life Support

There is a general ethical and legal presumption in the United States that life is preferable to death. The medical profession is generally expected to preserve life and to maximize the patient's opportunities to experience and enjoy the benefits of life. Nonetheless, there comes a point in every life when continued existence does not serve the interests of the patient, usually because the burdens outweigh the benefits. This point is most clear when the patient has no apparent interests, such as an infant with anencephaly, who is incapable of experiencing any of the pleasures of biologic existence. Similarly, patients in perpetual coma seem to have no interests. Even the conservative "Baby Doe" regulations, supported by many groups with a strong "right to life" orientation, concede that medically beneficial treatment need not be provided to a patient who is irreversibly comatose. The debate is not about whether medically beneficial treatment can be withheld. The challenge is to define acceptable principles that can help identify those patients who should no longer be treated and determine who should decide.

There is strong consensus in ethics and law that there is no meaningful distinction between withholding and withdrawing life-sustaining treatment. The President's Commission on Ethical Problems in Medicine concluded that contrary to widespread feelings on the matter, withdrawing treatment was preferable to withholding for two reasons.[1] First, withdrawing treatment implies that there has been more time for assessment of prognosis and the likelihood of a successful outcome. It comes after a clinical trial. Good ethics starts with good facts, and a decision to withhold treatment generally is made with less data than the decision to withdraw after treatment has been tried. Second, a tradition of reluctance to withdraw treatment often led to inappropriate withholding of support from patients who, in retrospect, may have had a good chance for meaningful long-term survival. One common setting was the delivery room, where high-risk infants sometimes were not resuscitated because of the fear that treatment would succeed in the medical sense, but that the infant's prognosis for meaningful survival would vanish without any means of reversing the decision to treat. Allowing treatment to be stopped allows all patients to enjoy the potential benefits of initial intervention and the possibility of success. The central ethical issue is whether treatment serves the interests of the patient. If it does not, whether it is being considered or has already been tried is irrelevant.

Two types of errors can occur. A type I error is one in which a patient lives who, in retrospect, would have been better off had he or she died much earlier. A type II error is one in which a patient dies who, in retrospect, probably would have enjoyed life. There is consensus that the latter is generally more serious than the former for two reasons: first, because life is valued so highly and most people would prefer even a handicapped life or existence with suffering over death; and second, because a type I error usually is reversible whereas a type II error by definition is not. Particularly in the intensive care setting, prolonged survivors who are better off dead usually are dependent on some technology that can be discontinued to allow a natural death to occur. The increasing ethical and legal acceptance of discontinuing nutrition and hydration makes it theoretically possible to reverse any decision that, in retrospect, was not in the patient's interest.

A corollary of these observations is that uncertainty generally should be resolved by maintaining the patient's life, because resuscitation that on reflection may not have been indicated usually can be reversed, whereas failure to keep the patient alive cannot be corrected.

Active Versus Passive Euthanasia

Once a decision has been made that treatment is no longer serving the patient's interest, it would seem to follow that a quick and painless death would be preferred to a long dying process, with associated discomfort for the patient or his or her family. Active euthanasia can be defined as a physical act that causes the death of a patient and was intended to be in the patient's interest. Passive euthanasia is generally understood to include withholding or withdrawing treatment, with the intent and expectation that death will occur sooner rather than later, based on the belief that an early death is in the patient's interest. Both practices have the intent and usually the consequence that death will occur sooner rather than later. Active euthanasia is nearly universally prohibited, and passive euthanasia is widely tolerated. The major reason for the distinction is based primarily on concern for future patients, not the patient at hand. Indeed, active euthanasia often seems more merciful from the patient's perspective, precisely because the suffering is reduced. This concern is less relevant when suffering can be relieved with sedation and analgesia.

Some have claimed that terminal sedation constitutes active euthanasia, but there is broad consensus, in ethics and in law, that if the intent is to relieve suffering, the fact that death may be accelerated does not constitute active euthanasia.[2,3]

The major objection to active euthanasia is based on the concern that physicians and others will slide down a "slippery slope," meaning that they will become progressively less sensitive and careful about who is a suitable candidate for euthanasia. The claim is made that if the traditional barrier against killing is lowered, doctors will give in to pressures and temptations to end suffering, including the suffering of family, nurses, and the physician, by taking advantage of the quick release that killing provides.

There is some evidence for this view in studies of the two modern societies in which active euthanasia has been widely practiced and tolerated by the state. Lifton's interviews with physicians who worked in Germany in the 1930s and 1940s demonstrate a progression from killing patients with terminal or severely disabling conditions to the slaughter of healthy people in the death camps.[4] Physicians who were directly involved and responsible for the executions reported that they believed at the time that there was no moral distinction between the two types of killings. They justified and defended their involvement in the death camps primarily as an example of their duty as physicians to relieve suffering.

In contemporary Holland, active euthanasia is widely practiced and tolerated by state policy. Public policy limits the practice to clearly competent patients, but cases of children incapable of consenting who were killed at parental request have been reported.[5]

The prohibition of active euthanasia based on "slippery slope" concerns implies that present patients' interests may be sacrificed to those of future patients. However, if suffering can be eliminated with medications, there should be few, if any, patients whose interests will be harmed by prohibiting active killing. In fact, the vast majority of patients in the contemporary ICU depend on technologies whose discontinuation usually will not result in a long dying process. The major exception is patients who depend only on nutrition and hydration, whose deaths can take 1 week or longer but for whom sedation can reduce suffering.

Withholding Food and Water

Once the judgment has been made that continued existence no longer serves the patient's interest, it should not matter, from the patient's perspective, what treatment is being used to keep him or her alive. The only exception would be treatments that serve to keep the patient comfortable during the dying process. However, if the patient is incapable of experiencing discomfort, whether because of his or her condition or treatments that render him or her unconscious, then any treatment that keeps the patient alive contrary to his or her interests not only may be discontinued but also should be discontinued. It is not only permissible to discontinue treatments that are not serving the patient's interest, it is obligatory.

For these reasons, treatments that provide nutrition and hydration have come to be seen as analogous to other treatments that keep patients alive. In addition to the President's Commission,[2] the American Medical Association, numerous state courts, and the United States Supreme Court have ruled that food and water can be discontinued when other requirements for withdrawing life-sustaining treatment have been met.

It is understandable that discontinuing food and water is psychologically more distressing, particularly to nursing personnel, than withdrawing other forms of treatment, in part because feeding is such an innate human instinct, unlike transfusing, resuscitating, or providing oxygen. Therefore decisions to discontinue food and water often require more discussion and staff support.

One aspect of withholding or withdrawing food and water that distinguishes it from withholding other medical treatments is the extent of the opportunity for abuse. Because every patient requires nutrition and hydration, the power to withhold it gives the physician a power that is almost indistinguishable from active euthanasia.[6] This is not to say opportunities to discontinue other forms of technology, such as mechanical ventilators or surgery, are not subject to abuse. The concern about abuse arises not so much in the ICU, where almost all patients are utterly dependent on some technology, but elsewhere in or out of the hospital where food and water may be the only "treatment" keeping a seriously ill or handicapped patient alive.

Competence, Incompetence, and Baby Doe

Autonomy is a central principle in American medical ethics. It implies that a competent person has a nearly absolute right to decide what shall be done to his or her body. Courts have consistently upheld the right of competent patients to refuse lifesaving treatment, even if it appears foolish or unwise to others, whether for religious or secular reasons or for no reason at all.

The definition of competence is itself controversial,[7] but many adolescent patients meet the standard. The most common definition relies on the ability of the patient to understand the consequences of his or her decision. Physicians therefore should be sensitive to distinctions between the wants and the interests of pediatric patients.

The vast majority of PICU patients, regardless of age, are incompetent because of developmental status, disease, or medication. Traditionally, parents had nearly complete discretion to make decisions on behalf of their children. This

practice came under intense criticism in the 1970s and 1980s upon disclosure of many cases in which handicapped and critically ill infants who appeared to have good prospects for long, meaningful life were allowed to die.[8] These cases most commonly involved infants with Down syndrome or spina bifida. In some instances, infants with Down syndrome and duodenal atresia were allowed to die of dehydration. In one center, more than 50% of infants with spina bifida had standard treatment withheld with the intention that they would die.[9] This pattern of inappropriate undertreatment has been called the Baby Doe problem, named after a celebrated case involving a newborn with Down syndrome and esophageal atresia who was allowed to die without surgery.[10]

The response of pediatricians and state courts was generally to respect the wishes of parents, even when decisions appeared to be contrary to the interests of the child.[11,12] In 1982, the federal government promulgated regulations requiring reports to a hotline and investigations by "Baby Doe squads" of alleged withholding of medically beneficial treatment based on handicap. These regulations were found unconstitutional but were reinstated pursuant to amendments to a child abuse statute that provided funds to the states for implementation of child abuse and neglect programs.[12a] The most controversial aspect of these regulations is their apparent prohibition of withholding or withdrawing medically beneficial treatment from any infant based on handicap or prognosis for quality of life. The three exceptions allowed are (1) if the infant is permanently comatose, (2) if the infant is imminently dying, or (3) if the treatment would be "inhumane." The legal significance of these regulations and the role of the law in these cases in general have been the sources of continuing confusion and controversy.

Legal Implications of Withholding or Withdrawing Life Support

Involvement of state and federal legislatures and courts in decisions involving treatment of dying patients is rapidly evolving, and varies among jurisdictions.[13] Generalizations are difficult, and the law varies among states. Nonetheless, some legal aspects are reasonably clear.

The most widespread source of confusion is the failure to recognize the difference between the law in theory and the law in practice. Although a variety of statutes, court decisions, and regulations have been interpreted, in many cases, as prohibiting discontinuation of treatment, the empiric fact is that, in the United States, it is uncertain whether any physician has ever been found to have civil or criminal liability for withholding or withdrawing life-sustaining treatment from any patient unless the physician's conduct was "outrageous." The law in practice has been remarkably deferential to physician discretion.[14]

Even on theoretical grounds, there are reasons to believe that the Baby Doe regulations do not regulate decisions by physicians, parents, or hospitals. Although the substantive standards appear very restrictive, the implementation standards and sanctions defer to the states. All that is necessary for states to be in compliance with the law is to provide assurances to the federal government that reports of alleged medical neglect will be handled in a prescribed way. States are not required to initiate investigations but are permitted to rely on reports, in accordance with traditional regulations involving child abuse and neglect. A study by the U.S. Office of the Inspector General found all states were in compliance with the Baby Doe regulations, although the federal Civil Rights Commission argued that more restrictive legislation is needed.[15]

In 1990, the U.S. Supreme Court issued its first opinion on the specific issue of discontinuing treatment of an incompetent patient. The case involved Nancy Cruzan, a young adult who had been in a persistent vegetative state for 8 years and was being kept alive with nasogastric feedings. Her parents had requested that the feeding be discontinued and that she be allowed to die. The Court upheld a Missouri statute that required "clear and convincing" evidence that a patient had expressed her wish that she would want to die in that specific circumstance. It is unclear whether the decision has any relevance for children, even in Missouri, and it is important to realize that the decision has little or no relevance for decisions in the majority of states that do not have statutes as restrictive as those in Missouri. The central finding in the Court's opinion was that states are free to make their own laws in this area. The majority of states at present defer to physician judgment in theory and virtually all defer in practice. Even in Wisconsin, where an appellate court decision held that parents may never consent to withholding of lifesaving treatment of a child unless he/she is in a persistent vegetative state,[16,17] physicians and hospitals routinely ignore the decision, and there have been no prosecutions.

The difficulty of sustaining a legal challenge against decisions to discontinue treatment was dramatized in an Illinois case involving a 2-year-old child, Sammy Linares, who was in a persistent vegetative state and ventilator dependent for 8 months. The hospital refused the parents' request to discontinue the ventilator, based on the hospital attorney's claim that to do so would be illegal. The father held the medical staff at gunpoint while he discontinued the ventilator until his son died. Despite committing at least two prima facie felonies involving illegal possession and use of a deadly weapon, the district attorney could not convince a grand jury to indict the father. Despite the clear illegality of his action in theory, in practice the legal system was typically sympathetic and supportive of the decision because it appeared to violate no interests of the child.[18] In a similar case, a federal appellate court upheld the right of a hospital to discontinue life support, over parental objection, for a child with profound brain injury.[19]

Despite the nearly universal legal deference to physician judgment, many physicians overtreat infants because they either misunderstand the law or have an exaggerated fear of liability. A survey of neonatologists found that 30% to 50% would continue treatment even when they thought it was not indicated, based on their belief that the Baby Doe regulations required such treatment.[20] Another survey of a group of California neonatologists before and after the Baby Doe regulations also found a trend toward overtreatment.[21]

In a Virginia case, an anencephalic infant known as Baby K was kept alive for 2.5 years, including intermittent ventilator support, at the request of the mother. A federal court ruled that resuscitation was required under a federal statute known as the EMTALA Act, a law that was intended to prevent dumping of patients from emergency rooms. That ruling is generally not followed in other courts, and the Center for Medicaid and Medicare Services has ruled that EMTALA does not apply to inpatients.[22] It is also important to note that the courts generally rule only when asked. Nor does the ruling prove that there would have been liability if the doctors had refused to treat the

infant. In a related case, a jury acquitted a doctor at the Massachusetts General Hospital who discontinued life-sustaining treatment for a woman in a persistent vegetative state, over the objection of the family.[23] The contrast with the Baby K case is that court opinion was not sought.

Futility

The increasing success of technology in maintaining vital functions has led to an increase in survival of patients with little prospects for long or meaningful life, resulting in conflict between parents who want "everything" done, and medical staff, who believe continued treatment is not in the interests of the child. The debate over withholding or withdrawing treatment against family objection frequently focuses on the claim that treatment is futile, and therefore need not be offered. When treatment is truly medically ineffective—such as mechanical ventilation in a child with extreme pulmonary hypoplasia—a claim of medical futility is warranted. More commonly, however, those who wish to make a unilateral decision to limit treatment, over family objection, are relying on a social notion of futility; that is, a claim that even if the treatment is medically effective, it will not result in a life worth living, or is not worth the cost. These judgments may be defensible, but they are not medical judgments, and physicians have little basis for assuming authority to make such judgments unilaterally. These difficult cases usually need to be resolved through negotiation and persuasion, with the help of institutional ethics committees.[24,25]

Hospital Ethics Committees

With the difficulty in reaching a consensus on substantive standards for decisions to discontinue life support, interest grew in procedural guidelines. The conceptual basis for the guidelines is the general notion that because one can never know whether a decision actually is right, the question of whether or not a decision is morally defensible depends on the process by which the decision is made. The process is similar to other areas of decision making, including the judicial process, in which the legal correctness of a decision resides almost completely in the process by which it is made; in the scientific method, which concedes the impossibility of ultimately knowing the truth but accepts successive approximations if they withstand scrutiny of the process by which they are made; and judgments about the quality of medical care, which ultimately depend less on outcomes than on process.

One procedural theory of ethical decision making that influenced the formation of ethics committees is called ideal observer theory.[26] The theory argued that a decision is morally right if it could receive approval from an ideal ethical observer with the following characteristics: 1) omniscient, meaning access to the relevant and available facts; 2) omnipercipient, meaning the ability to empathize, to vividly imagine how others feel, or to put one's self in another's shoes; 3) disinterested, having no vested interest in the outcome; 4) dispassionate, not being overwhelmed with emotion at the time critical decisions must be made; and 5) consistent, meaning that similar cases will be decided similarly.

In retrospect, decisions that appeared to be indefensible could be analyzed in this framework. In most cases, the failure to appreciate readily available facts appeared to be at the center of controversial decisions. Erroneous assumptions about prognosis, the availability of alternative care arrangements, or misunderstandings about the law are common examples. Because no single person can have the godlike qualities of an ideal ethical observer, interest arose in a process that might better emulate the model than traditional doctor–parent decisions. The federal Baby Doe regulations recommended but did not require such committees, which they referred to as "Infant Care Review Committees." Since 1994, the Joint Commission on Accreditation of Hospitals has required ethics committees or some other mechanism for resolving disputes about terminal care, and they have become a standard method for resolving controversial decisions.[27] These committees typically are interdisciplinary groups of 10 to 20 people, including hospital-based professionals and community members, which advise and recommend but do not typically decide on treatment plans.[28] Some hospitals have ethics consultants who work independently of an institutional ethics committee. Studies of their activities are limited,[29] but their growth has been accompanied by an apparent disappearance of the problem of undertreatment. That problem has been replaced by an apparent growth in overtreatment, which may be aggravated by the influence of hospital attorneys or risk managers on committees.[30] Consultation with committees usually is voluntary, though some hospitals require consultation for specified complex cases, such as "futility" cases.

Ethics committees often serve other functions besides ethical consensus development. They have been used to protect decision makers from liability. Malpractice charges require a finding of negligence, which means the physician failed to take adequate care in how a decision was made. Review and approval by an ethics committee may not only be helpful in defending against such a charge but may deter initiation of a suit. Similarly, a district attorney or judge considering legal charges may be less likely to pursue a case in which there was a special effort to obtain consultation and in which there was broad consensus beyond the family and attending physician. Committees have also served a therapeutic role, helping to manage tensions among medical staff, particularly nurses, when they do not necessarily disagree with a decision but appreciate the opportunity to review it in a broader forum than can be found within the ICU.

Caring for the Terminally Ill

Once a decision has been made that continued treatment is no longer in the patient's interest, attention can turn to implementing the decision in a way that minimizes suffering for the patient, family, medical staff, and other patients.

Decisions to terminate care should be well documented in the chart and in the orders. With regard to legal liability, inadequate documentation is more likely to create vulnerability than the opposite. Because the decision to terminate care should have the support of all involved, there should be no reason to conceal the decision or the reasons for it. Consultation with an ethics committee should be documented, either by the attending physician or by a representative of the committee.

If a judgment has been made that the patient would be better off dead, there is rarely a reason to continue some treatments while stopping others. The common practice of discontinuing one life-prolonging measure—resuscitation—while

maintaining other life-supporting treatments may be illogical. These seemingly contradictory measures are sometimes motivated by concerns for the feelings of family or staff.[31] As long as the patient is not suffering from continued treatment, this practice may be justified for a brief period, but prolonged treatment while waiting and hoping that a patient will die despite the treatment at some point becomes a misuse of limited resources, whether of personnel or an ICU bed.

Similarly, "limited codes" or "partial codes" generally should not be tolerated if their only purpose is to treat the sensitivities of medical and nursing staff. One hazard of partial resuscitation is that it may succeed in keeping the patient alive but result in additional damage to the patient because of inadequate oxygenation or perfusion. In summary, if a decision has been properly made that a patient is better off dead, it usually is best to effect that decision as soon as possible by discontinuing all measures that might prolong the patient's life.

Definition of Death and Organ Retrieval

Determining that a patient is dead is of special interest because of its implications for organ retrieval (see Chapter 13). Death traditionally has been considered a necessary condition for organ retrieval from critically ill patients, although there are increasing challenges to this assumption.[32]

Brain Death

All states now support brain death as a legal standard for determination of death, although there is growing controversy about the moral and clinical relevance of the concept. This standard requires irreversible cessation of all brain activity, including the brainstem. The criteria for determining that brain death has occurred are medical criteria not established by statutes or court cases. They change as new technology and research evolves; therefore it is incumbent on the physician to keep abreast of developments in this area. One study showed considerable ignorance and confusion on the subject.[32] The clinical criteria promulgated by a Harvard committee 20 years ago have come under increasing criticism, as it is clear that many patients declared to be brain dead by standard criteria have not lost all brain function, particularly the hypothalamus, evidenced by normal regulation of antidiuretic hormone activity.[33] Guidelines have been developed for applying clinical standards to children, including neonates.[34] Infants born alive with anencephaly typically have brainstem function and therefore do not meet any current definition of brain death.[35]

Organ Retrieval

There is a wide gap between the number of patients who could benefit from organ transplantation and the supply of organs. There also is a gap between the number of people who say they are willing to donate their own organs or those of family members when death has occurred and the number who actually do donate. These observations led to a national "required request" law, which requires hospitals to inform relatives in appropriate cases that organ donation is an option. The law has not resulted in the anticipated increase in organ supply, for a variety of reasons. Nonetheless, the ICU staff not only has a legal duty to ask but also should realize that organ donation is generally perceived as a benefit to those who consent to it, not as a burden.

Questions may arise regarding who should ask and when. It is a longstanding principle that those involved with the care of potential recipients, such as members of the transplant team, should not be in contact with the family of the potential source of the organ because of the obvious conflicts of interest. It is important to coordinate such decisions to maximize the efficiency and effectiveness of the transplantation; therefore it is appropriate that those caring for the "donor" communicate with the transplant team. It also may be appropriate for members of the transplant team to meet with the family of the "donor" after the decision has been made, to answer questions.

The shortage of organs has also stimulated new efforts to remove organs more efficiently from patients who are not brain dead and who die by traditional criteria of cessation of heart and lung function. Protocols have been established for discontinuing ventilator support in the operating room so that organs can be removed promptly after death is declared—donation after cardiac death and before organ viability is threatened by warm ischemia (see Chapter 13).[36]

References are available online at http://www.expertconsult.com.

Chapter 12

Palliative Care

Jeffrey Burns and Cynda H. Rushton

PEARLS

- "Palliative care begins when illness is diagnosed, and continues irrespective of whether or not a child receives disease-directed treatment…providers should evaluate and alleviate a child's physical, psychological, and social distress; effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited…it can be provided in tertiary-care facilities, community health centres, and at home." (World Health Organization definition of pediatric palliative care)
- During the past 25 years, an ethical and legal consensus has emerged in the United States that supports proportionate palliative sedation and analgesia; that is, administration of the minimum amount of medication to relieve refractory physical symptoms is not only a defensible practice but the desired practice. More controversial are such practices as administering medication to dying patients with the intended end point of hastening death.
- Effective communication is consistently reported to be one of the most important determinants of parent's satisfaction with the care of their dying child in the pediatric intensive care unit. Studies in this area support the importance of relational skills such as physician availability, attentive listening, and expressions of empathy, and indicate that these skills are more important than the precise words spoken to parents.
- Prior to the withdrawal of mechanical ventilation in particular, it is important for clinicians to hold a team meeting to anticipate the abrupt and unpredictable change in patient symptoms with the cessation of assisted ventilation and to have in place a flexible and effective plan of care to address changes as they arise.

What Is Pediatric Palliative Care?

Pediatric palliative care aims to improve the quality of life of patients (and their families) facing life-threatening illnesses through the prevention and relief of suffering by early identification and treatment of pain and other problems, whether physical, psychosocial, or spiritual.[1] It is comprehensive care provided throughout the child's illness, not solely at the very end of life. The World Health Organization[2] says of pediatric palliative care:

- "Palliative care for children is the active total care of the child's body, mind, and spirit, and also involves giving support to the family."
- "Palliative care begins when illness is diagnosed, and continues irrespective of whether or not a child receives disease-directed treatment."
- "Health providers should evaluate and alleviate a child's physical, psychological, and social distress."
- "Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited."
- "Palliative care can be provided in tertiary care facilities, community health centers, and at home."

Palliative care is broadly viewed as a model for the relief of suffering and the improvement of quality of life across the spectrum of illness. The National Consensus Project for Quality Palliative Care has released Practice Guidelines intended to serve as a blueprint from which to build optimal palliative care.[1] The guidelines outline several domains of palliative care, including communication, ethical decision making, management of pain and suffering, and psychological and spiritual well-being (National Consensus Project for Quality Palliative Care, *Clinical Practice Guidelines for Quality Palliative Care, Second Edition,* 2009; available at http://www.nationalconsensusproject.org/guideline.pdf).

Issues of Concern in Palliative Care

From the time of the patient's admission to the critical care unit, a mindful awareness of the potential for death or altered life span and quality of life is paramount. Given the enormous uncertainty that surrounds the care of critically ill children, palliative care principles are relevant to their care regardless of the ultimate outcome, providing clinicians with a "road map" for working with families and colleagues. Communication, decision making, pain and symptom relief, and clinician support are highlighted here.

Communication

Communicating with patients and families who face a serious progressive disease is extraordinarily difficult because of the associated issues of prognostic uncertainty, the potential for

death and dying, and the loss of hope. Embedded in these situations is the existential pain of witnessing the suffering of children and their families; discomfort about speaking truthfully with children, especially older adolescents; and reluctance to fully share decision making with parents because of the magnitude and lifelong burden of the decisions and concerns about abandonment of patients or families when values or decisions conflict.[3] The quality of communication with physicians and nurses is consistently reported as one of the most long-remembered and important determinants of parent's satisfaction with the care of their dying child in the pediatric intensive care unit.[4,5] Most clinicians recognize from experience that parents are not uniform in their preferences about communication. Nevertheless, repeated findings from the literature document a deficit in physician empathy and availability in establishing adequate communication patterns with parents. Meert and colleagues[6] examined the audio recordings from semi-structured telephone interviews of 56 parents of 48 children who had died 3 to 12 months earlier at six children's hospitals in the National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Of the 56 parents interviewed, 40 (71%) wanted to provide feedback on the way information about their child's terminal illness and death was communicated by pediatric intensive care unit (PICU) physicians. The most common communication issue identified by parents was the physicians' availability and attentiveness to their need for information. These investigators concluded that parents want physicians to be accessible and to provide honest and complete information with a caring affect, using lay language, and at a pace in accordance with their ability to comprehend. They also concluded that withholding prognostic information from parents often leads to false hopes and feelings of anger, betrayal, and distrust.

As with other skills that are important in the intensive care unit, the quality of clinician communication can be improved. Just as there is now a strong emphasis on identifying the communication skills that can contribute to, or protect against, preventable medical errors, so too a developing body of literature describes approaches and tools that may have a positive impact on the perceived quality of end-of-life communication. Interventions that teach critical care practitioners how to speak less and listen more would be likely to improve the experience of the parents of dying children. For example, Meyer[7] audiotaped 51 family meetings in Seattle hospitals during which discussions about withdrawing life support were likely to occur. They found that clinicians did more than two thirds of all the talking over an average family meeting lasting nearly 30 minutes. Meyer also found that an increased proportion of family speech was significantly associated with increased family satisfaction with the physician's communication and with decreased family ratings of conflict with the physician. Interestingly, in this study the families' opportunity to talk and knowledge that they were being attentively listened to by the clinicians was more important to their overall satisfaction with communication from the physician than even the total duration of the conference.[7]

Most clinicians recognize that ineffective communication can compound a family's suffering or unleash emotional responses that only add to a painful experience, yet few receive any formal or informal training on optimal practice for a difficult conversation in this context. Expressing the "right words" and avoiding words that unintentionally provoke harm is a source of anxiety for most clinicians in the PICU, especially when a child is dying. An educational program for pediatric critical care physicians and nurses recently has been developed to address this gap in training. Meyer and colleagues[20] describe the philosophy and pedagogical approach of an innovative educational program that is grounded in principles of relational learning and designed to improve the preparedness of health care professionals for engaging in challenging conversations with patients and families. Some examples of effective and ineffective communication styles suggested by the investigators who developed this course are outlined in Table 12-1.

Palliation of Symptoms or Relief of Suffering?

Few issues are as difficult and contentious for clinicians as the effective and ethical management of distressing patient symptoms and the suffering that often accompanies them. Witnessing the suffering of patients and their families is a source of concern for clinicians, and when interventions aimed at relieving the patient's distress, pain, or suffering are ineffective, clinicians often feel helpless or morally distressed.[9-13] The conceptual foundation of palliative care is that there is more to improving the quality of life for a child with a life-threatening illness than treatment with medications such as opiates. Rather, all of the child's physical, emotional, psychological, and spiritual needs must be continually assessed and managed comprehensively and not in isolation. Many reviews of comprehensive pediatric palliative care management have been reported in the literature in the past several years.[1,14-16]

Yet no other issue in palliative care is as contentious as determining how much is too much sedation and analgesia for a dying patient.[17-21] Clinicians struggle with the obligation to relieve suffering versus intentionally ending life. Such issues raise the full spectrum of ethical and legal concerns for which there is not universal agreement. Despite this situation, during the past 25 years an ethical and legal consensus has emerged in the United States that proportionate palliative sedation and analgesia, that is, administering the minimum amount of medication to relieve refractory physical symptoms, is not only a defensible practice but the desired practice.[22] More controversial are such practices as administering medication to dying patients with the intended end point of hastening death. To address these concerns, the Society of Critical Care Medicine has published a consensus recommendations intended to provide information and advice for clinicians who deliver end-of-life care in intensive care units.[23] A practical guide to end-of-life care, based on these guidelines, is provided in this chapter.

The provision of medical nutrition and hydration to a child at the end of life raises equally contentious issues.[24,25] Must it be continued because it is ethically required or provides symptom relief benefits, or may it be withheld or withdrawn because it may induce unwanted symptoms and is not ethically obligatory? There is broad consensus that withholding or withdrawing medical interventions is morally permissible when requested by competent patients or, in the case of patients without decision-making capacity, when the interventions no longer confer a benefit to the patient or when the burdens associated with the interventions outweigh the

Table 12–1 Communication with Families at Clinically Significant Times

Clinical Context	Suggested Explanation	Potential Pitfalls
Uncertain neurologic prognosis	"Lindy has had a very serious head injury and we are worried about her. Right now, we are doing everything to support her and to treat her head injury. Lindy's prognosis—our estimate of how she will do—is uncertain at this time. We expect that her clinical situation will become clearer over the next 24 to 48 hours. We can talk with you often to keep you updated as best we can."	Being overly optimistic or pessimistic in prognostication; setting an unrealistic time frame regarding clinical course; avoiding or not answering the family's difficult questions
Patient not responding to treatment, prognosis grim, need for brain death examination	"We are concerned that, despite our best treatment efforts, we have not seen the improvement in Lindy that we were all hoping for. Lindy is not waking up, and there are signs that the injury to her brain has gotten worse. Patients may be declared dead when either their heart or their brain ceases to function. Unfortunately, we are at the point now where we need to do an examination to see if Lindy's brain is still functioning. We will keep you informed of the results of our tests and what they will mean for Lindy."	Provision of conflicting information by different staff members; being vague and indirect in communication with the family
Providing results of first brain death examination	"Our preliminary testing indicates that Lindy's brain has ceased to function. We need to confirm this testing again in several hours. Unfortunately, if the testing is confirmed, it will mean that Lindy has died."	Being unprepared for families to raise questions about organ donation even before the diagnosis of brain death has been established
Waiting period between brain death examinations	"We will hold Lindy's second brain death examination at 10 AM tomorrow morning. Following that examination, we would like to sit down with you and let you know the results of the examination and what it means for Lindy. In the meantime, we will provide the best care for Lindy and be here for you, too."	Avoiding the family and contributing to the family's experience of feeling abandoned or under-informed; "hovering over" patient and family, providing too little privacy and special time between child and family
Brain death confirmation and withdrawal of life support	"We are sorry to say that, based on the results of Lindy's two examinations, we are now certain that your daughter has no brain function, and has died." The death certificate should be completed at this point, indicating the time the second examination was completed as the time of death.	Using language that suggests the child is dying, not dead; do not say, "Your child is being kept alive until you decide if you want to donate organs," or "Now we need to decide whether to withdraw life support"
Potential organ donation	"I would like to introduce you to some colleagues of mine who can help explain to you the options that are available at this point and who can assist you in making the best decisions for Lindy and your family."	Going beyond your limits of expertise regarding explanation about organ donation; hesitancy or reluctance to refer to the Organ Procurement Organization in a timely manner; not conveying trust or confidence when referring to the organ donor representative

From Truog RD, Christ G, Browning DM et al: Sudden traumatic death in children: "we did everything, but your child didn't survive," *JAMA* 295:2646–2654, 2006.

benefits received. The withdrawal or withholding of measures such as attempted resuscitation, ventilators, and critical care medications is common in the care of terminally ill adults and children. The American Academy of Pediatrics also has recently endorsed a position that the withdrawal of medically administered fluids and nutrition for pediatric patients is ethically acceptable in limited circumstances and preferably with an ethics consultation.[26]

Spiritual and Environmental Needs

A child's death is undoubtedly one of the most stressful experiences a human being can endure, and parents' views of longstanding relationships and beliefs can be shaken, if not in effect shattered, and their spiritual needs can be intense. Meert and colleagues[27] interviewed 32 parents of 26 children after their child's death in the PICU and reported that the main spiritual need described by parents was that of maintaining connection with their child. Parents maintained connection at the time of death by physical presence and after the death through memories, mementos, memorials, and altruistic acts such as organ donation, volunteer work, charitable fundraising, support group development, and adoption. Using a similar methodology, Robinson and colleagues[28] examined the experience of 56 parents whose children had died in three Boston PICUs after the withdrawal of life-sustaining therapies. These investigators found that four explicitly spiritual/religious themes emerged (prayer, faith, access to and care from clergy, and belief in the transcendent quality of the parent-child relationship that endures beyond death) in three quarters of the respondents and concluded that staff members should be explicit in their hospitality to parents' spirituality and religious faith to foster a culture of acceptance and integration of spiritual perspectives. Recent guidelines that have been promulgated for addressing the spiritual aspects of care for people facing life-threatening illness call for greater awareness and emphasis for patients across the life span and spectrum of disease.[29]

Support of Clinicians

Caring for critically ill children is uniquely rewarding and uniquely stressful. Clinicians who listen to and witness the pain and suffering of children and their families also may experience pain and suffering because they care.[9] The moral, emotional, and physical distress of clinicians caring for critically ill children, and their grieving process, has recently received more thorough examination. Clinicians—nurses, physicians, respiratory therapists, social workers, chaplains, child life specialists, and others—have unique needs for support. Hamric and Blackhall[30] and Rushton[31] have noted that nurses shoulder a large proportion of the stress in caring for dying children by the very nature of their proximity and sustained involvement with patients and families and are especially vulnerable to moral distress. Moral distress arises in situations where the clinicians are "unable to translate their moral choices into moral action…the costs of unrelieved moral distress are high; ultimately, as with all unresolved professional conflicts, the quality of patient care suffers."[31] Despite the predominance of literature focusing on moral distress in nursing, there is increasing recognition that moral distress and burnout affect the entire interdisciplinary team.

Programs that train clinicians to cope with the psychosocial and spiritual aspects of caring for dying children, including the high levels of moral distress, grief, and professional exhaustion, have been lacking until recently.[28,32] The American Association of Critical Care Nurses (AACN) has developed a program to address the issues of persons experiencing moral distress in the ICU entitled "Rise Above Moral Distress." This program describes four "A's": ask, affirm, assess, and act.[33] The AACN also calls for the implementation of interdisciplinary strategies to recognize and name the experience of moral distress; the establishment of mechanisms to monitor the clinical and organizational climate to identify recurring situations that result in moral distress; and taking corrective action, including the development of employee assistance programs, protocols for end-of-life care, critical stress debriefings, and grief counseling. Similarly, forums where troubling questions can be deliberated upon openly and intentionally among the interdisciplinary team members are essential for the well-being of each of the team members.[34] Unquestionably, physicians and respiratory therapists experience all of the same concerns as nursing professionals, and all clinicians need a variety of strategies to enhance their resilience and personal well-being, including stress reduction strategies, mindfulness, mind-body interventions, end-of-life care training, and a sense of community.[31,35-38]

Practical Aspects of Care at the End of Life

Optimal palliative care begins with the patient's admission to the PICU and continues without disruption through discharge from the hospital, regardless of whether the child lives or dies. All of the rapidly evolving clinical and ethical decisions underlying this care surface most dramatically when the issue arises of whether to withdraw life-sustaining treatment with the intention of allowing the child to die—in particular, discontinuation of mechanical ventilation.

Failure of the clinical team to anticipate the abrupt and unpredictable change in patient symptoms with the cessation of assisted ventilation and have in place a flexible and effective plan of care to address changes as they arise can lead to hasty decisions, and this situation can leave both the patient's parents and clinicians with lasting emotional distress that optimal and ethical end-of-life care was not provided.[39] How can clinicians provide care within an ethical framework consistent with the values of the medical profession and our society and yet still respond effectively to the evolving physiologic, emotional, and spiritual needs of the patient and their family members in a timely manner? A practical guideline, such as the one provided in the following section of this chapter (adapted with permission from the protocol used at the Division of Critical Care Medicine at Children's Hospital Boston and based on the Society of Critical Care Guidelines[23]), outlines the steps that should be taken.

The Anticipatory Clinical Team Meeting

Effective and cohesive end-of-life care must be led and supervised by the attending physician at all times. This begins with a brief meeting of all clinicians who will be providing end-of-life care prior to the withdrawal of life-sustaining treatments.[16] Among the questions that should be briefly addressed in this ad hoc meeting are the following:

What Treatments May Be Withheld or Withdrawn?

- We never withdraw care, only treatments and interventions.
- It is ethical and legal to withhold or withdraw any medical treatment when the patient's legal surrogate, as informed by a recommendation from the clinical team, determines that the burdens of such treatments outweigh the benefits.[40,41]
- Any medical intervention, from extracorporeal membrane oxygenation and pacemakers to the use of physiologic monitors, may be withheld or withdrawn from the dying patient in the ICU.
- A guiding concept in determining what treatments to continue and what treatments to withhold or withdraw is that any intervention that appears to promote the patient's comfort or dignity (as well as ameliorate emotional, psychological, or spiritual concerns) should be continued. Those that do not appear to promote the patient's comfort or dignity should be withdrawn.

Where and When Will Mechanical Ventilation Be Withdrawn?

- Will mechanical ventilation be withdrawn in the ICU, or in a private but appropriate area in another part of the hospital? Is it feasible to offer to transport the patient home for withdrawal of the ventilator?

How Should Mechanical Ventilation Be Withdrawn?

- An artificial airway may be removed (extubation), or the patient may have supplemental oxygen and/or positive pressure ventilation gradually reduced (i.e., a terminal wean with no plan for extubation). The method of withdrawal should be guided by the specific circumstances of the patient.
- How will mechanical ventilation be withdrawn—by terminal wean or extubation? Consider a terminal wean if the patient is likely to have pulmonary edema/hemorrhage or severe gasping from a low lung compliance or high airway resistance process.

- A terminal wean is performed by the gradual reduction in fraction of inspired oxygen and/or ventilator rate at a pace not faster than pharmacologic sedation is administered to treat objective signs of distress from the effects of hypoventilation and hypoxia.
- Studies suggest that the most rapid descent into unconsciousness with the least agitation occurs when hypoxia is allowed to progress in the face of normocarbia.
- Many parents will request that mechanical ventilation be withdrawn by having their child extubated. In this case, the abrupt removal of respiratory support will likely lead to the abrupt escalation in symptoms of respiratory distress. In this case the patient generally should receive sedation or analgesia prior to extubation in anticipation of respiratory distress, with subsequent doses titrated to the patient's level of discomfort.

Preparation and Support of the Family

- After the clinician meeting, preferably the senior physician and bedside nurse should meet with the family to provide clear and explicit explanations about the process of withdrawal of life-sustaining treatments and assurance that symptoms of patient suffering will be treated. Meeting with the family is essential to prepare them for what to expect and may alleviate some of their anxiety around the process.
- It is best to avoid making firm predictions about the patient's clinical course after withdrawal of mechanical ventilation or other forms of life-sustaining treatment, because often they are inaccurate. Substantial loss of credibility may result when predictions about death or the timing of death are inaccurate.
- When predictions are incorrect, clinicians and families frequently get very anxious as if something has gone "wrong," and this situation can lead to hastily made and poor decisions. The mindset of everyone in the room should be that the patient's trajectory after the withdrawal of mechanical ventilation can be different from what was expected and that any outcome will be treated calmly and compassionately for as long as necessary.
- When answering questions about what will happen, it is better to say, for example, "We think it is unlikely that your child will survive after the ventilator is withdrawn, but whether he/she breathes only for a short time or for a very long time, we can assure you that we will treat any symptoms that appear to be causing her/him discomfort."
- At times it will be necessary for the clinicians to anticipate, ask, and answer questions that the family appears to be afraid or unable to verbalize. For example, a clinician might say, "Sometimes after the ventilator is withdrawn patients experience a change in skin color, or unusual breathing noises, and this is to be expected. Our job is make sure that your child does not experience symptoms of suffering or discomfort. If we see signs of discomfort, we will treat them."
- Families should have the opportunity to be helpful and be invited to participate in activities to relieve discomfort, such as mouth care, bathing, and repositioning. They should be encouraged to participate in assessment of the patient's pain and suffering. The family also may be encouraged to provide other means of comfort to the patient that had been important to them in the past, such as holding or rocking their child, wrapping the child in a special blanket, or giving their child a massage.

Determining Who Will Care for the Patient at This Time

- Care of the dying patient is a solemn professional responsibility too important to delegate to one individual. It requires the presence of an experienced physician who can be immediately available at the bedside to work in collaboration with the nurse in guiding appropriate and timely therapies.

Determining How Signs of Apparent Discomfort Will Be Treated

- Pharmacologic and nonpharmacologic strategies to treat apparent discomfort should be discussed, and one person should be assigned to be the "circulator," that is, someone who is free to get additional supplies without leaving the patient alone.
- Palliative measures should be comprehensive and not rely solely on sedation and analgesia. For example, simple positioning or massage may be effective alone or in conjunction with pharmacologic agents.
- Assessment of breathing patterns can be complicated in dying patients. Irregular breathing patterns are a natural part of dying and may not be uncomfortable for the patient. Unfortunately, the irregular pattern that accompanies dying is often referred to as "agonal," which may imply to the family and other clinicians that the patient is in "agony."
- Gasping is a medullary reflex and can occur in the absence of consciousness. Similarly, noisy respirations from airway secretions (the "death rattle") are more likely to be distressing to the family and other observers than they are to the patient. Not all gasping need be treated with escalating doses of sedatives or narcotics. Ideally the decision to treat should be made based on consensus between the family and clinicians at the bedside regarding whether the breathing pattern appears to be causing, or is a manifestation of, suffering.
- In general, the clinician's obligation is to treat objective signs of discomfort as experienced by the patient. The distress of the family should be addressed by continued reassurance and emotional support.

Neuromuscular Blockade and the Withdrawal of Mechanical Ventilation

- Neuromuscular blocking drugs have no sedative or analgesic properties and may mask symptoms of suffering at the end of life. As a general rule, therefore, pharmacologic paralysis should be avoided at the end of life.[23,42]
- In most cases, the effect of these agents can be reversed or allowed to wear off within a short period, allowing for the withdrawal of mechanical ventilation in the absence of the confounding effects of paralysis. Patients who have been receiving neuromuscular blockades chronically for

management of their ventilatory failure occasionally can present a more difficult ethical dilemma. In some situations, restoration of neuromuscular function may not be possible for several days or even weeks. When faced with this problem, the clinician must choose between withdrawal of the ventilator while the patient is paralyzed versus continuation of life support well beyond the point at which the patient and family have determined that the burdens of such treatments outweigh the probable benefits. In this circumstance, it may be preferable to proceed with withdrawal of life support despite the continued presence of neuromuscular blockade.

Consideration of the Level of Sedation and Analgesia to Be Used

- Current ethical and legal guidelines place importance on the intentions of clinicians in administering analgesics and sedatives at the end of life. Specifically, clinicians should administer doses that *are intended to relieve pain and suffering but not intended to directly cause death.* We cannot, however, give more sedation than what the patient needs to be comfortable (thus, one should be prepared for the request, "Please, can't we just get this over with?").
- The goal is to ensure that objective signs of apparent discomfort are treated as needed. The goal of treatment is not to ensure that the patient's death is intentionally hastened or to avoid giving any treatment for fear of hastening death.[18,20,43-45]
- Because intentions are essentially subjective and private, the only ways to infer the nature of a clinician's intentions are through self-report and by an analysis of his or her actions.[46]
- Accordingly, documentation of one's intentions in the patient's chart is an important part of providing end-of-life care. When "prn" orders are written for analgesics and sedatives, the indication for administration should be stated clearly (e.g., pain, severe upper airway obstruction). This step reduces the likelihood of misinterpretation or abuse.
- With regard to actions, when a clinician titrates morphine in doses of 1, 5, or 10 mg every10 or 20 minutes, it is plausible to conclude that the clinician intends to make the patient comfortable and not to directly cause the patient's death. On the other hand, when a clinician administers 2000 mg of morphine acutely to a patient who is not profoundly tolerant, it raises the concern that the clinician may have primarily intended the death of the patient.
- Sedation and/or analgesia should be titrated to effect, and the dose should not be limited solely on the basis of "recommended" or "suggested" maximal doses. In most cases, patients who do not respond to a given dose of an opioid or benzodiazepine will respond if the dose is increased—there is no theoretical or practical maximal dose.
- The concept of "anticipatory dosing" (as opposed to reactive dosing) also should guide clinicians in the use of sedation and analgesia at the end of life. The rapid withdrawal of mechanical ventilation is an example of the need for anticipatory dosing. At the time of ventilator withdrawal, the clinician can anticipate that there will be a sudden increase in dyspnea. It is not sufficient simply to respond to this distress with titrated doses of an opioid (reactive dosing). Rather, clinicians should anticipate that the abrupt withdrawal of assisted breathing will trigger increased respiratory distress, and therefore they should provide adequate sedation or analgesia beforehand (anticipatory dosing). As a general rule, the doses of medication that the patient has been receiving hourly should be increased by twofold or threefold and administered acutely before withdrawing mechanical ventilation.

The Goal of Using Sedatives and Analgesics in This Context

- The goal of titrating sedatives and analgesics after withdrawal of mechanical ventilation is only to treat objective signs of discomfort that evolve; it is not to bring about a certain outcome. Stated another way, the target is to make the patient comfortable; the target is not some arbitrary maximum dose, and the target is not the death of the patient.
- If there are no objective signs of discomfort and the patient breathes effectively after extubation, despite the prediction that death would immediately follow withdrawal of ventilation, there should be no panic among the clinicians that something is wrong and further sedatives or analgesics must be administered. If the patient is unexpectedly breathing comfortably after extubation, all other non-medication measures of palliative care should be continued and ongoing and comprehensive support should be provided for the family.
- On the other hand, multiple boluses of escalating doses of sedatives and analgesics may be required to treat clear signs of discomfort after extubation in order to keep the patient comfortable.
- Either way, the team's frame of mind before the withdrawal of life-sustaining treatments must be that the patient will proceed to die at his or her own time and pace. Clinicians need to respond to what evolves, but it is not their intention in administering sedatives and analgesics to ensure that a certain outcome evolves.
- The sole focus is that a patient for whom life-sustaining treatments have been withheld or withdrawn will not experience suffering that is untreated.

Issues After Death

- In most jurisdictions, after a patient dies, physicians are required to notify other caregivers not in attendance, such as the pediatrician and consultants, along with the local organ procurement organization (if not prior to death for consultation about organ donation questions), because every cadaver is potentially a tissue donor of corneas, skin, heart valves, and bone. In some cases the medical examiner or coroner will need to be notified.
- Seeking permission for an autopsy raises special issues.[47] First, a child's death is an unparalleled time of stress for parents, and the physician who approaches a family for permission to perform an autopsy should have "earned the right" by virtue of his or her prior clinical relationship with the patient and family.

- Second, physicians involved in obtaining consent to perform an autopsy must be fully knowledgeable on (1) the autopsy procedure; (2) limitations to the procedure; and (3) the storage, use, and disposition of organs. Not only are physicians who are poorly educated about autopsies likely to misinform families and potentially generate subsequent medicolegal issues, but they are also more likely not to request an autopsy.
- A follow-up telephone call within 4 weeks of the patient's death to assess the family's grief status and to screen for problems and provide resources for continued support in the community should be provided by a bereavement support program.

Essential Basic Documentation

- A brief description should be placed in the patient's medical record of the decision-making process that led to the withholding or withdrawal of life-sustaining treatment and the palliative care provided.
- In describing the palliative care measures provided, it is important to briefly document the rationale used to titrate sedation and analgesia, if administered. For example, "Signs of suffering were noted with the onset of gasping respirations and increased work of breathing after the patient was extubated. Morphine and Versed were ordered by Dr. Burns and administered by C. Rushton, RN, and titrated to treat these signs of patient suffering. The patient's signs of suffering were relieved after three boluses over 20 minutes. The patient died at 3:45 PM."

Support of the Caregivers

- Caregivers should be provided opportunities for informal debriefing immediately after the death, and programmatic formal debriefing for other staff members not present should be provided at some reasonably close future date.[1,39,48]

References are available online at http://www.expertconsult.com.

Chapter 13

The Process of Organ Donation and Pediatric Donor Management

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PEARLS

- Involvement of critical care specialists, specifically in pediatrics, where there are a limited and decreasing number of donors, has improved the quality and number of organs recovered.
- Donor management is crucial to the successful recovery of organs for transplantation. Management of the potential pediatric organ donor requires knowledge of the physiologic derangements associated with this specific patient population.
- It is imperative to involve the organ procurement organization coordinators in a timely manner for any impending death. Best practices have allowed organ procurement organization coordinators and medical professionals to dialogue and improve consent rates while assisting families with end-of-life care issues.
- The diagnosis of brain death in children is based on clinical criteria that are consistent across the age spectrum.
- Donation after circulatory determination of death allows patients with a catastrophic brain injury who do not progress to meet brain death criteria to donate organs. Success with organs transplanted from this type of donor is occurring in many centers.

Overall, the demand for organs continues to increase at a rapid pace, far exceeding the number of organs available for transplantation. Approximately 2% of the patients on the national transplant wait list are children 18 years of age or younger.[1] However, in contrast to the increasing number of adults on the wait list, the number of children has decreased during the past several years. The reason for this decrease in large part is because more organ transplants are occurring in children.[1] Additionally, patients in need of a transplant who in the past would have died from organ failure while waiting are now living longer lives as a result of improved pharmacologic and medical management. Some of these patients may not require a transplant at all, further reducing the number of children on the national wait list. Nonetheless, children continue to die while waiting for a life-saving transplant, with the highest death rate observed in children younger than 1 year.[1] Additionally, another 40 to 50 children are removed from the pediatric wait list annually because their condition has deteriorated to a degree where transplantation is no longer an option.[1] The need for more organs is clear in this patient population.

The number of adult donors has continued to increase during the past 10 years, while the number of pediatric donors has decreased.[1] This decline in pediatric donors has occurred for many reasons, including improved medical and surgical treatments, vaccinations that have reduced deaths associated with childhood infectious diseases, safety restraints, education and awareness regarding health hazards affecting children, and pediatric critical care specialists who have reduced morbidity and mortality for children who are critically ill or injured.

Missed opportunities for organ donation occur in many medical institutions nationally.[2] Frequently these losses occur when families decline the option of donation, but in some cases families are not even being given the opportunity for donation. Organs available for transplantation may be lost because of caregivers' lack of familiarity with appropriate donor management, or opportunities for donation may be denied by medical examiners who fear losing evidence and the ability to successfully prosecute homicide cases in situations where abusive trauma has claimed the life of a child.

Unique issues are associated with the process of organ donation and transplantation in children. Parents and guardians must act as surrogate decision makers without benefit of being guided by the donor's wishes, as is often possible with adults. Size and weight constraints can limit acquisition and use of organs recovered from children. Technical challenges related to surgical procedures in smaller children and infants and age-related variation in the timing associated with declaration of brain death can result in organ deterioration and affect viability of organs for transplantation. Specialized care required for the management of critically ill children and pediatric organ donors may be lacking at institutions that have limited expertise and support for children. This includes expertise from nursing and critical care specialists, as well as support from pediatric neurologists, neurosurgeons, general surgeons, and other pediatric specialists.

The process of donation begins when a critically ill or injured child is identified as a potential donor with a timely referral to the organ procurement organization (OPO). Early involvement of the OPO enhances chances of recovering viable organs for transplantation while allowing coordination

of the donation process. Medical management of the potential pediatric organ donor requires knowledge of the physiologic derangements associated with this patient population. Hemodynamic instability, alterations in oxygenation and ventilation, metabolic and endocrine abnormalities, and coagulation disturbances are common. Support and care of the family provided by a team of physicians, nurses, social workers, chaplains, and other support staff trained in the unique aspects of pediatric medicine are integral to the care of these children and their families.[3,4] Each of these elements is essential to ensure successful recovery of organs from this select group of patients.

Role of the Pediatric Intensivist and Critical Care Team in the Process of Organ Donation

Effective donor management is crucial to the successful recovery of organs for transplantation. The integral involvement of pediatric critical care specialists in the management of critically ill and injured children has been a foundation of the clinical practice of critical care in many successful pediatric centers. Caring for the critically ill child and his or her family through all phases of illness, including end-of-life issues, should be a seamless transition. The continuum of care for the dying patient who progresses to death and becomes a donor requires the expertise of the pediatric intensivist and critical care team to manage and prevent deterioration of organ systems and loss of transplantable organs. Involvement of critical care specialists, especially in pediatrics, where there is a limited and decreasing number of donors,[1] improves the quality and number of organs recovered.

It is federally mandated to inform the OPO of any impending death in a timely manner. Suitability of the potential donor needs to be determined and issues regarding donation need to be discussed with the medical team and the family. The model utilizing OPO coordinators and designated requestors to obtain consent from families has been successful in the adult arena; however, we continue to learn that the situation with children and their families is different. One study found that parents seem to prefer discussions regarding donation with the pediatric intensivist or a member of the health care team they have come to trust, rather than the OPO coordinator.[5] Timing of the first request relative to discussions of brain death did not influence the decision to donate organs, but consent for donation was more likely when parents had sufficient time to discuss this issue.[5] These concepts are vastly different from the traditional approach in which the OPO coordinator requests consent and decouples the death and consent process. Improved communication between the health care team and the OPO remains important, however. A team approach has been adopted by many institutions for discussing donation with families. This practice is encouraged in the United States Department of Health and Human Services Organ Donation Collaborative's final report on best practices.[6] Best practices promote coordinated efforts between OPO coordinators and medical professionals to improve consent rates while assisting families with end-of-life care issues. Involvement of palliative care teams also has been identified as another resource to assist the intensive care unit (ICU) team, parents, and families facing end-of-life issues with their child.

Determination of Brain Death

The "dead donor rule" states that patients must be declared dead before removal of vital organs for transplantation can occur.[7] Therefore, accurate determination of brain death is essential before efforts at organ recovery proceed. Determination of brain death must occur in a timely and efficient manner for several reasons: it allows the family to begin the grieving process as they prepare for the loss of a loved one; it allows the process of organ preservation and preparation for recovery to begin; and if donation is not planned, medical therapies can be stopped, allowing redistribution of scarce ICU resources to other critically ill and injured patients.

Good donor management is imperative for recovery of viable organs for transplantation. Hemodynamic instability and organ dysfunction account for a loss of up to 25% of potential donors when donor management is not optimized.[8] Furthermore, the institution of hormonal replacement therapy (HRT) early in the donation process may assist with stabilization of the donor, improve the quality of organs recovered, and enhance posttransplant graft function.[9-13]

The determination of brain death in children is a clinical process based on clinical criteria that are consistent across the age spectrum. No unique legal issues differentiating declaration of brain death exist for children. However, age-related issues can make determination of irreversible injury and declaration of brain death more difficult in younger patients, resulting in age-based recommendations.[14] The clinical history, cause of coma, and brain injury must be determined to ensure that an irreversible condition has occurred. Physical examination criteria rely upon the coexistence of coma and apnea in a child who is neither hypothermic nor hypotensive for age and whose examination is not affected by sedatives or neuromuscular blocking agents. Neurologic criteria to determine brain death in infants and children are listed in Box 13-1. Absence of neurologic function is defined by the

Box 13–1 Neurologic Examination Criteria for Brain Death in Children

1. Coma. The patient must exhibit complete loss of consciousness, vocalization, and volitional activity.
2. Apnea. The patient must have the complete absence of documented respiratory effort (if feasible) by formal apnea testing demonstrating a $Paco_2$ ≥60 mm Hg.
3. Loss of all brain stem reflexes, including:
   - Midposition or fully dilated pupils that do not respond to light
   - Absence of movement of bulbar musculature including facial and oropharyngeal muscles
   - Absent gag, cough, sucking, and rooting reflexes
   - Absent corneal reflexes
   - Absent oculocephalic and oculovestibular reflexes
4. Flaccid tone and absence of spontaneous or induced movements, excluding spinal cord events such as reflex withdrawal or spinal myoclonus.
5. Reversible conditions or conditions that can interfere with the neurologic examination must be excluded prior to brain death testing.

Data from American Academy of Pediatrics Task Force on Brain Death in Children: Report of Special Task Force: guidelines for the determination of brain death in children, *Pediatrics* 80:298-300, 1987.

following features on physical examination: mid-position and fully dilated nonreactive pupils, absence of spontaneous eye movements induced by oculocephalic or oculovestibular testing, absence of bulbar function, cough, corneal, gag, and rooting reflexes, and absence of respiratory effort when challenged with elevated carbon dioxide levels that otherwise would induce respiratory effort in such a patient. Serial neurologic examinations are necessary to establish the diagnosis of brain death. The duration of observation between examinations and the need for ancillary studies is based on age, history, and clinical examination. The examination results must remain consistent with brain death throughout the observation and testing period.

Determination of brain death for any infant or child requires establishing and maintaining normal physiologic parameters. Before neurologic examination or neurodiagnostic testing for brain death can be meaningful, correction of hypotension and hypothermia must occur. The 1987 guidelines for determination of brain death in children provided no definition of hypothermia.[14] Current adult and Canadian guidelines use a core body temperature of >35° C (95° F).[15,16] Conditions that can interfere with the neurologic examination or factors capable of imitating brain death must be excluded. Conditions such as severe hepatic or renal dysfunction, inborn errors of metabolism, or metabolic disturbances may play a role in the clinical presentation of the comatose infant or child. These conditions should be considered and, if identified, appropriate treatment should be instituted to correct the derangements resulting in coma. Instances may occur in which these conditions cannot be corrected and additional ancillary testing may be required to confirm brain death. Testing for drug intoxications including barbiturates, opiates, and alcohol should be performed as indicated. The half-life of sedative agents must be considered when determining the appropriate timing of the clinical examination. Longer acting or continuous infusion of sedative agents and recent administration of neuromuscular blocking agents can interfere with the neurologic examination. These agents should be discontinued for a reasonable amount of time to allow adequate clearance of the drug(s) prior to initiating electroencephalogram (EEG) testing and clinical examination for brain death testing. Barbiturates reduce cerebral blood flow (CBF); however, no evidence exists that high-dose barbiturate therapy completely arrests CBF. Evidence suggests that radionuclide CBF study or cerebral arteriography can be utilized in patients who have undergone high-dose barbiturate therapy to demonstrate absence of CBF.[17,18] Clearance of neuromuscular blockers can be confirmed by use of a nerve stimulator.

The apnea test is a critical and essential component of the clinical examination to determine brain death. Testing for apnea must allow adequate time for the partial pressure of carbon dioxide, arterial ($Paco_2$) to increase to levels that would normally stimulate respiration. Apnea testing must be performed while maintaining normal oxygenation and stable hemodynamics. Patients should be preoxygenated with 100% oxygen to prevent hypoxia. Mechanical ventilatory support should be adjusted to eliminate ventilation, allowing the carbon dioxide tension (Pco_2) to rise while observing the patient for spontaneous respiratory effort. False reports of spontaneous ventilation have been reported while patients were maintained on continuous positive airway pressure for apnea testing despite having sensitivity of the mechanical ventilator reduced to minimum levels.[19] Attaching a self-inflating bag valve system, such as a Mapleson circuit, to the endotracheal tube or tracheal insufflation of oxygen using a catheter inserted through the endotracheal tube also has been used to provide supplemental oxygen. High gas flow rates with tracheal insufflation may promote carbon dioxide washout, preventing adequate $Paco_2$ rise during apnea testing. Additionally, adequate gas outflow must be ensured to prevent barotrauma. The $Paco_2$ should be measured and allowed to rise to 60 mm Hg or greater while continually observing the patient for any spontaneous respiratory movements over a 5- to 10-minute period. If no respiratory effort is observed during this time, the apnea test is consistent with brain death. The patient is reconnected to mechanical ventilator support until death is confirmed with either a repeat clinical examination or an ancillary study. If the apnea test cannot be completed because of hemodynamic instability, desaturation, or an inability to reach a $Paco_2$ of 60 mm Hg, an ancillary study should be pursued to make the diagnosis of brain death. Infants and children with chronic respiratory disease or insufficiency may only breathe in response to supranormal $Paco_2$ levels. In this instance, the $Paco_2$ level should rise to ≥20 mm Hg above their baseline $Paco_2$ level. If there is any concern regarding the validity of the apnea test, an ancillary study should be pursued.

Recommended clinical observation periods between examinations in children differ from those for adults, with a greater duration suggested for younger children. Box 13-2 lists the recommended observation periods based on the age of the infant or child from the Task Force Guidelines for Brain Death in Children.[14] Observation periods have never been validated. Many authors have argued that except in very immature, preterm newborns, the same criteria to declare brain death can be applied to full-term newborns, infants older than 7 days of age, children, and adults.[20-27] Despite this controversy, the only published guideline to determine brain death in children recommends observation periods based on the age of

Box 13–2 Recommended Observation Period to Determine Brain Death in Infants and Children

7 Days to 2 Months

- Two examinations and EEGs separated by at least 48 hours

2 Months to 1 Year

- Two examinations and EEGs separated by at least 24 hours
- A repeat EEG is not necessary if a cerebral radionuclide scan or cerebral angiography demonstrates no flow or visualization of the cerebral arteries

Older than 1 Year

- When an irreversible cause exists, ancillary testing is not required and an observation period of 12 hours is recommended
- The observation period may be decreased if the EEG demonstrates electrocerebral silence or the cerebral radionuclide or cerebral angiography study demonstrates no flow or visualization of the cerebral vessels

EEG, Electroencephalogram.
Data from American Academy of Pediatrics Task Force on Brain Death in Children: Report of Special Task Force: guidelines for the determination of brain death in children, *Pediatrics* 80:298-299, 1987.

the child.[14] The Special Task Force for the determination of brain death provided no guidelines to diagnose brain death in infants younger than 7 days of age.[14] Guidelines for this age group were not defined because of limited clinical experience, lack of sufficient data, and concerns about the ability to reliably confirm irreversibility of brain injury in this patient population.[25,26] This situation does not imply that brain death does not occur in this patient population, only that it can be more difficult to diagnose. Diagnosing brain death can occur in the term infant, even in those younger than 7 days of age; however, an observation period of 48 hours has been recommended to confirm the diagnosis. It has been suggested that the observation period can be reduced to 24 hours if ancillary studies demonstrate no CBF or an isoelectric EEG.[26,27] The younger the child, the more cautious one should be in determining brain death.

Ancillary studies can provide additional supportive information to assist in declaring brain death. These studies are useful when the clinical examination or apnea testing cannot be safely completed because of the underlying medical condition of the patient, if there is uncertainty about the findings of the neurologic examination, or if a confounding medication effect may be present. Ancillary studies are not necessary if determination of brain death can be made based on clinical examination criteria in the older child. They are, however, recommended by the Task Force for children younger than 1 year.[14] Ancillary studies may be utilized to expedite the diagnosis of brain death by reducing the clinical observation period, potentially increasing the viability of transplant tissue. However, in the circumstance that an ancillary study is equivocal, the observation period can actually be increased until another study or clinical examination is performed to confirm brain death. Ancillary studies can be helpful for social and medical reasons. These studies may allow family members to better comprehend the diagnosis of brain death and may be important in situations where death is the result of homicide. Ancillary studies are not a substitute for a complete physical examination.

Four-vessel cerebral angiography evaluating anterior and posterior cerebral circulation remains the gold standard to determine blood flow for brain death testing; however, this test is difficult to perform in small children and requires technical expertise that may not be available in every facility. Furthermore, transporting a potentially unstable patient to the angiography suite carries additional risk that can complicate this process. For these reasons, cerebral angiography is rarely performed. EEG documentation of electrocerebral silence and absence of CBF using radionuclide CBF study remain the most widely available and useful ancillary studies to assist with the diagnosis of brain death in infants and children. These studies are more easily accomplished at the bedside, without the need for extraordinary technical expertise. Radionuclide CBF studies have been used extensively with good experience.[28] Use of the portable gamma camera for radionuclide angiography has made CBF studies more accessible, allowing for the study to be undertaken at the bedside.[28,29] This study is becoming a standard in many institutions, replacing EEG as an ancillary study to assist with the determination of brain death in infants and children.[30] EEG and radionuclide CBF studies are both accepted ancillary studies used to assist the clinician in determining brain death in children. EEG may be more specific, although less sensitive, than the radionuclide CBF study. EEG testing evaluates cortical and cellular function, while radionuclide CBF testing evaluates flow and uptake into brain tissue. Each of these tests requires the expertise of appropriately trained and qualified individuals who understand the limitations of these studies to avoid misinterpretation. Transcranial Doppler sonography and brain stem audio-evoked potentials have been utilized[29,31] but have not been studied extensively or validated in children.[25,32,33] These studies, along with computed tomography angiography, perfusion magnetic resonance imaging, and magnetic resonance angiography-magnetic resonance imaging cannot be relied upon as dependable ancillary studies at this time.[32,33]

Ancillary studies are least sensitive in the neonatal age group.[26,34] Limited experience with ancillary studies performed in the newborn younger than 30 days of age indicates that EEG is less sensitive than CBF in confirming the diagnosis of brain death. Sensitivity remains quite low, however, even with CBF, for this age group.[25,27,34,35] Diagnosing brain death in the neonate can be more difficult; therefore, serial examinations are essential to ensure that the clinical examination remains consistent throughout the observation and testing period. The younger the child, the more cautious one should be in diagnosing brain death. If there is any uncertainty about the examination or the ancillary study, continued observation and clinical examination or a repeat ancillary study should be performed to make the diagnosis of brain death.

Diagnosing brain death has great implications with profound consequences. The clinical diagnosis of brain death is highly reliable when made by experienced examiners using established criteria.[36,37] There are no reports of children recovering neurologic function who met adult brain death criteria upon neurologic examination.[35] Diagnosis must never be rushed or take priority over the needs of the patient or the family. Appropriate emotional support for the family should be provided, including adequate time to grieve with their child after death has occurred. Each state has laws or regulations for determination of death that have, in most cases, been modeled after the Uniform Determination of Death Act.[38] The Uniform Determination of Death Act states that a person who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards. The reader is encouraged to become familiar with guidelines in his or her institution. At the time this chapter was being written, guidelines for the determination of brain death in infants and children were being reviewed and revised by a committee formed by the Society of Critical Care Medicine and The American Academy of Pediatrics.

Brain Death Physiology

As the patient with severe intracranial pathology progresses to brain death, neuroendocrine dysfunction often requires specific interventions. These physiologic derangements reflect the powerful neuroendocrine changes that occur during progression to brain death. Efforts to control cerebral perfusion pressure, hemodynamic manifestations of herniation, and loss of central nervous system function all contribute to the instability that routinely occurs during and after progression to brain death. These physiologic changes clearly affect end-organ viability in the prospective organ donor. Understanding

the physiologic changes and anticipating associated complications with brain death therefore is critical for organ recovery.

Loss of central nervous system function causes diffuse vascular regulatory and cellular metabolic injury.[39] Brain death and cerebral ischemia increase circulating cytokines,[40] reduce cortisol production,[41] and precipitate massive catecholamine release. The combination of these factors results in physiologic deterioration and ultimately end organ failure if left untreated.

CBF is approximately 50 mL/100 g/min and consumes 15% of the cardiac output.[42] Without consumption by the brain, glucose needs are reduced and the patient is prone to hyperglycemia. Furthermore, with this reduction in cerebral metabolism, carbon dioxide production falls, resulting in a reduction in $Paco_2$. Hypothermia should be anticipated as a result of hypothalamic failure and loss of thermoregulation. Additionally, impaired adrenergic stimulation results in loss of vascular tone with systemic vasodilation and increased heat loss. Neuroendocrine dysfunction occurs because of inhibition or loss of hormonal stimulation from the hypothalamus, resulting in fluid and electrolyte disturbances and eventually cardiovascular collapse if left untreated.

Hemodynamic deterioration that occurs with brain death is initiated by a massive release of catecholamines, commonly referred to as sympathetic or autonomic storm, associated with cerebral ischemia and intracranial hypertension. This deterioration manifests clinically with systemic hypertension and tachycardia.[39,43] During this autonomic storm, organs are exposed to extreme sympathetic stimulation from direct neural stimulation or from significant increases in endogenous catecholamines. The local effects of such sympathetic stimulation include increased vascular tone, effectively reducing blood flow and potentially causing ischemia to these organs.

This autonomic storm also has direct effects on the myocardium as the surge of catecholamines increases systemic vascular resistance, myocardial work, and oxygen consumption.[44] This imbalance between myocardial oxygen supply and demand[39,45] can cause ischemic changes. Myocardial injury can impair cardiac output and lead to dysfunction of other organs. Left ventricular end diastolic pressure rises, causing pulmonary edema. This condition may be exacerbated by displacement of systemic arterial blood into venous and pulmonary circulations as a result of catecholamine-mediated systemic vasoconstriction. Increased pulmonary vascular resistance and right heart volume overload may displace the ventricular septum into the left ventricle, further impairing cardiac output by impeding left ventricular filling.[46]

Following determination of brain death, and once a decision has been made by the family to proceed with organ donation, the focus of care shifts toward the preservation of vital organs. Subsequent care may differ from management before death. Efforts to reduce intracranial pressure are abandoned and care shifts toward providing ample blood flow and oxygen delivery to transplantable organs. Hemodynamic management goals are directed at maintaining normal peripheral perfusion and blood pressure for age. Decreased intravascular volume, caused by efforts to reduce CBF and control intracranial pressure (e.g., volume restriction and diuretic agents), must be corrected. Attention to volume loss from derangements such as diabetes insipidus (DI), must be anticipated and addressed. Additional donor management goals include the normalization of Pco_2, normalization of temperature, and correction of metabolic disturbances. Donor management goals are listed in Box 13-3. Progression from brain death to somatic death and loss of transplantable organs can result if appropriate care is not instituted.[8,46] Aggressive donor management optimizes organ function and affects the quality of organs recovered.[11,46] This scenario can result in more transplantable organs and improved graft function,[9-12] potentially reducing the length of the hospital stay and decreasing the incidence of morbidity and mortality for the transplant recipient.

Box 13–3 Pediatric Donor Management Goals

Hemodynamic Support

1. Normalization of blood pressure
2. Systolic blood pressure appropriate for age
   NOTE: Lower systolic blood pressures may be acceptable if biomarkers such as lactate and Svo_2 are normal
3. CVP <12 mm Hg (if measured)
4. Dopamine <10 μg/kg/min
5. Normal serum lactate

Oxygenation and Ventilation

1. Maintain Pao_2 >100 mm Hg
2. Fio_2 0.40
3. Normalize $Paco_2$ 35-45 mm Hg
4. Arterial pH 7.30-7.45
5. Tidal volumes 8-10 mL/kg
6. PEEP 5 cm H_2O

Thermal Regulation

1. Core body temperature 36°-38° C

Blood Pressure

	Systolic (mm Hg)	Diastolic (mm Hg)
Neonate	60-90	35-60
Infant (6 mo)	80-95	50-65
Toddler (2 y)	85-100	50-65
School age (7 y)	90-115	60-70
Adolescent (15 y)	110-130	65-80

Fluids and Electrolytes

1. Serum Na^+ (mEq/L)	130-150
2. Serum K^+ (mEq/L)	3-5.0
3. Serum glucose (mg/dL)	60-150
4. Ionized Ca^{++} (μmol/L)	0.8-1.2

CVP, Central venous pressure; Fio_2, fraction of inspired oxygen; *PEEP,* positive end-expiratory pressure; Svo_2, venous oxygen saturation.
Data from: Nakagawa TA: *North American Transplant Coordinators Organization (NATCO) updated donor management and dosing guidelines*, Lenexa, KS, 2008, North American Transplant Coordinators Organization.

Treatment of Hemodynamic Instability

Cardiac instability is the greatest limiting factor to successful organ recovery. Of all the physiologic abnormalities encountered in the prospective organ donor, the cardiovascular system is fraught with the greatest complexity and variation. The tremendous physiologic derangements associated with neuroendocrine dysfunction require specific interventions to restore normal physiology.

The sympathetic storm associated with cerebral ischemia and intracranial hypertension is a predictably transient phenomenon. Although end-organ ischemia can occur transiently, treatment with antihypertensive agents may not be warranted and indeed can create additional problems with perfusion when this phase of sympathetic outflow has passed. If hypertension is severe and treatment is believed to be indicated, a single intravenous dose or continuous infusion of a short-acting antihypertensive agent such as hydralazine, sodium nitroprusside, esmolol, or labetalol can be administered and titrated to effect.

Once brain death occurs, there is an associated drop of sympathetic outflow, leading to loss of sympathetic tone and vasodilation. This situation results in profound and abrupt hypotension. Management goals during this phase of patient care are directed at aggressive restoration of circulating volume, optimizing cardiac output and oxygen delivery to the tissues, and maintaining normal blood pressure for age (see Box 13-3). Aggressive restoration of circulating volume and utilization of catecholamines to support blood pressure are mainstays of treatment.[47] The use of artificial plasma expanders such as Hespan or dextran for volume resuscitation should be avoided because large volumes of these agents can promote coagulation disturbances.[48,49] Inotropic agents such as dopamine, dobutamine, and epinephrine can be titrated to effect. Catecholamines and dopamine appear to have immunomodulating effects that may help blunt the inflammatory response associated with brain death and improve kidney graft function.[50,51] Although sometimes necessary, the administration of high-dose vasoactive agents can be associated with reduced perfusion to donor organs, potentially jeopardizing their viability prior to recovery and transplantation. The use of HRT with agents such as thyroid hormone, steroids, vasopressin, and insulin is commonly used during donor management, especially in situations in which significant inotropic support is required.[10-12,47,52] Clinical characteristics such as blood pressure and central venous pressure (CVP) and biomarkers such as mixed venous oxygen saturation and serum lactate levels serve as guides to adequate cardiac performance and tissue oxygen delivery. Some clinical indicators may not be reliable once brain death has occurred. Urine output may not be a good clinical indicator of intravascular volume if DI is present. After death of the brain stem, heart rate may not be a reliable sign of intravascular volume status because there is loss of beat-to-beat variation and lack of vagal tone and a fixed heart rate. Perfusion also may be affected because temperature instability and hypothermia can result in delayed capillary refill time. Biomarkers such as mixed venous oxygen saturation and serum lactate levels may usefully guide cardiac management and manipulation of oxygen delivery to tissues. Elevations in serum lactate and the development of a metabolic acidosis provide evidence of tissue ischemia and should prompt immediate attention.

Arrhythmias can occur during the progression to brain death or following brain death. The catecholamine storm triggered by adrenergic stimulation can promote rhythm disturbances and myocardial ischemia. Hypotension from hypovolemia and vasodilation causes poor cardiac output and metabolic acidosis. Other factors that contribute to arrhythmias include hypoxemia, hypothermia, cardiac trauma, and the pro-arrhythmic properties of inotropes. Electrolyte and metabolic disturbances—specifically hypomagnesemia, hypocalcemia, and hypokalemia that occur with DI—also may precipitate rhythm disturbances. Identification and correction of the underlying cause of the arrhythmia is essential to address rhythm disturbances.

Hormonal Replacement Therapy

Significant volume resuscitation and inotropic support are commonly required to correct severe cardiovascular derangements following brain death. Thyroid and cortisol depletion may contribute to the hemodynamic instability encountered in patients who have progressed to brain death. Common strategies used to support this patient population are the initiation of HRT to augment blood volume and inotropic support to optimize cardiac output. The use of HRT has allowed a management strategy in which blood pressure and normovolemia are maintained using a minimum amount of vasoactive agents.

HRT in adult donors is controversial because the correlations of hormone use, cardiac function, and clinical outcome are variable.[9-12,53-57] However, in one adult series HRT has been shown to reduce the need for vasoactive infusions in 100% of unstable donors and to abolish the need in 53% of such donors.[57] Decreased inotropic requirements also have been noted in children who received levothyroxine and vasopressin as part of management following brain death.[58,59] Although limited studies are available, HRT seems to be a reasonable consideration in situations in which the hemodynamic status of the child is refractory to conventional therapy with fluid and inotropic administration. HRT has been associated with an increased number of organs recovered from donors.[8,10-12,60] No published studies are available in children; however, one unpublished abstract retrospectively reviewed 1903 pediatric donors.[61] HRT was associated with significantly increased odds of having the liver and at least one kidney and lung transplanted. There was no significant increase in the odds of the heart being transplanted. The greatest benefit of HRT in donor management may in fact be improved graft function following transplantation.[9,60,62-64] Given these observations, many OPOs have adopted the use of HRT as a routine part of donor management. Commonly used agents and doses for hormonal resuscitation in pediatric donors are listed in Table 13-1.

Impaired cardiac performance following brain death is due to vascular injury associated with the catecholamine storm. Additionally, reduced free triiodothyronine (T_3) levels may impair mitochondrial function and deplete energy stores. Animal studies have shown that diminished circulating levels of T_3 and thyroxine[39] impair oxygen utilization. The effects of thyroid hormone on myocardial contractility are complex and can be immediate or delayed. The acute inotropic properties of T_3 may occur as a result of β-adrenoreceptor sensitization or may be completely independent of β-adrenergic

Table 13–1 Pharmacologic Agents Used for Hormonal Resuscitation in Children

Drug	Dose	Route	Comments
Desmopressin (DDAVP)	0.5 μg/h	IV	Terminal half-life = 75 min (range, 0.4-4 h) Titrate to effect to control urine output (2-4 mL/kg/h) May be beneficial in patients with an ongoing coagulopathy
Vasopressin (Pitressin)	0.5 mU/kg/h	IV	Half-life = 10-35 min Titrate to effect to control urine output (2-4 mL/kg/h) Hypertension can occur
Levothyroxine (Synthroid)	0.8-1.4 μg/kg/h	IV	Titrate to effect Bolus dose 1-5 μg/kg can be administered; smaller infants and children require a higher bolus and infusion dose
Triiodothyronine (T_3)	0.05-0.2 μg/kg/h	IV	Titrate to effect
Methylprednisolone (Solu-Medrol)	20-30 mg/kg	IV	Dose may be repeated in 8-12 h; fluid retention and glucose intolerance can occur
Insulin	0.05-0.1 U/kg/h	IV	Titrate to effect to control blood glucose levels; monitor for hypoglycemia

IV, Intravenous.
Data from Nakagawa TA: *North American Transplant Coordinators Organization (NATCO) updated donor management and dosing guidelines*, Lenexa, KS, 2008, North American Transplant Coordinators Organization.

receptors.[62,65,66] Furthermore, T_3 administration may play an important role in maintaining aerobic metabolism at the tissue level after brain death has occurred.[67] Beneficial hemodynamic effects in brain-dead patients receiving T_3 administration have been variable.[62,64] Levothyroxine (Synthroid) and T_3 are the two intravenous thyroid agents available for administration. T_3 is used in some centers for HRT; however, the cost of this medication may be prohibitive. Dosing of thyroid hormone for the pediatric organ donor is not well established. Thyroid hormone dosing is based upon weight. One retrospective study in which younger children received larger bolus and infusion doses than did older children demonstrated enhanced weaning of inotropic support in children who progressed to brain death.[58]

Steroids such as hydrocortisone are another pharmacologic agent routinely used by many centers for HRT to assist with hemodynamic support. Few data exist to show that hydrocortisone provides hemodynamic benefit in the potential pediatric organ donor.[47] The potential benefit of hydrocortisone and other steroids may lie in their ability to alter adrenergic receptors and regulate vascular tone by increasing sensitivity to catecholamines.[68,69] Steroids also have been shown to stabilize pulmonary function, reduce lung water accumulation, and increase lung recovery from donors.[70-73]

The combination of thyroid hormone and steroids may be used to reduce vasoactive agent dose requirements in children. Additionally, vasopressin for control of DI can reduce the need for inotropic support.

Management of Pulmonary Issues for the Potential Pediatric Organ Donor

Increasing success with lung transplantation for the treatment of patients with end-stage lung and pulmonary vascular disease has placed a premium on the acquisition of lungs from the donor pool. Children waiting for a lung transplant comprise less than 10% of the national pediatric wait list.[1] However, the demand far exceeds availability. Experience has shown that lungs are the organs most likely to be found unsuitable for transplantation. Recovery of lungs for transplantation accounts for 7% to 22% of the multi-organ donor pool.[74,75] The low percentage of lung recovery for transplantation reflects stringent donor selection criteria and lack of suitable organs for transplantation. Lung protective strategies have the potential to salvage marginal lungs for transplantation; however, in many instances these strategies are not implemented, resulting in the loss of potential lung donors.[75]

Many factors contribute to the limitations associated with acquisition of lungs for transplantation. Blunt trauma in children resulting in pulmonary contusion/hemorrhage accounts for a large portion of injuries to the thoracic cavity. Inhalational or thermal injury can injure the lungs and airway structures. Infectious etiologies can compound the effects of existing lung disease or injury. Often these injuries are the reason the patient has become an organ donor. Furthermore, the lungs are particularly vulnerable in the face of critical illness, leaving them susceptible to complications such as fat emboli, pulmonary emboli, aspiration pneumonia, ventilator-associated pneumonia, and atelectasis.[71] Each of these disorders is associated with lung injury and impaired ventilation and oxygenation that diminishes lung suitability for transplantation.

The physiologic aberrations that accompany brain death also can result in end organ damage, rendering lungs unsuitable for transplantation. Management of pulmonary physiology is often complicated by the development of pulmonary edema from the progression of brain injury.[46] The sympathetic storm associated with brain death causes systemic and pulmonary vasoconstriction. Neurogenic pulmonary edema occurs as pulmonary venous pressure rises, causing pulmonary capillary wall disruption and evolution of pulmonary edema.[76] This predictable deterioration of pulmonary function increases the vulnerability of the lungs to injury in the brain-dead donor.[75,77] Massive brain injury may in fact act as a preconditioning factor that renders the graft more susceptible to subsequent lung damage and increases the risk of post-transplant graft failure.[77]

Lung protective management strategies have been developed as a result of the complex physiology and vulnerability of the lungs following brain death. Measures to protect donor

lungs have resulted in improved recovery and successful transplantation of these organs.[78,79] Management strategies include measures such as diligent pulmonary toilet with frequent suctioning, patient turning, clearance of mucous plugs, and airway evaluation with flexible bronchoscopy.[71,80] Ventilator management with attention to recruitment maneuvers such as sustained inflations and positive end-expiratory pressure (PEEP) have been advocated to avoid the development of atelectasis and to treat the pulmonary edema associated with the catecholamine storm that occurs with brain death.[79,80] The benefit associated with the use of inflation maneuvers and PEEP must be balanced against the risk of barotrauma and effects on preload that can potentially adversely affect cardiac output in the donor with myocardial dysfunction. Volume administration and inotropic support may be required if blood pressure is affected by this maneuver. These cardiovascular effects can be minimized if adequate preload is provided prior to escalation of PEEP. Colloid solutions have been recommended to minimize accumulation of pulmonary edema.[80] Additionally, albuterol has been shown to enhance clearance of pulmonary edema in an animal model[53] and to improve mucociliary clearance.[71] Steroids are frequently utilized in the donor and have been shown to reduce lung water accumulation and stabilize pulmonary function.[70-73] Another novel therapy involves the use of naloxone to improve gas exchange in donor lungs.[81]

Ventilatory requirements may become minimal in the donor as brain death occurs. Respiratory alkalosis is common as metabolic production of carbon dioxide from the brain ceases and compliance of the chest wall changes. Restoring normocarbia with a goal of 35 to 40 mm Hg in the child who has progressed to brain death is ideal given the effects of pH on unloading characteristics of oxygen from hemoglobin. Avoiding overdistention of the lungs during mechanical and manual ventilation is crucial to reduce the risk of barotrauma or further pulmonary injury.[71,79] Donor management goals include achieving a Pao_2 of greater than 100 mm Hg, oxygen saturation of greater than 95% using the least amount of oxygen necessary, tidal volume of 10 mL/kg, and PEEP of 5 to 10 cm/H_2O to ensure adequate alveolar recruitment. Elevation of the head of the bed and use of a cuffed endotracheal tube with high cuff pressures to reduce aspiration risk also are advocated.[70] Donor management guidelines for oxygenation and ventilation are summarized in Box 13-3.

An oxygen challenge test is routinely performed to determine the suitability of the lungs for transplantation. A Pao_2/fraction of inspired oxygen (Fio_2) higher than 300 on an Fio_2 of 1.0 and a relatively clear chest radiograph are preferred by transplant surgeons. Early flexible bronchoscopic evaluation of the lungs is advocated by many OPOs to address correctable issues and maximize ventilation strategies to improve lung function.

Fluid and Electrolyte Disturbances

Fluid and electrolyte disturbances in the pediatric donor are the result of physiologic abnormalities, as well as consequences of earlier medical management. Commonly encountered derangements include dehydration, hyperglycemia, and sodium, potassium, and calcium disturbances. Metabolic fluctuations associated with progression toward brain death require meticulous management of fluids and electrolytes. If left untreated, these abnormalities can adversely affect organ viability.

Intravascular volume depletion is frequently encountered in the child with traumatic brain injury who has progressed to brain death. Fluid restriction, along with hypertonic solutions and osmotic diuretics, are commonly used in the management of cerebral edema. Another contributor to intravascular volume depletion is osmotic diuresis from hyperglycemia resulting from steroid and catecholamine use and increased availability of glucose from loss of cerebral metabolism. Furthermore, DI compounds sodium and water imbalance if not ideally treated. The intravascular volume of the potential donor must be adequately resuscitated, as guided by CVP, perfusion, serum electrolyte concentrations, and serial lactate measurements. Restoring intravascular volume is crucial to maintaining organ viability.

Diabetes Insipidus

DI occurs in many brain-dead patients, and if left untreated, it can have profound effects on the donor. Uncontrolled free water losses result in severe hypernatremia and significant dehydration with eventual cardiovascular collapse. Hypernatremia can affect organ suitability for transplantation and has been associated with graft failure following liver transplantation.[82]

In addition to hourly maintenance intravenous fluids, one quarter or half normal saline solution can be used to replace urine output in excess of 3 to 4 mL/kg until pharmacologic replacement therapy is implemented. The use of glucose in renal replacement fluids should be avoided to prevent further exacerbation of hyperglycemia and osmotic diuresis. Enteral free water supplementation administered through a nasogastric tube can be used for correction of severe hypernatremia. Rapid osmolar shifts during correction of hypernatremia are inconsequential because brain death has already occurred. DI frequently requires pharmacologic treatment with antidiuretic hormone to reduce ongoing free water loss. Pharmacologic agents such as vasopressin or desmopressin (DDAVP) are routinely utilized in HRT protocols to control urine output. These pharmacologic agents have specific indications and adverse effects that must be considered when contemplating their use to treat DI.[83] Donor management goals for treating DI include maintaining a normal serum sodium level and reducing excessive urine output. Pharmacologic treatment is not intended to completely stop urine output.

Vasopressin is a polypeptide hormone secreted by the hypothalamus and stored in the posterior pituitary. Vasopressin acts on V_1 and V_2 vasopressin receptors to stimulate contraction of vascular smooth muscle with resultant vasoconstriction. It has a short half-life of 10 to 20 minutes, and unlike desmopressin, it has no effect on platelets.[84] Vasopressin can be administered by bolus or continuous intravenous infusion. The most desirable features of this agent derive from its ease of titration to control urine output. When discontinued, its effects are short lived. Vasopressin is administered at doses of 0.5 mU/kg/h and can be titrated to control urine output to 2 to 4 mL/kg/h.[83,84] By titrating in this way, one preserves renal function and avoids volume overload and metabolic abnormalities such as hyponatremia and hyperkalemia. Vasopressin infusions commonly require rapid titration to control

excessive urine output, then avert complete loss of urine output[85] during rapid swings in renal output. High doses of vasopressin may potentially reduce splanchnic perfusion, including hepatic and pancreatic blood flow. Additionally, vasoconstriction and increased smooth muscle contractility may affect coronary and pulmonary blood flow.[45] Excessive dosing of vasopressin should be avoided to preserve end organ function.

Desmopressin acetate is a more potent synthetic polypeptide structurally related to vasopressin. This agent lacks smooth muscle contractile properties and is more specific for the V_2-vasopressin receptor. Desmopressin enhances platelet aggregation and has a longer half-life of 6 to 20 hours when administered as a single intravenous dose.[86] Desmopressin may be a preferred agent for the correction of hypernatremia given its lack of hemodynamic effects. Desmopressin can be administered by continuous infusion at 0.5 μg/h and titrated to control urine output.[83,88] Intramuscular and intranasal administration can result in erratic absorption and should be avoided. The terminal half-life of desmopressin administered by continuous intravenous infusion is 75 minutes, with a range of 0.4 to 4 hours.[88] The longer half-life of desmopressin may be less desirable than the shorter half-life of vasopressin in potential kidney donors. Desmopressin therapy may be discontinued 3 to 4 hours prior to organ recovery.[83] Fluid replacement for excessive urine output can be administered as needed for the short period prior to organ recovery.

Oliguria

Oliguria can be seen with volume depletion, acute renal insufficiency or failure, and overly aggressive pharmacologic management of DI. If urine output falls to less than 1 mL/kg/h and does not improve after decreasing or discontinuing vasopressin, intravascular volume status must be evaluated and appropriately treated. If urine output is not improved following volume expansion, initiation of inotropic or vasopressor support may improve urine output. Furosemide (Lasix) or mannitol can be used to stimulate urine output in the patient with adequate intravascular volume status. A selective dopamine agonist such as fenoldopam can be used to enhance urine output and may provide renal protection in the normotensive or hypertensive patient.[89]

Glucose, Potassium, and Calcium Derangements

Hyperglycemia as a result of steroid and catecholamine use and increased availability of glucose as a result of the loss of cerebral metabolism can lead to an osmotic diuresis, exacerbating an already depleted volume status in the donor. Hyperglycemia can be avoided by frequently assessing blood glucose concentration and making appropriate adjustments in the dextrose concentration in intravenous fluids. If these simple maneuvers are unsuccessful in controlling blood glucose levels, an insulin infusion should be instituted to maintain glucose levels between 60 to 150 mg/dL. Serum glucose levels should be closely followed to avoid hypoglycemia.

Potassium derangements can result from diuresis, renal insufficiency, steroid administration, and acid-base disturbances. Potassium can be supplemented if hypokalemia is significant. The adverse effects of hyperkalemia are clearly more hazardous than those of hypokalemia. The adverse effects of hypokalemia most likely to affect the potential donor are dysrhythmias.

Hypocalcemia occurs commonly as a result of large volume replacement with colloids such as albumin; massive blood transfusions, which result in large amounts of citrate-reducing free calcium concentrations; and sepsis. The use of calcium supplementation should be guided by ionized calcium levels.

Coagulation Abnormalities and Thermoregulatory Instability

Coagulation abnormalities can arise as a result of the release of tissue thromboplastin and cerebral gangliosides from injured brain.[45] Additionally, the catecholamine surge associated with traumatic brain injury may contribute to coagulation disturbances.[90] Thrombocytopenia and platelet dysfunction can be induced by common drugs such as heparin, antibiotics, β-blockers, calcium channel blockers, histamine H_2 receptor antagonists, tromethamine, and hespan.[91] Patients with liver disease have reduced synthesis of vitamin K–dependent clotting factors. A dilutional coagulopathy can occur from massive transfusions if coagulation factors are not replenished. Coagulation abnormalities also can be exacerbated by hypothermia. Correction of the coagulopathy can be treated using fresh frozen plasma, platelets, and cryoprecipitate, and by restoring and maintaining normothermia. The goal of blood product replacement for coagulopathy should be tailored accordingly based on the abnormalities encountered.

Coagulation abnormalities should be addressed prior to transport of the donor to the operating suite for organ recovery. A minimum platelet count of 75,000/mm^3 should be obtained prior to recovery of organs in the operating suite. The use of aminocaproic acid (Amicar), an antifibrinolytic agent, and other similar hemostatic agents are not recommended for treatment of bleeding because microvascular thrombosis may be induced in donor organs.[45]

Hypothermia commonly occurs following brain death. Vasodilation with an inability to compensate for heat loss by shivering or vasoconstriction is a common cause of thermoregulatory instability in this patient population. Additionally, the infusion of large volumes of room-temperature intravenous fluids to treat DI and volume depletion contributes to hypothermia. Hypothermia can promote cardiac dysfunction, arrhythmias, coagulopathy, a cold-induced diuresis resulting from decreased renal tubular concentration gradient, and a leftward shift of the oxyhemoglobin dissociation curve, resulting in decreased oxygen delivery to the tissues.[92] Radiant warmers, warm blankets, thermal mattresses, warm intravenous fluids or a blood warmer for infusion of blood products, and environmental warming will help maintain body temperature. Additionally, heating inspired gases can assist in controlling body temperature. Prevention of hypothermia is essential to prevent deterioration of the potential organ donor.

Medical Examiner/Coroner Issues and Organ Donation for Children

Many children who die from head injuries are victims of nonaccidental trauma. When nonaccidental trauma has resulted in the death of a child, great sensitivity is required to preserve

the integrity of the criminal investigation. Successful recovery of organs from these patients can still occur in most cases with close cooperation between forensic investigators, treating physicians, the transplant team, and the OPO.[93-97] Protocols to facilitate organ recovery in child abuse victims can decrease denials for organ donation by medical examiners/coroners.[96-99] Involvement of the district attorney during protocol development also should be a consideration. Efforts to reduce the number of medical examiner denials for donation are occurring at a national level and supported by the National Association of Medical Examiners.[100] Despite these national efforts, many potential pediatric donors continue to be lost because of medical examiner/coroner denials.[2]

Donation After Circulatory Determination of Death

Whereas the vast majority of recovered organs will be recovered from brain-dead donors, donation after circulatory determination of death (DCD)—that is, the organ donor without a beating heart—provides another source of valuable organs for transplantation.

DCD allows donation to occur from patients with catastrophic brain injury who do not progress to brain death. The discussions and decision to donate organs can only occur after the decision to withdraw life support has been made. This step avoids the perceived ethical conflict that we are allowing the patient to die to recover organs. Routine end-of-life care, including comfort measures, are provided for these patients just as they would be for any patient in whom withdrawal of medical support occurs.

Criteria must be met for organs to be recovered by this method. Circulatory arrest must occur within 60 minutes of withdrawing support. The time constraint is important because longer periods to achieve circulatory arrest will result in organ ischemia, rendering potential transplant tissue useless. Following loss of cardiac electrical activity (electrical asystole) or pulse pressure (mechanical asystole), the patient is observed for 2 to 5 minutes before recovery of organs can occur. This 2- to 5-minute observation period is crucial to ensure that auto resuscitation of the heart with restoration of circulation does not occur. If electrical or mechanical asystole is consistent with circulatory death following the observation period, organs are recovered for transplantation. Families must be prepared for the possibility that death may not occur within the specified time period. If this situation occurs, continued comfort measures are provided for the patient and family support continues.

DCD is not a new method of organ recovery. In fact, DCD is the foundation of modern transplant medicine. Organs were routinely recovered by this method prior to institution of brain death guidelines. The reevaluation of this method of donation was prompted by the increasing need to meet the demands of a growing national transplant wait list.[101,102] Between 2005 and 2006, there was almost a 100% increase in the number of pediatric DCD donors nationally. This sustained practice during the past few years is reflected by an average of 72 pediatric DCD donors per year, accounting for approximately 10% of all DCD donors during this period.[1] DCD has the potential to increase organ donation in children.[103-105] Individual numbers of DCD donors may be small at any one pediatric center, but the collective impact from all pediatric centers actively recovering organs from this type of donor has the potential to significantly increase the number of organs available for transplantation.[101-106]

DCD focuses on recovery of the two most commonly needed organs for children, the liver and kidney. Success with transplantation of DCD organs, primarily the kidney and liver, is occurring in many centers. Rates of graft survival for these organs appear to be similar to those of organs recovered from brain-dead donors.[107-111] Although experience is limited, lung transplants from DCD donors have occurred in several institutions.[112,113] Additionally, the successful transplantation of three hearts recovered from neonatal DCD donors, under an established research protocol, has occurred[114]; however, ethical concerns about when circulatory death occurs have been raised and continue to be debated.

Although some controversy exists over this mode of donation, the Society of Critical Care Medicine, the Institute of Medicine, the American Medical Association, and the American Academy of Pediatrics support DCD as an acceptable means to recover organs for transplantation.[93,115-118] Education regarding this mode of donation is crucial so that all health care personnel can successfully identify and recover organs from this population of children.[119,120]

Summary

The process of organ donation begins when a critically ill or injured child is identified as a potential donor with a timely referral to the OPO. Identifying and caring for the organ donor requires a skilled team of specialists who deal not only with the deceased child, but also the family. Early involvement of the OPO allows coordination with physicians, social workers, chaplains, and family support services, enhancing the chance for the family to understand and agree to organ donation. Timely and accurate determination of brain death allows the focus of medical management to transition toward care and preservation of organs for transplantation once consent is obtained. Management of the pediatric organ donor is a natural extension of care for a critically ill or injured child. Meticulous care of the potential donor can result in more transplantable organs with improved graft function. The option for organ donation should be made available to every family. It should be the expectation that the family will be approached in a professional, compassionate manner that allows for open discussion during the most difficult, agonizing time in their lives. Pediatric critical care specialists working together with other dedicated professionals to provide specialized care to the donor can affect the lives not only of the donor family, but also of many potential recipients and their families through the effects of a life-saving and life-changing transplant.

References are available online at http://www.expertconsult.com.

Chapter 14

Pediatric Transport: Shifting the Paradigm to Improve Patient Outcome

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PEARLS

- In transport, patients are subjected to a high-risk moving environment with limited resources and few monitoring capabilities. The goal during transport should be to provide the same or better quality care than the patient received before transport.
- A retrieval system has a responsibility to the referral community to make tertiary care accessible. The components include a communication center, administrative staff, appropriately trained team members, reliable equipment, and education and safety programs.
- A hospital should not transfer a patient until (1) the patient has been stabilized within the ability of the transferring hospital, (2) the patient consents to transfer having been informed of the risks of transfer, and (3) the referring physician certifies that the medical benefits expected from the transfer outweigh the risks. The transferring hospital has responsibility for providing copies of the medical records and imaging studies to accompany the patient. The receiving facility must have available space and qualified personnel and agree to accept the patient. The transport must be made by qualified personnel.
- The pathophysiology of acute respiratory and hemodynamic embarrassment in children differs from adults in ways that may impact care during transport.
- Underutilization of acquired procedural or assessment skills often leads to decrement in skill level. It is a major challenge for multidisciplinary teams to acquire and maintain the knowledge and skills to provide competent care for critically ill children and adults.
- Evidence that early resuscitation of pediatric shock improves outcome is mounting. The paradigm of transport in which speed of transport takes precedence over quality of care must be abandoned if we are to realize improved outcomes in the critically ill child who requires transport to a critical care center. Goal-directed therapy should begin in the prehospital arena and continue throughout the critical care continuum.

Along with the regionalization of pediatric emergency and critical care centers has come the growth of interfacility transport programs, allowing geographic expansion of tertiary medical care. Eighty-nine percent of pediatric emergency department (ED) visits occur in nonpediatric EDs, where the extent of illness or injury is assessed and initial stabilization is provided.[1] Most community hospitals do not have the personnel, space, or facilities to provide critical care to infants or children beyond the period of initial stabilization, necessitating transfer to a tertiary facility. In transport, children are subjected to a high-risk environment with limited resources and monitoring capabilities. The goal during transport should be to provide care commensurate with the degree of illness severity in a safe and effective manner, minimizing the risk of deterioration and unplanned events before transport and en route. Little research exists to support the choices about mode of travel or makeup of the transferring team that are made every time a child is transferred to a tertiary facility.

Improvements in critical care are incremental: There are no miracle drugs or technologies. The major improvements in care in the last decade involve early, aggressive administration of simple therapies: timely initiation of resuscitation fluids, inotropes via peripheral intravenous line, and antibiotic therapy can improve outcomes.[2,3] If appropriate resuscitation waits until the child arrives in the pediatric intensive care unit (PICU), the benefits of early, aggressive action are likely to be lost. Goal-directed therapy must begin before and continue during transport for the benefits noted in these studies to occur. Significant barriers to realizing this ideal exist.

In this chapter we will briefly discuss the barriers that have stifled progress. Information about appropriate vehicles, medication, and equipment for transport is summarized elsewhere, in the American Academy of Pediatrics (AAP) Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients.[4] This chapter is designed to challenge the pediatric intensivist, whose patient population is largely derived from transport, with the important concept that a well designed and staffed pediatric critical care transport system can have a dramatic impact on patient outcomes, and deserves great attention from pediatric intensivists.

The Problem: An Adult-Oriented Retrieval System Focused on Rapid Movement

Emergency medical services (EMS) and regional flight teams are focused on the major causes of mortality in the adult population, such as myocardial infarction and trauma, for which rapid transfer to a center that can provide definitive care is an important determinant of outcome.[5] Adult-oriented ED and EMS services do not provide ideal care for children. Still, multidisciplinary teams transport the majority of critically ill children. Many argue that pediatric specialized transport systems are not necessary, for the reasons given in Box 14-1.

With the support of other interested bodies, the American Academy of Pediatrics recently issued a policy statement detailing the recommended pediatric equipment for ambulances.[2] It is not known what percentage of ambulances are adequately equipped, but two independent studies reported that as recently as 2003, only 6% of emergency rooms were appropriately equipped to care for children. Items frequently not available included laryngeal mask airways and infant and neonatal equipment.[6]

Limited pediatric training coupled with limited exposure to pediatric patients may hamper the ability of EMS providers to respond appropriately to pediatric emergencies. In 2000, nationally registered paramedics received a median 358 total hours of instruction, less than 5% of which were dedicated to pediatrics. Moreover, most paramedics in this study were not required to take pediatric continuing medical education (CME) training.[7] Without repeated reinforcement, cognitive and interventional skills deteriorate over time. Fewer than 10% of all EMS runs nationwide are for infants and children, and a small percentage of these involve advanced life support (ALS) or critical care.[8,9] Babl et al.[10] demonstrated that in a program with 50 active ALS providers, each provider is expected to have one pediatric bag-valve-mask (BVM) case every 1.7 years, one pediatric intubation every 3.3 years, and one intraosseus cannulation every 6.7 years. Su et al.[11] demonstrated that the knowledge acquired in didactic sessions deteriorates rapidly over a 6-month period. Henderson[12] also demonstrated that the ability of a provider to intubate or provide BVM ventilation for a child deteriorates significantly over the course of 6 months.

Underutilization of an acquired skill can lead to a decrement in skill level and a fear-related aversion to performing the procedure. With any given scenario in the EMS setting, adult patients are more likely to receive an appropriate intervention compared with a child having the same problem.[13,14] Prehospital care providers are reluctant to attempt intubation, even when it is clearly indicated. Aijian et al. examined a population of pediatric patients who had suffered a prehospital cardiopulmonary arrest and determined that endotracheal intubation was attempted only 68% of the time, with a success rate of only 64%.[15] In patients younger than 1 year, endotracheal intubation was attempted only 38% of the time, with a success rate of only 50%.[15] Multiple investigators have documented a decrease in the percent of successful intubations in children compared with adult patients, both in ground EMS systems and air ambulance systems.[16-19]

Studies of pediatric trauma victims make it clear that prehospital providers could do a better job with children. Children were twice as likely to die of trauma in the field compared with adults, which was attributed to the lack of pediatric training.[5,8,20] Ramenofsky et al. determined that 53 of 100 deceased pediatric trauma victims in their study could have been salvaged given an optimally functioning emergency medical system and that in 79% of the potentially salvageable cases, mortality was associated with prehospital iatrogenic or secondary insults.[9]

Referring hospitals that lack pediatric expertise may create suboptimal situations prior to transport. Esposito et al. found that frequent errors occur in ED management of pediatric trauma, leading to preventable mortality of approximately 9%.[21] In addition, they reported a 64% error rate in the management of children, including gross violations of basic trauma care.[21] Han et al.[22] found that resuscitation practice in a community ED was consistent with American College of Critical Care Medicine-Pediatric Advanced Life Support (ACCM-PALS) guidelines in only 30% of children who presented with septic shock. Athey et al.[23] found that nearly 10% of all U.S. hospitals without pediatric intensive care facilities admit critically ill and injured children, and that 7% of these hospitals routinely admit these children to adult intensive care units rather than transferring the children to a more appropriate facility. Of the facilities that keep children, few have protocols for obtaining pediatric consultation for emergencies, and most did not have appropriate-sized equipment to care for children.[23] Those referring hospitals that do transport children to pediatric facilities are often inadequately equipped to care for children or unfamiliar with established guidelines and protocols and, as a result, may be in a rush to send children, sacrificing stabilization and eschewing transport by a more experienced team in the interests of saving time. When facilities and physicians lack

Box 14–1 Arguments Against and for Use of Specialized Pediatric Transport Teams

Arguments against	Arguments for
• Expensive and resource-intensive	• Resource use may be justified by improved outcomes
• The patient is already packaged to go—what else is there to do?	• A specialized team brings goal-directed ICU care to the patient and continues attentive resuscitation as the patient changes en route
• Limitations of the transport environment—what more can a specialist do?	• For most transports, the critical time is time to initiation of appropriate therapy, NOT time to arrival at the tertiary care center
• Specialized teams spend too much time on the scene; no appreciation for what is time-critical	• Nonspecialized teams lack experience with children and have difficulty maintaining learned skills
• Requires two-way transport; takes longer to get to the critical care center	• Improved outcome may justify development of specialized teams
• ABCs (airway, breathing, circulation) are no different for children	
• Not available in many settings	

insight about their ability to care for children, requests for transfer may come too late, after irreparable organ damage has already occurred.

Critical Pediatric Physiology Relevant to Transport Medicine

There are some critical differences between the respiratory mechanics and cardiovascular physiology in adults and children that lead to a need for earlier, more aggressive intervention in children with common pediatric problems. Failure to understand these differences can lead to a potentially injurious delay in advanced airway management and shock resuscitation. Airway interventions should be planned carefully and performed early in the course of respiratory failure to avoid having to deal with a respiratory crisis while en route.

Peripheral airway resistance in children younger than 5 years is approximately four times higher than in adults or older children, in whom the upper airway is the major contributor to airflow resistance.[24] Because of this, young children are more likely to have lower airway obstructive disease and less likely to respond to airway positioning, an intervention which is commonly used by paramedics to defer intubation in adults.

Infants and small children have more compliant chest walls with low elastic recoil compared with older children and adults, increasing the risk of lung collapse.[25] In infants and small children, muscular effort is required to stabilize the chest wall, and a portion of the force of contraction of the diaphragm is wasted in distorting the rib cage.[26] This mechanical disadvantage leads to increased energy expenditure, and increases the likelihood that infants with lung disease may fatigue and stop breathing.[27] Gastric distension can further decrease the efficiency of the diaphragm in children and should be prevented or treated with a nasogastric tube. Positive pressure breathing applied early in the disease process can stop the progression of atelectasis and respiratory failure.

Functional residual capacity is only slightly higher than critical closing volume in infants and small children, leading to alveolar collapse much earlier in the course of respiratory failure. Lung growth appears to involve both an increase in the number of alveoli and an increase in the size of alveolar spaces,[28] which may also predispose the infant lung, with its smaller alveoli, to collapse. In addition, the adult lung contains anatomic channels that allow ventilation distal to an obstructed airway, also known as collateral ventilation; the absence of these pathways in young children further increases the risk for atelectasis.[29] The diffusing capacity across the alveolar-capillary membrane in a child is only about one third that of an adult, making gas exchange less efficient.[30]

The delivery of goal-directed therapy may be hampered by the inability of practitioners to recognize shock. Infants and children have a greater capacity to increase systemic vascular resistance in shock states and tend to preserve blood pressure until very late in the evolution of shock.[31] Pediatric shock resuscitation protocols developed by the consensus of experts in the field call for treatment of shock using clinical signs, including age-specific targets for heart rate and blood pressure, and relatively subtle indicators of perfusion as therapeutic endpoints.[32]

Rapid Transfer, Goal-Directed Therapy, and the Golden Hour

EMS and regional flight teams focused on adult experience work under the assumption that the time between the moment of injury and arrival at a center capable of delivering definitive care is among the most important determinants of survival. This "golden hour" is the driving force for clinical decision-making and usually translates into providing minimal care and moving quickly (Figure 14-1). The concept of the "golden hour" often is described as having its origin in a surgical commentary by Cowley et al.[33] on the success of implementing a helicopter-based program for trauma, during an era when prehospital care consisted of providing supplemental oxygen and a fast-moving vehicle. "Scoop and run" and the "golden hour" remain the prevailing philosophies in the transport of infants and children, few of whom benefit from the speed of transport alone.

There are a few disease processes, such as aneurysms requiring neurosurgical intervention or complete transposition of the great arteries requiring urgent atrial septostomy, in which rapid transport to a center that can provide definitive care is the most pressing issue. These are rarities. Respiratory insufficiency and shock are common reasons for referral of pediatric patients. A recent study identified shock in 37% of children transferred to tertiary centers *regardless of the reason for referral.*[34] It is increasingly recognized that rapid resuscitation is critical to the management of pediatric shock.[32] In adults and children, protocolized, aggressive, early therapy of septic shock has proven vastly more effective than any pharmacological intervention.[2,22,34,35] Aggressive fluid resuscitation and initiation of inotropes and antibiotics should be accomplished within the first hour after presentation. In adults with septic shock, a delay in antibiotic therapy is associated with worse survival, with mortality increasing by 7% for every 30 minutes that passes without delivery of appropriate antibiotic therapy.[3]

The American College of Critical Care Medicine (ACCM) clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock are divided into specific

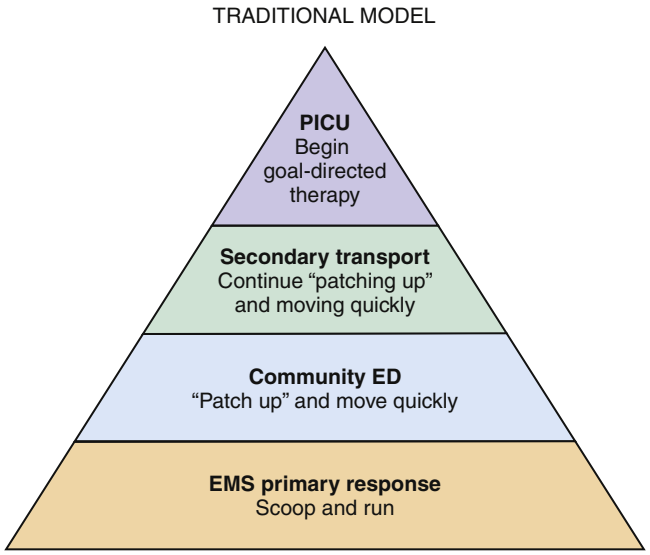

Figure 14–1. Traditional model of emergency care based on the concept of the "golden hour." *ED,* Emergency department; *EMS,* emergency medical services; *PICU,* pediatric intensive care unit.

tasks to be accomplished in the first 5 minutes, the first 15 minutes, and the first hour. The recommended treatments are simple interventions that can be initiated in community EDs and continued and refined in transport, provided that the treating physician and transferring team appreciate the urgent need and are sensitive to the subtle signs of shock in children. Han et al. reported that when community physicians aggressively resuscitated and successfully reversed shock before a transport team arrived, patients had a ninefold increase in their odds of survival.[22] These studies defy the popular notion that out-of-hospital stabilization "wastes time" and "delays" definitive therapy that should be rendered at the receiving facility. Initiating treatment in the referring facility to the best of the institution's ability and bringing skilled transport personnel to the child rather than transporting the child with inadequately skilled personnel may markedly decrease the time to effective treatment.

Specialized Teams Improve Outcome

In 1978, Chance et al.[36] demonstrated reduced mortality and more stable physiology in neonates weighing less than 1.5 kg who were transported by a specialized team. Improved acid-base balance and hemodynamic stability on arrival to tertiary care centers has also been noted in pediatric patients transported by specialty teams.[37] Macnab[38] found fewer preventable insults occurred in children transported by a pediatric intensive care team. Edge et al.[39] demonstrated that patients who were transported by nonspecialized teams had a tenfold increase in transport-related adverse events (such as loss of an endotracheal tube) compared with specialized teams, after adjusting for severity of illness (Pediatric Risk of Mortality [PRISM]) and number of interventions (Therapeutic Intervention Scoring System [TISS]). In a prospective risk assessment of 1085 children transported to a children's hospital, Orr et al.[40] found that patients who were transported by nonspecialized transport teams were more likely to suffer from an unplanned event (odds ratio, 22.2) and in-hospital death (odds ratio, 2.4) compared with children transported by a specialized team, after adjusting for severity of illness, age, and diagnosis. Mobilization time, scene time, and total transport time did not predict unplanned events or death. In a case-control study of head-injured children, Macnab et al.[41] found more preventable insults among the patients transported by untrained escorts compared with trained escorts. The authors determined that the additional cost of care resulting from secondary adverse events occurring during transport by untrained escorts was $135,952.

In a prospective cohort study in which allocation of teams depended on team availability, not severity of illness, Orr et al.[42] showed that use of a specialized team resulted in fewer unplanned adverse events and lower mortality compared with use of a nonspecialized team. Most importantly, mortality was high in children transported by nonspecialized teams compared with specialized teams (23% vs. 9%) a difference that remained significant when controlling for pre-ICU PRISM score.

The Solution: A Retrieval System Focused on Improving Outcome

Pediatric transport is part of a critical care continuum that includes EMS, the referring ED, secondary transfer, and the receiving critical care facility (Figure 14-2). In our experience, the continuum is often fragmented, primarily by territorial issues, resulting in poor communication, isolation, lack of continuity of care, and inadequate quality assessment (Figure 14-3). The most effective system provides excellent communication between the referring hospital and the tertiary center with clear advice to support the referring staff's care, brings critical care and goal-directed therapy to the patient at the referring institution, and continues optimal care through transport and into the PICU (Figure 14-4). Bringing evidence-based recommendations and then skilled transport personnel to the child rather than transporting the child with inadequately skilled personnel may markedly decrease the time to effective treatment. Ideally, if optimal care is to be provided,

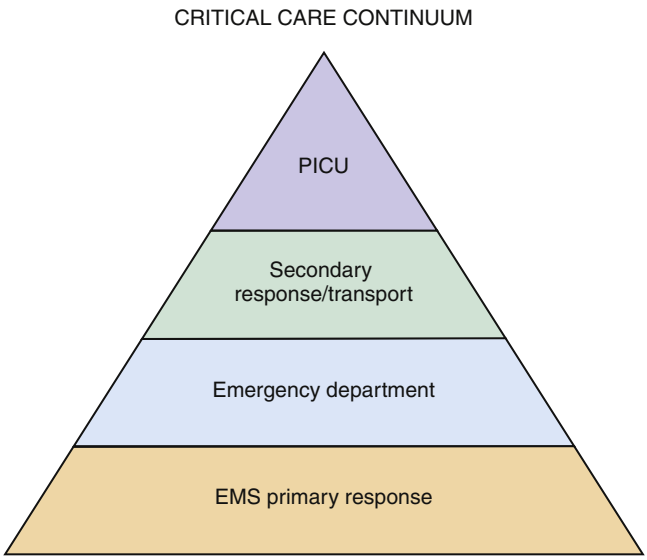

Figure 14–2. Pediatric transport as part of the critical care continuum. *EMS,* Emergency medical services; *PICU,* pediatric intensive care unit.

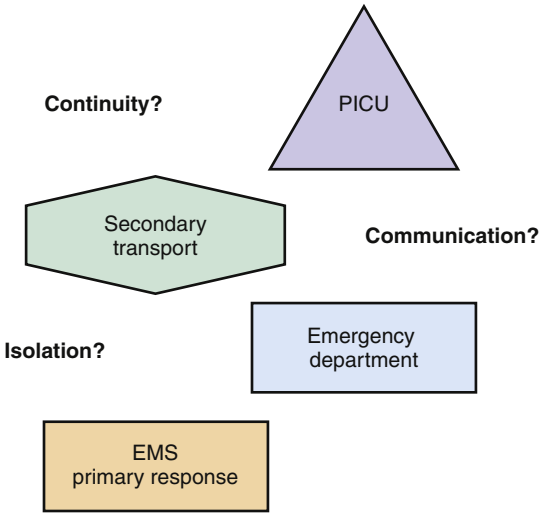

Figure 14–3. Authors' depiction of fragmented critical care continuum within a disjointed system. *EMS,* Emergency medical services; *PICU,* pediatric intensive care unit.

physicians and other caregivers from emergency medicine, neonatology, surgery, and intensive care all take an active role in designing each segment of the continuum and maintaining quality assurance. The critically ill child ultimately will be the responsibility of the pediatric intensivist, so it behooves him or her to have significant input into system design and protocols.

Responsibility of the Retrieval System

The retrieval system has a responsibility to the referral community to make tertiary care accessible, including transport. The referring community's expectations of the regional center's response to transport requests vary according to the standard of care and topography for that region. Regardless of its origin, a retrieval system should include a communications center, administrative staff, appropriately trained team members, reliable equipment, and a safety program.

Communications

The communications center for the retrieval system should be easily accessible to both the referring physician and the transport team.[43,44] It should be staffed round-the-clock by full-time communication specialists who are trained in handling emergency calls and who have no other distracting duties that would delay a response. The communication specialist should follow a prescribed protocol to minimize the number of calls necessary to organize efforts, notify the appropriate personnel, and arrange all aspects of the transport so that the referring physician can direct his or her attention to patient care. A detailed log of transport requests, including time, demographic data, diagnosis, and vehicle availability, should be kept for both administrative review and medical-legal documentation. Equipment for direct communication with the center should be available in every transport vehicle. The receiving physician who is responsible for the transport maintains contact with the communications center and with the referring physician.

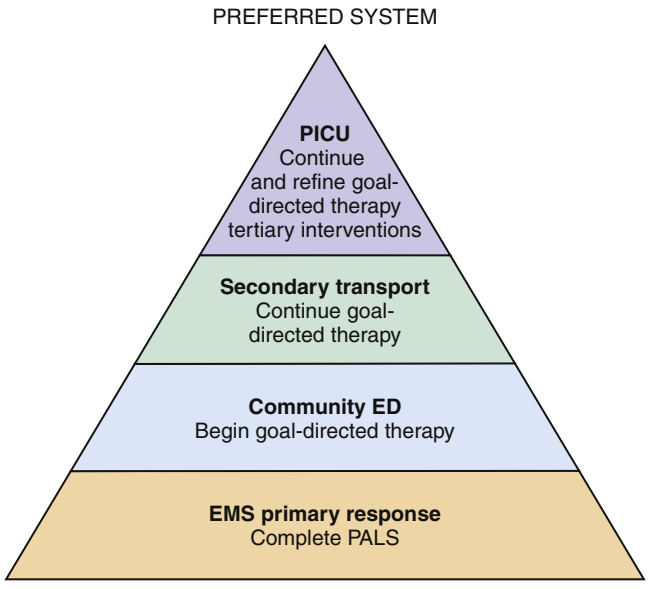

Figure 14–4. Authors' depiction of preferred system of goal-directed care model. *ED,* Emergency department; *EMS,* emergency medical services; *PALS,* pediatric advanced life support; *PICU,* pediatric intensive care unit.

The receiving physician should obtain a brief history of the patient's present illness and a summary of initial interventions and should give recommendations tailored to the capabilities of the referring hospital and pertinent to the current problem. This information should be documented on a log that remains a part of the patient's medical record.

Staffing

The administrative staff of a retrieval system should include, at a minimum, a program director, medical director, transport coordinator, and medical command.[43,44] The program director is responsible for the structure, activities, and organization of the transport system and assumes overall program responsibilities; acts as a liaison between the team and hospital administration; and develops and implements quality management.

The medical director should be a specialist in critical care or emergency medicine. He or she might have training in a surgical subspecialty (trauma) or in pediatrics (neonatology). He or she is a licensed physician who is responsible for supervising and evaluating the quality of medical care provided by the transport team, and must have educational experience in the areas of medicine that are commensurate with the mission of the retrieval service. The medical director should be experienced in both air and ground transport (as appropriate to his or her specific system), should understand patient care capabilities and limitations in the transport environment, and should be educated in infection control, stress recognition and management, altitude physiology,[45] and stressors in the transport and flight environments. The medical director must be actively involved in quality management, administrative decisions affecting medical care, and the hiring, training, and continuing education of all transport personnel. He or she must orient those physicians who provide online medical direction to the policies, procedures, and patient care protocols and should act as a liaison to the referral community for teaching and outreach.[43,44]

The transport coordinator, usually a nurse or paramedic, collaborates with the medical director with regard to training, protocols, scheduling, data collection, quality management, and marketing. The medical director and transport coordinator should participate in patient transport, whenever possible, to maintain skills and perspective. A command physician should oversee every transport and provide advice to the referring physician and transport team as necessary.

The command physician must be experienced in handling transport calls and offering management suggestions for the period before arrival of the transport team. He or she should be knowledgeable about the availability of resources and have the authority to accept transferred patients without further consultation, to perform triage, and to activate backup systems when necessary. Medical control is usually accomplished in one of two ways: online or offline.[46] Online medical control is direct real-time voice communication (radio, telephone, cellular telephone, or satellite phone) between the medical control physician and the transport team. The transport team must always know who the command physician is throughout the transport process. Responsibility for medical control varies based on local practices and the policies of the transport service. Medical control physicians must be experienced in critical care transports to ensure that the crews provide appropriate care. For specialized transports, the transport service

should have a mechanism in place for medical control physicians to have timely consultation with subspecialists or the receiving physician. Alternatively, the critical care transport team should have the ability to consult with the receiving physician and to provide updates to the receiving facility. Offline medical control consists of written protocols or standing orders for patient management by the transport team. There is no direct communication between the team and the medical control physician. The medical director is responsible for developing and renewing transport protocols and procedures used for offline medical control.

Team composition and training strategies vary considerably among transport programs. The choice of personnel usually depends on the availability of professionals in the sponsoring facility, the anticipated patient population, financial support for the program, and other practical considerations. Selection of team members is critical to the success of a transport program. Members should be selected based on their experience and competence in the care of children in the inpatient setting. Techniques for training personnel depend on the team members' anticipated role in the care of transported patients, their experience providing care for neonates and older children, and their familiarity with the transport environment.

Although the specific requirements of training depend on the professional background of the team members, their experience, and their roles in inpatient care, the goals and general content of training are the same for nurse, respiratory therapist, physician, and paramedic. Transport crew members should be experienced in the care of critically ill patients and be able to deal with complex environments and limited resources. They must be highly skilled in airway management, resuscitation, and vascular access. They should have a fundamental knowledge of field priorities and be able to make decisions independently. All team members should have specific training in transport medicine, which includes methods of functioning in a moving environment, aeromedical physiology, and troubleshooting for equipment-related problems.

The team transporting a critically ill pediatric patient should include a team leader who is experienced in diagnosing and managing life-threatening illnesses or injuries in neonates and children. This caregiver must (1) understand pathophysiology and the usual clinical course and complications of common pediatric illnesses, (2) understand how to use appropriate laboratory and radiographic tests as diagnostic aids, and (3) have experience in managing neonates and children who require intensive pharmacologic intervention. The team should be capable of performing all standard emergency procedures required in the care of critically ill neonates and children. A very high level of expertise in performing these procedures is necessary, because they often are performed under adverse conditions.

The team leader role is commonly filled by either an experienced nurse or physician. Many dedicated pediatric transport teams include a physician, although little objective evidence indicates this configuration results in improved outcome compared with nonphysician teams. Physician attendance is particularly controversial when the role is filled by physicians-in-training, since all but the most advanced trainees lack the knowledge and experience needed in the transport environment.

A transport program should define the cognitive knowledge and technical skills required for each professional group and should include a method to document the acquisition of these skills. Procedure performance proficiency should be approved by the base facility and, where appropriate, by state regulatory agencies that govern the activities of each professional group. Instruction typically includes didactic sessions designed to assist personnel to acquire cognitive knowledge, a skill development and maintenance program, and a supervised orientation period. Simulation has been shown to improve adherence to protocols in the training of crisis-response teams and may be a useful adjunct to team member training.[47] The supervised orientation period should end only when the training program director and the trainee are confident in the trainee's abilities. A continuing education program must follow and include transport case conferences and review and ongoing competency-based training.

Equipment

Equipment taken on transport should be complete and adequate to provide continuing intensive care throughout the trip. Oxygen reserve should be calculated for each patient transported and should be at least twice the amount needed for the expected duration of the trip, in case of delays or equipment malfunction. Portable, compartmentalized equipment packs must be designed for easy access and must be able to withstand the stress of the transport environment. For air medical transport, weight and space restrictions must be considered when selecting equipment and range of medications. Transport monitors should have battery power that will last beyond the expected duration of transport, because of the possibility of unexpected delays or vehicle breakdowns, and should be free of movement artifact. Most important, the transport team should be self-sufficient and not dependent on the referring hospital for supplies. All equipment should be routinely checked and maintained after transport by a team member dedicated to that task.

Safety

Safety should be a high priority in any transport program. Emergency vehicle operation carries substantial risks, not only to the crew and the patient but also to others in its vicinity. The medical director is responsible for thoroughly researching vendors of air or ground transport services in the areas of maintenance, safety records, experience of drivers and pilots, and reliability of equipment. Written contracts between the institution and the vendor should include specific insurance details. Ambulance drivers should be discouraged from exceeding the speed limit because no evidence indicates that use of lights and sirens has any positive effect on patient outcome.

Aeromedical transport involves a unique set of safety issues. The four leading causes of accidents are weather, engine failure, collision with an obstacle, and loss of control. Pressure on pilots to fly, competition among aeromedical services within a region, and failure to observe minimal weather standards are among the components contributing to these accidents. In order for pilots to make sound decisions based on the flight conditions, they must be isolated from patient care issues. In regions with competing aeromedical services, the services should act jointly to establish regional safety guidelines, minimum weather standards, and a quality assurance program that examines compliance.

Transport team members must have a good understanding of aviation medicine and of how the aeromedical environment

affects both them and the patient. Barometric pressure changes that occur with increasing cabin altitude lower alveolar oxygen tension and increase the volume of any entrapped gas (e.g., in the bowel, sinuses, pneumothorax, and endotracheal tube cuffs)[48] and may affect intravenous infusion rates. The results of poor eating habits (hypoglycemia), sleep deprivation, and drugs (e.g., alcohol, marijuana, antihistamines) are potentiated by increasing altitude. Vibration can produce fatigue, and accelerating and decelerating forces can produce vertigo. Night vision is decreased at cabin altitudes above 5000 feet. The transport team should be adept at survival techniques for their region and should always be prepared to deal with an off-airport landing. Regular sessions to review safety and emergency procedures for each transport mode should be provided for the transport team members.

Referring Hospital Responsibilities

Transfer of patients from one institution to another is regulated by federal statute. The legislation that created the patient stabilization and transfer requirements for hospitals and physicians was the Consolidated Omnibus Budget Reconciliation Act (COBRA) of 1986, also known as the "antidumping law," and its amendment, the Omnibus Reconciliation Act of 1989.[49,50] This is the current legal standard. One of the main objectives of this resolution was to guarantee equal access to emergency treatment to all citizens regardless of their ability to pay. COBRA attributes responsibility for the patient's transfer to the referring hospital and physician. Violations can result in a number of penalties, including termination of Medicare privileges for the physician and hospital. A hospital can be fined between $25,000 and $50,000 per violation, and a physician can be fined $50,000 per violation. A patient can sue the hospital for personal injury in civil court. The Emergency Medical Treatment and Labor Act (EMTALA) established by the COBRA legislation governs how patients can be transferred from one hospital to another. Hospitals cannot transfer patients unless the transfer is "appropriate," the patient consents to transfer after being informed of the risks of transfer, and the referring physician certifies that the medical benefits expected from the transfer outweigh the risks. Appropriate transfers must meet the following criteria: 1) the transferring hospital must provide care and stabilization within its ability; 2) copies of medical records and imaging studies must accompany the patient; 3) the receiving facility must have available space and qualified personnel and agree to accept the transfer; and 4) the interfacility transport must be made by qualified personnel with the necessary equipment.

Emergent interfacility transport should occur after initial stabilization and determination by the referring facility that the patient's needs for definite care are beyond the scope of local capabilities. Transfer of the critically ill patient occurs with the expectation that appropriate care will continue en route to the receiving facility and that complications will be identified and treated. These goals frequently require specialized personnel and equipment. Coordination between referring and receiving institutions and medical direction during transport are fundamental to guarantee continuation of care and optimal utilization of resources. Interfacility transport can be performed by a transport team from the referring facility, by the receiving facility, or by a third party. It is the responsibility of the referring physician in consultation with the receiving physician to decide the best mode of transportation (air vs. ground) and to ensure that the transporting personnel have the necessary expertise and equipment to deal with the patient's condition and possible complications.

Complete copies of all patient care records must be sent. This documentation includes results of all therapeutic and diagnostic interventions, copies of all imaging studies performed, and patient consent for transfer. Teleradiology has a role in allowing receiving centers to review a patient's studies prior to arrival. It is essential that the transport team establish direct communication with both referring and accepting physicians. Communication with the referring physician must detail the following information: 1) identification of the patient and medical history; 2) interventions performed during initial stabilization and patient's response; 3) pertinent physical examination findings; 4) ongoing therapy; and 5) potential complications that may occur during transport.

Summary

The limited pediatric training and exposure of EMS personnel, coupled with the differences in size, anatomy, physiology, and psychosocial aspects unique to children, will continually challenge the EMS provider. The approach that prioritizes rapidity of transport over stabilization and initiation of care, a pattern that is commonly accepted for adult patients, will not result in the best outcomes for most children. Children transported by nonspecialized teams are at higher risk of transport-related adverse events and mortality.

As the evidence mounts that earlier initiation of aggressive therapy for shock improves outcomes, we must realize that the need for pediatric-specific intensive care begins long before the patient arrives in the tertiary care center. The primary goals in the vast majority of pediatric transports should be anticipatory management of respiratory insufficiency and early and attentive application of the principles of goal-directed shock resuscitation. Most pediatric patients with septic shock survive their acute illnesses, and emergency providers rarely witness development of organ dysfunction from seeds sown in the first few hours of the shock state. The unique perspective of the pediatric intensivist is valuable and could help to change practice in the referring community. The goal of the pediatric intensivist should be to extend his or her sphere of influence in order to make this happen.

References are available online at http://www.expertconsult.com.

Chapter 15

Pediatric Vascular Access and Centeses

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PEARLS

- Intraosseous infusion is a convenient means of emergency vascular access with new mechanical devices available. Vigilant observation of the needle insertion site is necessary to recognize extravasation and prevent serious complications.
- Pericardiocentesis may be required for both diagnostic and therapeutic purposes. Ultrasound imaging improves success and reduces complications, and should be performed in all cases except with life-threatening tamponade.
- Umbilical arterial and venous access may be useful in neonates up to 2 weeks of age.

Intraosseous Infusion

Venous access in critically ill infants and children can be one of the most challenging aspects of their care. Peripheral veins in infants can be quite difficult to cannulate, particularly in the event of shock with shunting of blood away from the periphery and collapse of small veins. Because of these challenges, intraosseous (IO) infusion has become widely accepted as a quick, reliable means to establish short-term emergency venous access.

IO infusion was first described in 1922 and became widely used in the 1930s and 1940s.[1] With the development of disposable needles and catheters, use of IO infusion fell out of favor. It was not commonly used again until the mid-1980s, when a series of publications demonstrated the utility of the technique for rapid venous access in critically ill children.[2,3]

The marrow space provides a noncollapsible access point to the vascular system. Marrow sinusoids drain into medullary venous channels that empty into the systemic circulatory system. Because of the noncollapsible nature of the marrow space and the direct connection to the venous circulation, fluids and medications infused into the marrow space are distributed rapidly through the venous circulation.

Indications

IO infusion is indicated in situations requiring the rapid acquisition of intravenous (IV) access in which the establishment of conventional peripheral access is difficult or impossible. The situations in which it is most often used include cardiopulmonary arrest, shock, burns, and status epilepticus. In these situations, one or two attempts at standard peripheral access are usually made prior to placing an IO needle. In cardiopulmonary arrest, one should immediately gain vascular access via the IO procedure. In addition to its use in the hospital, IO access has been successful in the prehospital setting as well as in critical care transport.[4,5]

The success rate with the technique is high, greater than 95% with experienced practitioners.[6] Equal success using the new mechanical intraosseous devices has also been demonstrated.[7] Most fluids and medications that can be given through a conventional IV line can be given via an IO infusion with comparable results. In the event of cardiac arrest or severe shock, IO access is at least as effective as peripheral venous access in providing fluids and medications to the central circulation. Studies have shown that commonly used resuscitation, antiepileptic, and antibiotic drugs all can be given effectively through an IO line. Three antibiotics produce subtherapeutic levels when given via an intraosseus line at standard IV doses: chloramphenicol, vancomycin, and tobramycin.[8]

In addition to the administration of fluids and medications, IO access can be used for certain clinical laboratory studies. No significant differences were found when comparing electrolytes, chemistries, pH, PCO_2, or hemoglobin from IO marrow specimen with either arterial or venous blood samples.[9] A marrow specimen can be cultured in lieu of a blood culture.[10] Finally, the marrow can be used for blood type and crossmatching.

Contraindications

IO infusion has few absolute contraindications. A fractured or previously punctured bone should not be used because infused fluid will extravasate and possibly cause compartment syndrome. Alternate sites in other bones can be used in such situations. Bone diseases such as osteogenesis imperfecta and osteopetrosis have been suggested as contraindications to intraosseous infusion,[11] but a case of successful IO access in a patient with osteogenesis imperfecta has been reported.[6] Placing the needle into an area of cellulitis or burn could cause osteomyelitis or other infectious complications and is a relative contraindication although if limited sites are available, placing the IO needle through burned skin is acceptable.

Figure 15–1. Bone Injection Gun. *(Courtesy Persys Medial and Waismed USA.)*

Figure 15–2. EZ-IO. *(Courtesy Vidacare Corporation.)*

Supplies and Equipment

Access to the bone marrow space is accomplished with one of several different types of needles. Conventional bone marrow needles (e.g., Jamshidi needle, CareFusion, San Diego, Calif.) work well. Needles made specifically for IO infusion use are available, including a straight needle or a needle with a threaded screw device (e.g., Sur-Fast, Cook Medical, Bloomington, Ind.). Usually a 15- or 18-gauge needle is chosen. The smaller 18-gauge should be used in infants. Studies have shown no significant differences in time required to insert the needle, success rate, or extravasation rates between standard and threaded IO needles.[12,13] If bone marrow or IO needles are not available, standard lumbar puncture needles can be used,[6,14] although they are prone to bend. In neonates, even a 19- or 21-gauge butterfly needle can be used.[14] Needles with a stylet are preferred to prevent clogging of the needle by bone.

Two new mechanical devices appropriate for the pediatric population have been introduced: the Bone Injection Gun (B.I.G., Waismed Ltd., Herzliya, Israel) and the EZ-IO (Vidacare Corporation, San Antonio, Tex; see Figures 15-1 and 15-2). The B.I.G. is a spring-loaded device, while the EZ-IO is a small battery-powered drill; both of these penetrate the bone marrow more quickly as compared to the manual method.

Other equipment required for IO placement includes a towel or sandbag, syringes with saline or heparinized saline flush solution, IV fluid and tubing, a T-connector or stopcock, and antiseptic prep solution (iodine). Optional supplies include a pressure bag and materials for local anesthesia (syringe with 25-gauge needle and 1% lidocaine).

Technique

The IO needle can be placed into the bone marrow at one of several sites, including the proximal tibia, distal femur, distal tibia, iliac crest, and sternum. The proximal tibia is the site most commonly chosen. The sternum has been used in adults but should be avoided in children because of the possibility of perforating the smaller chest cavity.[15] In addition, placing the needle in the sternum can interfere with airway and circulatory resuscitative efforts. When the needle is placed in the proximal tibia, the insertion site is located by palpation on the flat anterior tibial surface 1 to 3 cm (two fingers breadth) distal to the tibial tuberosity (Figure 15-3). This site is chosen to avoid the proximal growth plate. The midshaft should not be used because of increased risk for fracture. Placing a towel or sandbag under the child's leg helps stabilize the leg and makes insertion easier. The skin overlying the area should be prepped with antiseptic solution. Because IO lines are usually placed in obtunded patients, local anesthetic is not always necessary. Local anesthesia by infiltration with 1% lidocaine can be performed if the patient is awake. If a needle with a plastic sheath is being used, adjust the sheath so that an adequate length of needle protrudes beyond the sheath. Some authors have suggested inserting the needle at a 60- to 75-degree angle away from the tibial growth plate, but others recommend using a perpendicular or 90-degree angle. The perpendicular angle helps prevent the needle from sliding along the bone. The needle is advanced using firm pressure and a twisting or rotary motion until a "give" or loss of resistance is felt, indicating entry into the marrow space. The force needed to penetrate the bony cortex is considerable; the twisting motion helps significantly in needle insertion. One disadvantage of using a threaded needle is that the "give" or loss of resistance that occurs when the needle enters the marrow space may not be felt; however, the needle may be more secure in the bone once the needle is placed.[25] The stylet is removed and a syringe is attached to the needle to attempt to aspirate marrow. Correct placement of the needle should be confirmed to avoid extravasation. Aspiration of bloody fluid into the syringe confirms that the needle is correctly placed.

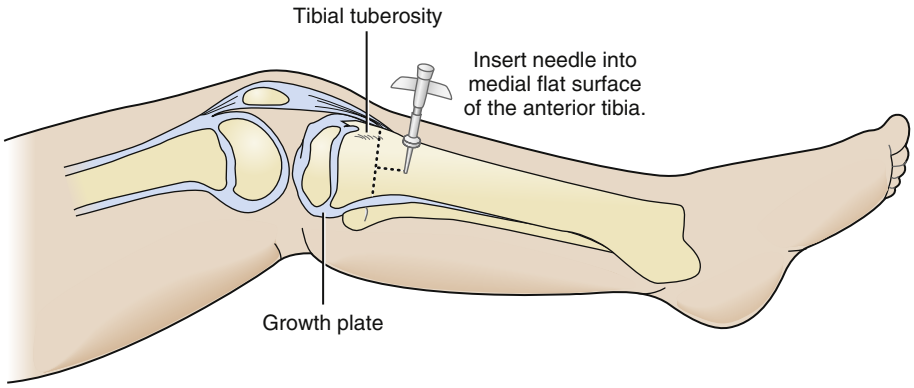

Figure 15–3. Insertion of the intraosseous needle into the anterior tibia.

Additional evidence of correct needle placement includes the observation that the needle stands upright in the bone without support and lack of resistance when flush solution is infused into the needle with the syringe. Sometimes, marrow cannot be aspirated even if the needle is correctly placed. If the "give" is felt on insertion and the needle stands alone in the bone but marrow cannot be aspirated, infusion of a small amount of fluid with the syringe can be attempted. Fluid should infuse easily with little pressure and without noticeable swelling of the soft tissues or extravasation of fluid.

In small studies, placement of IO needles with the new mechanical devices have success rates equal to or higher than traditional manual methods, with the added benefit of easy use and less risk to the user.[7] However, the high cost of this equipment may be a major limitation for use. In children, prehospital providers preferred the IO drill over the spring-loaded injection gun.[16,17]

When using the spring-loaded injection gun, after choosing the desired needle depth of penetration by dialing to the patient's age, the B.I.G. is positioned over the desired site with one hand while the other squeezes and pulls out the safety latch. The free hand is then used to activate the device at a 90-degree angle to the surface. The device is removed by pulling upward with a slight side movement to clear the needle. The stylet trocar is pulled out, then the safety latch should be slid over the needle and the apparatus taped as necessary for stabilization.

When using the IO drill, first ensure that driver and needle set are securely seated. After removing and discarding the needle set safety cap from the IO needle, position the driver at the insertion site with the needle set at a 90-degree angle to the bone and gently power or press the needle set until the needle set tip touches bone. Ensure that at least 5 mm of the catheter is visible. The bone cortex is penetrated by squeezing the driver's trigger and applying gentle, steady downward pressure. The trigger should be released when a sudden "give" or "pop" is felt upon entry into the medullary space and a desired depth is obtained. If excessive force is used, the driver may stall and not penetrate the bone. Gentle pressure and the catheter tip rotation will provide the necessary penetrating action. After placement, remove the power driver and stylet and confirm catheter stability. A primed extension set is then attached to the catheter hub's Luer lock and the apparatus is flushed. The manufacturer does not recommend attaching a syringe directly to the IO needle hub, to reduce the risk of needle dislocation.

The possible insertion sites are the same whether using the manual or mechanical needles. When the needle is placed in the distal femur, it should be placed approximately 2 to 3 cm proximal to the patella in the midline. In the distal tibia, the needle is placed 1 cm proximal to the medial malleolus in the midline, posterior to the saphenous vein. The proximal tibia is usually selected in children younger than 4 years, but the distal tibia has been recommended in older children in whom the proximal tibial cortex is thicker. The proximal humerus may be used for adolescents.

Maintenance

Once correct placement of the needle is confirmed, fluids and medication can be administered with a syringe via a stopcock or T-connector, or a standard IV infusion set can be connected to the needle. The needle is secured using gauze pads and tape. Some have suggested taping a clear plastic cup over the needle to help prevent dislodgment.[6] The site should be observed carefully visually and by palpation for signs of extravasation, both immediately after placement and frequently (every 5 to 10 minutes) during use. If evidence of extravasation is seen, the needle should be removed to avoid compartment syndrome. If needle placement is attempted at one site and the cortex is penetrated but the line cannot be used because of extravasation, another bone must be chosen for subsequent attempts.

IO access is intended only for short-term use in emergency resuscitative situations; long-term use increases the risk of extravasation, compartment syndrome, and infection.[38,43] Therefore, once IO access is secured, efforts should be directed toward obtaining conventional IV access. Once alternate access is obtained, the IO needle should be removed, manual pressure applied for 5 minutes, and a dressing applied to the site.

Complications

Significant complications of IO infusion are rare. The most common complication is extravasation of fluid. The causes of extravasation include incomplete penetration of the bony cortex, movement of the needle such that the hole is larger than the needle, dislodgment of the needle, penetration of the posterior cortex, and leakage of fluid through another hole in the bone, such as a previous IO site or fracture. Extravasation of a small

amount of fluid is usually not problematic, but compartment syndrome may result after extravasation.[18] One report documented a compartment syndrome after infusion of only 35 mL of fluid via the IO line.[19] Use of the IO line for prolonged periods and use of the IO line with pressure infusion appear to be risk factors for compartment syndrome. Compartment syndrome associated with IO infusion can result in the need for fasciotomy and amputation. Careful frequent observation of the IO site is necessary to detect extravasation and to prevent compartment syndrome. If extravasation occurs, the needle should be removed and the extremity observed for signs of compartment syndrome. Initial experience suggests the complications of the new mechanical devices are similar to the traditional IO needle.

Other rare complications include infection and bone fracture. Osteomyelitis, cellulitis, and sepsis have been reported in conjunction with IO infusion.[20] Risk for infection is increased when IO access is used in a bacteremic patient and when the line is used for a prolonged period. The risk of osteomyelitis is low. Although IO access is usually obtained in emergency situations, precautions to prevent infection should be taken, including use of sterile gloves and equipment and preparation of the skin with antiseptic solution (iodine or alcohol). Fracture of the bone has been reported.[21] One report of fracture associated with IO infusion is the case of a 3-month-old in whom a 15-gauge needle was used; a smaller needle size (18-gauge) should be used in small infants.

There are some theoretical complications that are probably not significant in clinical practice. Fat embolism occurs with infusion into the bone marrow space. An animal study found fat emboli in the lung with IO infusion, but no changes were seen in oxygen saturation or intrapulmonary shunt.[35] There are no reports of clinical fat embolization associated with IO infusion in humans in the English literature. However, intravascular air was discovered on postmortem studies in two patients.[22] Because of the risk of fat embolization, children with a right-to-left shunt may be at increased risk for cerebral emboli with IO infusion.[6]

The physical effects of infusion on the growing bone seem to be self-limited. Both animal studies and human follow-up studies of the bone and bone marrow show only short-term, minor changes and no long-term changes in bone structure, growth, or bone marrow.[23,24]

Summary

IO infusion is a valuable means of obtaining temporary, emergency vascular access in the critically ill infant or child. It has a high success rate and is associated with rare complications. Complications can usually be prevented by using appropriate technique and vigilantly monitoring the site for extravasation.

Arterial Catheter Placement

Frequent access to arterial blood is essential for complete and thorough assessment of acid-base status, oxygenation, and ventilation in the critically ill patient. Because of the dynamic, often rapidly evolving nature of critical illness in children, including the potential for rapidly changing hemodynamic status, continuous measurement of blood pressure can be invaluable in planning timely interventions aimed at improving systemic oxygen delivery. For these reasons, use of indwelling arterial catheters became routine in the 1970s, and now arterial catheters are an indispensable tool in the care of critically ill children. Placement of an arterial catheter allows continuous measurement of systolic, diastolic, and mean blood pressure, and provides a visible pressure waveform that may contribute additional diagnostic information. An arterial catheter also provides direct access to arterial blood for frequent, painless sampling. Hence the ability to place an arterial catheter is a fundamental skill in pediatric critical care medicine.

Indications

Indications for an arterial catheter include the following:

1. Need for frequent measurement of blood pressure to assess the patient's hemodynamic status and to allow for timely assessment of interventions aimed at improving hemodynamic status, such as fluid administration and titration of vasoactive infusions. Consider placement of an arterial catheter in any patient supported with vasoactive infusions.
2. Need for frequent sampling of arterial blood for laboratory analysis. Access to arterial blood through an indwelling catheter increases the ease of painlessly obtaining blood samples for analysis. Obtaining arterial samples through a catheter also eliminates skewing of results by physiologic changes related to the stress of arterial puncture or venipuncture, such as increased respirations with crying or localized poor perfusion or tourniquet use. Most notably, an indwelling arterial catheter allows for frequent assessment of arterial blood gas measurements, thereby providing the most accurate information on a patient's acid-base status, as well as measurement of Pa_{O_2}. Other laboratory tests may be obtained from an arterial catheter as well, thereby conserving peripheral veins.
3. Need for continuous monitoring of cerebral perfusion pressure (CPP) in patients with traumatic brain injury or other causes of increased intracranial pressure (ICP). Cerebral perfusion pressure is equal to mean arterial pressure minus intracranial pressure.
4. Need for arterial access to facilitate therapeutic procedures, such as exchange transfusions and continuous arteriovenous hemodiafiltration.

Contraindications

Very few absolute contraindications for placement of an arterial catheter exist. The skin at the site of arterial access must be intact prior to insertion of a catheter. Any evidence of infection of the skin or underlying structures is a contraindication to catheter placement at this site. Other disruptions in skin integrity, such as burns, are a relative contraindication. Severe coagulopathy and systemic anticoagulation increase the risk of hemorrhage from unsuccessful arterial punctures associated with attempted arterial catheter placement, as well as the risks of bleeding at the site of arterial catheter insertion. These risks must be weighed against the potential benefits of improved monitoring when deciding to place an arterial catheter in a coagulopathic or anticoagulated patient.

A catheter should not be placed in an extremity with compromised perfusion. Evidence of adequate collateral

Box 15–1 Supplies and Equipment for Arterial Catheterization

1. Appropriate size catheter (24 gauge for infants, 22 gauge for toddlers and older)
2. Sterile gloves
3. 10% povidone-iodine or chlorhexidine solution
4. Sterile towels
5. Syringe with 1% lidocaine and 25-gauge needle for local infiltration
6. Topical anesthetic cream
7. Luer-Lok connector with heparinized flush
8. 3-0 silk suture
9. Instrument tray with needle holder and scissors
10. Cloth tape
11. Plastic, nonocclusive dressing
12. Connecting tubing
13. Transducer
14. Fluids containing heparin (1 U/mL) and papaverine

circulation is desirable prior to placement of an arterial catheter. The traditional means of assessing collateral circulation to the hand is the Allen test. The radial and ulnar arteries are compressed until the distal extremity is blanched. Pressure over one artery then is released. Capillary refill should return to the distal extremity in less than 5 seconds. The test then is repeated by unblocking the other contributing artery after the distal extremity becomes blanched. Some practitioners question the utility of the Allen test because a normal test result does not guarantee adequate collateral circulation, nor does an abnormal test necessarily indicate possible complications.[25] The Allen test is considered less reliable for patients in shock. Additionally, an arterial catheter is often placed without assessing collateral circulation in emergent circumstances.

Procedure

Box 15-1 lists the supplies and equipment required for arterial catheterization.

Technique

The initial step in placing an arterial catheter is site selection. The radial, posterior tibial, and dorsalis pedis arteries are usually optimal sites, due both to the ease of access to these sites and to the typically good collateral circulation. Placement of the catheter in distal arteries of the extremities also allows for ease of site observation and hemorrhage control with direct pressure. Preductal placement in the right radial artery is preferred in infants with ductal-dependent heart lesions.

Catheters also can be placed in the axillary or femoral arteries if no peripheral sites are suitable. Insertion of a catheter into the axillary artery is technically more difficult than the other sites mentioned and is associated with a risk of brachial plexus injury due to hematoma compressing the neurovascular bundle.[26] Traditionally, many physicians have been reluctant to place arterial catheters for long-term use into the femoral artery, particularly in infants and young children, for fear of complications, most notably severe ischemia of the limb. A recent review of 745 femoral artery catheterizations in critically ill pediatric burn patients revealed a 1.1% rate of loss of distal pulse. In this retrospective study, limb ischemia was associated with younger age, smaller patient size, and increased severity of the burn injury. Patients who suffered limb ischemia were managed, for the most part, with immediate catheter removal and systemic heparinization. Three underwent thrombectomy. All patients in this series showed complete recovery of limb perfusion, except for one who required amputation of the fifth toe on the ipsilateral side.

Traditional teaching has held that the brachial arteries should not be used for arterial catheters because of the lack of collateral blood flow and risk of distal extremity ischemia. In a review of arterial catheter placements performed at a pediatric cardiac surgical center, the authors reported on the use of 386 brachial artery catheters in infants weighing 20 kg or less. None of these catheterizations were reportedly associated with permanent ischemic damage, and only three were associated with what was described as temporary loss of distal perfusion.[28] Despite these encouraging results, the complete lack of collateral circulation at the brachial artery requires careful consideration of risks and benefits before placement of a brachial artery catheter. Additionally, the superficial temporal arteries also should not be used because of poor collateral flow as well as the fact that retrograde flow from a catheter placed in this artery could result in showering of emboli into the cerebral circulation.

The selected site must be properly immobilized prior to placement of the indwelling catheter. If placing a radial artery catheter, the wrist is hyperextended 30 degrees to develop a straighter course and to bring the radial artery into a more superficial position. Typically, the radial pulse can best be palpated and catheter insertion should first be attempted in a position just proximal to the proximal crease, or usually about 1 to 2 cm from the wrist. Recently, the technique for placement of a radial arterial catheter has been expertly summarized in the "Videos in Clinical Medicine" series in the *New England Journal of Medicine*.[29] The following discussion of insertion technique can be applied to catheter placement at any of the sites discussed above. First, the site is prepared with a chlorhexidine solution and draped with sterile towels. Lidocaine (1% without epinephrine) is infiltrated locally. Alternatively, lidocaine/prilocaine (EMLA) cream can be used as a local anesthetic. Systemic narcotics and/or anxiolytics can be administered as well, although they should be used cautiously in a patient who is not being ventilated. Percutaneous placement of the catheter can be accomplished using one of several techniques. The first method uses a catheter over a needle, very similar to placement of a peripheral IV catheter. The needle is inserted through the skin at a 30-degree angle (bevel up or down). When a flashback of blood is obtained in the hub, the catheter is advanced another 1 to 2 mm. While holding the needle stable, the catheter is advanced over the needle into the lumen of the vessel. Blood should be flowing continuously into the catheter hub prior to attempting to advance the catheter. Once the catheter is inserted through the skin to the hub, a flushed Luer-Lok connector is attached to the hub while pressure is applied over the cannulated artery. Correct placement of the catheter is verified by aspirating arterial blood into a syringe attached to the connector. The catheter is then flushed and securely sutured or taped into position. A transparent dressing is placed over the catheter as a protective

barrier. Before the final dressing is placed, many centers use a chlorhexidine-impregnated patch at the site of catheter insertion to decrease catheter-associated bloodstream infections.[30]

Transfixation, the second percutaneous technique, involves inserting a catheter over a needle as described earlier. However, when a flashback of blood is seen in the hub, the needle and catheter are further advanced until the needle and catheter pierce the posterior wall of the artery and transfix this wall to the underlying structures. The needle is pulled out, leaving the catheter in place. The catheter is then slowly withdrawn until the tip is again intraluminal, with blood flowing back into the hub. The catheter is then advanced into the artery up to the hub. Catheter advancement can be facilitated by attaching a syringe filled with flush to a connecter and gently flushing as the catheter is advanced. The position of the catheter is confirmed, and the catheter secured as described earlier.

The final percutaneous method for catheter placement involves use of the Seldinger technique. A needle is used to pierce the anterior wall of the artery. When return of arterial blood is seen through the introducer needle, a guidewire is placed through the needle and advanced into the lumen of the artery. The needle is then removed, and a catheter is advanced over the guidewire into the lumen of the vessel. This method also can be used with a catheter over a needle. Confirmation of correct positioning and securing the catheter completes the procedure. A recent study in adults undergoing general anesthesia found no difference in the success rate or time to insertion when arterial catheters were placed using wire guides or without wire guides.[31] Placement using the Seldinger technique is the preferred method when placing a catheter into larger vessels such as the femoral artery. When placing a catheter into a central artery using Seldinger technique, a longer catheter (e.g., 2.5 to 3 Fr, 5 to 8 cm) should be used. Such catheters are available in commercially made kits.

Recently, interest has grown in ultrasound-assisted placement of arterial catheters. A study of adult patients requiring arterial catheter placement in an emergency department setting demonstrated decreased time to insertion and decreased number of attempts at catheter placement using ultrasound-guided technique compared to traditional pulse palpation technique.[32] A pilot study in pediatric patients undergoing surgery found that ultrasound-guided placement of radial arterial catheters had a higher success rate and required fewer attempts compared to traditional techniques.[33] However, a larger pediatric study that randomized patients receiving radial arterial catheters to placement via ultrasound-guided versus traditional techniques by pediatric subspecialty trainees or anesthesiologists found no difference in success rate at the first cannulation site, total number of attempts, or time to successful cannulation.[34]

If attempts at percutaneous cannulation of an artery are unsuccessful, a cutdown approach is an alternative means of obtaining arterial access. A superficial incision is made perpendicular to the artery through the skin. The subcutaneous tissues are bluntly dissected parallel to the vessel using hemostats. When the artery is identified, the posterior wall is gently dissected away from the adjacent structures. Two loops are placed around the vessel: one proximal and one distal. These loops are used to elevate the artery during the cannulation process; they should never be used to tie off the vessel. After dissection is completed and the loops are in place, the artery is cannulated under direct visualization using the needle over the catheter method. The catheter is secured with a suture through the skin, and the wound is closed with interrupted stitches. If excessive bleeding persists, the proximal loop can have gentle traction applied in an attempt to control the hemorrhage.

Maintenance of an Arterial Catheter

To prolong patency of an arterial catheter, heparinized fluid is most commonly infused through the catheter. A common practice is to infuse 0.9% sodium chloride containing heparin 1 U/mL at 3 mL/hr, although slower infusion rates may occasionally be used in small infants with a need for fluid restriction. Studies of perioperative arterial catheters in adults have found no difference in the rate of catheter patency using heparinized or nonheparinized solutions,[35] but this does not take into account the smaller vessel size in children or the need for more prolonged catheter patency common to the care of the critically ill child. A meta-analysis of randomized controlled trials of heparin use to maintain either peripheral venous catheter or peripheral arterial catheter patency demonstrated a positive effect of heparinized fluid on duration of arterial catheter patency and the risk of clot formation.[36] Comparison of normal saline to 5% dextrose in water, both with heparin, revealed that infusion of saline resulted in longer catheter life.[37] Papaverine is a smooth-muscle relaxant that can decrease vasospasm when used in arterial catheter maintenance fluids. A randomized, controlled trial of the addition of papaverine (60 mg/500 mL) to routine arterial catheter fluids demonstrated a significantly lower rate of catheter failure and longer catheter life in the papaverine group.[38] This study evaluated patients from 3 weeks to 18 years of age and recommended avoiding the use of papaverine in neonates due to a perceived increased risk of intraventricular hemorrhage (IVH). More recently, the use of papaverine-containing arterial catheter fluid in neonates from 25 to 36 weeks' gestational age was shown to prolong catheter life without an increased risk of IVH.[39] Despite these results, many institutions routinely avoid the use of papaverine in arterial catheter fluids in preterm neonates and in patients with traumatic brain injury or other preexisting intracranial hemorrhage for fear of causing or worsening an IVH.

The arterial catheter should always be visible so that any bleeding around the catheter site or caused by inadvertent disconnection of the tubing from the catheter, which can quickly result in significant hemorrhage, can be immediately observed. Securing the catheter with suture and using a Luer-Lok connector to connect the catheter to the tubing help to decrease the possibility of accidental detachment. The site of catheter insertion should be closely monitored for any signs of infection or compromised perfusion. Mottling of the skin proximal and/or distal to the catheter may be indicative of intraarterial thrombus formation, and discoloration of fingers or toes distal to a catheter may result from emboli. The catheter must be removed if any of these complications are observed.

For accurate direct measurement of blood pressure with an arterial catheter, one important consideration is the positioning of the transducer in relation to the catheter and the patient's position. Standard practice for hemodynamic monitoring involves having the transducer zeroed to atmospheric pressure for accurate pressure measurement. The transducer is often maintained as close as possible to the level of the right

atrium for accurate blood pressure measurements, particularly when the patient is in the supine position.[40] Studies in animal models have demonstrated that positioning the transducer level with the aortic root results in accurate measurement of mean arterial pressure regardless of patient position or catheter site, while placement of the transducer level with the catheter tip resulted in significant error in mean arterial pressure measurement when the patient was in positions such as reverse Trendelenburg.[41] It is common practice at present to change the fluids and tubing every 72 hours. A study that investigated increasing the interval for changing arterial catheter fluids and tubing from 48 to 72 hours showed no increased risk for catheter-associated infection.[42] The overlying dressing also is changed on a scheduled basis.

Inability to draw blood from a catheter or flattening of the waveform on the monitor is suggestive of either a kinked catheter or thrombus formation at the end of the catheter. If evidence of compromised perfusion distal to the catheter is present, the catheter should be removed. If no evidence of compromised perfusion is present, changing the catheter over a guidewire may be considered. However, strong consideration should be given to removing the existing catheter and placing a fresh arterial catheter in a new position, as changing a catheter over a guidewire has been associated with an increased risk of catheter-associated bloodstream infection (CABSI), at least in central venous catheters.[43]

Complications

Complications related to arterial catheters include hemorrhage, thrombus formation, emboli, distal ischemia, and infection. Permanent ischemic complications related to radial artery catheters in adult patients are a very rare event.[25] A recent study used ICD-9 codes to define arterial catheter complications in a large multi-institutional administrative database in an effort to examine the prevalence of and risk factors for arterial catheter complications in critically ill children.[44] This study found a complication of some sort in 10.3% of patients with arterial catheters, most often infection/inflammation, and found a rate of thrombotic or embolic complications of 7.5%. Complications were more common in younger children and tended to be associated with longer hospital courses. Arterial catheter complications were independently associated with cardiac surgery, bone marrow transplantation, and dialysis, probably reflecting an effect of the severity of illness. In addition to bleeding, infection, and distal limb ischemia, an uncommon but well-recognized complication of arterial catheter placement is growth arrest due to physeal injury from extravasation, aneurysm formation, or ischemia.[45] Such injury can occur to the femur, tibia, radius, or ulna.

Catheter-related infections can be local or the focus for systemic sepsis. The risk of catheter-related infection has previously been thought to be lower for arterial catheters than for central venous catheters. Recent studies, however, have found very comparable rates of catheter-related infection in critically ill patients having both types of catheters.[46] The risk of arterial catheter infection has been related to the duration of catheter use and to placement of a catheter in the femoral artery. [46-48] In one recent study of catheter-related infections in children, the presence of an arterial catheter was noted to be a risk factor for any type of catheter-related infection, but in this study the arterial catheter most likely represents a surrogate marker for greater severity of illness.[49] Regardless, however, the arterial catheter should be considered a possible source of sepsis, as is the central venous catheter, and strong consideration should be given to removing an arterial catheter when it is no longer absolutely necessary for optimal care.

Summary

Arterial catheters are a routine part of the monitoring of many critically ill children, and the ability to place an arterial catheter is a necessary skill for the pediatric intensivist. As with any procedure, the potential risks and benefits of arterial catheter placement should be carefully weighed prior to the procedure. Recent publications demonstrate that the rates of and risk factors for complications of arterial catheterization in critically ill children need further study.[44]

Pericardiocentesis

Pericardiocentesis is the aspiration of fluid or air from the pericardial space. The most compelling indication for the procedure is relief of cardiac tamponade, but it also can be performed to diagnose the cause of a pericardial effusion. Pericardiocentesis can be performed emergently without imaging guidance techniques; however, this should only be undertaken in dire circumstances because of the risk of the procedure and the higher failure rate when no guidance is used.

Indications

Drainage of a pericardial effusion of any cause is absolutely indicated when cardiac tamponade is present. Often drainage is recommended if the effusion is large, even in the absence of tamponade, for diagnosis and fluid removal.[50] For small effusions, pericardiocentesis may be indicated for diagnosis alone. In pediatric patients, pericardial effusions most commonly occur with postviral or idiopathic pericarditis, but they are also seen with postpericardiotomy syndrome, collagen vascular disease, oncologic disease, and, rarely, uremia. Purulent pericarditis resulting from *Staphylococcus aureus* or *Streptococcus pneumoniae* infection can be seen in cases of concomitant pneumonia with empyema. Although rare in developed countries, tuberculous pericarditis can occur. Drainage of purulent pericarditis is indicated for relief of tamponade, prevention of constrictive pericarditis, diagnosis, and drainage of infection. With purulent pericarditis, open drainage may be more effective because of the difficulty in draining thick pus.[51] If using a tube pericardiocentesis and drainage, instillation of a thrombolytic such as alteplase (recombinant tissue plasminogen factor) or urokinase may be considered with purulent effusions.[52] Traumatic pericardial effusions secondary to penetrating trauma often require surgical drainage of the blood, because tamponade is common. Pneumopericardium secondary to pulmonary air leaks in mechanically ventilated patients is usually well tolerated hemodynamically but may require drainage, especially in small infants, because of the development of tamponade.

Contraindications

When acute tamponade is present, pericardiocentesis is unequivocally indicated. However, when elective or diagnostic pericardiocentesis is to be performed, the presence

of a bleeding diathesis is considered a contraindication. The presence of aortic dissection is considered a major contraindication.[50] Lack of experience with the procedure is a relative contraindication for elective pericardiocentesis. Open drainage is preferred to closed drainage when the patient has traumatic tamponade and is in cardiac arrest.[53] When the effusion is loculated in a location not easily reached using the subxiphoid approach, needle pericardiocentesis is contraindicated because the risk of complications increases and the possibility of successful drainage becomes remote.

Procedure

Drainage of a pericardial effusion can be performed either by simple needle aspiration or by insertion of a drainage catheter. If the procedure is for diagnosis only and the effusion is small, then needle drainage is adequate. However, if tamponade is present, the effusion is sizable, or effusion likely will continue, insertion of a catheter for continuous drainage is indicated.

Equipment

1. **Needle for drainage.** The size of the needle ranges from 14 to 20 gauge, depending on the type of fluid and the size of the patient. For thicker fluids, such as pus or blood, a larger-bore needle is used. A steel needle, such as a vascular introducer needle or a spinal needle, can be used, but often an IV catheter is more effective because once the fluid is reached, the steel inner needle can be removed from the IV catheter, leaving the softer, needleless catheter in place while the fluid is aspirated. This process decreases the risk of cardiac puncture.
2. **Syringes, three-way stopcock, and short extension tubing** are assembled for aspiration. A 5- or 10-mL slip-tip syringe is used when accessing the pericardium for easier manipulation. A larger 20- to 30-mL syringe may be needed for fluid drainage, depending on the predicted volume. The stopcock and short tubing are useful when draining large amounts of fluid.
3. **Equipment for insertion** includes 2% chlorhexidine solution, sterile gloves and drapes, and 1% lidocaine for local anesthesia.
4. Appropriate **sterile sample tubes** should be available for collection of fluid for chemical, cellular, and microbiologic analysis.
5. **Cardiac monitor** is essential for determination of arrhythmias during the procedure.
6. **Catheter, dilator, and flexible J-wire** are necessary when the catheter will be left in place. Placement in the pericardial sac of a 5 to 8 Fr pigtail catheter with multiple side holes is recommended. The size of the catheter is determined by the size of the patient and the viscosity of the fluid. If the fluid is fibrinous in appearance by echocardiography, then a larger-bore catheter should be placed. Several pigtail catheters are manufactured specifically for fluid drainage, often available as kits that also contain an appropriate-size dilator and J-wire guide. If a kit is not available, then a venous dilator of appropriate size with a separate J-wire can be used. A J-wire is used to prevent another puncture of the pericardium or heart using a straight wire. Before the needle is inserted, the wire, dilator, and catheter must be checked to ensure their sizes are compatible.

Technique

Needle aspiration can be performed blindly in the event of a true emergency such as traumatic tamponade; however, the technique has higher complication and failure rates. Fluoroscopy has been useful but is cumbersome because it requires patient transport to a radiologic or catheterization suite in the absence of portable fluoroscopy.

Echocardiographic guidance is recommended for most pericardiocenteses because it can be done at the bedside and is logistically less complex. The most common technique uses transthoracic scanning, which can easily visualize the effusion. Echocardiographic scanning is indicated prior to needle drainage or catheter insertion for any reason except tamponade with cardiac arrest. Pericardial fluid can be identified by computed tomography or magnetic resonance imaging. Because these techniques are cumbersome and time consuming, they should not be used in acute tamponade because echocardiography is more readily available at the bedside and is usually fast in skilled hands. The echocardiogram can show the size of the effusion, its distribution around the heart including any loculations, the presence of fibrin or clots, and evidence of tamponade.[54] Tamponade can be diagnosed using two-dimensional imaging when the right atrium collapses during late diastole. Normally the right atrial free wall is concave throughout the cardiac cycle. With tamponade, the pericardial pressure exceeds the right atrial pressure at end-diastole and causes the right atrial free wall to collapse toward the center of the right atrium. The worse the tamponade, the longer into systole the collapse occurs.[55] Echocardiographic guidance in patients with tamponade has been shown in adults to have a 99% success rate in relieving the tamponade.[56] After the fluid has been echocardiographically evaluated, the patient is placed supine with the head elevated approximately 30 degrees. The subxiphoid approach is the safest and most common approach, although other approaches have been described. The approach is extrapleural and, in patients with normal anatomy, avoids major vessels such as the internal mammary, coronary, and pericardial arteries.[50] The subxiphoid and lower costal margin are prepared with 2% chlorhexidine. The area is draped in sterile fashion. Lidocaine local anesthesia is infiltrated at the junction of the xiphoid and the left costal margin. The needle is inserted at a 30- to 45-degree angle with the needle directed toward the left clavicle (Figure 15-4). The slip-tip syringe is attached and is aspirated continually while the needle is inserted (Figure 15-5). Needle advancement is halted when air or fluid is aspirated. If blood is obtained, analysis is necessary to determine whether the blood is of pericardial or intracardiac origin. Several techniques are helpful for this determination. The hematocrit of pericardial fluid will be lower than that of intracardiac blood, which will be equal to the patient's hematocrit. Dropping a few milliliters of the fluid on gauze sponges determines whether the fluid will clot. Fluid that does not clot is pericardial; fluid that does clot is most likely intracardiac blood.[57] Another technique involves injection of small amounts of saline microbubble contrast (saline in a syringe that has been agitated) through the introducer needle while imaging with echocardiography.[58] If contrast bubbles are seen in the heart, then the tip of the needle is intracardiac. If bubbles appear in the pericardial sac, then the needle is appropriately placed in the pericardium.

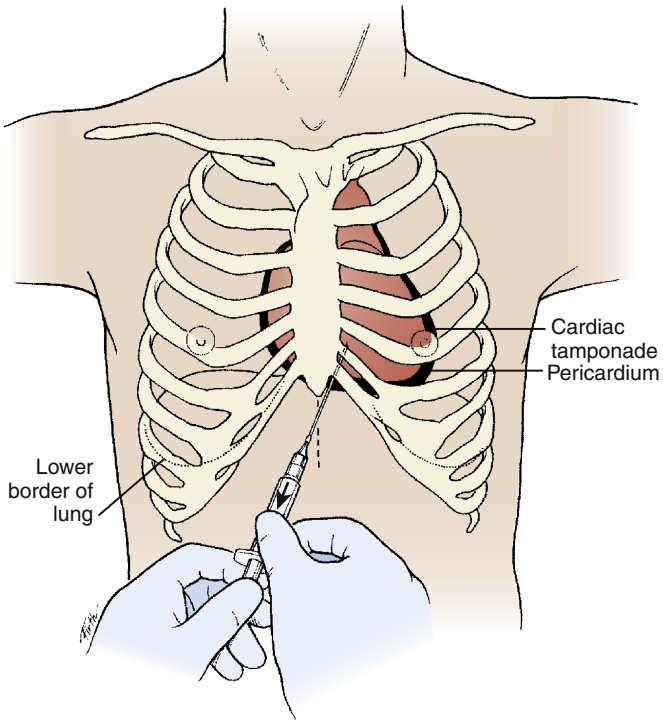

Figure 15–4. Insertion of needle for pericardiocentesis at the junction of the xiphoid and the left costal margin, aiming toward the left shoulder. *(From Brundage SI, Scott BG, Karmy-Jones R et al: Pericardiocentesis and pericardial window. In Shoemaker WC, Velmahos GC, Demetriades D, editors:* Procedures and monitoring for the critically ill, *Philadelphia, 2002, Saunders Elsevier.)*

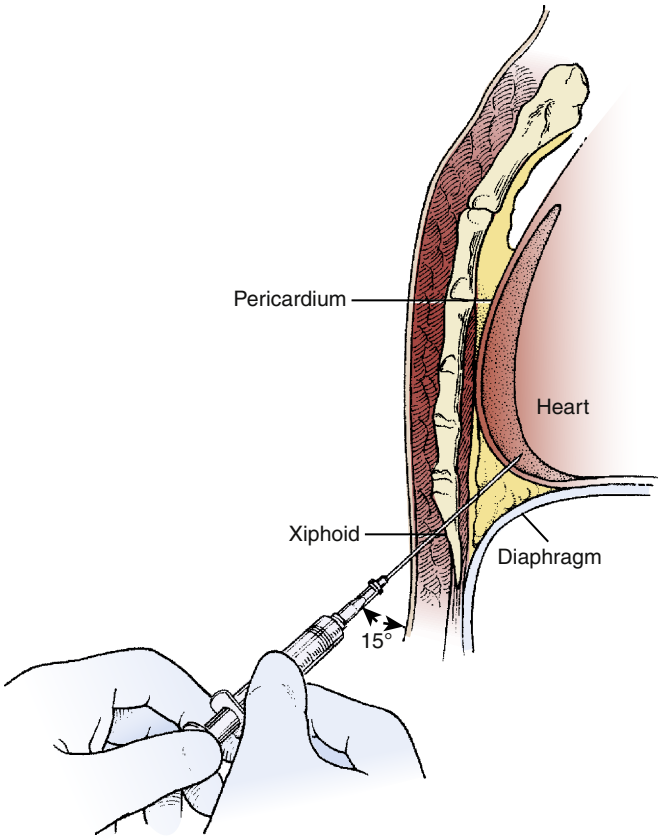

Figure 15–5. In pericardiocentesis, the needle is inserted slowly, under continuous aspiration, toward the heart at a 15-degree angle to the skin. *(From Brundage SI, Scott BG, Karmy-Jones R et al: Pericardiocentesis and pericardial window. In Shoemaker WC, Velmahos GC, Demetriades D, editors:* Procedures and monitoring for the critically ill, *Philadelphia, 2002, Saunders Elsevier.)*

During insertion the needle is guided using two-dimensional echocardiography. The echocardiographic probe is placed on the chest where the fluid is best seen. The needle tip is identified by ultrasound and followed as the needle is advanced.[59] Another technique involves mounting the needle on the echocardiographic probe, which has been placed in a sterile sleeve. The needle is advanced while the operator also handles the probe. This technique allows the use of locations other than the subxiphoid approach for insertion of the introducer needle, with the potential for better fluid visualization.[60]

Previously, the most common guidance technique used electrocardiography to guide the needle. Alligator clamps were placed on the steel insertion needle and connected to an electrocardiogram monitor. The ECG complexes were visualized while the needle was inserted. If an injury pattern was noted in the ST segment, then the heart presumably had been touched by the needle. The needle was pulled back into the pericardial sac, and the ECG trace would return to normal. Although this technique is simple to perform, echocardiographic guidance offers more specific information about needle position and fluid location, allowing for a safer and more successful procedure.

Once the needle is determined to be well-positioned in the pericardial sac, if a catheter is to be inserted, then the J-wire can be passed through the needle as with standard Seldinger technique. The needle is removed, and the dilator is passed over the wire to open the tissues outside the pericardium and enlarge the puncture in the pericardium. The dilator is removed, taking care to leave the J-wire in good position. The catheter is passed over the wire into the pericardial sac. Its position can be confirmed echocardiographically. The wire is removed. The connecting tubing and three-way stopcock are connected and the fluid is aspirated. The tubing can be connected to a drainage bag for removal of fluid that continues to accumulate. A sterile sample of the aspirated fluid should be sent to the laboratory for appropriate analysis. The catheter is secured with suture and covered with an occlusive dressing. A chest radiogram should be taken at the end of the procedure, and daily to confirm the catheter position.

Maintenance

The catheter is simple to maintain. The dressing should be changed according to the ICU protocol for central venous lines. The fluid in the drainage bag should be measured and the amount recorded on a regular schedule. If fluid is no longer draining, then a small amount (1 to 2 mL) of heparinized saline can be infused into the pericardium through the stopcock after preparation with antiseptic solution. This process can release any fibrinous material occluding the catheter. If no fluid is forthcoming, then echocardiography can be performed to determine if residual pericardial fluid remains. If more fluid is present, flush the catheter again in an attempt to open up the catheter. If the fluid had originally been purulent, then instillation of a fibrinolytic agent may allow better drainage. If no fluid remains, the catheter can be removed, depending on the patient's condition and the underlying cause of fluid development.

Complications

Cardiac puncture is not an uncommon complication of the procedure. If the ventricle is entered and the needle quickly withdrawn, then the injury is minor and of no clinical consequence. Coronary laceration occurs rarely, resulting in acute ischemia, and has been associated with death from the procedure.[61] The pleural space can be entered with the insertion needle or the catheter, resulting in a hemothorax or pneumothorax. Hemoperitoneum and pneumoperitoneum can occur. Injury to the diaphragm, intestines, and stomach have been reported. Infection of the indwelling catheter can occur, but is rare because the catheter usually is not in place for more than 3 to 4 days. Cardiac arrest and death have been reported during pericardiocentesis.[62, 63] In a retrospective study of pericardial drainage catheters in pediatric patients, Zahn et al.[64] noted only five complications in a total of 43 procedures. Four of the complications were considered minor and included myocardial perforation with no hemodynamic alteration, pneumopericardium, and ST-segment elevation. One critically ill neonate who had suffered a myocardial perforation during cardiac catheterization died. The results of the study indicated that pericardial catheter placement in pediatric patients is a relatively safe procedure. Most complications of pericardiocentesis with or without catheter placement can be prevented by careful guidance of the needle with echocardiography and greater experience of the practitioner.

Interpretation

Laboratory analysis of pericardial fluid includes cell count and differential, microbiologic evaluation, cytology, and blood chemistry workup, which may include protein, glucose, pH, lactate dehydrogenase (LDH) and triglycerides. Normally, pericardial fluid is clear and straw-colored. Cloudiness may indicate purulence resulting from infection, or chyle if the patient has undergone recent chest or cardiac surgery. Serosanguinous fluid can be seen with multiple diagnoses, including trauma, postpericardiotomy syndrome, collagen vascular disease, infection, and neoplastic disease.

The presence of white blood cells with a predominance of polymorphonuclear cells greater than 1000 per milliliter is indicative of bacterial infection. When the predominant cell type is lymphocytic, then tuberculous pericarditis should be suspected. In idiopathic or postviral pericarditis, the fluid contains fewer than 1000 cells per milliliter, and the cells are mostly monocytic or lymphocytic. Occasionally, the fluid is hemorrhagic with a preponderance of red blood cells. Neoplastic effusions may contain neoplastic cells, which may be missed on routine cell count but will be visible on cytologic examination. With purulent pericarditis, the protein level is high and the glucose level and pH are low. LDH is elevated with neoplastic effusions. With purulent effusions, the ratio of LDH in the fluid to LDH in the blood is increased to greater than 0.6. With chylous effusions, the fluid has an increased triglyceride level.

With acute nonpurulent pericarditis the fluid should be evaluated for viruses; Coxsackie viruses are the most common causes of viral pericarditis. Viral culture can be performed, although the yield is generally low. Polymerase chain reaction has been used successfully to diagnose viral and bacterial etiologies.[65] For purulent pericarditis, Gram stains and acid-fast bacilli stains should be performed, as should appropriate bacterial (both aerobic and anaerobic) and fungal cultures, as well as bacterial PCR analysis. If tuberculous pericarditis is suspected, adenosine deaminase (ADA) and PCR for mycobacteria are indicated.[50]

Summary

Pericardiocentesis, with or without catheter placement, is a straightforward procedure that is indicated for relief of cardiac tamponade and for diagnosis of certain pericardial effusions. It is a lifesaving technique for patients with tamponade. Used in conjunction with guidance techniques such as echocardiography or electrocardiography, pericardiocentesis can be performed safely in patients of all ages.

Umbilical Arterial Catheter and Umbilical Venous Catheter Placement

When a baby is born, regardless of the gestational age, the umbilical vessels are readily accessible for catheterization. However, catheterization of umbilical vessels should not be taken without due consideration. The decision to place umbilical catheters should be based on the patient's gestational age, the expected duration and severity of illness, and underlying disease processes. The risk and benefits should be weighed carefully against peripheral venous catheterization. Umbilical catheters can be an avenue to rapid venous and arterial access in neonates up to age 1 week, and in some up to 2 weeks.

Umbilical Artery Cannulation

Indications for umbilical artery cannulation (UAC) placement include the need for frequent monitoring of acid-base balance, continuous measurement of blood pressure, angiography, resuscitation, and exchange transfusions. Infusions of medications or fluids may be warranted when a UAC is present, but placement of a UAC is not indicated for infusions alone. UAC placement is contraindicated in patients with omphalitis, peritonitis, necrotizing enterocolitis, omphalocele, hypercoagulable states, or known ischemia of the perineum, or lower extremities.[66,67]

Supplies and Equipment

A bed with adequate lighting and a heat source are essential. Prepackaged UAC trays are commercially available and contain different sizes and types of catheters. Umbilical catheters should be radiopaque with rounded tips and single holes. A Luer-Lok system is available on some catheters and has some advantages; others need trimming and attachment of a blunt needle to connect them to a three-way stopcock. Babies weighing less than 1500 g need a 3.5 Fr catheter; infants weighing more than 1500 g require a 5 Fr catheter.[68] Other supplies needed include povidone-iodine or chlorhexidine solution; umbilical tie; sterile drapes; gloves; scalpel; scissors; iris forceps; pick-ups; gauze pads; 3-0 silk suture; 3-mL, 5-mL, or 10-mL syringes; tape; and heparin flush (1 unit heparin per milliliter of normal saline).[69]

Technique

Prior to UAC placement, gently restrain the baby and determine the catheter insertion distance. Restrain the infant in a supine position by using soft restraints of the arm and legs. Alternatively, restrain the baby by swaddling technique.

High or low placement of the catheter is based on the vertebral level at which the catheter resides in the aorta. Complications have been reported with both low and high UACs.[70-72] A low UAC should lie at or below the third lumbar vertebra (caudal to the origins of the renal arteries).[73] A high UAC should have its tip between the sixth and ninth thoracic vertebrae. A high UAC position is the preferred position and a low UAC should only be used if a high UAC is not attainable.[74] The calculation for insertion length can be determined using various methods, such as birth weight, shoulder-to-umbilicus length, and total body length.[75-77] A simple method for calculating insertion depth for high placement is as follows: for babies weighing more than 1500 g (3 × birth weight [in kg]) + 9 = centimeters of catheter to insert to the umbilical ring; for babies less than 1500 g, use the formula (4 × birth weight [in kg]) + 7 = centimeters of catheter to insert to the umbilical ring.[78,79]

Next, attach the UAC to a three-way stopcock, and also attach to the stopcock a 3- or 5-mL syringe filled with heparin flush. Fill the stopcock and UAC with heparin flush solution. Turn the stopcock off to the catheter prior to insertion. Prepare the cord with antiseptic solution and drape the baby, sparing the head and chest to allow for patient monitoring during the procedure. Place an umbilical tie snugly around the epithelialized portion of the umbilical cord using a one-looped tie. The umbilical tape should be able to apply pressure to the cord in the event of acute hemorrhage, but should not be so tight as to hamper introduction of the catheter. Use a scalpel to cut the cord horizontally approximately 1 to 2 cm above the umbilical ring. The larger thin-walled umbilical vein is typically in the 12 o'clock position (cephalad) and two small thick-walled umbilical arteries can be identified at the 5 and 7 o'clock positions. Grasp the cord securely with a hemostat (or forceps) near one of the umbilical arteries. Use the iris forceps to dilate an arterial lumen by first inserting the forceps in the closed position, finally allowing both prongs to spring open and dilate the lumen. Holding the catheter with the iris forceps, introduce the catheter into the dilated artery, taking care to ensure that the catheter is in the lumen of the vessel. Insert the catheter approximately 0.5 cm and pull the umbilical cord toward the infant's head before attempting to advance the catheter. Aspirate blood and flush the catheter once it has been advanced to the desired length. Ensure air bubbles are cleared prior to flushing the catheter. If the catheter meets resistance, apply gentle steady pressure for approximately 30 seconds to determine if the catheter will advance. Do not force the catheter. If the catheter will not advance or no blood return is seen, a false passage may have been created. A double-catheter technique can be attempted in this situation.[80] Leave the catheter that is meeting resistance in place and carefully advance a second catheter beside it to the appropriate distance. If the double-catheter technique fails, the second umbilical artery can be cannulated. Suture the catheter in place, using a pursestring stitch cinched tightly to provide hemostasis and wrapping both ends of the suture around the UAC before tying a square knot. Secure the line using a tape bridge or other available securing device. Finally, loosen the umbilical tie and keep it in place for any needed hemostasis. A transducer may be attached for continuous blood pressure monitoring while still allowing for blood sampling. Anteroposterior and lateral x-ray films of the abdomen are needed to confirm proper positioning of the catheter. A malpositioned catheter should be adjusted promptly. If it is too high, it should be pulled back; if it is too low or in a vessel other than the aorta, the catheter should be removed and replaced.[67] Never advance a UAC once the sterile field has been broken.

Maintenance

A continuous infusion is needed to keep the lumen of the catheter clear, and catheters should be flushed after blood draws to keep the catheters free of clot. An infusion containing heparin should be used containing 1 U heparin per milliliter at 0.5 mL/hr for a 3.5 Fr catheter or at 1 mL/hr in a 5 Fr catheter. As little as 0.25 U/mL of heparin can be used successfully without increased risk of catheter occlusion.[81] The composition of the heparin-containing fluid varies by institution and may be influenced by gestational age and electrolyte status. A typical solution includes 38 or 77 mEq/L sodium chloride or sodium acetate, or an isotonic amino acid solution with heparin 1 U/mL running as a continuous infusion.[82] Infants can be placed in the supine position or on their sides; prone positioning is usually not used. A dressing should not be applied to the umbilicus so that the catheter insertion site and cord can be easily inspected. The UAC should be removed when the original indication for placement no longer exists or continuous blood pressure monitoring and frequent blood gases are no longer needed. It is generally recommended, while using a UAC, to avoid or limit enteral feeds. To remove the UAC, withdraw it slowly in increments of 1 cm/min. This process should allow the artery to spasm and provide hemostasis. If bleeding occurs, apply pressure to the cord.[69,83] The sutures should be removed at the time of catheter removal.

Complications

A variety of complications are associated with UACs. Malpositioned catheters, vascular-related complications, infections, and hemorrhage are common categories of complications related to UACs. Intimal injury almost universally occurs to some degree with UAC placement. With malpositioned UACs, especially in the branches of the iliac artery, gross disfigurement can result.[71,84] Unusual complications related to vascular injury include acquired coarctation of the aorta and umbilical arterial rupture.[85,86] Blanching of the legs or buttocks secondary to vasospasm may occur in the ipsilateral leg to the UAC. If blanching does not improve, catheter removal is warranted to prevent severe ischemic complication. Thrombotic and embolic complications resulting from fibrin deposition on the catheter are not clinically significant in most patients, but thrombosis of the aorta or its major branches can be devastating.[71,87] Infectious complications are similar to those associated with other central vascular lines. Acute hemorrhage is an infrequent complication that can result in significant morbidity and mortality. Significant blood loss can occur with accidental withdrawal of the catheter or disconnection from the blunt needle. Close monitoring and proper securing of the catheter can prevent most of these problems. Hypertension secondary to UAC placement has been frequently reported.[88] Catheter-related sepsis occurs in neonates possessing UACs, with coagulase-negative *Staphylococcus* the most commonly identified pathogen. Some complications infrequently associated with UACs are development of aneurysmal dilatation of the aorta, peritoneal perforation, bladder injury, breaks or transection of catheters, intravascular knots

of catheters, a catheter looping back on itself, umbilical artery rupture, and others.[67]

Summary

UACs are commonly used in the care of severely ill neonates. Often overlooked by the pediatric intensivist, they can be extremely valuable tools for infants up to 2 weeks of age for assessment and management, but their use is not without problems. Because of the clinical significance of complications associated with UACs, alternative noninvasive tools for patient monitoring have been developed.

Umbilical Vein Cannulation

The umbilical vein is catheterized for emergency fluid or medication administration. In the first few hours of life, the umbilical vein is much easier to cannulate for central access than the umbilical arteries but can become more difficult as the ductus venosus constricts. In addition to resuscitation, the umbilical vein can be catheterized for prolonged central venous access in severely ill neonates. Other indications include exchange transfusion and monitoring of central venous pressure.

Equipment

The materials required for umbilical venous catheter (UVC) placement are identical to the materials required for UAC placement. Double-lumen UVCs are commercially available and are preferred unless the catheter is being placed for exchange transfusion. Typically, a 3.5 Fr catheter is used for neonates weighing less than 1000 g, 5 Fr for neonates weighing 1000 g to 3500 g, and 8 Fr for those weighing more than 3500 g.

Technique

UVC placement requires the same preparation and aseptic technique as described for umbilical artery cannulation. The umbilical vein is located at the 12 o'clock position when the umbilical cord is cut 1 to 2 cm above the umbilical ring. Apply a hemostat or forceps to the cord near the umbilical vein. The umbilical vein is not constricted when compared with the umbilical arteries and does not routinely require dilation prior to introduction of the catheter. The umbilical cord should be gently pulled toward the feet during placement to straighten the course of the vein and reduce resistance during insertion of the UVC.[66,67,83]

The length of catheter insertion is determined by the size of the infant and by the indication for placement. In emergency situations (resuscitation) and exchange transfusion, the catheter should be placed only to a depth where rapid blood return is achieved, which is 3 to 5 cm in most infants. A long-term UVC should reside at the junction of the inferior vena cava and right atrium. The formula ([3(weight in kg) + 9]/2) + 1 or the shoulder-to-umbilicus distance can be used to estimate depth of UVC insertion in centimeters from the umbilical ring.[67,78] A malpositioned UVC in the portal vein is indicated by resistance and bouncing at an insertion depth of 4 to 5 cm. If this type of resistance is encountered, a new catheter can be gently inserted (with a 50% success rate) using a side-by-side technique.[89] Remove the misdirected catheter after successful insertion of the second catheter. A catheter should never be forcefully advanced when resistance is met. Catheter position must be confirmed radiographically with both anteroposterior and lateral radiographs of the abdomen and chest. A malpositioned UVC may be missed if both views are not evaluated after placement of the line. The catheter should be sutured using a pursestring stitch and secured with a tape bridge, as described for the UAC. A malpositioned catheter should not be used for infusion of fluids. Never advance a UVC once the sterile field has been broken.

Maintenance

The UVC should be maintained as part of a closed system to prevent air embolism. Normally, infants are not placed prone while the UVC is in place, and careful observation of the umbilicus for signs of infection is warranted. Sterile technique should be used to minimize the risk of infection. A malpositioned catheter should never be advanced, and low catheters should only be used in extenuating circumstances. If placed for exchange transfusion, the catheter should be removed immediately after the procedure. If the UVC was placed for central venous access, it should be removed when it is no longer needed. Generally, UVCs should be discontinued within 10 days to 2 weeks after placement to decrease the likelihood of complications, although in babies weighing less than 1250 g it may be safe to leave a UVC in place for up to 28 days.[90,91] UVCs should be removed in the manner described for UACs.

Complications

Infection is the most common complication associated with UVC placement, with increased risk when the catheter is left in place for prolonged periods of time.[71,90] Thrombosis is another reported complication of UVC placement and can lead to late portal hypertension when it occurs in the portal venous system.[92,93] Associated hepatic necrosis, liver abscess, cardiac infections, arrhythmias, cardiac tamponade, cardiac perforation, necrotizing enterocolitis, and peritoneal perforation or peritoneal fluid extravasation have been described in the literature, with some being life-threatening.[67,71,92,94-96]

Summary

UVCs provide emergency access during resuscitation of a severely ill neonate. In low-birth-weight infants, UVCs can be the initial route for providing valuable high-calorie nutrition. Appropriate catheter placement should be confirmed with two-view radiographs. Complications from UVCs are more likely if the catheters are left in place for prolonged periods or are incorrectly positioned. Ideally, UVCs should be removed within 7 days due to increased risk of infection.

Central Venous Line Placement

Intensivists must be expert in central venous line (CVL) placement and use. The need for central access should be anticipated so that circumstances surrounding the procedure, such as sterile technique and the patient's safety and comfort, can be optimized.

Indications and Contraindications

Indications for CVLs include:

- The need for reliable and durable venous access:
  - In the face of lack of or inadequate peripheral venous access.
  - For administration of vasoactive infusions, TPN, and other medications that require central vascular access.

- Frequent blood sampling.
- Monitoring of central venous pressure and central venous oxygen saturation.
- Providing access for certain extracorporeal support modalities such as continuous renal replacement therapy and apheresis.

Contraindications to central access are not absolute and are primarily related to catheter placement at specific sites. In the presence of increased bleeding risk, sites where bleeding may be difficult to control, such as the subclavian, should be avoided if possible. In patients with significant intraabdominal or pelvic trauma, femoral catheters may pose increased risk. Bacteremia present at the time of catheter placement likely will colonize to central venous catheters. Catheters should not be inserted through obviously infected skin. The relative risk and benefit of catheter placement should be carefully considered before each procedure.[97]

Technique

Critically ill pediatric patients vary greatly in size, and the pediatric intensivist should have an awareness regarding the dimensions of the vein that is being accessed and the proximity and anatomical relation of the respective artery to the vein. The diameters of the central veins vary across the pediatric age groups (Table 15-1), and those veins and their respective arteries can be very vulnerable to damage during the cannulation process due to variations of the anatomical relationship that exist among patients.

Appropriate-sized catheters for CVL placement in pediatric patients should be readily available. In acutely ill patients requiring central access for a relatively short period (days to weeks), plastic polymer catheters are commonly used. These catheters are available in a variety of diameters, lumen numbers, and lengths. They can be packaged with appropriate-sized introducer needles, guidewires, and tissue dilators, along with other necessary equipment such as local anesthetic, skin cleanser, drapes, and suture for securing the catheter. Currently available antibiotic-impregnated catheters may decrease the risk of catheter-related bloodstream infection.[98]

Table 15–1 Approximate Mean Femoral and Internal Jugular Vein Diameter Across the Pediatric Age Period

Age	Mean IJV Diameter (mm)	Mean FV Diameter (mm)
25-27 weeks PCA*	2.1	1.5
31-33 weeks PCA*	3.3	1.9
37-39 weeks PCA*	4.2	2.3
1 month	5.5†	4.5‡
1 year	6.2†	5.4‡
2 years§	6.7	6.3
4 years§	7.8	7
6 years§	8.9	7.7
8 years§	10	8.5
10 years§	11.1	9.2
13 years§	12.8	10.4
16 years§	14.5	11.5
19 years§	16.2	12.6

IJV, Internal jugular vein; *FV,* femoral vein; *PCA,* postconception age.
*Author's experience, data not published.
†Reference 110.
‡Reference 115.
§Steinberg C, Weinstock DJ, Gold JP, et al: Measurements of central blood vessels in infants and children: normal values, *Cathet Cardiovase Diagn* 27(3):197-201.

Adequate sedation and analgesia not only provide patient comfort during the procedure but also make the procedure easier and safer with less patient movement. Agents with rapid onset and short duration of action, such as midazolam, propofol, and ketamine, are ideal. Even with sedation, local anesthesia should be used to reduce pain and the depth of sedation required for a patient to be comfortable and still.

Full barrier precautions should be used whenever a CVL is placed in the PICU and should include hair cover, mask, careful handwashing, sterile gown and gloves, a large area of skin prepped with antiseptic solution, and a draped sterile field large enough to eliminate the possibility of inadvertent contamination of equipment and sterile surfaces. This technique, when properly applied, has been shown to decrease the risk of catheter-related infection.[99] Skin disinfection with chlorhexidine is superior to povidone-iodine.[100]

The majority of CVLs placed in the PICU are placed using the Seldinger technique[101] This technique is essentially the same regardless of the site used. An introducer needle is placed in the desired vein while aspirating with a syringe. This step can be facilitated by using a bedside ultrasound with appropriate probe designed to visualize the vessel of interest (see later discussion). When the lumen of the needle is fully within the lumen of the vein, blood flows freely into the syringe. The needle should be held in place with one hand while the syringe is disconnected with the other hand. The rate at which blood passively flows from the open needle hub is dependent upon the gauge of the needle and the venous pressure; however, it should not be obviously pulsatile. A J-tipped guidewire is inserted into the open hub of the needle and advanced into the vein (Figure 15-6, *A*). The wire should meet little or no resistance as it is advanced. If resistance is met, attempts to advance the wire should cease. The position of the needle should be adjusted, by either advancing or withdrawing slightly or changing the angle of entry. The wire can be carefully withdrawn and the syringe reattached to the needle in order to reidentify the lumen of the vein. If resistance is met while withdrawing the wire, the needle and wire should be withdrawn as a unit rather than risk breaking or cutting the wire. Once the guidewire is well within the lumen of the vein, a small incision is made adjacent to the needle to enlarge the puncture site to more easily accommodate the dilator and catheter. Next, the introducer needle is carefully withdrawn along the wire holding the wire completely stationary. A dilator of appropriate size is advanced along the wire into the puncture far enough to dilate all tissue planes into the lumen of the vein. The dilator is withdrawn, and the desired catheter is advanced into position along the wire (Figure 15-6, *B*). The guidewire is removed, leaving the catheter in place. Blood should be easily aspirated from all lumens. Each lumen should be filled with sterile saline or heparinized saline to prevent thrombosis.

Several systems for securing catheters are commercially available. The most common technique uses silk suture. A large loop of suture should be placed in the skin, attached through the wings of the catheter hub, and tied tightly

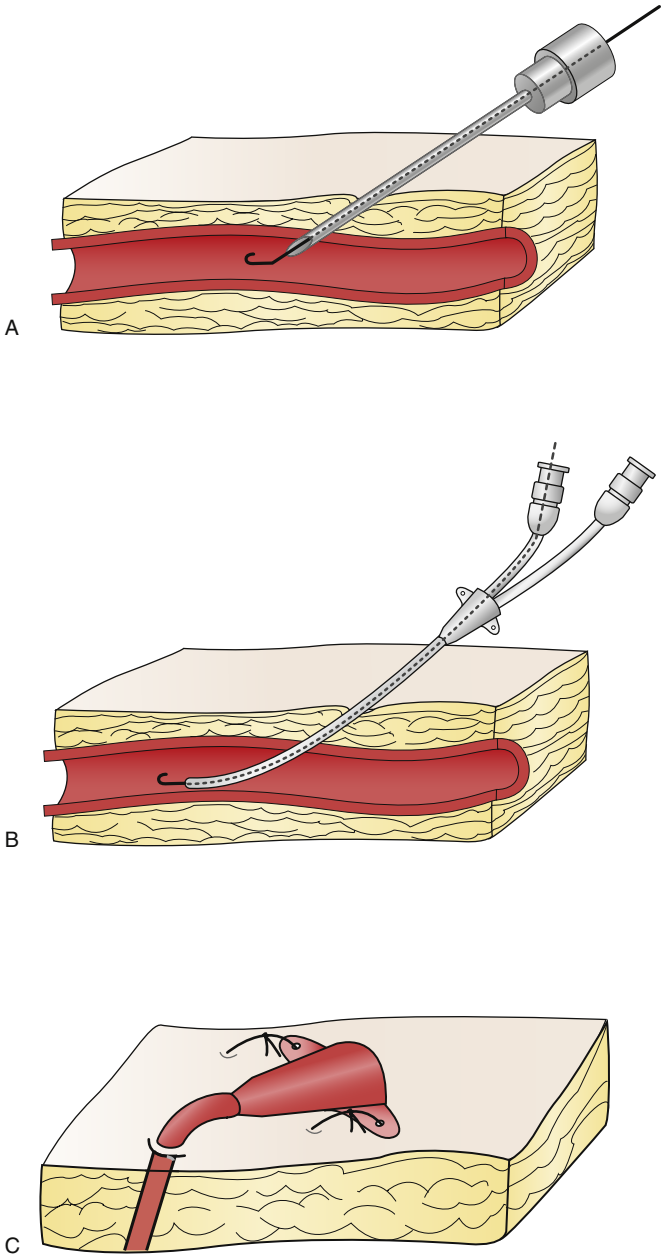

Figure 15–6. **A,** Guidewire is placed through the introducer needle into the lumen of the vein. **B,** Catheter is advanced into the vein lumen along the guidewire. **C,** Hub of the catheter is secured to the skin with suture.

enough to prevent catheter movement but not so tightly as to cause necrosis of the skin within the loop of suture material (Figure 15-6, *C*).

Internal Jugular Vein Cannulation

Multiple approaches can be used to cannulate the internal jugular vein. For each of these approaches, the patient is supine in slight Trendelenburg position, with a roll of bed linen under the shoulders to extend the neck and with the face turned to the contralateral side. The middle or low approach is most commonly used (Figure 15-7, *A*). The introducer needle enters the skin at the apex of the triangle formed by the clavicle and the heads of the sternocleidomastoid muscle at a 30-degree angle to the skin directed toward the ipsilateral nipple. For the anterior approach, the introducer needle enters the skin along the anterior margin of the sternocleidomastoid halfway between the mastoid process and the sternum and is directed at the ipsilateral nipple (Figure 15-7, *B*). Using the posterior approach, the needle enters the skin along the posterior border of the sternocleidomastoid halfway between the mastoid process and the clavicle and is directed toward the suprasternal notch (Figure 15-7, *C*).[102]

Subclavian Vein Cannulation

Place the patient supine in a slight Trendelenburg position. A narrow roll of bed linen is placed beneath the patient, between his or her shoulders. The introducer needle enters the skin inferior to the junction of the middle and lateral third of the clavicle and is directed toward the suprasternal notch. The needle passes slightly inferior to the clavicle and enters the subclavian vein (Figure 15-8).[102]

Femoral Vein Cannulation

The patient is placed in a supine position either flat or in slight reverse Trendelenburg position. A pad of bed linen is placed under the hips to slightly raise them off the bed surface. The leg on the side of catheter placement is slightly abducted and externally rotated. The femoral artery pulse is palpated just distal to the inguinal ligament about halfway between the anterior iliac crest and the pubic symphysis. The femoral vein is approximately 5 mm medial to the femoral artery in infants and toddlers and approximately 10 mm in adolescents and adults. The introducer needle enters the skin 1 to 2 cm distal to the inguinal ligament at an approximately 30-degree angle with the skin surface and in line with the course of the vein, approximately parallel to the axis of the thigh (Figure 15-9).[102]

Use of Ultrasound for Central Venous Line Placement

Since the first description of the Seldinger technique by Sven Seldinger in 1953, percutaneous CVLs have been placed by relying on certain surface anatomic landmarks at the site of insertion. This method is a "blind" method since the operator does not have direct visualization of the central vein that is being accessed. Recently, the use of ultrasound technology to facilitate CVL placement has been described, and since the first report by Legler in 1984, the use of ultrasound to guide CVL placement has become increasingly more popular among many practitioners.

Small, portable bedside ultrasound machines with transducers designed for visualization of vessels are commercially available. Sterile ultrasound gel and transducer covers exist, and they maintain full barrier precautions while placing the CVL.

The ultrasound is used in either of two ways to help with CVL placement:

- Continuous real-time visualization of the central vein and the needle while the needle is being introduced into the lumen of the vein. This can be performed by two operators (one operator holds the ultrasound probe while the other operator introduces the needle) or by a single operator (the ultrasound probe is held with one hand and the needle is introduced with the other hand).

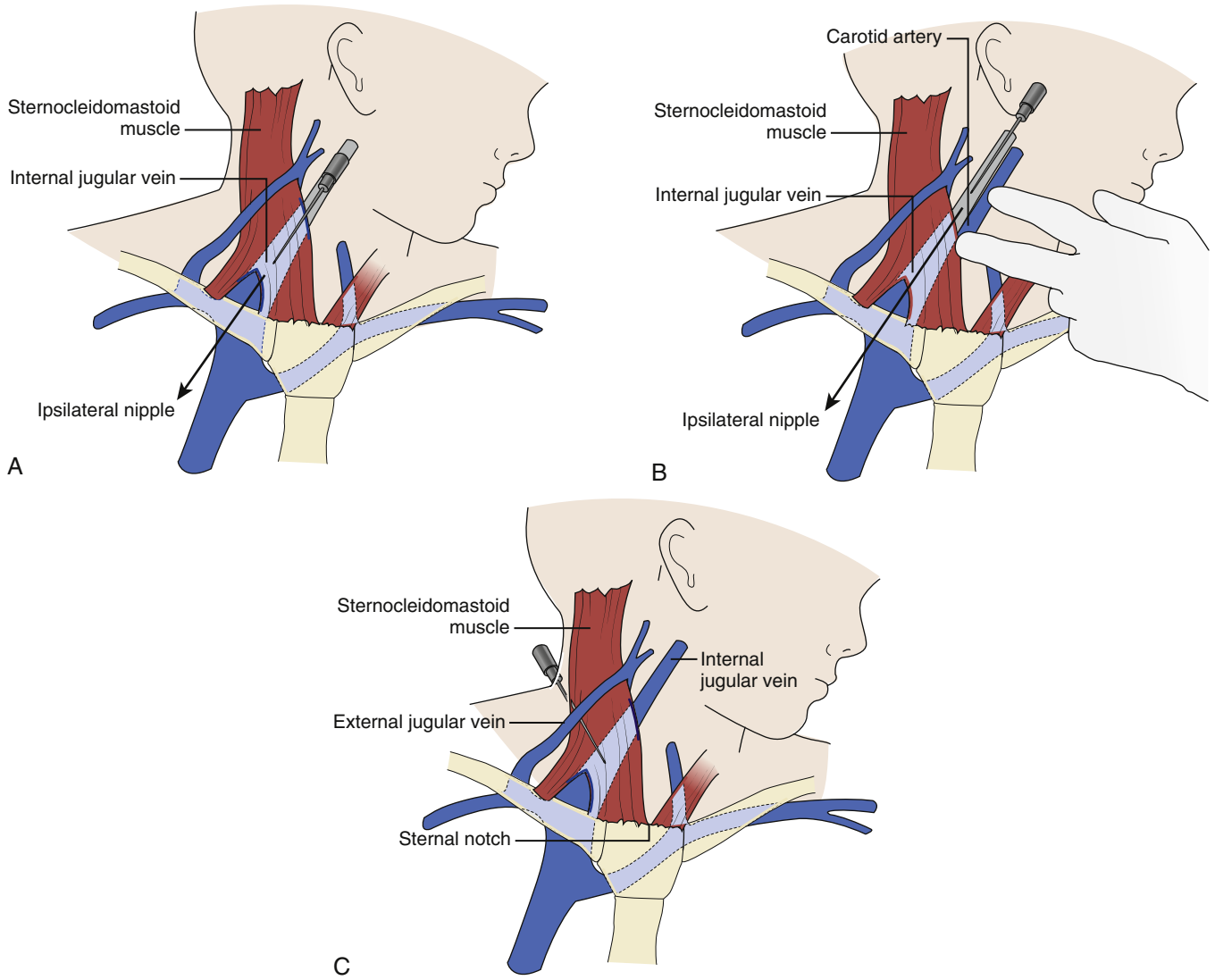

Figure 15–7. Approaches to the internal jugular vein. The patient is supine, in slight Trendelenburg position, with the neck extended over a shoulder roll and the head rotated away from the side of the approach. **A,** Middle approach. The introducer needle enters at the apex of the triangle formed by the heads of the sternocleidomastoid muscle and the clavicle and is directed toward the ipsilateral nipple at an angle of approximately 30 degrees with the skin. **B,** Anterior approach. The carotid pulse is palpated and may be slightly retracted medially. The introducer needle enters along the anterior margin of the sternocleidomastoid about halfway between the sternal notch and the mastoid process and is directed toward the ipsilateral nipple. **C,** Posterior approach. The introducer needle enters at the point where the external jugular vein crosses the posterior margin of the sternocleidomastoid and is directed under its heads toward the sternal notch.

- Direct one-time static visualization of the vein and its respective artery prior to needle insertion, then insertion of the needle without continuous visualization.

In a randomized controlled trial, real-time ultrasound guidance for CVL placement outperformed the static method.[103] The use of ultrasound guidance for CVL placement has been shown in many studies, both in adult and pediatric patients, to result in better success rates and fewer complications as compared to the "blind" surface landmarks method.[104-106] A recent study in pediatric patients showed that ultrasound guidance during CVL placement decreased the complications rates and the placement attempts but did not improve success rates.[107] In experienced hands, ultrasound can be of great help to facilitate CVL placement with fewer complications. Ultrasound offers many benefits that help facilitate CVL placement. It identifies the size of the central vein and the exact relation of the vein and its respective artery, which has been shown in many studies (both in adults and children) to frequently vary from what is depicted in the "classic" anatomy.[108-115] Ultrasound also shows the guidewire inserted inside the vein prior to using the dilator. In addition, ultrasound identifies the patency of the central vein and helps to avoid attempting CVL placement in an already thrombosed central vein. Use of real-time ultrasound for CVL placement is strongly encouraged, and pediatric intensivists should be familiar with this technology.

Complications

The risk of bloodstream infection is significantly increased by the presence of a central venous catheter. The increased risk is true for all catheter locations and increases with the total

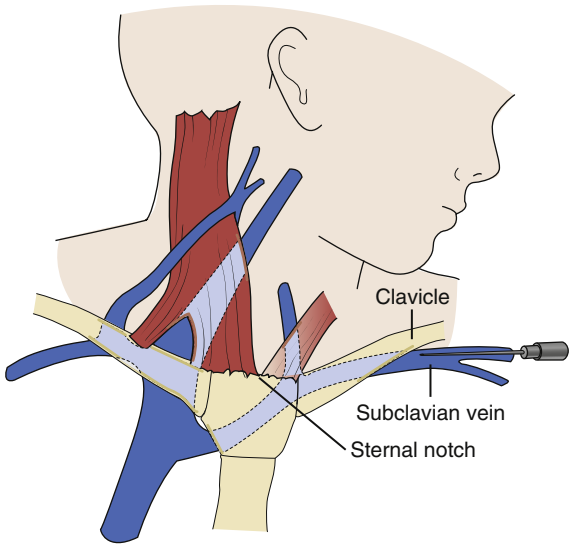

Figure 15–8. Approach to the subclavian vein. The patient is supine, in slight Trendelenburg position, with a small roll along the spine between the shoulders. The needle enters the skin at the junction of the lateral and middle thirds of the clavicle and is directed toward the sternal notch in the horizontal plane.

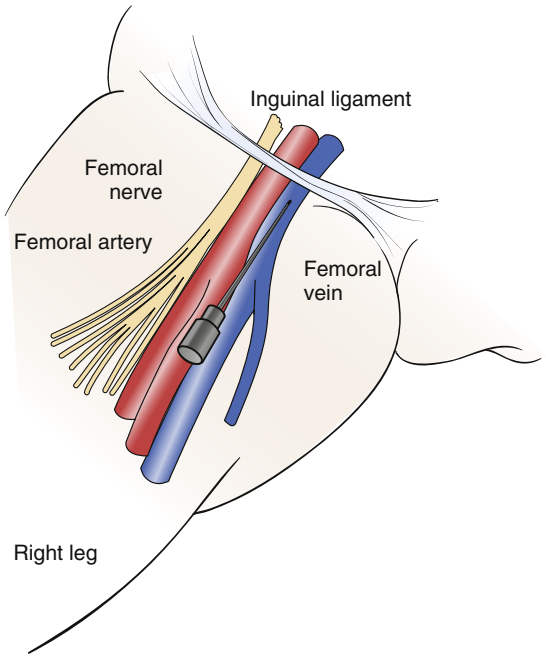

Figure 15–9. Approach to the femoral vein. The patient is flat and supine, with the thigh slightly abducted and externally rotated. The introducer needle enters the skin 2 to 3 cm distal to the inguinal ligament and 0.5 to 1 cm medial to the pulse of the femoral artery.

number of catheter days. Routine changing of uninfected catheters either over a guidewire or to a different anatomic site does not change the risk. Coagulase-negative staphylococci, *Enterococcus* species, *Staphylococcus aureus*, *Enterobacter* species, and *Candida* species account for the majority of infections. The risk of infection is decreased by use of antibiotic-impregnated catheters, full barrier precautions at the time of placement, and careful aseptic technique when the line is accessed.[98,99]

Pneumothorax may result if the lung is punctured during internal jugular or subclavian placement. This complication is less likely with careful patient positioning and attention to anatomic landmarks as the introducer needle is advanced. Chest radiography should be performed after an internal jugular or subclavian catheter is attempted to document that a pneumothorax has not occurred. Thrombosis may occur in the vessel surrounding the catheter. The catheter lumen may become thrombosed.

Bleeding at the time of placement can be serious and potentially life-threatening. Bleeding at the skin puncture site from an inadvertent arterial puncture is easily controlled by direct pressure. However, bleeding caused by injury to a deeper vascular structure may result in difficult-to-control hemorrhage. Veins and arteries may be perforated or lacerated distant from the intended puncture site by the introducer needle, guidewire, vessel dilator, or the catheter itself. Injury to the femoral or iliac vessels may result in pelvic or retroperitoneal bleeding. Lacerations of the internal jugular, subclavian, or innominate veins or the superior vena cava may communicate with the thoracic cavity and result in hemothorax and bleeding that cannot be controlled by direct pressure. Perforation of the heart during catheter placement may cause cardiac tamponade. Bleeding complications are more severe in the presence of a coagulopathy or thrombocytopenia and should be treated, if possible, before central access is attempted, especially if the internal jugular and subclavian sites are to be used.[116,117]

A central venous catheter positioned such that it applies pressure to the wall of the vessel or to the wall of the heart risks causing perforation. This situation may result in acute blood loss or tamponade. Undesirable positioning of a CVL can be detected radiographically and should be corrected as soon as possible.[116,117]

Venous Cutdown

With the widespread use of central venous access and the use of intraosseous access during emergencies, venous cutdown is less commonly performed. Venous cutdown is indicated when percutaneous access is not achievable and the need for IV access warrants the more invasive procedure. Materials needed depend upon the technique of vein cannulation used. The skin should be prepped and draped, and sterile technique should be used. The skin overlying the intended site is opened perpendicularly with respect to the vein. The tissue surrounding the vein is bluntly dissected to completely expose the vein. Ligatures are passed around the vein distal and proximal to the intended site of cannulation. A small venotomy is created and, using the ligatures to control the vein, a catheter is directly passed into the lumen of the vein. The distal ligature can be tightened to control bleeding and the proximal ligature to help secure the catheter (Figure 15-10). Alternatively, an over-the-needle IV catheter can be directly introduced into the exposed vein without creating the venotomy or using ligatures. An introducer needle and then a guidewire can be inserted into the lumen of the vein for Seldinger technique placement. The latter approach is particularly useful for femoral venous cutdown. After the catheter is in place, it is secured with suture material and the wound is closed around the catheter.

The complications of venous cutdown are similar to the complications of other venous access techniques. The risk of bleeding from the open wound should be considered,

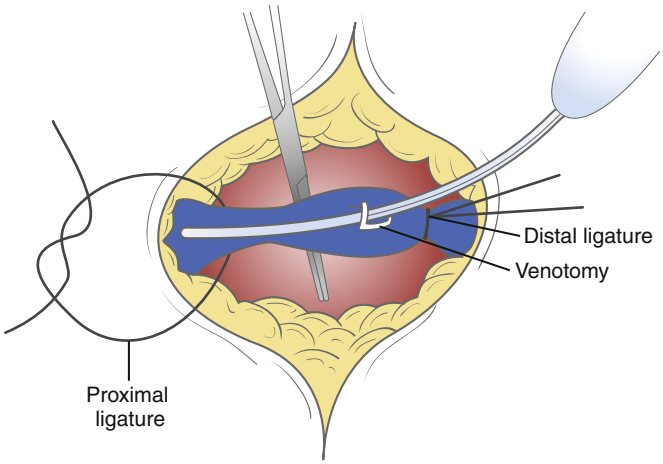

Figure 15–10. Venous cutdown.

especially in patients with increased risk for bleeding (anticoagulation or other coagulopathy). The open wound also increases the risk of infection. Injury to adjacent structures, such as arteries and nerves, during incision and blunt dissection is a risk with cutdown.[102,118,119]

Peripherally Inserted Central Venous Catheters

Peripherally inserted central venous catheters (PICCs) are increasingly used in pediatric intensive care unit (PICU) patients. Historically, these catheters have been used most in neonatal ICUs. For infants and smaller children, often only a single-lumen catheter can be placed. Multilumen catheters may be placed in older children. While PICC lines can often be placed by visible location and/or palpation of veins in the antecubital fossae, ultrasound is frequently used to place these catheters above the antecubital fossa to allow unimpaired elbow flexion. Success is more common when the catheters are inserted in the basilic vein.[120]

PICC lines are most often constructed of soft silicone material. The catheter length is measured prior to catheter insertion, and the catheter trimmed to the appropriate length. Placement of PICC lines is most commonly performed using a modification of the Seldinger technique. A needle or catheter is inserted into the vein, then a guidewire is placed, followed by a dilator. A soft "peel-away" introducer is often inserted next, with the catheter inserted through the introducer sheath, then the sheath is peeled away after the catheter is in place.

When placed by interventional radiologists, the catheter position is frequently verified by real-time fluoroscopy.[121] Outside of interventional radiology suites, chest radiography remains the primary method for documenting the location of the catheter tip.

While PICC lines are associated with a lower risk of placement-related complications, they are subject to the same complications as percutaneous central venous catheters, including catheter-associated infection, thrombosis, perforation, embolization, and fracture.[122-125] When PICC lines become fractured, the catheter may be repaired using manufacturer-provided kits for some catheters. Catheter repair may be associated with increased infection risk.

Pulmonary Artery Catheterization

Pulmonary artery catheter (PAC) monitoring was introduced into practice in 1970 by Swan and Ganz. Recently, because of the invasivness of the procedure and the lack of proven survival benefit for patient management, other less invasive surrogate techniques have significantly decreased the use of the PAC technology.[126-129]

The placement of the catheter can be done at the bedside, but skill is required to avoid complications and for proper interpretation of the hemodynamic data. Most catheters are balloon-tipped and flow-directed, and are able to measure right atrial, pulmonary artery, and pulmonary capillary wedge pressures as well as to determine cardiac output and oxygen saturations in the right heart chambers. Single-lumen catheters may be placed directly into the pulmonary artery at the time of cardiac surgery. Both techniques are used in pediatric patients, but the single-lumen catheter is especially used because of the frequency of pulmonary hypertension complicating the postoperative management of pediatric cardiac patients. The flow-directed, balloon-tipped catheter is usually placed in the ICU to assist in determining the etiology of shock, lactic acidosis, pulmonary edema, pulmonary hypertension, as well as to help guide fluid and vasoactive therapy over time.[130] There are different sizes of pulmonary artery catheters, with different lumens and a thermistor at the tip. Some use a fiberoptic spectrophotometry for continuous measurement of mixed venous oxygen saturation.

Pulmonary artery catheters are indicated for use in pulmonary hypertension, as well as in select patients with severe respiratory failure or severe shock. Pulmonary hypertension may beither be primary or secondary, the latter including pulmonary hypertension in postoperative congenital cardiac patients. These patients are prone to wide swings in PA pressures associated with variations in oxygenation, ventilation, and even sedation. When nitric oxide is used for management of postoperative pulmonary hypertension, direct measurement of PA pressure helps guide therapy. In patients with severe respiratory failure requiring high positive airway pressure with associated hemodynamic compromise, PACs may aid in the diagnosis of the cause of low cardiac output and direct therapy. When oxygen delivery in these patients is significantly limited because of hypoxemia, low cardiac output, or both, measurement of oxygen delivery using variables derived from information provided by the catheter may be useful. In children with severe shock unresponsive to fluid resuscitation and requiring vasoactive infusions, the PAC may better define the hemodynamic profile, thus allowing more specific therapy.

Significant controversy exists regarding the benefits and potential harms caused by this invasive form of hemodynamic monitoring.[131-133] Some randomized clinical trials documented that routine bedside pulmonary artery catheterization not only is not beneficial but may be associated with increased morbidity and mortality,[127] but other centers did not find differences in morbidity or mortality with or without PACs.[131] No studies in pediatric patients have demonstrated better outcomes with the use of the PAC.

Multiple barriers exist to PAC use, including patient risk with placement, the ability to measure similar variables via less invasive measures, increased cost, inaccurate measurement leading to misuse of PAC-derived variables, and incorrect

interpretation and clinical application. Additionally, with the decreased use of this technology, the skill required to maintain competency in placement and interpretation of the data provided presents a significant challenge to many institutions.

Contraindications

There are no specific contraindications to placement of a Swan-Ganz catheter, but there are several relative contraindications, including bleeding diathesis increasing the risk for percutaneous access, as well as severe tricuspid or pulmonary insufficiency, which can make bedside catheter placement prohibitively difficult. Unstable cardiac arrhythmias that are easily triggered by catheter manipulation are also a relative contraindication. Catheter placement for measurement of cardiac output using the thermodilution technique is contraindicated in the presence of intracardiac shunts, tricuspid insufficiency, or pulmonary insufficiency, as the thermodilution measurement will be inaccurate.

Procedure and Equipment

Choosing the most appropriate size and type of catheter is often difficult because a variety of balloon-tipped, flow-directed catheters are available on the market. Catheters are available with two diameters, 5 Fr and 7 Fr. The 5 Fr diameter catheter is most appropriate for patients weighing less than 15 kg, and the 7 Fr diameter catheter is best for patients weighing more than 15 kg. Single-lumen PACs are most commonly placed in the operating room at the time of heart surgery.

The standard PAC is 1 m long. The distance between the proximal variables depends on the catheter. The standards are 10, 15, 20, and 30 cm. Using the correct distance is crucial in order to monitor the appropiate pressure.The PAC is equipped with proximal and distal ports facilitating measurement of intravascular pressures, infusion of vasoactive agents, fluids, and blood sampling. At the tip are a thermistor used to calculate cardiac output and a balloon that may be inflated and deflated as necessary. Some catheters have an additional right ventricular port for temporary pacemaker insertion, and some have a fiberoptic oxygen saturation sensor for continuous measurement of mixed venous oxygen saturation. Other necessary equipment includes a monitor with cardiac output capability or a computer to determine cardiac output using thermodilution, as well as compatible pressure transducers. Carbon dioxide is used in some centers to inflate the balloon so as to minimize the risk of air embolization, although room air is most common. The catheters are placed through a percutanous introducer sheath, which is placed with the same technique as described for central venous catheters.

Before placement, the catheter should be flushed and filled with fluid through which intravascular pressures are transmitted to a transducer. The equipment is then zeroed to atmospheric pressure at the level of the patient's left atrium (midaxillary line, fourth intercostal space) and calibrated. If all air bubbles are not removed from the tubing, they may result in "damping" of the waveform tracing, and consequently, erroneously low systolic pressure. Clots at the tip of the catheter may also alter the wave form.

The site is prepared in sterile fashion with chlorhexidine solution and draped with sterile towels. It is important to drape a wide area with sterile sheets in order to avoid exposure of the

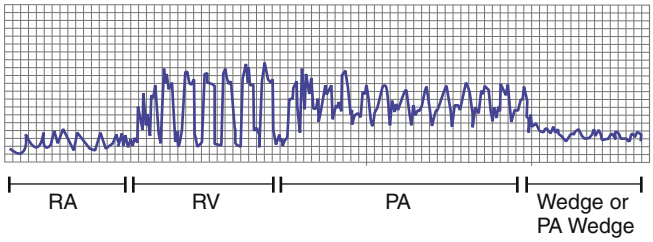

Figure 15–11. Pressure tracing during placement of a pulmonary arterial catheter showing pressures from the right atrium (RA), right ventricle (RV), and pulmonary artery (PA), then pulmonary capillary wedge pressure. *(From Adatia I, Cos P: Invasive and noninvasive monitoring. In Chang AC, editor:* Pediatric cardiac intensive care, *Baltimore, MD, 1998, Lippincott Williams & Wilkins.)*

catheter, because of the length of the PAC. The PAC is inserted through the introducer sheath. A sterile sleeve is placed on the end of the sheath and the catheter is passed through the sleeve, then through the diaphragm and into the sheath.

Anatomically, the preferred sites of insertion are the right internal jugular, left subclavian, right subclavian, and left internal jugular veins. Usually, the placement of the catheter is guided by pressure wave form monitoring (Figure 15-11), but fluoroscopic visualization will occasionally be needed, particularly if the PAC is placed from a femoral site. Once the catheter tip enters the venous circulation, the balloon is inflated with air. From this point, the catheter should be advanced with the balloon inflated so as to prevent damage to the myocardium, cardiac valves, or pulmonary artery branches. If the catheter is withdrawn, the balloon must first be deflated to avoid valvular injury.

The catheter is advanced to the right atrium (RA), then across the tricuspid valve into the right ventricle (RV), and across the pulmonary valve into the pulmonary artery (PA). As the catheter continues to float with the balloon inflated, it will wedge in a branch PA, occluding the blood flow. The pulmonary artery occlusion pressure (PAOP), or wedge pressure (PAWP), will be recorded from the distal lumen. If the balloon is deflated, a PA pressure tracing will be recorded. If the wave forms are not obtained, the balloon should be deflated and the catheter pulled back to the RA before attempting placement again.

After insertion, a chest radiograph is obtained to ensure proper catheter placement and rule out pneumothorax. The caheter tip should be visualized within the proximal third of the hemithorax.

The pressure wave forms are characteristic; when the catheter is advanced to the RA, the atrial trace has a respiratory variation that helps to confirm the catheter is in the thorax. Once in the atrium the balloon is inflated and advanced to the RV, where the trace is characterized by a rapid upstroke in early systole with an equally rapid downstroke at the end of systole. Turning the catheter with a clockwise motion usually helps in passing the PAC. The catheter is advanced to the PA. The PA trace has the same peak systolic pressure of the RV, but as systole ends, the trace shows a slower fall that continues through diastole, because the diastolic pressure in the PA is higher than the RV diastolic pressure. Once in the PA, advance the catheter slightly until a pulmonary wedge trace is seen. This trace is similar to the RA trace, although usually with a higher pressure. PAWP is obtained when the balloon

is inflated and the catheter floats into the wedge position (see Figure 15-11). Because the catheter floats to an area of greatest blood flow in the lung, it most likely will be in an area consistent with West zone III. Zone III is an area where arterial pressure is higher than both venous and alveolar pressure.

Measurement of PAWP is best done at end-expiration to minimize the effect of changes in pleural pressure. Once the wedge is measured and the balloon is deflated, the PA trace should return. If the trace does not change, the catheter should be retracted until the PA trace is seen. The catheter should not be left inflated in the wedge position because of the risk of pulmonary infarction. The catheter is appropriately positioned when the PA pressure trace is present when the balloon is not inflated and the pulmonary capillary wedge trace is present when the balloon is inflated. Once it has been confirmed that the PAC is in good position by pressure trace and radiography, the catheter should be secured in the sleeve and taped to the patient.

Information Acquisition

Much hemodynamic and oxygen delivery information can be obtained from the Swan-Ganz–type pulmonary artery catheter. Multiple hemodynamic pressures can be obtained, including RA pressure, PA pressure, and PAWP. Right atrial pressure is useful for determining preload of the right ventricle. pulmonary artery pressure is useful for determining the presence of pulmonary hypertension both at baseline and with manipulation of oxygenation, ventilation, ventilator pressures, nitric oxide, and other procedures.

PAWP reflects left ventricular preload. In most patients with normal cardiac function and anatomy, right atrial or central venous pressure adequately reflects LV preload as well. However, in the presence of certain congenital heart defects, with significant ventricular dysfunction, or with high mechanical ventilatory pressures, a significant discrepancy may exist between right and left ventricular preload. In such circumstances, measurement of PAWP is useful for guiding fluid and inotropic therapy.

Systemic mixed venous oxygen saturation (Svo_2) can be determined directly and continuously with a catheter containing the fiberoptic oximeter. In the absence of the oximeter, intermittent blood sampling from the distal port when in place in the pulmonary artery allows for Svo_2 measurement.

The thermistor at the tip of the catheter allows for measurement of cardiac output, using the thermodilution method. This method uses the Fick principle, based on the law of conservation of thermal energy. A specific amount of known temperature fluid is injected in the proximal port (upstream), and the temperature change downstream (at the thermistor) is recorded. The change in temperature over time allows for measurement of blood flow, in this case cardiac output. According to Jansen this measure of cardiac output is accurate if the following conditions are met: 1) no loss of cold occurs between the injection site and the thermistor, 2) mixing of the cold injectate (indicator using Fick terms) and the blood is complete, and 3) the temperature change caused by the injection of cold fluid is sufficient to be detected by the thermistor.

To perform thermodilution cardiac output measurements, the catheter must be connected to the thermodilution computer, which is either freestanding or part of the cardiac monitor. A specific volume of injectate, either room temperature or iced, is injected rapidly into the proximal port of the catheter. The temperature difference over time that is detected at the thermistor is recorded as a curve. The computer then integrates the area under the curve, which is inversely proportional to the cardiac output. The cardiac output is calculated and projected. For pediatric patients, this number should be divided by their surface area in meters, giving the cardiac index. The injectate can be either iced or room temperature. The disadvantages to iced injectate include risk of hypothermia in pediatric patients requiring frequent cardiac output measurements, the poor accuracy of the first injection because of warmer fluid in the catheter, and a greater signal-to-noise ratio. Room temperature injectate prevents these problems and yet is accurate when cardiac output is stable. However, in conditions of high or low cardiac output, less variance occurs with iced injectate compared with room temperature injectate. However, for convenience and the safety of pediatric patients, room temperature injectate is recommended.

Usually three to five injections yield adequate results. Some error can be introduced by faulty technique. Injecting variable volumes or injecting with variable rates can result in inaccurate measures. Multiple injections and averaging of the results can overcome these problems. The presence of tricuspid or pulmonary insufficiency can lead to overestimation of cardiac output. Echocardiography may be necessary to rule out the presence of valvular insufficiency. Intracardiac shunts, such as a ventricular septal defect, result in false values for cardiac output. Mechanical ventilation has been shown to alter stroke volume, which can result in variable measures of cardiac output. Therefore, one should perform the injection at the same time in the ventilator cycle to standardize the cardiac output measurements.

Maintenance

Care of the PAC is similar to that for any central venous line. The catheter and sheath should be dressed sterilely at all times and the dressing changed according to protocol. The catheter is housed in a sterile sleeve that allows for aseptic technique if further manipulation is necessary. Pressure transduction of the distal (PA) and proximal (RA) ports and continuous electrocardiographic (ECG) monitoring are mandatory. This setup continually confirms proper placement of the catheter. Whenever the balloon is inflated to determine PAWP, allow the balloon to deflate passively by opening the balloon port and removing the syringe. This step helps prevent balloon rupture. Balloon rupture should be suspected if blood is obtained when aspirating the balloon port. In this situation, remove and then replace the catheter if it is still clinically indicated. As noted earlier, arrhythmias can occur, particularly if the catheter becomes dislodged. A chest radiogram should be assessed daily for catheter position.

Interpretation

The hemodynamic data obtained or calculated with the PAC should be interpreted to make therapeutic decisions.

There are not isolated "good" or "bad" cardiac output (CO) values, but appropriate cardiac output is that which permits an adequate oxygen delivery (Do_2). As a global index of adequacy between consumption (Vo_2) and Do_2, Svo_2 is the target of choice for therapeutic decisions. Svo_2 should be kept above

a threshold value and all other PAC parameters should be used to choose how to maintain Svo_2 above this value. A value between 65% and 70% should be used. This Svo_2 goal can be achieved by fluid administration, blood transfusion, increasing or decreasing inotropic support, and/or vasopressors.[134-136]

Complications

PA catheterization is a significantly invasive procedure. Complications can occur during the Seldinger procedure to access the vein, during the passage of the PAC (across two heart valves), or during catheter use. Bleeding, infection, and pneumothorax may occur during venous access. Arrhythmias can be seen during placement of the PAC or due to dislodgment of the catheter. Their spectrum goes from supraventricular tachycardia while in the RA to premature ventricular beats or even ventricular tachycardia while in the RV. Usually, the arrhythmias cease when the catheter reaches the pulmonary artery. Occasionally lidocaine, amiodarone, and defibrillation may be needed, so they should be readily available. Once the catheter is in place, pulmonary infarction or hemorrhage is a risk. Rupture of the distal pulmonary artery, endothelial damage, and valvular damage have been reported, as well as knotting of the catheter requiring fluoroscopic retrieval. Remove the pulmonary artery catheter as soon as possible to avoid complications.

Summary

Since the introduction of the PAC, controversy has surrounded the technology regarding the benefits and potential harms caused by this invasive form of hemodynamic monitoring. In adult clinical trials, the usefulness of PAC has been challenged because no benefit in patient outcome has been observed, and some retrospective studies have described worse outcomes. Accurate acquisition and interpretation of the data is paramount for making appropriate therapeutic decisions.

Thoracentesis and Tube Thoracostomy

Thoracentesis

Thoracentesis, first described in 1852, is a procedure used to remove fluid or air from the pleural space. In pediatric patients, thoracentesis is most frequently indicated as a diagnostic procedure. Pleural effusions in children are most commonly the result of an infectious process (50% to 70% parapneumonic effusions), with congestive heart failure (5% to 15%) and malignancy being less common causes.[1] Many other conditions may, rarely, cause pleural effusions in children (Box 15-2).

Indications

Thoracentesis may be used to help diagnose the cause of a pleural effusion. It can also be used therapeutically to relieve respiratory distress resulting from large accumulations of fluid or air. If ongoing evacuation is required, tube thoracostomy should be considered (see below). Ultrasound is a useful technique to identify fluid accumulations when there is complete opacification of the hemithorax on chest radiograph, and to help characterize fluid consistency (complicated vs. simple effusions).[2] Ultrasound may also help to identify optimal locations for successful aspiration. [137]

Box 15–2 Causes of Pleural Effusion

- Infection (exudates)
  - Bacterial
  - Viral
  - Fungal
  - Mycobacterial
  - Mycoplasma
- Cardiovascular
  - Congestive heart failure
  - Constrictive pericarditis
  - Superior vena cava obstruction
- Pulmonary
  - Pulmonary infarction
  - Atelectasis
  - Asbestos exposure
  - Drug-induced pleuritis
- Intraabdominal disease
  - Abdominal surgery
  - Pancreatitis
  - Hepatitis
  - Peritonitis
  - Subdiaphragmatic abscess
  - Intrahepatic abscess
  - Meigs syndrome
  - Cirrhosis with ascites
- Iatrogenic
  - Extravascular central venous catheter placement
- Collagen vascular disease
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögren syndrome
  - Wegener granulomatosis
- Neoplastic
  - Lymphoma/leukemia
  - Mesothelioma
  - Chest wall tumors
  - Metastatic carcinoma
  - Bronchogenic carcinoma
- Renal
  - Uremia
  - Urinary tract obstruction
  - Nephrotic syndrome
  - Peritoneal dialysis
- Miscellaneous
  - Esophageal rupture
  - Hemothorax
  - Chylothorax
  - Lymphedema
  - Hypoalbuminemia
  - Myxedema
  - Sarcoidosis
  - Radiation therapy
  - Immunoblastic lymphadenopathy
  - Familial Mediterranean fever

Contraindications

Thoracentesis has no absolute contraindications. Small fluid accumulations make this procedure difficult and may increase the risk of pneumothorax. Positive pressure ventilation may also increase the risk of pneumothorax. Uncorrected coagulopathy and thrombocytopenia predispose to bleeding complications; however, thoracentesis can generally be accomplished in this setting utilizing a small needle and careful technique. An uncooperative patient can lead to damage to the underlying vascular structures and lung parenchyma. This can be avoided by generous use of sedation and analgesia in pediatric patients.

Preparation

Sedation and analgesia are frequently required to safely perform thoracentesis in pediatric patients. Proper monitoring techniques and medication administration should be utilized in this setting, and are discussed in Chapter 77. Topical local anesthetic agents may reduce the discomfort associated with infiltration of local anesthetics.[138] These agents should be placed at the intended puncture site approximately 15 to 30 minutes prior to the procedure (depending on the agent used) and covered with an occlusive dressing.

Procedure

Box 15-3 lists the supplies and equipment required for thoracentesis.

Technique

If thoracentesis is being performed for evacuation of a pneumothorax, the patient should be placed in the supine position. Aspiration is performed at the second or third intercostal space in the midclavicular line. For the removal of pleural fluid, the patient should, if possible, be place in the upright, seated position. Infants and young children may be held in the burping position by an assistant. The normal site for fluid aspiration is the seventh intercostal space in the posterior axillary line (near the tip of the scapula).

Box 15–3 Supplies and Equipment for Thoracentesis

- Pillows or towels for positioning patient
- Sterile gloves
- Povidone-iodine or chlorhexidine solution
- Commercial thoracentesis tray (for older children and adolescents)
- Or assemble the following items:
  - Sterile gauze sponges
  - Sterile towels or drapes
  - 3- to 5-mL syringe for local anesthetic; 27- to 30-gauge needle for skin infiltration
  - 1% lidocaine; consider sodium bicarbonate to buffer lidocaine
  - Over-the-needle catheter: 14 to 20 gauge depending on the size of the patient
  - 10- or 20-mL syringes for fluid collection
  - Three-way stopcock or tubing extension set with clamp
  - Sterile dressing
  - Tape to secure dressing

The previously placed occlusive dressing should be removed and the site prepped with chlorhexidine and draped with sterile towels. The skin entry site is then generously infiltrated with a local anesthetic using a 27- to 30-gauge needle. The needle is then advanced perpendicular to the skin to infiltrate the underlying subcutaneous tissues, superior portion of the rib, and periosteum. A longer 22- to 25-gauge needle may be needed to accomplish this. The needle is then advanced over the superior border of the rib while applying gentle aspiration until the pleural space is reached. The depth of the needle where fluid aspiration occurs should be noted. An over-the-needle catheter of sufficient length is then used for aspiration of fluid with a syringe. If infection is suspected, a larger catheter (16- to 18-gauge) may be needed.

Aspiration is continued until a sufficient quantity of fluid for diagnostic studies is obtained. A three-way stopcock with attached tubing may be placed on the catheter to facilitate this process. If fluid is being removed for release of respiratory distress, aspiration is continued until fluid flow ceases. The catheter is subsequently removed and a sterile dressing is applied over the entry site.

Complications

The most common complication of thoracentesis is pneumothorax.[137] We recommend that all patients undergoing thoracentesis have a follow-up chest radiograph to evaluate for this possible complication. Hemothorax may occur in patients with abnormal coagulation studies and thrombocytopenia. A platelet count of greater than 50,000 and normal coagulation studies are ideal, but the procedure can be safely performed with careful technique and avoidance of the neurovascular bundle found on the inferior border of the rib. In more urgent settings, platelets and clotting factors may be administered during the procedure. Soft tissue infections can be avoided with use of proper sterile technique. Reexpansion pulmonary edema has been reported in adult patients with removal of large fluid volumes and usually occurs in the first hour following thoracentesis.[139,140] This complication has not been reported in children.

Interpretation

Analysis of pleural fluid is separated into two basic categories: exudates and transudates. The criteria used to distinguish between the two are largely dependent on adult work from 1972 by Light.[141] Box 15-4 lists the Light criteria for differentiating between transudative versus exudative fluid. Elevated triglyceride levels (greater than 110% of serum value) and lymphocyte predominance suggests chylothorax. Elevated amylase suggests pancreatitis or esophageal rupture.[142] Recent advances in polymerase chain reaction (PCR)

Box 15–4 Interpretation of Pleural Fluid

Characteristics of exudative effusions:

- Pleural to serum protein ratio >0.5
- Pleural to serum LDH ratio >0.6
- Pleural fluid LDH more than twice the upper limit of the normal serum value

technology allows for rapid and accurate diagnosis of *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycoplasma* in pleural fluid.[143]

Summary

Thoracentesis is a useful diagnostic procedure for pediatric pleural effusions. It can also be a useful technique for resolution of respiratory distress with significant fluid accumulations and/or pneumothoraces. Thoracentesis is a simple technique that can be performed with high yield and a minimal complication rate.

Tube Thoracostomy

Tube thoracostomy placement is a common procedure in the pediatric critical care setting. Tube drainage of the chest is a therapeutic option employed since the days of Hippocrates. Many options, including less invasive techniques, are now available and are discussed below. Tube thoracostomy is required for a variety of reasons in critically ill pediatric patients. Pneumothoraces can develop spontaneously or as a result of acute lung injury. Large parapneumonic effusions and empyemas resulting from infectious pulmonary processes often require chest tube placement. Hemothoraces or hemopneumothoraces resulting from trauma frequently require drainage. Finally, chylothoraces in postoperative cardiac patients frequently require tube placement and continuous drainage. The technique utilized for placement depends on the nature (thick, thin, transudative, exudative) of the material to be removed.

Contraindications

As with thoracentesis, tube thoracostomy has no absolute contraindications. Attempts should be made to correct coagulopathy to prevent bleeding complications. This can be accomplished via transfusion of serum clotting factors and platelets as needed. However, when emergent or urgent intervention is required, tube thoracostomy should not be delayed to correct coagulopathy.

Supplies and Equipment

Many institutions have specially designed chest tube trays with sterile instruments. Typical requirements include sterile gauze sponges, sterile towels for draping, syringes and needles for local anesthesia, a scalpel and blade, curved Kelly clamps of various sizes, needle driver, suture, and suture scissors. Other materials required are an appropriately sized chest tube, chlorhexidine solution, sterile gloves, a drainage apparatus (such as Pleur-Evac), local anesthetic, and tape.

Technique

Pediatric patients should receive sedation and analgesia for tube thoracostomy placement as for thoracentesis, as described in the previous section. In addition, local anesthesia should be generously used. Up to 0.5 mL/kg of 1% lidocaine (5 mg/kg) or 0.7 mL/kg of 1% lidocaine with epinephrine (7 mg/kg) can be used. The technique for placement depends on the type of material to be removed from the chest. Thin, transudative fluid and pneumothoraces can often be evacuated with placement of a small caliber tube. These tubes, also known as pigtail catheters, range in size from 5 Fr to 9 Fr and are placed via a modified Seldinger technique.[144]

After proper sedation and analgesia, the overlying skin is prepped with chlorhexidine and draped in sterile fashion. A needle attached to a syringe (5 or 10 mL) is inserted in the fourth or fifth intercostal space in the midaxillary line. Continuous suction is applied and the needle is advanced until fluid or air is obtained. A guidewire is then placed through the needle into the pleural space. A small skin incision is made and the overlying skin and subcutaneous tissues are dilated with a skin dilator. A small catheter with multiple side holes is then placed over the wire and advanced into the pleural space. The guidewire is removed and the catheter is attached to a standard chest tube suction device. The tube is anchored to the skin with a suture or a commercially available sutureless skin anchoring device. Placement of pigtail catheters tends to be less painful than traditional tube thoracostomy (described below); however, the viscous fluids encountered with hemothoraces and empyemas generally do not drain well via this technique. Successful treatment of empyema with placement of pigtail catheters and use of fibrinolytic agents (alteplase and streptokinase) has been described.[145]

A variation of this technique allows for placement of larger caliber tubes. After placement of the guidewire as above, progressive skin dilators are used allowing placement of a more standard-sized chest tube. Kits for placement of these over-the-wire devices are commercially available. Caution should be used with placement of these devices in diseases with poor pulmonary compliance and/or pulmonary hyperinflation, as these conditions may predispose to intraparenchymal tube placement and the development of bronchopleural fistulas, which are difficult to treat.[146]

Traditional techniques for tube thoracostomy may be required for drainage of viscous fluids, including cases of empyema and hemothorax. Tube thoracostomy is a painful procedure and requires generous use of sedation and analgesia. Following administration of sedation and analgesia, the patient is placed in the supine position. The skin is prepped with chlorhexidine and draped in sterile fashion. The proper position for placement is the fourth or fifth intercostal space in the midaxillary line. The skin, subcutaneous tissues, intercostal muscles, underlying rib, and periosteum should be generously infiltrated with local anesthetic as described above.

A skin incision in the fourth or fifth intercostal space, large enough to allow placement of the chosen tube, is made parallel to the axis of the rib in the midaxillary line. A curved Kelly clamp is used to bluntly dissect the underlying subcutaneous tissue until the superior border of the upper rib is reached. The clamp is then used to push through and dilate the pleura above the superior border of the rib. In a larger child, the index finger can be used to further dilate the subcutaneous tissues and intercostal muscles. Any intrapleural adhesions can also be manually broken up. The end of the tube is then attached to a clamp and inserted into the pleural space. The clamp is opened and the tube advanced to the proper depth, ensuring all side holes are past the parietal pleura. If possible, the tube should be advanced anteriorly for pneumothoraces and posteriorly for effusions. The tube is then attached to a pleural drainage system.

Many techniques are available for suturing the chest tube in place. The most important aspect of the choice of anchoring method is that the operator removing the tube knows how the tube was secured. Some operators prefer a

horizontal mattress suture on both sides of the tube; others prefer to place a "pursestring suture" that can be pulled together after the tube is removed. If the latter technique is used, no knot is placed at the skin level, but extra suture is wrapped around the body of the tube and then tied to the tube itself. Upon removal, the extra suture serves as skin suture for the wound. Rarely, a suture is inadvertently placed through the tube while the device is anchored. In this event, a technique for cutting the suture using endoscopic scissors has been described.[147] "Needleless" anchoring devices for anchoring tubes without suture (e.g., StatLock Multipurpose, Venetec International, San Diego, Calif.) are commercially available.

Maintenance

Following successful chest tube placement, a chest radiograph should be obtained to verify proper position and to evaluate for resolution of pleural fluid or pneumothorax. Tubes should be evaluated for continued air leak by checking for air bubbles in the leak chamber of the suction apparatus. Ongoing air leak with no evidence of pneumothorax by chest radiograph suggests development of a bronchopleural fistula or airway injury. Some authorities suggest intermittent external negative pressure to "strip" the tube in order to maintain patency, although little evidence supports this practice.[148] Alteplase may also restore patency of tubes clogged by proteinaceous material.[145] Some advocate prophylactic antibiotic use, but little evidence supports this practice.[149]

Timing of tube removal depends on the indication for placement. Tubes placed for pneumothoraces may be removed following resolution of air leak. Our practice is to place these tubes to water seal for at least several hours and obtain a chest radiograph prior to removal. The practice of placing tubes to water seal and evaluating with a chest radiograph is supported in the adult literature.[150] Tubes placed for drainage of pleural fluid may be safely removed once fluid drainage has decrease to 2 to 3 mL/kg over 24 hours. Removal of large tubes may be painful and require analgesia and/or sedation, especially in small children. Tubes may be safely removed during either the inspiratory or expiratory phase.[151]

Complications

Several potential complications exist with placement of chest tubes. Any structure within the thorax may be inadvertently penetrated with use of undue force. For this reason, trocar chest tubes are not recommended for use in children, even in emergent situations. Placement in the lung parenchyma is a relatively common occurrence.[152] This may predispose to development of a bronchopleural fistula. Vascular injury may occur with high placement, and subclavian artery obstruction has been reported as well.[153] Left-sided placement can lead to thoracic duct injury and development of chylothorax. Deep placement may lead to mediastinal perforation.[154] Computed tomography may be used to evaluate the exact placement of chest tubes in cases where inadvertent misplacement or complications are suspected.

Summary

Tube thoracostomy is a common procedure in pediatric critical care. With attention to detail, this procedure may be accomplished safely and with minimal risk. New techniques and smaller caliber tubes may be utilized in select cases. Fibrinolytic agents such as alteplase may be used to restore patency of clogged tubes and may be of therapeutic benefit in cases of empyema.

Paracentesis

Paracentesis is the percutaneous sampling of peritoneal fluid by needle aspiration through the abdominal wall. It is a relatively safe procedure and is useful as a diagnostic tool in the evaluation of patients with ascites. Analysis of ascitic fluid, combined with history and physical examination, frequently confirm the cause of ascites. Paracentesis may also be used for the relief of respiratory distress secondary to massive ascites-induced abdominal distention.

Indications

Paracentesis is indicated in any patient with new-onset ascites, patients with chronic ascites and clinical deterioration, and cases of suspected bacterial peritonitis.[155] Paracentesis with placement of an indwelling catheter and ongoing fluid drainage has been used in the management of abdominal compartment syndrome.[156]

Contraindications

Paracentesis in patients with ascites has no absolute contraindications. Coagulopathy is not a contraindication to paracentesis, although caution should be used in patients with moderate-to-severe coagulopathies.[157-159] Some data suggest that prophylactic transfusion of fresh-frozen plasma, platelets, or other clotting factors prior to paracentesis in patients with coagulopathy is not necessary.[160,161]

To reduce the chance of introducing bacteria into the peritoneal cavity, paracentesis should not be performed through an area of cellulitis.

Procedure

The presence of ascites must be confirmed prior to paracentesis. While the physical examination findings of flank dullness, shifting dullness, and fluid waves support the presence of ascites, in most circumstances ultrasonography should be performed to confirm ascites prior to paracentesis. Ultrasonography is more sensitive than physical examination in diagnosing ascites, can detect small amounts of fluid, and can differentiate free from loculated fluid.[162] Ultrasound guidance may improve the safety and efficacy of paracentesis.[163,164]

Supplies

Box 15-5 lists the supplies required for diagnostic paracentesis.

Technique

For most critically ill patients, the patient is positioned in semisupine (trunk flexed at the hips and upper torso elevated 30 to 45 degrees) or lateral decubitus position.[158,165] The bladder should be emptied by voiding or catheterization. The

site of needle insertion is selected by physical examination or ultrasound location of ascitic fluid, with the preferred site being in the midline, 2 cm below the umbilicus, in the area of the avascular linea alba. In patients with portal hypertension, the linea alba may become vascularized, so a lateral approach may be preferred to reduce the chance of hemorrhagic complications.[166] A lateral approach can be used in the right or left lower quadrant a few centimeters above the inguinal ligament and lateral to the rectus abdominus muscle.[165] Puncture sites in the area of surgical scars should be avoided due to the risk of underlying bowel adhesions.

The entry site is prepared with antiseptic solution such as chlorhexidine or povidone iodine and is draped in sterile fashion. The skin and peritoneum is infiltrated with lidocaine using a small-gauge needle. After attaching a syringe to a needle or catheter appropriate for the patient's age, the needle is inserted through the site of infiltration while traction is applied to the skin in a caudal direction. Use of this Z-track method of insertion is recommended to prevent a direct linear needle track, which could result in a fluid leak after the procedure is completed. The needle is advanced slowly, using negative pressure on the syringe, until a "pop" is felt as the needle passes through the peritoneum and free flow of fluid into the syringe is noted. A spinal needle, if used, can be secured in place with a free hand or hemostat. An over-the-needle catheter, if used, is advanced into the peritoneal cavity, the needle is removed, and the syringe is replaced. Approximately 20 to 40 mL of fluid is collected for diagnostic evaluation. If fluid return stops or is sluggish, changing the patient's position may be helpful. Following removal of the needle or catheter, direct pressure is applied to the insertion site and then a sterile pressure dressing is applied. When ongoing drainage is needed, a pigtail catheter can be placed using Seldinger technique.

Box 15–5 Supplies for Diagnostic Paracentesis

- Antiseptic solution
- Alcohol preps
- Sterile gauze
- Sterile drapes
- Sterile gloves
- 1% lidocaine with or without epinephrine
- 3- to 10-mL syringe with small-gauge needle for local anesthesia
- 22- to 16-gauge spinal needle or intravenous catheter (22- to 20-gauge needle for small children, 16- to 20-gauge needle for larger children)
- 20-mL (or larger) syringe
- Specimen vials

Complications

Potential complications of paracentesis are few but may include persistent leakage of ascitic fluid, bladder or intestinal perforation, introduction of infection with resultant peritonitis, subcutaneous abdominal wall hematoma, and bleeding.[165,171] Persistent leakage of ascitic fluid can be minimized by using the Z-track method for needle insertion. Ongoing fluid leaks can be managed by closing the defect with a suture or applying cyanoacrylate skin adhesive.[167] Bladder emptying decreases the risk of bladder perforation.[166] The risk of intestinal perforation with subsequent complications is minimal, but is increased in patients with previous abdominal surgical procedures and adhesions. This risk can be minimized by avoiding abdominal surgical scars as the needle insertion site.[168,169] The risk of intestinal perforation can be increased if the bowel is markedly distended (as in bowel obstruction), so in these cases, decompression should be considered prior to paracentesis. Appropriate selection of the needle insertion site

Table 15–2 Characteristics of Ascitic Fluid in Various Conditions

Condition	Clinical Characteristics	Laboratory Findings
Portal hypertension	Straw colored, sterile	Total protein <2.5–3 g/dL WBC <250–500, <1/3 neutrophils
Spontaneous bacterial peritonitis	Cloudy or turbid Gram stain positive <10%, cultures may be negative, single organism*	Neutrophils >250 Total protein <1 g/dL LDH and glucose similar to serum
Secondary bacterial peritonitis	Multiple organisms	Total protein >1 g/dL
Chylous ascites	Milky with recent fat ingestion	WBC 1000–5000, predominately lymphocytes Triglycerides >200 mg/dL, cholesterol >48 mg/dL†
Pancreatic ascites	Turbid, brown or bloody	WBC and total protein increased Amylase and lipase levels > serum Amylase levels may be falsely low in young infants‡
Urinary ascites		Protein <1 g/dL; creatinine >serum§
Malignant ascites	Bloody	Protein and LDH elevated
Nephrotic syndrome	Straw colored	Total protein <2.5 g/dL‡
Tuberculous ascites	Yellow or bloody, may have fibrin clots	Total protein >2.5 g/dL WBC >1000, primarily lymphocytes PCR useful¶

*Kandel G, Diamant NE: A clinical view of recent advances in ascites, *J Clin Gastroenterol* 8(1):85–99, 1986.
†McGibbon A et al: An evidence-based manual for abdominal paracentesis, *Dig Dis Sci* 52(12):3307–3315, 2007.
‡Glauser JM: Paracentesis. In Roberts JR, Hedges JR, editors: *Clinical procedures in emergency medicine,* Philadelphia, 1991, WB Saunders.
§Runyon BA: Care of patients with ascites, *N Engl J Med* 330(5):337–342, 1994.
¶Uzunkoy A, Harma M: Diagnosis of abdominal tuberculosis: experience from 11 cases and review of the literature, *World J Gastroenterol* 10(24):3647–3649, 2004.

minimizes the risk of bleeding. Visible collateral venous channels on the abdominal wall should be avoided. Strict adherence to sterile technique and avoidance of areas of skin or soft tissue infection decrease the risk of infection. Scrotal edema from fluid dissection through fascial planes following paracentesis has been described, typically in patients with massive ascites.

Interpretation

Analysis of ascitic fluid may not yield a definitive diagnosis but is useful in the evaluation of ascites. Clinical assessment identifies the most likely diagnosis, helps determine which tests which should be ordered, and influences the interpretation of results.[155,170]

Studies that should be obtained include total protein, glucose, albumin, LDH, cell count with differential, Gram stain, and aerobic and anaerobic cultures. Other studies to consider are pH, amylase, triglycerides, bilirubin, creatinine, electrolytes, cytology, and cultures and stains for tuberculosis. Corresponding serum chemistries should be obtained for comparison.

Gram stain should be performed on the cell pellet generated from centrifuged fluid.[155] These measures increase the likelihood of recovering or identifying organisms from infected fluid.

Analysis of the serum-ascites albumin gradient (SA gradient) is useful for differentiating between ascites caused by portal hypertension and ascites resulting from other causes. The SA gradient is calculated by subtracting the albumin concentration of the ascitic fluid from the albumin concentration of the serum. An SA gradient of 1.1 g/dL or higher correlates with portal hypertension with 97% accuracy.[155]

The characteristics of ascitic fluid in various conditions are shown in Table 15-2.

Summary

Needle aspiration of ascitic fluid is a relatively safe procedure when performed with appropriate precautionary measures. Analysis of ascitic fluid obtained by paracentesis is useful in the evaluation of patients with new-onset ascites, chronic ascites with clinical deterioration, or suspected bacterial peritonitis. Ongoing drainage through a catheter placed at the time of paracentesis may improve ventilation in patients with massive ascites or reduce complications secondary to intrabdominal compartment syndrome.

References are available online at http://www.expertconsult.com.

Chapter 16

Pediatric Intensive Care in Developing Countries

Frank Shann, Andrew C. Argent, and Suchitra Ranjit

PEARLS

- In the world's 66 high-income countries, the total annual expenditure on health averaged U.S. $4033 per capita in 2006, which was 175 times the $23 per capita available in the 43 low-income countries.
- Overseas development aid from members of the Organisation of Economic Co-operation and Development amounted to only 0.30% of their gross national income in 2007, which was well short of the United Nations' target of 0.70%.
- More than 98% of all child deaths occurred in developing countries in 2007, and 8.4 million of the 9.2 million deaths in children younger than 5 years were preventable.
- Pneumonia is the most common cause of death in children. It causes approximately one third of all deaths in children younger than 5 years.
- Gastroenteritis is the second most common cause of child mortality. It causes approximately 2 million child deaths every year.
- The diagnosis of tuberculosis may be difficult in children because of the paucity of organisms in sputum and other body fluids. Often treatment for tuberculosis must be started without bacteriologic confirmation of the diagnosis.
- Malnutrition contributes to 56% of child deaths, and 83% of this effect is associated with mild to moderate rather than severe malnutrition.
- When treating severe malnutrition, sodium and water intake should be limited, protein intake should be restricted initially, intravenous administration of albumin should be avoided, and calorie intake should be increased gradually.
- Ideally, every child in the world should have access to an intensive care unit with facilities for endotracheal intubation and mechanical ventilation. No ethical justification exists for providing these treatments to children in rich countries while denying them to children in poor countries.
- Providing intensive care is not in the interests of a child if the prognosis is very poor because such care simply prolongs suffering, and it is not in the interests of health services if such care results in poor utilization of limited resources. If the mortality rate in an intensive care unit is greater than 10%, patient selection probably is inappropriate.
- When mortality in children younger than 5 years is greater than 30 per 1000, many deaths are caused by infections. A high proportion of these deaths can be prevented by immunization and primary health care, which are far less expensive than intensive care.

In the year 2007, 136 million children were born in the world. Of these children, 9.2 million died before age 5 years, with 98% of the deaths occurring in developing countries.[1] If the entire world had an mortality rate for children younger than 5 years equal to that of the developed world, only 0.8 million deaths would occur in this age group each year.[1] Therefore, of the 9.2 million deaths in children younger than 5 years that occur each year, 8.4 million are preventable.

Why Lower Child Mortality Rates?

If too many people already exist in the world, is it sensible to try to reduce child mortality rates? First, this question is always asked about other people's children. Second, reducing child mortality rates is important both for humanitarian reasons and to enable lower birth rates.[2] Governments of poor countries are not able to provide old-age or sickness benefits, so having children who survive to adulthood is crucially important to provide security. To increase their chances of having their children survive when mortality rates are high, people need to have many children. A vicious circle is created because high birth rates perpetuate poverty so that governments cannot provide social security, people need children who survive to adulthood, and birth rates remain high. Therefore reducing child mortality rates is a necessary (but not sufficient) condition for reducing birth rates and slowing the growth of the world's population.[2]

Expenditure on Health

In 2006, 1.3 billion people lived in the world's 43 poorest countries (with an annual gross national income of less than U.S. $976 per capita), with an average total annual expenditure on health of only U.S. $23 per capita.[3] In the world's 66 high-income countries, annual expenditure on health averaged U.S.

$4033 per capita, which is 175 times the amount available in low-income countries.

Child Mortality, Infections, and Intensive Care

Most of the unnecessary child deaths in developing countries are caused by infectious diseases, and most of these deaths can be prevented by immunization and basic primary health care. Figure 16-1 shows the relationship between the mortality rate among children younger than 5 years and the percentage of deaths caused by infection.[4] When the mortality rate among children younger than 5 years is less than 20 per 1000 live births, few deaths are caused by infections, and intensive care can make an important contribution to reduce mortality from noninfectious causes such as congenital heart disease and trauma. As the mortality rate among those younger than 5 years increases from 20 to 30 per 1000, the proportion of deaths caused by infections increases rapidly, and the role of intensive care becomes less clear. When the mortality rate among children younger than 5 years is greater than 30 per 1000, many deaths are caused by infections, and a high proportion of these deaths can be prevented by immunization and primary health care, which are far less expensive than intensive care.

Role of Intensive Care

Optimal use must be made of the limited resources available to treat critically ill children in developing countries. Many lives can be saved with effective use of relatively inexpensive therapies, such as intravenous (IV) fluids, oxygen, antibiotics, thermal control, and good nutrition. However, if we define intensive care as endotracheal intubation with the capacity for mechanical ventilation, publicly funded pediatric intensive care probably has little place in communities with a mortality rate among children younger than 5 years that is greater than 30 per 1000 live births. In the rapidly increasing number of communities with intermediate mortality rates among children younger than 5 years of approximately 20 to 30 per 1000, there is a place for the use of either continuous positive airway pressure (CPAP) or intubation and ventilation for carefully selected patients using basic equipment. When resources are limited, admitting only children who have a good chance of long-term survival is important. If the mortality rate among patients in the intensive care unit (ICU) is greater than 10%, patient selection probably is inappropriate.

The main argument in favor of providing endotracheal intubation and ventilation to children in developing countries is that every child in the world should have access to these therapies. No ethical justification exists for providing intensive care to children in developed countries while denying it to children in poor countries. In addition, educated families in developing countries reasonably demand that their children have access to intensive care.

The main argument against providing intensive care in areas with a high mortality rate is that intensive care diverts scarce resources away from far more effective low-cost interventions such as immunization and primary health care. Skilled staff, in particular, are in short supply in many developing countries; if they are used to provide curative services in urban hospitals, the rural poor are at grave risk of being neglected. Strong arguments exist for providing basic public and primary health care to all children rather than intensive care to a small proportion of children.[5] In addition, intubation and ventilation are difficult to do well. Done poorly, they may actually increase the incidence of mortality. For example, a study in six pediatric ICUs in Mexico and Ecuador found that endotracheal intubation and central venous cannulation were associated with an increased incidence of mortality in low-risk admissions.[6]

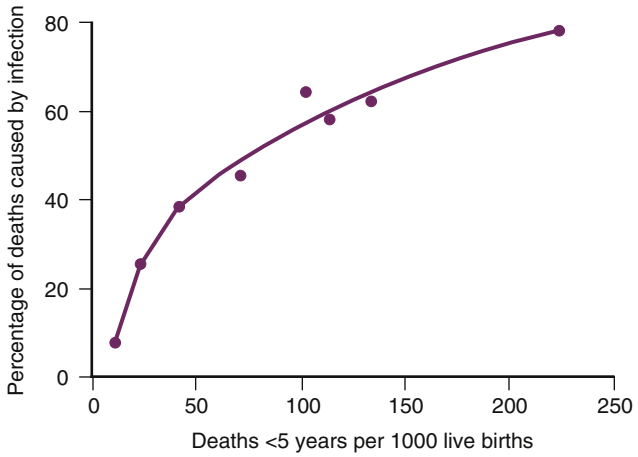

Figure 16–1. Mortality rates in children younger than 5 years and percentage of deaths caused by infection throughout the world. *Data from Murray CJL, Lopez AD:* Global comparative assessments in the health sector: disease burden, expenditures and intervention packages, *Geneva, 1994, World Health Organization.*

Ethical Dilemma

An ethical dilemma exists: children in rich countries have access to intensive care, whereas in poor countries, we can either deny intensive care to children (and perhaps increase the probability that they will be immunized and receive primary health care) or provide intensive care (often at the expense of immunization and primary health care).

This dilemma cannot be resolved while extreme poverty persists in developing countries. Unfortunately, rich countries are doing even less to help now than in the past. Overseas development aid from members of the Organisation of Economic Co-operation and Development amounted to only 0.30% of their gross domestic product in 2007, which was well short of the United Nations' target of 0.70%.[7] Even worse, Organisation of Economic Co-operation and Development member countries now spend more than U.S. $1 billion every day on agricultural subsidies, which is more than six times the amount given in aid and seriously undermines primary producers in developing countries. If developing countries could increase their export share by just 5%, it would generate U.S. $350 billion per year, which is seven times more than the total amount they receive in aid.[8,9]

Causes of Death

More than 98% of all child deaths occur in developing countries, and 8.4 million of the 9.2 million deaths in children younger than 5 years are preventable.[1] Table 16-1 shows that

Table 16–1 Causes of Death in Children Younger than 5 Years in 2005

Cause	No. of Deaths (in Millions)
Pneumonia	2.0
Diarrhea	1.8
Prematurity	1.1
Neonatal sepsis	1.0
Birth asphyxia	0.9
Malaria	0.9
Measles	0.4
Human immunodeficiency virus	0.3
Congenital abnormalities	0.3
Pertussis	0.3
Neonatal tetanus	0.3
Other	1.3
Total	10.6

Data from World Health Organization: *The World Health Report 2005: make every mother and child count,* Geneva, 2005, World Health Organization.

Table 16–2 Approximate Annual Number of Deaths in Children Younger than 5 Years Caused by Individual Pathogens in 1999

Pathogen	No. of Deaths (in Millions)
Pneumococcus	1.2
Measles	1.1
Haemophilus (a, b, c, d, e, f, nonserotypable)	0.9
Rotavirus	0.8
Malaria	0.7
Human immunodeficiency virus	0.5
Respiratory syncytial virus	0.5
Pertussis	0.4
Tetanus	0.4
Tuberculosis	0.1
Hepatitis B	<0.1
Influenza virus	<0.1
Meningococcus	<0.1
Parainfluenza virus	<0.1
Varicella	<0.1
Total	6.7

Data from Shann F, Steinhoff MC: Vaccines for children in rich and poor countries, *Lancet* 354(suppl ii):7, 1999.

most of the deaths are caused by infectious diseases, particularly pneumonia, diarrhea, neonatal sepsis, and malaria, with malnutrition an important contributing factor.[10,11] Table 16-2 shows that the major pathogens are *Streptococcus pneumoniae*, measles, *Haemophilus influenzae*, rotavirus, malaria, human immunodeficiency virus (HIV), and respiratory syncytial virus.[12] The following sections of this chapter discuss individual diseases that are common causes of mortality in children in developing countries, starting with the diseases that cause the most deaths (see Table 16-1). On rare occasions, children with these diseases require intensive care in developed countries. The suggested treatments assume that the child is in a hospital that can deliver a high standard of intensive care. Other hospitals should follow the World Health Organization (WHO) guidelines for the care of children in developing countries.[13-16]

Pneumonia

Pneumonia is the most common cause of death in children. It is the direct cause of 2.0 million deaths each year in children younger than 5 years. It also contributes to mortality from neonatal sepsis, measles, pertussis, and HIV, so pneumonia is an important contributory factor in approximately one third of all deaths in children younger than 5 years.[17,18] A total of 156 million episodes of acute lower respiratory tract infection occur in children each year, 11 to 20 million of which are severe enough to require hospital admission.[17]

Fatal pneumonia in children usually is caused by *S. pneumoniae* or *H. influenzae*. The etiology of pneumonia can be determined accurately only by culture of lung aspirates from children with no antibiotic activity detectable in serum or urine.[19] Most cases of pneumonia in children are caused by aspiration of bacteria from the nasopharynx, and mixed infections with *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis* are common.[20] *H. influenzae* pneumonia often is caused by nonserotypable strains, as well as by type b and the other serotypes (a, c, d, e, f).[21]

For children who do not respond to penicillin and gentamicin, one should consider differential diagnoses of staphylococcal pneumonia (for which cloxacillin and gentamicin should be administered), HIV infection (often with pneumocystis), chlamydia or mycoplasma (for which azithromycin should be administered), and tuberculosis (see the section in this chapter on tuberculosis).

Antibiotic Treatment

Children with pneumonia who are sick enough to require hospitalization usually should be treated with benzyl penicillin, and they should be treated with benzyl penicillin plus gentamicin if they have very severe pneumonia.[15] The combination of benzyl penicillin and gentamicin has synergistic activity against many strains of *S. pneumoniae* and is always active against *H. influenzae*. Penicillin resistance is *not* an indication for the use of third-generation cephalosporins to treat pneumococcal pneumonia, because they are no more effective than penicillin alone,[22] let alone penicillin plus gentamicin. However, if meningitis caused by a partially resistant strain is present, vancomycin or a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone) should be used if available.

Staphylococcal pneumonia is suggested by a poor response to penicillin and gentamicin, pneumatoceles, pneumothorax, empyema, or associated soft tissue or joint infection. Cloxacillin (or oxacillin, flucloxacillin, or dicloxacillin) and gentamicin given intravenously are appropriate treatments.

Oxygen and Ventilation

Oxygen therapy may be lifesaving in patients with severe pneumonia.[23,24] The most efficient means of administration is 1 to 2 L/min of humidified oxygen via an 8F nasopharyngeal catheter inserted 2 cm less than the distance from the side of the nose to the front of the ear. As well as providing oxygen, this method delivers low levels of CPAP.[25] Care should be taken to (1) remove and clean the catheter every 12 hours, (2) verify that the catheter is not inserted too far (to avoid delivering oxygen into the esophagus), and (3) limit the flow to a maximum of 2 L/min (to avoid distending the stomach). A special low-flow oxygen flow meter with a scale of 0 to 2 or 0 to 3 L/min should be used.

If mechanical ventilation is not available, oxygenation and ventilation can be improved using mask or nasopharyngeal CPAP up to 12 cm H_2O pressure. If endotracheal intubation and mechanical ventilation are available, a sensible plan is to start with low tidal volumes of 6 to 8 mL/kg, positive end-expiratory pressure 8 to 10 cm, inspiratory time 1 second with a rate of 20 to 30 per minute in an infant (assuming no bronchiolitis or asthma is present), and peak pressure less than 30 cm to minimize ventilator-associated lung injury (see Chapters 49 and 50). Failure of the right ventricle may occur as a result of pulmonary hypertension[26]; in this situation, nitric oxide, 5 to 10 ppm (or sildenafil) and high-frequency oscillatory ventilation may be helpful if available.

Fluid Therapy

Patients with pneumonia often exhibit increased secretion of antidiuretic hormone (syndrome of inappropriate antidiuretic hormone secretion),[27,28] and thus children with pneumonia should not be given too much fluid. Hyponatremia usually is caused by excess water rather than sodium deficiency and should be treated by fluid restriction rather than administration of hypertonic saline solution. A small proportion of children with pneumonia have septic shock with capillary leak and hypovolemia, which may be exacerbated by positive pressure ventilation (causing severe hypoperfusion). A helpful procedure in children with this condition may be to insert a central venous catheter and give 10 mL/kg boluses of 4% to 5% albumin or 0.9% saline solution to achieve a central venous pressure of 10 to 12 mm Hg (see Chapters 29 and 103). In the absence of extensive skill and experience, femoral venous catheters are probably the safest to use. Large amounts of fluid initially may be needed to restore the intravascular volume, but thereafter fluid requirements often are only 30% to 40% of normal because the child may have high antidiuretic hormone concentrations.

Feeding

The blood glucose level should be monitored closely and the glucose infusion rate should be adjusted to prevent hypoglycemia. If necessary, 50% dextrose can be infused via the central venous catheter. Continuous small nasogastric feedings should be started from the time of admission as long as no cardiovascular compromise is evident. Full enteral feedings usually can be achieved within 24 to 48 hours. If gastric feedings are not tolerated, nasojejunal feedings may be successful if a nasojejunal tube can be placed (see Chapter 75).

Gastroenteritis

Gastroenteritis is the second most common cause of child mortality. It causes 2 million child deaths every year (see Table 16-1). Particular problems include shock, acid-base abnormalities, electrolyte abnormalities, and secondary bacterial infection.[29] Diarrhea may be a symptom of other disease processes, including sepsis and metabolic abnormalities, so it should not be assumed to be caused by gastroenteritis.

The consequences of fluid loss depend on the rate and the amount of loss. In gastroenteritis, fluid moves from the intravascular space into the gut lumen. Depending on the relative rates of fluid loss and fluid replacement from the extracellular fluid space, patients may be in shock with no clinical signs of dehydration, dehydrated with no features of shock, or dehydrated and in shock. Clinical signs of dehydration occur when approximately 30 to 40 mL/kg of fluid is lost from the body (i.e., 3% to 4% dehydration).[30]

Hypovolemic shock requires immediate and vigorous replacement with isotonic IV fluids. Dehydration can be corrected over 2 or 3 days and usually can be adequately treated with oral ingestion of fluids. The management of dehydration is complicated by the relative inaccuracy of the clinical signs of dehydration (particularly in malnourished or obese children)[30] and by the variable amount of ongoing stool losses (see Chapter 29). During rehydration, the serum sodium concentration should be measured every 4 hours and the rate of fluid and sodium administration adjusted accordingly.

Shock

Shock in patients with gastroenteritis usually is caused by hypovolemia resulting from fluid loss. However, there is a high incidence of bacterial sepsis in patients with severe gastroenteritis. The initial therapy for shock should include provision of oxygen and rapid IV administration of fluid with an electrolyte content similar to plasma (e.g., 0.9% sodium chloride). Shock should be corrected rapidly over 10 to 15 minutes with continuous or frequent assessment of the response. Intraosseous or sagittal sinus vascular access may be required if venous access is difficult.[31] Additional aliquots of fluid should be given under close observation until the patient is normovolemic. Once the patient is normovolemic, inotropic support will be required if the patient still exhibits symptoms of shock. Patients who are hypovolemic from gastroenteritis do not require colloid as volume replacement.

Fluid and Electrolyte Abnormalities

Once intravascular volume has been restored, attention should be paid to the management of the sodium derangements and dehydration (see Chapter 67). Normal hydration should be achieved over 48 to 72 hours. If renal function is normal, the kidneys will resolve most of the electrolyte abnormalities given adequate treatment of shock and gradual replacement of fluid and electrolyte deficits.

Calculation of fluid therapy is more difficult in the presence of ongoing diarrhea, which may amount to 300 mL/kg in 24 hours. Fluid therapy is best monitored using a combination of serial weighing (if accurate scales are available) and electrolyte measurement. If any doubt exists about urine output, a urinary catheter should be inserted to help distinguish between

renal losses and diarrhea. A "metabolic bed" may be used so that stool and urine output can be measured separately. Oliguric renal failure is common, but polyuric renal failure also may occur, particularly in children with severe hypokalemia or hyperglycemia.

Sodium Abnormalities. Hypernatremia may result from excessive water loss, excessive salt intake (usually in poorly constituted rehydration solutions), or a combination of both. It is associated with significant morbidity (especially of the central nervous system) and mortality. Hypernatremia is more common in infancy than in later life and may be associated with the use of formula to feed infants.[3]

Once shock has been treated, the goal of therapy is to reduce the sodium concentration no faster than 0.5 mEq/L/h.[32] Once hypovolemia has been corrected, the remaining fluid deficit should be replaced over 48 to 72 hours using a solution containing approximately 70 mEq/L of sodium.

Hyponatremia may be related to errors of measurement, excessive fluid intake, or excessive sodium loss. Pseudohyponatremia occasionally is seen secondary to hyperlipidemia. Factitious hyponatremia is seen in the context of hyperglycemia or mannitol infusions; measured sodium levels decrease by approximately 1.6 mEq/L for every 100 mg/dL (approximately 5.5 mmol/L) increase in glucose concentration. This factor must be taken into account when calculating fluid management. Severe symptomatic hyponatremia should be treated by giving 4 mL/kg of 3% saline solution intravenously over 2 hours, but the serum sodium concentration should rise by no more than 8 mEq/L on any day of treatment. This rate is ideally monitored with measurement of sodium levels every 2 to 4 hours.

Hypokalemia. Hypokalemia is common in patients with severe gastroenteritis, particularly if rehydration solutions without potassium are used. In the face of bradycardia secondary to severe hypokalemia that is causing poor cardiac output, rapid replacement of potassium may be required to establish a heart rate that is appropriate to the circulatory status of the child. In all other situations, IV potassium supplementation should not exceed 0.5 mEq/kg/h. If polyuria occurs, a safe approach is to provide maintenance fluids and replace urinary losses greater than 2 mL/kg/h with fluid that has an electrolyte content similar to that of the urine.

Hypophosphatemia. Hypophosphatemia is common in patients with severe gastroenteritis and should be treated with IV potassium or sodium phosphate if the child exhibits symptoms. Joules' solution can be provided enterally but may exacerbate diarrhea. Phosphate concentrations less than 0.3 mEq/L usually are associated with severe symptoms and should be treated, but phosphate supplementation is not required with concentrations greater than 0.6 mEq/L unless the child has other associated symptoms.

Metabolic Acidosis. Metabolic acidosis is common in children admitted to the ICU with gastroenteritis. It may be related to hypoperfusion (usually with elevated serum lactate), renal dysfunction with renal tubular acidosis, or ingestion of medication (e.g., salicylates or toxins from traditional remedies). If acidosis persists despite correction of hypovolemia, consider measuring serum lactate and urine ketone levels, excluding the ingestion of toxins such as salicylates and iron, and screening for metabolic disease. Inborn errors of metabolism may be manifested following the stress of an illness such as acute gastroenteritis.

If acidosis is related to excessive loss of bicarbonate via stool or urine, bicarbonate administration may be appropriate. To reduce the risk of sodium overload, a solution of 5% dextrose containing 50 to 70 mEq/L of sodium bicarbonate should be used, with potassium added according to requirements.

Low Birth Weight

Babies born weighing less than 2500 g are said to have a low birth weight. Approximately 1 million low-birth-weight infants die each year (see Table 16-1 and Chapter 46). Small-for-gestational-age births are relatively more common in developing countries than in developed countries. The decision about whether a low-birth-weight baby should be considered premature, small for gestational age, or both is important. Problems associated with prematurity (i.e., babies younger than 37 weeks of gestation) include respiratory distress syndrome, apnea, poor feeding, intraventricular hemorrhage, jaundice, infection, and hypothermia. Problems associated with infants who have a small-for-gestational-age status are intrauterine hypoxia, birth asphyxia, meconium aspiration, hypoglycemia, and infection.

Only the general principles of management of low-birth-weight infants are outlined in this chapter; more detailed information is available elsewhere.[14,33] Vitamin K (1 mg) is administered intramuscularly after birth. The baby should be kept warm (i.e., well wrapped up in a room kept at 27° to 30°C, which is crucially important) and handled as little as possible. Apnea monitors should be used for babies younger than 32 weeks of gestation, and caffeine or aminophylline should be provided if apnea occurs. Cultures are obtained and penicillin and gentamicin administered if there are any signs of infection, including respiratory distress. Use of breast milk and strict handwashing procedures help prevent cross-infection in the nursery. Desaturation can be treated with nasopharyngeal CPAP. Intubation and mechanical ventilation may be helpful if facilities are available, but nasal CPAP is much safer and often is just as effective.[34,35]

Kangaroo care is defined as skin-to-skin contact between the mother and baby with frequent and exclusive or nearly exclusive breastfeeding and early discharge from hospital. Many of the controlled trials of kangaroo care are of poor quality. A Cochrane Review concluded that kangaroo care appears to reduce morbidity, but more well-designed trials are needed.[36]

Breastfeeding on demand is preferred if the baby is active and sucks well. If the baby does not feed well, feeding him or her expressed breast milk with a cup and spoon (not a bottle) is appropriate. If the baby is too weak to feed with a cup and spoon, nasogastric tube feedings are indicated. Close attention to serum glucose is warranted with IV and/or enteral glucose administration as needed to provide 5 to 10 mg/kg/min.

Poliomyelitis, bacille Calmette-Guérin (BCG), and hepatitis B vaccines should be administered before discharge at a time when the baby is fully breast-fed and gaining weight. The mother should be given a solution of ferrous sulfate to give to her child at a dose of 2 mg/kg/day of elemental iron, and follow-up should be scheduled.

Neonatal Asphyxia

Approximately 900,000 infants die every year from asphyxia (Table 16-1).[10,37] This condition may be caused by an hypoxic-ischemic insult during labor or by fetal abnormalities that were present before labor. Asphyxia is more common in small-for-gestational-age babies and carries a grave prognosis in preterm babies. Even if improvement occurs during the first few hours after delivery, the baby should be observed closely for at least 24 hours because rapid deterioration may occur at 6 to 24 hours as cerebral edema develops.

Oxygen should be provided as required to maintain an oxygen saturation greater than 90%. Intubation and mechanical ventilation should be used in the event of airway or breathing compromise and should not be discontinued too early because deterioration may occur 6 to 24 hours after delivery.

Poor cardiac output is common in patients with severe asphyxia because of hypovolemia from capillary leakage and impaired myocardial contractility. Echocardiography may help distinguish among hypovolemia (small left atrium), poor ventricular contractility, and pulmonary hypertension (which should be treated with nitric oxide, if available). After correction of hypovolemia, the total fluid intake initially should be limited to 30 to 40 mL/kg/day.

The baby's temperature should be kept below 37° C. Controlled trials suggest that mild hypothermia with a core temperature of 32° to 33° C is beneficial.[38-40] The blood glucose should be kept in the normal range.

Close surveillance should be undertaken for neonatal sepsis, which can be manifested as asphyxia. Treatment with penicillin and gentamicin is appropriate, and cefotaxime or ceftriaxone should be added if evidence of meningitis is present. Convulsions should be treated with phenobarbital, 20 mg/kg, administered intravenously over 60 minutes. One small study reported that administration of 40 mg/kg of IV phenobarbital to all babies with asphyxia was beneficial,[41] but this treatment may cause dangerous levels of sedation unless ventilation is performed.

Hypocalcemia is treated with IV 10% calcium gluconate, 0.5 mL/kg, over 10 minutes. Corticosteroids are not indicated. Coagulopathy should be treated with fresh-frozen plasma, if available. Vitamin K should be given to all babies. Paralytic ileus and necrotizing enterocolitis are common after severe asphyxia; accordingly, enteral feeds should not be started until bowel sounds are present and the baby passes meconium. Renal failure and hyperkalemia may require treatment with glucose and insulin, an ion-exchange resin enema, or peritoneal dialysis. Babies who do not start to breathe within 48 hours rarely make a good recovery. It is important not to continue treatment if there is no realistic chance of intact survival.

Malaria

Severe malaria is caused by *Plasmodium falciparum*, which is the only species of malaria that causes parasitized erythrocytes to adhere to endothelial cells and produce microvascular disease. At any one time, more than 1 billion people are infected with malaria, and the disease causes 0.9 million deaths each year.[10,42]

Malaria starts with fever, and the patient may exhibit coughing and vomiting. Especially in nonimmune patients, the illness may progress very rapidly over 1 to 2 days, with coma (cerebral malaria), shock, convulsions, anemia, hypovolemia, hypoglycemia, jaundice, respiratory distress, renal failure, and coagulopathy being exhibited.

Diagnosis

The diagnosis is made by examination of thick and thin blood smears (false-negative results may occur with inexperienced staff) or by detection of *P. falciparum* antigen using enzyme-linked immunosorbent assay, polymerase chain reaction (PCR), or immunoassay for parasite lactate dehydrogenase. Commercially available rapid blood tests use a dipstick or test strip with monoclonal antibodies directed against a parasite antigen.[42] They have a sensitivity and specificity greater than 90% for *P. falciparum*.

Severe malaria is present if the patient has severe anemia (hemoglobin <6 g/dL) or hypoglycemia (blood glucose <2.5 mmol/L). In nonimmune patients, severe malaria is present if there is hyperparasitemia (>250,000 parasites/μL or >5% parasitemia), but partially immune patients may have more than 5% parasitized erythrocytes without evidence of clinical illness.

Initial Treatment

Patients exhibiting coma or shock should be intubated and undergo ventilation. Insertion of a femoral venous cannula to allow monitoring of central venous pressure and infusion of drugs should be considered. Hypovolemia should be corrected with 10 mL/kg boluses of 0.9% saline solution; if it is available, 4% to 5% albumin may be preferable to saline solution.[43] If poor perfusion persists despite an adequate central venous pressure, echocardiography may aid in assessing intravascular volume and ventricular contractility (see Chapter 23). Hypoglycemia is common in small children, and their blood glucose concentration should be monitored closely. Convulsions are treated with IV phenobarbital, 20 mg/kg administered over 1 hour, then 5 mg/kg daily.

Routine use of phenobarbital may increase the incidence of mortality in patients who do not undergo ventilation but likely does not do so in patients who do undergo ventilation.[44] Administration of pentoxifylline, N-acetylcysteine, and mannitol probably is not helpful, but use of levamisole may be beneficial.[45]

Antimalarial Drugs

The choice of antimalarial drug depends on which drugs are available and on local drug resistance patterns. The best choice usually is either quinine or artesunate. Evidence suggests that artesunate clears parasites faster than quinine does and increases survival rates,[46] but resistance has been reported recently in Southeast Asia.[47] Patients with severe malaria are infected by a large number of parasites and should always be treated with two antimalarial drugs to reduce the risk of selecting resistant strains with recrudescence of disease.[48]

Artesunate is given in an initial IM or IV dose of 2 mg/kg, then 1 mg/kg/day after 6 hours if the infection is hyperparasitic, then 2 mg/kg daily until the child can swallow.[49,50] When the child can swallow, artesunate should be administered orally. After 7 days of therapy with artesunate, oral mefloquine, 15 mg/kg followed by 10 mg/kg 12 hours later, should be given.

Quinine sulfate (or quinine dihydrochloride) is given in an initial IV dose of 20 mg/kg over 4 hours, then 10 mg/kg is administered intravenously over 2 hours every 12 hours for 7 days.[15] Quinine can be given orally when the child can tolerate it. After 7 days of therapy with quinine, mefloquine, 15 mg/kg orally followed by 10 mg/kg 12 hours later, should be provided.

Quinidine can be used if artesunate and quinine are not available, but quinidine is more likely than quinine to cause cardiac toxicity.[15] Following an IV loading dose of 15 mg/kg quinidine over 4 hours, the drug is administered at a dose of 7.5 mg/kg over 4 hours, every 8 hours, for 7 days. After 7 days of therapy with quinidine, mefloquine, 15 mg/kg orally followed by 10 mg/kg 12 hours later, should be given.

Other Treatment

Bacterial infection is common in children with clinical findings suggestive of cerebral malaria. Following a blood culture, cefotaxime (or penicillin if cefotaxime is not available) and gentamicin are appropriate empirical treatments. Lumbar puncture should be deferred until the child recovers consciousness. Antibiotics are discontinued after 48 to 72 hours if the blood culture is negative and results of a lumbar puncture are normal.

Children with a hemoglobin level of 4 g/dL or less require urgent transfusion with packed erythrocytes. Children with a hemoglobin level of 4 to 6 g/dL should receive a transfusion if they are in a coma or in shock or have more than 10% parasitized erythrocytes.[15,49] Transfusion should occur slowly over 6 hours until a hemoglobin level of 10 g/dL is achieved, taking care to avoid fluid overload in children with severe malnutrition. Use of furosemide is not indicated unless there is evidence of fluid overload (i.e., pulmonary edema with a high central venous pressure). Exchange transfusion, if it can be performed safely, may be beneficial in patients who are in a coma or have renal failure, adult respiratory distress syndrome, or a parasitemia of 10% or more.[51]

No evidence supports the use of corticosteroids,[52] cyclosporin, dextran, heparin, iron chelating agents,[53] or prostacyclin in patients with malaria. The patient should be turned every 2 hours, hypoglycemia should be prevented, and vital signs and fluid balance should be monitored carefully. Acidosis may be associated with severe hyperkalemia initially, but total body potassium often is low and hypokalemia may occur in the recovery phase.

Measles

Despite the effectiveness of measles immunization, more than 400,000 children still die every year as a result of measles (see Table 16-1). It is a devastating viral infection with a case fatality rate up to 30%, particularly in malnourished children. Measles is highly infectious, and its course frequently is complicated by a secondary infection with adenovirus or bacteria.[54,55]

Diagnosis

Measles has a 3- to 5-day prodromal period consisting of coryzal symptoms, fever, cough, and conjunctivitis. Koplik spots develop in the mouth from days 2 to 4. They are seen on the inner surface of the cheeks and have the appearance of salt granules on a red background. A maculopapular rash appears from day 4. The rash starts on the head and neck and spreads to the trunk and the rest of the body over several days. The rash darkens 5 to 6 days after it appears. The skin may peel and have a scaly appearance. Diarrhea is common throughout the early phase of the disease. Upper respiratory tract symptoms may progress to involve the larynx with croup and the remainder of the respiratory system with severe bronchopneumonia.

Persistence of fever for longer than 3 days after the appearance of the rash suggests that there is secondary bacterial infection, often involving the respiratory system. Measles may precipitate features of acute malnutrition. Vitamin A deficiency may be exacerbated by the illness and cause acute xerophthalmia with blindness. An acute allergic encephalitis with demyelination may occur, typically during the second week of the illness as the rash is clearing. Acute measles inclusion body encephalitis may occur and is more common in immunocompromised children. Subacute sclerosing panencephalitis presents some years after the acute infection. Bronchiectasis may be a complication of severe measles pneumonia with secondary infection.

Infection Control

Children are infectious before the rash appears and for up to 7 days after the first symptoms appear. The incubation period is 10 to 12 days. Ensure that all children who came into contact with the infected child have been immunized with measles vaccine. In children older than 4 months, immediate immunization at the time of exposure protects against infection. Younger infants usually are protected by maternal antibodies; however, in communities where maternal antibody levels may be low, every effort should be made to ensure that young infants are not exposed to measles patients, and immunoglobulin should be administered to contacts if possible.

General Measures

The common complications of measles are pneumonia, diarrhea, croup, conjunctivitis, keratitis, xerophthalmia, malnutrition, otitis media, stomatitis, and nosocomial infection.[54,56] Treatment of the acutely ill child includes ensuring adequate oxygenation, obtaining cultures and providing penicillin and gentamicin as needed, and initiating mechanical ventilation. Fluid therapy should be closely tailored to the clinical situation, taking into account factors such as diarrhea and fever. Because hydration status may be difficult to assess clinically, regular weighing facilitates fluid balance assessment. Vitamin A, 200,000 IU/day, should be administered orally for 2 days to reduce mortality and prevent xerophthalmia.[57] Whether immunoglobulin has a role in the treatment of severe measles is not clear.[54] Measles may exacerbate tuberculosis and malnutrition.

Human Immunodeficiency Virus

The vast majority of HIV-infected children are located in the developing world (see Chapter 93). In southern Africa, HIV-related pneumonia is the main cause of admission to hospital[58] and is an important cause of admission to intensive care.[59,60] In the past, children admitted to the ICU with respiratory disease had a very high incidence of mortality, but the rate

has improved gradually with time.[59] Much of the improvement came from the recognition that *Pneumocystis jiroveci* is a major pathogen in these children. Other studies have highlighted the importance of cytomegalovirus, tuberculosis, and bacterial infections, particularly *Staphylococcus aureus*.[58-61]

Little information is available about the long-term outcome of HIV-infected children requiring intensive care in the developing world. However, the impression is that, in the absence of antiretroviral therapy, the majority of these children die within months of being admitted to the ICU. A decision about whether to admit a child to the ICU should be influenced by the medium- to long-term prognosis and not just survival in intensive care.[62] It is not in the interests of a child to provide intensive care if the prognosis is very poor because such care simply prolongs suffering, and it is not in the interests of the health services if such care results in poor utilization of limited resources.

In the absence of antiretroviral therapy, admitting infants with severe infection to the ICU appears to be of limited benefit. However, one consequence of programs directed at reducing maternal-to-child transmission of HIV (using nevirapine or zidovudine) is that the diagnosis of HIV infection in the infant is more complex. Thus there is a place for admitting HIV-exposed (and possibly HIV-infected) infants with severe infection to the ICU while the diagnosis is being established. There is little or no place for prolonged intensive care when the diagnosis of HIV infection is established if antiretroviral therapy is not available. As antiretroviral therapy becomes more generally available in the developing world, the role of intensive care in the management of HIV-infected children will require review.

Pertussis

Pertussis syndrome is caused by *Bordetella pertussis* or *Bordetella parapertussis*. The WHO estimates that 300,000 children die from pertussis each year,[63] but PCR testing has shown that pertussis is much more common than previously thought,[64] so the total number of deaths may be even higher.

The illness starts with rhinorrhea, fever, and a cough that comes in spasms for approximately 10 days until the whoop starts. The cough may last for up to 3 months and recur with subsequent respiratory infections. A large amount of very thick sputum is produced, which may cause a paroxysm of coughing that lasts so long the child becomes cyanotic. After the paroxysm, the child may inspire so strongly that a loud stridor, or whoop, is heard. The cough may be accompanied by expectoration of tenacious mucus or vomiting. Young infants may have no whoop and may present with apnea.[65]

In endemic areas, encephalopathy is common in patients with severe pertussis, and up to one third of infants may present with coma or seizures.[66] The incidence of mortality is high in infants with severe pertussis if the total white blood cell count is greater than 40,000/μL, if they have encephalopathy, or if they need mechanical ventilation for pneumonia. Severe pulmonary hypertension may occur, particularly in children with a white blood cell count greater than 100,000/μL.[67]

Diagnosis

In developing countries, the diagnosis usually must be made on clinical grounds. Pertussis likely is present in children with typical clinical findings who have a lymphocyte count greater than 10,000/μL. Children with a lower respiratory infection and a total white blood cell count of 40,000/μL or more have a high mortality rate, and many of these children probably have pertussis even if they do not have typical symptoms.[68]

Obtaining a culture of *B. pertussis* is difficult, and the sensitivity is low even if the test is performed correctly. Immunofluorescent antibody testing is positive in approximately 80% of cases if the specimen is obtained within 2 weeks of the onset of the cough and erythromycin or chloramphenicol has not been given. PCR for pertussis is sensitive and specific,[64] but the test is difficult to perform and is expensive. In one study, 33% of children with pertussis also had respiratory syncytial virus infection.[64]

Treatment

Antibiotics probably do not alter the course of the illness unless they are given before the paroxysmal cough develops, but they do render the patient noninfectious. In developing countries, chloramphenicol usually is the antibiotic of choice. Chloramphenicol is active against *B. pertussis* and most of the bacteria that cause secondary pneumonia. Erythromycin also is active, but erythromycin stearate is less effective than the estolate and must be given in high doses for 14 days.[69,70] Clarithromycin and azithromycin are highly effective, but they are expensive.[70]

Severe paroxysms should be treated with oxygen and gentle suction. Convulsions can be treated with diazepam, followed by phenobarbital as prophylaxis. The available evidence does not support the use of diphenhydramine, pertussis immunoglobulin, or salbutamol.[71] Four controlled trials of systemic steroid use for pertussis all suggested a benefit, but the studies were not well designed.[72-75] Inhaled steroids appeared to be helpful in one report.[76]

CPAP administered via a nasal mask or prong may be helpful in infants with apnea as an alternative to mechanical ventilation.[77] The prognosis is poor if mechanical ventilation is required for pneumonia in children with pertussis.[78] Exchange transfusion should be considered if the total white blood cell count is more than 100 × 109/L or severe pulmonary hypertension is present.[67]

Tetanus

Tetanus is responsible for 300,000 child deaths each year (see Table 16-1). Most of the deaths result from neonatal tetanus caused by lack of maternal immunization and poor umbilical cord hygiene. Tetanus occurs occasionally in older children with infected wounds but has decreased substantially since the institution of adequate immunization practices. Tetanus toxins affect most body organs and not just the central nervous system. The prognosis depends on age (with higher mortality rates in newborn babies and elderly adults), the source of infection, and delay in treatment.[79] Children with tetanus present with difficulty feeding; trismus; muscle spasms; hypertonicity; convulsions; and autonomic, cardiac, and respiratory instability.

Treatment

If spasms are severe, oxygen should be provided until adequate sedation is achieved with diazepam and chlorpromazine. IV diazepam at a dose of 0.5 mg/kg is administered slowly every

15 to 30 minutes until severe spasms are controlled, and then 0.5 mg/kg is given every 12 hours by nasogastric tube. When given intravenously, diazepam should be diluted 1:20 with 0.9% saline solution and injected slowly over 5 minutes. Diazepam should not be given intramuscularly. After spasms have been controlled with IV diazepam, maintenance doses can be given orally or by nasogastric tube; up to 40 mg/kg/day may be needed as tolerance develops. In addition to diazepam or midazolam, administration of chlorpromazine, 5 mg/kg every 12 hours intramuscularly or by nasogastric tube, is useful. Tracheostomy should be performed in older children with a severe case of tetanus. Paralysis and mechanical ventilation will be needed if severe spasms persist despite heavy sedation.

Autonomic instability may cause large and sudden variations in blood pressure and pulse rate. In patients undergoing ventilation, morphine, 20 to 40 μg/kg/h, may be a helpful addition to diazepam and chlorpromazine. Atropine, clonidine, and magnesium have been used[12] but have not been demonstrated to be superior to careful use of large doses of chlorpromazine, diazepam, and morphine. β-Blockers should not be given.[80]

If human tetanus immunoglobulin is available in IV form, a total dose of 4000 U is recommended, although some centers now use only 500 U. The entire dose can be infused intravenously over 1 hour. Alternatively, 1.5 mL (approximately 100 units) can be administered intrathecally, 1.5 mL can be infiltrated around the umbilicus in patients with neonatal tetanus (after cleaning the stump with hydrogen peroxide), and the remainder can be infused intravenously. If immunoglobulin is given intrathecally, dexamethasone, 4 mg (2 mg in neonates) every 12 hours, should be administered intramuscularly for 5 days. The role of intrathecal administration of tetanus immunoglobulin is unclear,[2] but it may reduce the incidence of mortality if corticosteroids are given as well.[81] If human tetanus immunoglobulin is not available in IV form, 750 units (three ampoules) of intramuscular (IM) human or horse tetanus immunoglobulin on the first day and 500 units on the next 2 days should be given. IM preparations should not be administered by intrathecal injection.

After the site of infection is identified, any necrotic tissue is removed, and benzyl penicillin, 50 mg/kg, is given intravenously every 6 hours. A full course of immunization with tetanus toxoid should be given during convalescence (usually three doses at 2-month intervals).

Tuberculosis

Tuberculosis is common in the developing world. In association with the HIV pandemic, there has been an increase in the incidence of tuberculosis and multidrug-resistant tuberculosis. Most children with tuberculosis do not require intensive care. However, tuberculosis may be an unexpected additional finding during an ICU admission, or it may be the cause of an ICU admission. In one pediatric ICU, tuberculosis was not initially considered as a diagnosis in 30% of eventually confirmed cases.[82] In general, the sputum of children does not contain a large number of *Mycobacterium tuberculosis* organisms, so children are rarely a source of infection. However, in the ICU, children who have *M. tuberculosis* in the sputum may constitute a risk to staff because sputum is aerosolized from an endotracheal tube during suctioning. In the case of young children, the risk of at least one parent being infected is high. In one series of infants younger than 3 months with tuberculosis, 42% of the index cases identified by history were parents, and 30% of the mothers had previously unsuspected pulmonary tuberculosis.[83] Patients' relatives may be a source of infection for staff and other hospital patients.[84] If a child presents with tuberculosis, the public health authorities must be informed, the source of the infection investigated, and appropriate therapy instituted. Children are rarely the source of infection, whereas adults with tuberculosis are highly infectious.

Pathophysiology

In children, tuberculosis usually results from primary infection with *M. tuberculosis* inhaled into the lungs. The organism spreads into the lymphatic system and the mediastinal lymph nodes (setting up the primary focus) and then via the thoracic duct into the bloodstream, with hematologic dissemination throughout the lungs (miliary tuberculosis). Spread to the rest of the body may occur from erosion of the pulmonary vessels and subsequent dissemination via the systemic circulation.

Diagnosis

The diagnosis of tuberculosis may be difficult in children because of the paucity of organisms in sputum and other body fluids. Often treatment for tuberculosis must be started without bacteriologic confirmation of the diagnosis. However, particularly when resistant tuberculosis is possible, every effort should be made to isolate the organism from sputum, body fluids, tissue biopsy, or culture of the suspected sources of infection. Gastric lavage has been shown to be superior to bronchoalveolar lavage,[85] and inducing the expulsion of sputum may be superior to gastric lavage.[86] Table 16-3 summarizes the diagnostic approaches to tuberculosis.

Chest x-ray films showing a miliary pattern, a typical Ghon focus with associated lymphadenopathy, or more diffuse consolidation are strongly suggestive of tuberculosis. Pleural effusions are common, especially in older children. A computerized tomography scan of the chest demonstrates typical lymph nodes with rim enhancement after contrast administration.

Tuberculin tests can be used to aid diagnosis. False-negative results frequently occur in children with malnutrition, immune compromise, overwhelming disease, or recent significant illness. Induration of more than 10 mm at the site of tuberculin administration suggests infection in children who have not received BCG vaccination, whereas induration of more than 15 mm suggests infection in children who have received BCG vaccination.

Presentation to the Intensive Care Unit

Children with tuberculosis who require intensive care usually have an infection of the respiratory tract; however, central nervous system disease or abdominal complications also may cause critical illness. In areas where tuberculosis commonly occurs, the diagnosis should be considered in any child with

Table 16–3 Investigation for Tuberculosis in Children

Investigation	Technique	Problems and Possible Benefits
Gastric lavage	Lavage of the stomach with a variable volume of 0.9% saline solution	Should be performed when the patient has not fed for several hours to avoid contamination of specimen with food; not applicable once patient has been intubated because theoretically the sputum will be removed by suction and will not be swallowed; relatively noninvasive
Induced sputum	Aspirate of the nasopharyngeal secretions following nebulization with 5% saline solution; generally, patients should be given salbutamol prior to nebulization to decrease the risk of bronchospasm related to the hypertonic saline solution	Potential risk to staff because organisms can be nebulized to environment with coughing; better yield than gastric lavage
Bronchoalveolar lavage	Bronchoalveolar lavage of affected areas of the lung	Patient requires general anesthesia; technically difficult and requires expensive equipment if a particular area of the lung is lavaged; can be conducted nonbronchoscopically, but a particular area of the lung cannot then be lavaged; yield not as good as with gastric lavage

acute pneumonia that does not respond to therapy as expected. Radiologic changes in the lung may be surprisingly extensive for the severity of lung disease in patients with tuberculous bronchopneumonia.

Acute respiratory distress syndrome is a well-recognized complication of miliary and bronchogenic tuberculosis in adults but is less common in children.[87-93] Some reports have suggested that steroid therapy may be useful for persons with acute respiratory distress syndrome with miliary tuberculosis, whereas other reports suggest the outcome is worse. No randomized trials on steroid therapy for persons with acute respiratory distress syndrome with miliary tuberculosis have been performed.

Lower Airway Obstruction

Intrathoracic lymph node tuberculosis may cause severe airway obstruction as a consequence of external compression of the airways by circumferential lymph nodes, erosion of the bronchial wall with extrusion of caseous material into the bronchial lumen, or a combination of both. Clinical presentation of airway compression by lymph nodes includes features of lower airway obstruction and a "klaxon cough." Typically a wheeze that is worse on expiration, particularly with forced expiration, is heard. The trapping of air is less than expected based on the severity of the wheeze.

Acute obstruction may be temporarily relieved by use of inhaled epinephrine, and administration of steroids may ameliorate the symptoms.[94] If the airway obstruction does not resolve with steroid therapy or if the obstruction is so severe that supportive ventilation is required, relief may be achieved by surgical intervention.[95-98] Surgery should be preceded by bronchoscopy to define the site of compression and to remove any endobronchial material that is contributing to the obstruction. If the lymph nodes are compressing the trachea or major bronchi, surgical decompression may dramatically relieve symptoms; however, if segmental bronchi are being compressed, surgery is less likely to relieve the symptoms. Surgery usually is effective if the nodes are filled with fluid material. Relieving obstruction caused by hard caseous nodes with extensive surrounding fibrosis often is difficult.

Bronchoesophageal Fistula

An acquired bronchoesophageal fistula can be caused by erosion of peribronchial lymph nodes into both the esophagus and a bronchus.[99,100] The fistula may present either with features of bronchial aspiration of swallowed material and associated coughing or with respiratory failure. Ventilation in this situation is complicated by the constant leak of air from the bronchus into the esophagus and gastrointestinal tract. Fistulas from the esophagus into the pleural space have been described.

Laryngeal Tuberculosis

Tuberculosis may cause laryngeal obstruction, particularly in the setting of HIV infection.[44] In one study, laryngeal tuberculosis accounted for 15.8% of episodes of laryngeal obstruction in HIV-infected children admitted to the ICU.[101] Clinical features include hoarseness and laryngeal obstruction.

Tuberculous Meningitis

Children with tuberculous meningitis usually present to the ICU with a depressed level of consciousness or status epilepticus (see Chapter 65). A lumbar puncture should not be performed on a child who has a depressed level of consciousness, but a computerized tomography scan should be performed to determine if hydrocephalus, cerebral edema, or a mass lesion is present. The typical cerebrospinal fluid features include an increased cell count (usually >500/μL with predominantly lymphocytes, although neutrophils may predominate early in the disease); absence of other bacteria; and high protein levels, relatively low sugar levels, and low chloride levels. Hyponatremia is common because of increased secretion of antidiuretic hormone (which occurred in 71% of cases in one study).[102] Therapy should be started with high-dose antituberculous therapy and

Table 16–4 Drugs Used to Treat Tuberculosis in Children

Drug	Usual Daily Dose	Comment
FIRST-LINE THERAPY		
Isoniazid	10-15 mg/kg orally (max 300 mg), IV or IM	Part of usual three-drug regimen; has marked effect on rapidly dividing organisms dividing cells
Rifampicin	10-15 mg/kg (max 600 mg) orally or IV over 3 hours	Part of usual three-drug regimen; has significant postantibiotic effect
Rifabutin	Dosing for children not established	
Rifapentine	Dosing for children not established	
Pyrazinamide	15-30 mg/kg (max 2 g) orally	
Ethambutol	25 mg/kg orally (max 2.5 g); give 80% of oral dose if given IV	Can be used in young children if resistant organisms suspected; older children should undergo regular visual testing during therapy
SECOND-LINE THERAPY		
Cycloserine	10-15 mg/kg orally (max 1 g)	
Ethionamide	15-20 mg/kg orally (max 1 g)	
Streptomycin	20-40 mg/kg (max 1g) IM	
Amikacin or kanamycin	15-30 mg/kg (max 1 g) IM or IV daily; drug level monitoring essential	
P-aminosalicylic acid (pas)	200-300 mg/kg (max 10 g) in 2-4 divided doses orally	

IM, Intramuscular; *IV,* intravenous.

steroids.[103] Antituberculous drugs such as rifampicin may accelerate the metabolism of steroids, and a high dose may be required.

Tuberculous Pericarditis

Tuberculous pericarditis is an uncommon complication. Occasionally children present with features of shock. The most common presentation consists of long-standing symptoms of illness with some features of pericardial tamponade.[104] Tuberculous pericarditis requires urgent drainage only in cases of significant symptoms or diagnostic concerns. Antituberculous therapy should be started early, and steroids should be given to patients at risk of having constrictive pericarditis develop.[105,106]

Miliary and Abdominal Tuberculosis

Miliary tuberculosis is relatively rare in the ICU but may be associated with tuberculous meningitis and the development of acute respiratory distress syndrome. Abdominal tuberculosis is characterized by marked abdominal lymphadenopathy with associated malabsorption, gut obstruction, or protein-losing enteropathy.

Treatment Regimens

For patients with drug-susceptible tuberculosis, the usual treatment starts with isoniazid, pyrazinamide, and rifampicin,[107] but starting with just isoniazid and rifampicin is acceptable if use of pyrazinamide is contraindicated. If drug resistance is likely, ethambutol or streptomycin should be added. For children diagnosed with tuberculosis during an intensive care admission a daily treatment regimen usually is begun, although treatment subsequently may be given only two or three times per week. One (non-ICU) study showed that therapy with three drugs administered two times per week from the start was as effective as daily therapy.[108]

Many drugs interact with antituberculous therapy, and great care must be taken with all other medications given, particularly anticonvulsant agents, theophylline, paracetamol, antiretroviral drugs, and steroids.[109]

Metronidazole is not a first-line antituberculous agent; however, it has a marked effect against dormant M. tuberculosis under anaerobic conditions. One report from India showed significant improvement in clinical outcome when metronidazole was added to conventional therapy for adults with pulmonary tuberculosis.[110] Steroids may be useful in patients with tuberculous meningitis and when intrathoracic airways are compressed by tuberculous lymph nodes. Table 16-4 summarizes characteristics of tuberculosis antimicrobial drugs.

Poor absorption of drugs from the gastrointestinal tract may occur in critically ill children, especially those with abdominal tuberculosis. If there is doubt about the absorption of medication from the gut, rifampicin and isoniazid should be administered intravenously. Liver toxicity may occur, with adverse effects ranging from mild elevation of transaminases to acute severe hepatic failure and death. All the first-line antituberculous drugs have a marked postantibiotic effect, and daily administration is not essential.

Diphtheria

Diphtheria is an acute infectious disease caused by toxigenic strains of *Corynebacterium diphtheriae*. Since the introduction of immunization, the incidence of diphtheria has decreased

dramatically; however, the WHO estimated that the disease still caused 4000 deaths in children in 2004.[111] Colonization of chronic skin sores by *C. diphtheriae* often induces immunity; as standards of hygiene improve and chronic skin sores become rare, clinical diphtheria becomes more common unless it is prevented by immunization.

The organisms are transmitted by contact or droplet spread. After an incubation period of 2 to 4 days, the organisms invade the pharynx in 90% of pediatric cases, but they may infect the nose, mouth, or skin. Satellite lesions may occur in the stomach, esophagus, or lower airways.[112] Bronchial involvement mimicking bacterial tracheitis has been described.[113]

Course During the First Week

Nasal diphtheria initially may be indistinguishable from the common cold but later may be characterized by a serosanguineous nasal discharge, white patches on the septal mucosa, and erosions on the upper lip. Toxemia usually is mild. Pharyngeal diphtheria is characterized by the development of a pseudomembrane composed of sloughed mucosa plus an inflammatory exudate of neutrophils, fibrin, and bacterial colonies. The membrane typically forms over one or both tonsils and may extend throughout the nasopharynx, oropharynx, and soft palate and down into the larynx. The pseudomembrane initially is white and changes to a dirty gray over time. It is associated with intense underlying inflammation, and attempts to remove the pseudomembrane cause bleeding. The intense inflammation may obstruct the airway, and occasionally the entire pseudomembrane sloughs off and causes airway obstruction.[112] Pharyngeal diphtheria usually is associated with severe toxemia and the development of enlarged cervical lymph nodes with associated edema (bullneck).

Laryngeal and tracheobronchial diphtheria can be primary infections or extensions of pharyngeal lesions. These lesions are relatively rare but can cause severe airway compromise and are associated with severe toxicity.[112] Oral lesions in adults have been described but are rare in children. Skin involvement with formation of slough may occur at any site; toxicity, if present, is mild.

During the initial phase of the illness, systemic features such as pyrexia and toxemia are caused by absorption of toxin from the inflammation site. Disseminated intravascular coagulation, acute renal damage, and acute cardiac failure may occur.[114-116] Fever and toxemia usually resolve after approximately 1 week.

Subsequent Course

During the second or third week of the illness, myocarditis and neurologic problems may occur if the toxin has not been inactivated by administration of antiserum. Myocarditis has been described in 10% to 20% of patients presenting with oropharyngitis. The mortality rate associated with diphtheritic myocarditis ranges from 14% to 60%.[117] Clinical features include rapid onset of cardiac failure with cardiac gallop, muffled heart sounds, and apical murmurs; rhythm disturbances, including sinoatrial node dysfunction, extrasystoles, atrial flutter, atrial fibrillation, nodal rhythm, and ventricular tachycardia; and conduction abnormalities with bundle branch and atrioventricular block. Conduction abnormalities on electrocardiogram were a marker of severe myocardial damage and poor prognosis in one study.[118] A wide range of electrocardiographic changes is seen in persons with myocarditis, ranging from ST-segment changes to extensive infarctlike patterns.[119] On echocardiography, left ventricular dilatation with poor function but retained muscle mass has been described. Biochemical features of myocarditis include increased serum myoglobin, lactic dehydrogenase, and creatine phosphokinase.

Neurologic complications usually occur between 10 days and 3 months after the onset of oropharyngeal disease. Palatal palsies with difficulty swallowing are a common complication during the first 3 weeks of illness. Paralysis of the diaphragm, eye muscles, and skeletal muscles may occur up to 3 months after the onset of disease. Examination of affected nerves has shown degeneration of the myelin sheaths and axon cylinders.[112]

Diagnosis

Early diagnosis and treatment are important for limiting the effects of toxin and minimizing the severity of illness. The initial symptoms are those of any upper respiratory tract infection, but the presence of toxemia with a membrane on the pharyngeal surface in an unimmunized child (or a child immunized in a program in which the refrigeration chain may not have been maintained) should alert the clinician to suspect diphtheria. The organisms can be cultured from a portion of the membrane or from a swab taken from under it. The presence of diphtheroids on Gram's stain is not sufficient evidence of infection; complete cultures should be performed. The presence of an antibody titer to diphtheria toxin may help confirm the diagnosis.

Antibiotics

Penicillin, 50 mg/kg administered intravenously every 4 hours, is a first-line therapy. Once the toxemia settles, a change to intramuscular procaine penicillin, 25,000 to 50,000 units/kg/day or oral phenoxymethylpenicillin, 12.5 mg/kg every 6 hours, is appropriate.[15] Erythromycin is an alternative for patients allergic to penicillin, but some strains of the organism are resistant.[120]

Antitoxin

Antitoxin should be administered as soon as the condition is suspected. Clear evidence exists that mortality rates are higher in children who receive antitoxin late. The antitoxin is made in horses, and a test dose should be given to assess for possible allergy. Diphtheria antitoxin may be difficult to obtain. In the United States, the antitoxin is available only through the Centers for Disease Control and Prevention. In some other countries, less purified antitoxin is available but cannot be given intravenously. The dose of antitoxin is related to the severity of the disease and not to the size of the patient, as shown in Table 16-5.

Supportive Care

Oxygen administered via face mask or nasal prongs should be provided if the child has an oxygen saturation less than 92% in room air. Use of nasal or nasopharyngeal catheters is not advisable because they may precipitate airway obstruction. Performing a tracheostomy may be preferable to endotracheal

Table 16–5 Doses of Antitoxin Used to Treat Diphtheria

Severity of Disease	Dose
Mild disease (nasal and tonsillar)	20,000 U IM
Moderate disease (laryngeal with symptoms)	40,000 U IM or IV
Moderately severe (nasopharyngeal with symptoms)	60,000–100,000 U IV
Malignant disease (combined sites or delayed diagnosis)	60,000–100,000 U IV

IM, Intramuscular; *IV,* intravenous.

intubation if airway obstruction is evident.[121] If endotracheal intubation is attempted, gas induction should be used and great care must be taken not to dislodge pieces of the membrane into the trachea and obstruct the airway. Administration of dexamethasone may help decrease airway edema and relieve obstruction,[114] but it does not reduce the incidence of cardiac and neurologic complications.[122] Palatal palsies that make swallowing difficult may develop, and nasogastric tube feeding may be needed for some time. Patients must be regularly monitored for 3 months after the acute illness because neurologic problems may persist during this time.

Cardiac

Carnitine may have a role in therapy for patients with diphtheria carditis. Animal data and a randomized controlled trial show a decreased incidence of myocarditis and its complications when carnitine is administered.[50,123] Cardiac support may dictate use of inotropes and optimization of preload with diuretics or IV fluid. Ventricular pacing may improve the outcome in children with diphtheritic myocarditis and associated heart block, although one study reported that all patients with third-degree heart block died despite the use of a pacemaker.[118] Prolonged cardiac follow-up may be indicated because there may be a considerable delay between onset of symptoms and development of cardiac dysfunction.[124] Recovery from myocarditis may require more time than previously appreciated.[125]

Prevention of the Spread of Disease

All hospital staff in contact with children with diphtheria should be fully immunized. When possible, patients should be isolated. Alternatively, only fully immunized children should be housed in the same area of the ward. All the patients' contacts must be investigated for the possible presence of diphtheria by obtaining throat swabs and checking immunization status. Patients who have recovered from diphtheria should be immunized with diphtheria toxoid; the dose depends on the patient's age and immunization status.[126]

Dengue

Dengue is an acute febrile illness caused by four different dengue viruses transmitted by Aedes mosquitos (principally *Aedes aegypti*). Dengue symptoms include fever, myalgia, arthralgia, rash, leukopenia, and lymphodenopathy.[127] Dengue usually causes a nonspecific febrile illness. However, it also causes dengue hemorrhagic fever and dengue shock syndrome; the latter is characterized by increased vascular permeability.[127] The risk of severe dengue is greater with the second infection, especially in children. Associated thrombocytopenia, spontaneous bleeding, and disseminated intravascular coagulation are common. Severe dengue is one of the most common causes of pediatric admission to hospitals in Asia, with up to 500,000 cases reported annually to the WHO.[127] Dengue shock syndrome usually occurs between days 3 and 5 of the illness. The risk of death is highest when the pulse pressure is 10 mm Hg or less at the time of presentation.[128]

Fluid Therapy

The main treatment for dengue shock syndrome is prompt, vigorous fluid therapy. Boluses of 20 mL/kg of 0.9% saline solution should be given every 15 minutes until the pulse pressure is at least 30 mm Hg. No evidence exists that colloids are superior to crystalloids for resuscitation, although colloids are often used for severe dengue shock.[129] After resuscitation, normal maintenance doses of fluid are given, with extra boluses of 10 mL/kg if the pulse pressure falls below 30 mm Hg.

Other Treatment

Because of severe capillary leakage, pleural effusion and ascites are common in patients with severe dengue. However, because of the risk of bleeding, centesis should not be undertaken unless fluid accumulation is causing severe respiratory or circulatory embarrassment.[130] A small proportion of children do not respond to aggressive fluid therapy. Patients in respiratory distress may require administration of oxygen and nasal CPAP or mechanical ventilation.

The risks of central venous line insertion usually are greater than the benefits, but if shock persists despite vigorous fluid therapy, a central venous catheter should be inserted if this procedure can be done safely. The risk of bleeding can be reduced by using a femoral venous line. Central venous pressure should be maintained at 10 to 12 cm H_2O. However, if severe lung disease is causing right ventricular failure, central venous pressure may be normal or high even though the child is in a hypovolemic state. In these circumstances, echocardiography should be performed to assess left atrial size (as a measure of intravascular volume) and to locate evidence of impaired ventricular contractility. Hypovolemia should be corrected, and dobutamine, 5 to 15 μg/kg/min, should be administered if ventricular contractility is poor. Bleeding can be severe and often is associated with platelet dysfunction and intravascular coagulation; administration of low-dose heparin, 10 to 15 units/kg/h, and fresh-frozen plasma may be helpful. Platelets should be transfused only if the count is less than 20,000/mm^3 to 40,000/mm^3 with significant bleeding. IV administration of immunoglobulin, 500 mg/kg/day for 5 days, may decrease the rate of bleeding and increase the platelet count. Renal failure may require hemofiltration or peritoneal dialysis. Coma usually results from hypoxic-ischemic injury, cerebral edema, intracranial hemorrhage, or intravascular coagulation, but occasionally it is caused by dengue encephalitis. Corticosteroids and carbazochrome should not be used routinely to treat dengue.[131-133] A report of a single case from

Table 16–6 Management of Severe Malnutrition

	Stabilization		Rehabilitation
	Days 1-2	Days 3-7	Weeks 2-6
Hypoglycemia	→		
Hypothermia	→		
Dehydration	→		
Electrolytes	→	→	→
Infection	→	→	
Micronutrients	No iron	→	With iron
Initiate feeding	→	→	
Catch-up growth		→	→
Sensory stimulation	→	→	→
Prepare for follow-up			→

From World Health Organization: *Pocket book of hospital care for children: guidelines for the management of common illness,* Geneva, Switzerland, 2006, World Health Organization, p 176.

Tahiti has suggested that desmopressin may reduce capillary leakage in patients with severe dengue.[73]

Malnutrition

Malnutrition contributes to 56% of child deaths, and 83% of this effect is associated with mild to moderate rather than severe malnutrition.[11] The WHO has published detailed guidelines regarding the management of severe malnutrition for physicians and health workers at the first-referral level (Table 16-6),[15,16] and useful summaries of the management of malnutrition have been published.[134-137]

Severe malnutrition is defined as nutritional edema (kwashiorkor), severe wasting with weight-for-height more than three standard deviations below the median (marasmus), or severe stunting with height-for-age more than three standard deviations below the median.[16] Although improvements in the management of severe malnutrition have lowered the mortality rate from higher than 50%, it remains high, even with intensive management. Kwashiorkor now appears not to be caused by protein deficiency but rather by antioxidant deficiency.[138]

A diagnostic workup for malnutrition should include determination of a blood glucose level, a blood film for malaria, determination of a hemoglobin level, microscopy and culture of urine, microscopy of feces (blood suggests dysentery; Giardia lamblia cysts or trophozoites may be present), a chest x-ray film, and a Mantoux test. Measurement of serum proteins and electrolytes rarely is helpful and may lead to inappropriate therapy. Testing for HIV depends on local circumstances.

Malnutrition mimics many of the clinical signs of dehydration (e.g., sunken eyes, poor skin turgor, and apathy). Malnourished children often have excess body water and sodium, and giving them too much fluid is dangerous. On the other hand, severe sepsis in a malnourished child may be present with remarkably few clinical signs. In particular, no fever may be present, and the mortality rate is high in afebrile patients with malnutrition and sepsis. If the child exhibits shock, hypovolemia should be corrected with 10 mL/kg boluses of 0.9% saline solution (not albumin). Once hypovolemia is corrected, care should be taken not to administer excess sodium and water intravenously. Nasogastric feeding should be used whenever possible; use of IV fluids should be avoided.[15] Benzyl penicillin and gentamicin should be given parenterally after obtaining cultures. The child should be maintained in a normothermic state. The blood glucose level initially should be measured every 4 hours, and hypoglycemia should be treated promptly. Diuretics should not be given for treatment of edema.

The level of total body sodium is high in persons affected with malnutrition, even in the presence of hyponatremia, and thus sodium intake should be restricted. Deficiencies of potassium, magnesium, zinc, copper, selenium, iodine, vitamin A, and folic acid must be corrected immediately. Usually, correction of these deficiencies is best accomplished with the oral or nasogastric administration of an electrolyte solution.[15,135] Iron supplements should be given orally only when the child starts to recover (after the first week of treatment).

After the initial correction of hypovolemia and replacement of any continuing losses, water intake should be limited to 100 to 130 mL/kg/day. Hypoosmolar feedings should be given initially, with a moderate calorie intake of 80 to 100 kcal/kg/day, and protein intake should be restricted to 1.0 to 1.5 g/kg/day.[15,16,135] Albumin should not be given intravenously for treatment of hypoalbuminemia because the liver has a reduced capacity to metabolize protein in malnourished children.[16] Feedings usually are given every 2 hours for the first 2 days, every 3 hours on days 3 to 5, and every 4 hours thereafter. Appetite usually returns after the first 5 to 7 days. The strength of the feedings then can be increased gradually to supply 150 to 220 kcal/kg/day and protein can be increased to 4 to 5 g/kg/day, but fluids still are limited to 130 mL/kg/day.

During treatment of severe malnutrition, sodium and water intake should be limited, protein intake should be restricted initially, administration of IV albumin should be avoided, and calorie intake should be increased gradually. Deficiencies of potassium and magnesium should be corrected early, with empiric antibiotic therapy given and care taken to prevent hypoglycemia and hypothermia.

Conclusion

Ideally, every child in the world should have access to an ICU with facilities for endotracheal intubation and mechanical ventilation. No ethical justification exists for providing these treatments to children in rich countries while denying them to children in poor countries. However, attempting to make intensive care available to all children while many extremely poor countries have so little money to spend on health care is not helpful.

In countries in which the mortality rate in the first 5 years of life is greater than 30 per 1000 live births, most deaths are caused by infections. Using government funding to provide intensive care actually might increase the mortality rate if such care diverts resources away from immunization and primary health care. When the mortality rate for children younger than 5 years is between 20 and 30 per 1000, limited use of intubation and ventilation for carefully selected indications may

have a role. When the mortality rate for children younger than 5 years is less than 20 per 1000, fewer deaths can be prevented by immunization and primary health care, and intensive care can make an important contribution to further reducing child mortality rates.

Self-Assessment Question 1

Which one of the following statements is *not* true?

A. Pneumonia contributes to about one third of all child deaths.
B. Fatal pneumonia in children is usually caused by *S. pneumoniae* or *H. influenzae.*
C. Children with very severe pneumonia should be treated with ceftriaxone (or cefotaxime) if it is available, rather than benzyl penicillin (or ampicillin) and gentamicin.
D. After correction of hypovolemia, most children with pneumonia should be given *less* fluid than a normal child.

Statement C is false.[13,22] *Pneumonia contributes to approximately a third of child deaths, fatal pneumonia is usually caused by* S. pneumoniae *or* H. influenzae, *and maintenance water requirements are often reduced because of increased levels of antidiuretic hormone.*

Self-Assessment Question 2

Which one of the following statements is true?

A. In a child with gastroenteritis, the presence of abnormal tissue turgor, poor peripheral perfusion, or hyperventilation suggests greater than 5% dehydration.
B. Hypovolemia caused by acute diarrhea should be treated with 4% albumin, if available, rather than saline solution to reduce third-space fluid loss.
C. Children with diarrhea and malnutrition may have septicemia and should be treated with penicillin (or ampicillin) and gentamicin even if they are afebrile.
D. Children with diarrhea and malnutrition have large deficits of albumin, sodium, and water and should be given 4% albumin in saline solution at 10 mL/kg/h for the first 6 hours.
E. Hypernatremic dehydration is very dangerous, and the serum sodium should be reduced by at least 2 mmol/L every hour using 0.2% saline solution in 4% dextrose.

Statement C is true.[13] *These clinical signs of dehydration are evident with 3% to 4% dehydration*[30]*; dehydration caused by acute diarrhea should be treated with crystalloid rather than colloid,*[13] *administration of sodium and albumin may cause heart failure in persons affected by malnutrition,*[135] *and the serum sodium should fall no faster than 0.5 mmol/L/h in persons with hypernatremia.*[32]

References are available online at http://www.expertconsult.com.

Chapter 17

Educating the Intensivist

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PEARLS

- The principles of adult learning and how they relate to fellowship training are discussed.
- These principles include the influence of the learner's current experience and knowledge and the self-directed and autonomous nature of adult learners.
- The motivation for adults to learn comes from both intrinsic and extrinsic factors.
- Adults learn best by active participation and practice in educational activities.
- To improve practice, adult learners need timely feedback and reinforcement.
- Skill acquisition in medicine is similar to the continuum of human developmental stages with learning that progresses from novice, advanced beginner, competent, proficient, expert, and finally, master.
- The mature clinician is one who reflects upon his or her daily medical experiences to place them in a larger context of previous encounters and critically evaluates his or her own performance, acknowledging both effective and ineffective aspects of patient care.

Pediatric critical care medicine is a discipline dedicated to the care of the critically ill child. It focuses on the sick child as a whole and takes into account the impact of disease on all organ systems, addressing the physical, mental, and emotional needs of the child and those of his or her family as well. The education and training of pediatric intensivists are focused on patient care principles that include resuscitation, advanced life support, management of traumatic injury, postoperative care, application of all modes of mechanical ventilation, renal replacement therapy, cardiovascular support, hemodynamic and neurologic monitoring; management of poisonings, pulmonary, hematologic/oncologic, and metabolic disorders; pharmacologic principles; transplantation; procedural sedation; and infectious diseases. However, the complex needs of the critically ill child also require that intensivists be prepared to assume a leadership role in the coordination of this care among persons from multiple disciplines who are part of the team. In addition, the pediatric intensivist has to develop an understanding of the ethics of critical care medicine and be able to balance complex and high technology care with humanistic principles and respect for the patient as a human being. The intensivist must also develop skills for evaluating medical literature that reports clinical and/or basic science research and develop the ability to teach learners of different levels effectively.

Requirements

The American Board of Pediatrics

The required elements for the education and training of pediatric intensivists in patient care have been defined over time and continue to evolve (see Chapter 1 for the history of the specialty). The American Board of Pediatrics (ABP) has developed a list of content specifications for the subspecialty examination. While this list is not intended to serve as a curriculum, the pediatric intensivist sitting for the examination is expected to be familiar with more than 2000 items listed on 169 pages. The Pediatric Critical Care Medicine Content Outline has 16 sections that include the following: cardiovascular, respiratory, neurology and neuromuscular, infectious disease, immunology and inflammation, renal and electrolytes, metabolism and endocrinology, hematology/oncology, gastroenterology/nutrition, poisonings, toxins and overdoses, trauma and burns, pharmacology, anesthesiology and postoperative care, technical procedures, principles of monitoring, special critical care issues, and core knowledge in scholarly activities. To qualify for the ABP subspecialty examination, applicants are required to have certification in general pediatrics, to have completed training in critical care medicine in a program accredited by the Accreditation Council for Graduate Medical Education (ACGME), and to provide evidence of meaningful research during training.

The Accreditation Council for Graduate Medical Education

Pediatric critical care medicine is one of the accredited subspecialties of the ACGME. As such, oversight for the training programs is provided by the Pediatric Review Committee. In addition to meaningful scholarship by faculty members and trainees, requirements for program accreditation include faculty credentials such as subspecialty board certification, an active role in the training program, and research productivity and funding. Fellowship training requirements include but are not limited to defined patient numbers and adequate opportunity to develop procedural competence, a didactic curriculum that is comprehensive and is regularly implemented, formal education related to developing teaching skills, and evaluation of competency. These requirements are evaluated by the Pediatric Review Committee according

to six competencies, as outlined at the following Web site: www.acgme.org/outcome/comp/GeneralCompetenciesStandards21307.pdf.

ACGME Core Competencies

In 1999, the ACGME initiated an outcome project to design a conceptual framework for education and training according to six common program requirements or general competencies.[1] The objective of the outcome project was to "ensure and improve the quality of graduate medical education."[2] The ACGME recommends that trainees demonstrate the following:

1. *Patient care* that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health
2. *Medical knowledge* regarding established as well as evolving biomedical, clinical, and cognitive sciences, with the ability to apply these concepts to patient care
3. *Practice-based learning and improvement* involving self-evaluation with regard to patient care, appraisal, and utilization of scientific evidence
4. *Interpersonal and communication skills* that result in effective information exchange and partnership with patients, their families, and other health professionals
5. *Professionalism* manifested through a commitment to professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population
6. An awareness of and responsiveness to the health care system and the ability to utilize system resources to provide optimal care in a *systems-based practice*[1]

These core competencies should be used to inform the content of the education program and guide and coordinate evaluation of residents or fellows in their development of medical knowledge.[3]

Duty Hours

While many persons remember fellowship training that involved 16-hour days, being on call every other night, and working on research projects on weekends off, new regulations have led to major changes in fellowship training schedules. In the United States, duty hours are now limited and may be further shortened.[4] The duty-hour restrictions are based on studies suggesting that sleep deprivation causes significant decrements in physician performance in the areas of neurocognition and clinical tasks that result in medical and surgical errors. On July 1, 2003, the ACGME implemented duty-hour regulations for all ACGME-accredited programs. These regulations included limitation of total average work hours to 80 hours per week; limitation of the length of an individual shift to 24 hours plus 6 hours for task completion and handover; the requirement of at least 10 hours off between shifts; and the requirement of at least 4 days off over a 4-week period. More recently, the Institute of Medicine has suggested further shortening of duty hours.[4] Historically the limitation of duty hours is related to the Libby Zion case[5] and the findings of the Bell Commission in New York.[6] Whereas the death of Libby Zion was attributed to the physician trainees' long work hours, the Bell Commission findings indicate that the evidence was not convincing in this regard. Rather, this Commission believed that her death was more likely related to knowledge deficit and lack of supervision of trainees.

While few other issues in medicine have generated emotional discussions of such magnitude within the medical community in the United States, work-hour restrictions have long been in place in Canada, France, and other European nations. Since the implementation of duty-hour restrictions, a number of studies have evaluated the effects of this mandate on patient care. Landrigan et al.[7] studied the effect of work hours on serious medical errors in the intensive care unit (ICU) comparing a traditional work shift of 24 hours or more with every third night on call and an "intervention" schedule that eliminated extended work shifts and reduced work hours each week. The interns made 35.9% more serious medication errors while working under the traditional schedule. In addition, the interns made 5.6 times as many serious diagnostic errors while working a traditional work shift. However, in a more recent study, the same group evaluated the effects of the ACGME duty-hour limits on sleep, work hours, and safety in a group of 220 residents[8] and found no changes in the total numbers of work and sleep hours. More importantly, rates of medication errors, resident depression, and resident injuries did not decrease, and educational ratings did not improve. Volpp et al.[9] studied the effects of duty-hour restriction on the mortality rate of hospitalized Medicare beneficiaries[9] and found no worsening or improvement. On the other hand, Prasad et al.[10] conducted a retrospective cohort study comparing ICU mortality in teaching and nonteaching hospitals before and after implementation of duty-hour regulations and found that there was a decrease in in-hospital mortality rates among ICU patients following the implementation of duty-hour restrictions regardless of teaching or nonteaching hospital status.

Meanwhile, the amount of information and number of skills that have to be acquired and mastered by pediatric intensivists continue to increase. In spite of this situation, Chudgar et al.[11] showed that medical education and teaching methods in the ICU have not changed since the implementation of the ACGME duty hour restrictions. In addition, the program directors who were surveyed were concerned that the new restrictions have negatively affected resident attitudes, continuity of care, and their availability for educational activities. Kairys et al.[12] showed that there has been a decline in the total operative cases reported by graduating surgical residents. In addition to the potential to reduce clinical skills and fracture continuity of care, the plan to further reduce duty hours has generated other concerns. As the work hours of trainees are shortened, patient care tasks have fallen on attending physicians who do not have work-hour limits. This group of physicians tends to be older and they have many other responsibilities that include research, teaching, and administration. Mercurio and Peterec[13] aptly describe this dilemma in their 2009 article in *Pediatrics*, "Attending Physician Work Hours: Ethical Considerations and the Last Doctor Standing." Other concerns include the lack of continuity of physician-patient interactions. Charap[14] writes: "Reducing work hours limits the numbers of patients that residents care for and the extent of residents' involvement with individual patients. By limiting the diversity, intensity, and continuity of physician-patient interactions, our residents will probably have gaps in their clinical skills. These skills are not reflected in in-service or board certification examinations. They deal with recognizing patterns and discerning the very sick patients from the not-so-sick patients."[14]

Regardless of where the road of duty hours takes us, we have to develop novel ways of teaching to ensure that the training of future pediatric intensivists includes all aspects of patient care, education, research, and leadership and that this training takes place within the context of the duty-hour restrictions.

Box 17–1 Principles of Adult Learning

- Relate to learner's current experience and knowledge.
- Adults are self-directed and autonomous.
- Motivation comes from intrinsic and extrinsic factors.
- Adults learn best by active participation and practice.
- Multiple techniques/multiple exposures.
- Timely feedback and reinforcement.

Adult Learning

In developing a curriculum that allows understanding and utilization of the core competencies by trainees as well as continuing medical education for practitioners, the approach to teaching and feedback should be based on principles of adult learning (Box 17-1).[15] Adult learning is fundamentally different from childhood learning, and though a continuum between these two types of learning could be argued, the difference between them is based on several key distinctions. Adult learners have a greater depth and breadth of experiences and knowledge upon which to draw and relate new experience and learning.[15,16] To assimilate new information, adults need to be able to integrate new ideas with what they already know. Furthermore, information that conflicts with what is already believed to be true is integrated more slowly.[17]

Adults are self-directed and autonomous. As a consequence, their education is typically most effective when programs facilitate self-learning with specific goals of acquiring practical information. Motivation for learning is both intrinsic (personal need for new knowledge base or skill set) and extrinsic (professional expectations from colleagues or authority figures). Adults benefit from an appropriately challenging learning environment.[16,17]

Adults learn best when they are active participants in the learning process and are allowed to practice newly acquired skills and concepts.[16,18] Adults have varied experiences and knowledge and do not all learn in the same way. Therefore, a multimodal approach to teaching with multiple exposures to content is more effective than any single approach/exposure method. Finally, adult learners require and often seek out feedback, and therefore they learn more effectively when given timely feedback that reinforces newly acquired information.

The Dreyfus and Dreyfus Model of Skill Acquisition

Stuart Dreyfus, an applied mathematician, and Hubert Dreyfus, a philosopher, developed a model of skill acquisition based on their studies of fighter pilots.[19] This model addresses the stages in the development of professional skills. In addition to being studied in fighter pilots and military personnel, the model has been studied in chess players and car drivers; more recently it has been applied to skill acquisition in clinical medicine. The Dreyfus model proposes that skill acquisition is not different from the continuum of human development, with stages of skill acquisition designated as novice, advanced beginner, competent, proficient, expert, and finally, master. The learner needs to acquire certain skills and learn certain concepts at each level; therefore, teaching methods must match the level of development (Table 17-1).

Methods of Teaching

It is incumbent upon those who oversee the ICU to be responsible for the education of those who occupy it. There are different levels of learners and educators. The faculty physician is the expert or master and serves as the facilitator/educator for medical students, residents, fellows, nurses, and other allied health personnel. This tenet requires the faculty physician to strive constantly to attain and maintain the expert or master status. To have effective teaching in the ICU, the faculty physician must understand that a gap often exists between what faculty physicians and trainees perceive as adequate teaching.[20] Furthermore, one must overcome traditional barriers to education, which include lack of dedicated teaching time, high clinical workload, and poor continuity between faculty physicians and trainees,[20] especially with the requirement of alternative scheduling, such as shift work, to accommodate the 80-hour work week.[11]

Education in the ICU setting consists of teaching basic principles but also includes an ongoing, ever-changing process that depends on new literature and accumulation of medical knowledge. Teaching tools should be designed and selected to optimize improvement of both physician performance and health care outcomes.[18] A learning needs assessment is crucial to effective continuing medical education (CME) and interactive learning associated with opportunities to practice learned materials/skills in an environment that offers sequenced and multifaceted activities.[18] A systematic review that evaluated 37 studies of CME showed that "multiple media, multiple techniques of instruction, and multiple exposures to content are suggested to meet instructional objectives intended to improve clinical outcomes."[21] Many of the features that are instrumental in successful CME initiatives are also principles of successful adult learning. Hence, the tools necessary for educating intensivists should include these principles. Current teaching methods were assessed by a survey of critical care medicine program directors (pediatric, surgery, medicine, and anesthesia), and Table 17-2 summarizes the methods used. The most common method of teaching in the ICU is the bedside, case-based approach, with 80% of programs spending at least 2 hours a day on this activity.[11] Of the methods listed, 45% of the programs wished to have computer or human patient simulation, and 50% would incorporate more Web-based learning modules, which have been shown to be efficacious.[22] Other tools or teaching strategies include debriefing in the ICU,[23] competency-based conference morning report,[24] and changing didactic schedules to accommodate nonstandard work sessions (i.e., shift work).[25]

In 2004, the Society for Critical Care Medicine released "Guidelines for critical care medicine training and continuing medical education,"[26] which addressed the needs of physician education in critical care medicine on a continuum from the resident to the intensivist. Table 17-3 is a representation of the broad scope of educational objectives for critical care medicine fellows and intensivists that includes two broad areas of learning: clinical and administrative.

Teaching at the Patient's Bedside

Case-based teaching at the bedside is thought to be one of the most effective means of educating clinicians in the understanding of disease processes and evaluation and management of critically ill patients. Nothing is more dramatic and unforgettable

Table 17–1 Dreyfus and Dreyfus Model of Skill Development Applied to the Development of Competence in the Subspecialty of Critical Care Medicine

Level of Learning and Characteristics	Examples of Learner Level in Critical Care Medicine	Teaching Implications
NOVICE	**FIRST-YEAR PCCM FELLOW**	
Rule driven Uses analytical reasoning and rules to link cause and effect Synthesis of information is based on knowledge acquired during residency training Big picture may be elusive	Interviews patient and performs a physical examination that is focused on the critical illness May not be able to focus the information on the basis of a differential diagnosis Does not see the big picture	Teach basic critical care concepts Point out subtle but meaningful diagnostic information in the history and physical examination Eliminate irrelevant information Highlight discriminating features and their importance to the diagnosis Encourage reading about two diagnostic hypotheses at the same time
ADVANCED BEGINNER	**SECOND-YEAR PCCM FELLOW**	
Sorts through rules and information to decide what is relevant on the basis of past experience Uses analytical reasoning and pattern recognition to solve problems Able to abstract from concrete and specific information to more general aspects of a problem	Can generate more specific differential diagnosis while obtaining history and physical examination Capable of filtering relevant information to formulate a unified summary of the case Can abstract pertinent positives and negatives from the review of systems and incorporate them into the history of present illness	Expose learner to clinical cases proceeding from common to uncommon Emphasize the use of semantic qualifiers Encourage formulation and verbalization of differential diagnosis and treatment plan Good coaching: help learner become attentive to the meaningful pieces
COMPETENT	**THIRD-YEAR PCCM FELLOW**	
Emotional buy-in allows learner to feel appropriate level of responsibility More expansive experience tips the balance on clinical reasoning from methodical and analytic to identifiable pattern recognition of common clinical problems Sees the big picture Complex/uncommon problems still require reliance on analytical reasoning	Recognizes common patterns of illness based on previous encounters Sees consequences of clinical decisions, which leads to emotional buy-in to learning Will methodically attempt to reason through complex or uncommon problems Responsible for decision-making process	Balance supervision with autonomy in decision making Hold learners accountable for their decisions Don't tell them what to do; ask what they want to do Critical for learner to see a breadth and depth of patient encounters to construct and store in memory a large repertoire of illness scripts Tip the balance from clinical reasoning to pattern recognition
PROFICIENT	**CLINICAL INSTRUCTOR**	
Breadth of past experience allows reliance on pattern recognition of illness: problem solving intuitive Still needs to fall back to methodical and analytic reasoning for managing problems because exhaustive number of permutations and responses to management have provided less experience in this regard than in illness recognition Is comfortable with evolving situations, able to extrapolate from a known situation to an unknown situation Can live with ambiguity	Starts to match findings with those encountered in past experience Data gathering more effective and efficient Sees patient through different lens than the student Engages in process of clinical reasoning to find the best intervention	Needs to work alongside and be mentored by an expert Must develop capacity to know ones' limitations and step back and call on additional resources when stretched beyond one's capabilities
EXPERT	**ASSOCIATE PROFESSOR**	
Thought, feeling, and action align into intuitive problem recognition and intuitive situational responses and management Open to notice the unexpected Clever Discriminates features that do not fit a recognizable pattern	Broad repertoire of illness scripts, based on clinical experience that allows immediate action for majority of clinical encounters Likes to deal with diagnostic dilemmas When presented with diagnostic dilemma, will slow down and look it up	Keep up the challenge Needs ongoing experience and ongoing exposure to interesting and complex cases to avoid complacency and to help transcend beyond this level Should be apprenticed to a master who models the skills of the reflective practitioner and a commitment to lifelong learning

Continued

Table 17–1 Dreyfus and Dreyfus Model of Skill Development Applied to the Development of Competence in the Subspecialty of Critical Care Medicine—cont'd

Level of Learning and Characteristics	Examples of Learner Level in Critical Care Medicine	Teaching Implications
MASTER	**ASSOCIATE PROFESSOR/PROFESSOR**	
Exercises practical wisdom Goes beyond the big picture to that of culture and context of each situation Deep level of commitment to the work Great concern for right and wrong decisions that fosters emotional engagement Intensely motivated by emotional engagement to pursue ongoing learning and improvement Reflects in, on, and for action	The clinician that everyone goes to with problem cases Recognizes subtle features of a current case reminiscent of cases seen over the years Painstakingly revisits past cases or identifies common thread that will help treat the current clinical problem Vision extends beyond individual practice Contributes to bigger context to improvements in the field Intense internal drive to learn and improve Practical wisdom	Self-motivated to engage in lifelong learning and practice improvement

PCCM, Pediatric critical care medicine.
Adapted from Carraccio CL, Benson BJ, Nixon LJ, et al: From the educational bench to the clinical bedside: translating the Dreyfus Developmental Model to the learning of clinical skills, *Acad Med* 83:761-767, 2008.

Table 17–2 Methods Used in the Education of Physicians

Teaching Method	%
Bedside, case-based teaching	94.4
Lecture series	79.0
Morbidity and mortality conference	72.6
Syllabus of articles	63.7
Journal club	62.9
Multidisciplinary rounds	60.5
Rounding sheets	58.1
Web-based articles	29.0
Web-based lectures	27.4
Psychomotor skills laboratories	24.0
Full-body simulator	15.3
Cadaver/animal laboratories	8.1
Computer simulation	4.8
Palm pilot algorithms	3.2
Standardized patients	3.2

Modified from Chudgar SM, Cox CE, Que LG, et al: Current teaching and evaluation methods in critical care medicine: has the Accreditation Council for Graduate Medical Education affected how we practice and teach in the intensive care unit? *Crit Care Med* 37:49-60, 2009.

than seeing a patient with fulminant meningococcemia and purpura fulminans. Perhaps less dramatic but just as effective are instances when one palpates a thrill, hears a gallop, feels an enlarged liver or spleen, listens to wheezing or stridor, or performs a detailed neurologic examination in a patient who has experienced a middle cerebral artery stroke or a spinal cord injury. Even medical technology is better taught at the bedside. When the learner is introduced to a child with severe asthma exacerbation who is receiving mechanical ventilation and the learner is shown the flow volume loops exhibited at various ventilator rates and inspiratory:expiratory ratios, she or he is likely to come away with a much better understanding of the principles of mechanical ventilation in someone with a prolonged time constant. The different waveforms on bedside monitors can be used to demonstrate important pathophysiologic principles. Examples include malignant intracranial pressure waveforms with a wide systolic-diastolic variation reflecting the poor compliance of a diffusely swollen brain; the lack of a dicrotic notch in the arterial waveform of someone with hypovolemia; changes in systolic pressure associated with inspiration in a patient with pulsus paradoxus; and the right ventricular tracing of a subclavian venous catheter meant to be in the right atrium that has been inserted too far. Showing trainees extracorporeal membrane oxygenation circuits, continuous veno-venous hemodialysis and ultrafiltration machines, high-frequency oscillators, and ventricular assist devices while they are being used in patient care provides the "aha" moment often not attained while viewing slides in a darkened room during a lecture.

In addition, when trainees present the historical data and physical findings of their patients to the attending physician during bedside rounds, they can be taught to describe the information relating to their patients in a succinct manner and discriminate between important and less important information, develop a list of differential diagnoses, and formulate a treatment plan. They learn to "think on their feet" and can be taught how to put data together to determine a cohesive diagnosis that will lead them to the right conclusions regarding diagnostic and management decisions.

In these days of duty-hour limitations, electronic medical records, and computerized order entry, it is easy to lose sight of the patient and stray from the bedside. However, clinical acumen remains largely dependent on exposure to a large number of clinical cases in building medical knowledge and experience in each learner, no matter what level they are at. Therefore, case-based bedside teaching should always be a major component of clinical teaching. Historically, patients have always been and should continue to be our best teachers.

Procedural Training

In order to provide care to critically ill children, the intensivist needs to learn many procedural skills. These skills include endotracheal intubation, thoracostomy, use of pacemakers,

Table 17–3 Essential Clinical and Administrative Learning Points

Clinical	Administrative
Identify and teach others to identify the need for/provide care for all critically ill patients	Evaluate current ICU hospital policies and suggest improvements
Provide and teach others resuscitation for any patient sustaining a life-threatening event	Triage critically ill patients to optimize care delivery within the institution
Initiate, manage, and wean patients from mechanical ventilation and teach others new methods and devices for management of respiratory failure	Improve resource utilization and maintain patient care quality by facilitating triage of patients to limited institutional critical care beds and caregivers
Initiate critical care to stabilize and manage patients who require transport	Develop programs and change unit practice to improve care of critically ill patients
Instruct other qualified caregivers and the lay public in the theory and techniques of CPR	Develop programs for patient safety monitoring and error reduction
Treat cardiogenic, traumatic, hypovolemic, and distributive shock with conventional and state-of-the-art approaches	Actively participate in quality assurance processes, including morbidity and mortality conferences, process improvement teams, and Joint Commission Accreditation of Healthcare Organizations preparation
Recognize the potential for multiple organ failure and institute measures to avoid or reverse this syndrome	Support the process of assessing patient and family satisfaction and participate in tool development and implementation
Identify life-threatening electrolyte and acid-base disturbances, provide treatment, and monitor outcome	Encourage and enhance good relationships with other health care providers
Identify and initiate discussions involving ethical issues and parent/patients' wishes in making treatment decisions using advance directives and other methods	Understand advanced concepts important for compensation of critical care services and contractual issues related to providing critical care services and performing the business of medicine
Diagnose and treat common and uncommon poisonings	Develop skills for teaching critical care
Teach appropriate use and monitoring of procedural sedation and use advanced pain management strategies	Develop and evaluate curriculum changes for ICU caregivers, fellows, and residents
Diagnose malnutrition and use/monitor advanced nutrition support methodologies	Evaluate, modify, and approve ICU hospital policies
Provide invasive and noninvasive monitoring for titrating therapy; prioritize complex data to support action plan	Improve resource utilization and maintain patient care quality by planning for future needs for institutional and regional critical care resources
Use and teach medication safe practice guidelines and determine cost-effectiveness of therapeutic interventions	Develop programs and change unit, institution, and regional practice to improve care of critically ill patients
Develop skills of ICU nurses and ancillary personnel in caring for critically ill patients and provide in-service education	Use existing tool sets to assess patient and family satisfaction and direct the development of new tools when appropriate
Use, teach, and help enforce methods of infection control	Develop programs and document improvement in patient safety monitoring and error reduction
Communicate effectively with patients, families, and other involved members of the health care team about all treatment decisions and patient prognosis	Develop high-quality relationships with other health care providers
Continue to augment knowledge by assimilating peer-reviewed published medical literature through self-directed learning and CME activities	Teach the business of medicine
Diagnose and treat a sufficient number of patients with critical illness using conventional and state-of-the-art approaches to maintain clinical proficiencies	Develop collaborative and productive relationships with other specialist physicians and model joint clinical planning in managing complex ICU problems

CME, Continuing medical education; *CPR,* cardiopulmonary resuscitation; *ICU,* intensive care unit.
Adapted from Dorman R, Angood PB, Angus DC, et al: Guidelines for critical care medical training and continuing medical education, *Crit Care Med* 32(1):263-272, 2004.

central venous and arterial catheter placement, pericardiocentesis, and others. The ACGME and the ABP require documentation of competency in these skills. Teaching procedural skills should include didactic sessions on related anatomy, indications, and complications. Videos of certain procedures are available on Web sites such as that provided by the *New England Journal of Medicine* (http://content.nejm.org/misc/videos.dtl?ssource=recentVideos). If available, low or high-fidelity manikins should be used to teach proper technique and for practice sessions. Procedural training also should include the components required for the maintenance of aseptic technique, and quality improvement processes must be in place to reduce or eradicate nosocomial infections. Subsequently, trainees should be supervised during their initial attempts at each procedure until they demonstrate adequate skill to proceed independently without excessive risk to the patient.

Simulation Training

Simulation training has been used extensively in the aviation industry since the 1930s. Medical simulation began in the early 1960s with simple resuscitation manikins. This step was followed later by the development of more realistic manikins for training in anesthesiology. For many years, medical simulation did not progress because of the high cost of devices as well as the thought that it was unlikely that complex human physiology could be replicated in a simulator. In the past 20 years, however, much advancement has occurred in high-fidelity medical simulation. Medical simulators are now sophisticated and specialized, ranging from obstetric models to laparoscopic surgical simulators to a simulated premature newborn. In addition to providing a better representation of physiologic and pathophysiologic states, simulators also have become more specific in their design. Low-fidelity medical simulators include partial task trainers, also called procedural trainers, which are designed to train users to perform a defined psychomotor skill. Examples include a partial torso designed to teach central venous cannulation techniques and a manikin head utilized to teach endotracheal intubation. High-fidelity manikins are partial or whole-body manikins that are instructor-driven. Computer software is programmed to produce physiologic signals that are displayed on a computer screen designed to represent a patient on a monitor. Manikins are programmed to display physical findings such as chest rise, breath sounds, pulses, and vocalizations. In a simulated training session, the trainee can gather patient information via the monitor and physical findings demonstrated by the manikin, determine a course of action, and implement a treatment plan. Simulator responses are generated by the instructor via computer control or via preprogrammed algorithms in reaction to diagnostic choices and treatments provided by the trainee. The sessions can be recorded for use in debriefing immediately after the simulation scenario, affording a final opportunity to emphasize the educational objectives of the exercise.

Simulation is a medical educational tool with multiple advantages. Knowledge and skills can be integrated in a real-time fashion, providing opportunities for both teaching and evaluation. Training can be repetitive and standardized and the training environment is safe for the "patient" and "low-stress" for the trainee. Simulation is well suited to education in the ICU. ICUs have complex patients with rapidly changing physiology and acute needs. ICU caregivers work in a multidisciplinary environment that involves complex team dynamics, communication challenges, and high-risk situations. In addition, the ICU is often the site for high-risk procedures. These procedures include pericardiocentesis or emergent central venous catheter insertion and require expertise and the need for the procedure to be performed rapidly yet safely. In the past, these procedures were taught via the "see one, do one, teach one" philosophy. This paradigm was insufficient. The randomness of illness does not always provide trainees with ample opportunity to learn complex skills, and for certain procedures that are performed infrequently, trainees do not have sufficient practice to master the skills. In addition, patient safety frequently dictates that the most experienced caregiver perform the procedure.[27] Simulation allows instruction and psychomotor skills practice in a safe environment along with the ability to educate multiple trainees. Finally, in addition to teaching particular skills, simulators can be programmed to reflect procedure-related complications and medication errors to prepare trainees for such events.

Another advantage of simulation is the ability to provide on-site training. ICUs are filled with complex equipment, may have off-site supply locations, and have personnel with multiple competing demands. Simulators provide the opportunity to replicate this complex environment. They are portable and can be placed within the ICU. This feature provides the advantage of placing the trainee in the setting of patient care, with the opportunity to use actual ICU equipment and supplies within the environment in which they are expected to provide patient care. For example, in a scenario of ventricular fibrillation, the trainee must recognize the dysrhythmia, initiate cardiopulmonary resuscitation (CPR), and call for intravenous epinephrine and the defibrillator. Team members must perform adequate CPR while others obtain the resuscitation cart for access to emergency medications, and still other personnel must retrieve the defibrillator and set it up for use. The simulation exercise helps to emphasize knowledge not only of appropriate treatment of dysrhythmia but also tests the knowledge of resource location and teamwork organization.

It seems fitting to finish this section with a discussion of teamwork in simulation training, because it is one of the most vital components to a well-functioning ICU. Teamwork is necessary to accomplish many tasks in the ICU, from the traditional code team responding to a cardiac arrest to the routine vascular catheter placement in a patient. ICU personnel are expected to function as well-organized teams. However, team members often are unaware of basic teamwork principles and may not have had opportunities to practice teamwork skills. In addition, medical teams are usually ad hoc; that is, it is often unknown which physicians, nurses, or respiratory therapists will have to respond to a patient crisis at any given time. This characteristic adds another layer of difficulty to teamwork training. Again, aviation and anesthesiology have shown us the utility of simulation in teamwork training. In the mid 1980s, the aviation industry developed protocols for Cockpit Resource Management, later changed to Crew Resource Management, or CRM. The field of anesthesia adapted CRM principles to anesthesia training and eventually developed anesthesia crisis resource management protocols.[28,29] Principles of crisis resource management include effective leadership, organization, communication, effective use of resources, and stress management.[29]

Simulation is an effective tool for teamwork training. Hunt et al.[30] used simulated mock codes to evaluate team performance and target educational interventions during emergent resuscitations in North Carolina emergency rooms. Wayne and colleagues[31] also used simulation to assess adherence to Advanced Cardiac Life Support (ACLS) quality indicators during ACLS events. All trainees received traditional training, with some trainees receiving additional ACLS training using a human patient simulator. The simulator-trained group was several times more likely to adhere to American Heart Association standards than were the students who received only traditional training.[31] These are just two of the many studies that show that CRM principles can be effectively evaluated, learned, and applied via simulation with team performance improved when compared with traditional training.

Simulation offers a strong educational opportunity, creating instances to teach, practice, and evaluate. Cognitive and

psychomotor skills can be integrated in a realistic environment while patient and trainee safety is protected. Simulation tools still lack some sophistication that would be useful for ICU training, such as simulated neurologic findings, changes in skin color and temperature, or even capillary refill. Technology, though, continues to advance, and the future of simulation tools is very promising.

Web-Based Education

Numerous resources are available on a wide variety of Web sites. Information is readily available from PubMed and Google. Innumerable "podcasts" are available on various topics. Online textbooks such as *Goodman and Gilman's Pharmacologic Basis of Therapeutics* provide a wealth of information and include video clips of physiologic theories such as activity in the neuromuscular junction. Multiple critical care societies developed and sponsor a Web site on principles of pulmonary artery catheter monitoring called the Pulmonary Artery Catheter Education Program (http://www.pacep.org). Congenital heart lesions and related surgical repairs are shown on a variety of Web sites, including one from the Johns Hopkins Helen B. Taussig Children's Heart Center/Cove Point Foundation Web site (http://www.pted.org/). The Society of Critical Care Medicine hosts an educational Web site that includes the PICU course—a site with more than 30 PowerPoint lectures that can be downloaded for use (http://www.learnicu.org/Clinical_Practice/Fundamentals/RICU/Pages/default.aspx). Some of the presentations now have voice-overs and therefore can be used for independent study. A number of institutions have created Web-based distance education on programs such as Blackboard. The American Academy of Pediatrics has developed a Web-based critical care medicine certifying examination review product (PREP-ICU) containing questions and extensive discussions based on content specifications of the ABP (http://www.aap.org/profed.html). Although Web-based education can never replace patient bedside teaching, it provides ideal supplements for self-study in the context of duty-hour restrictions.

Evaluation and Assessment of Competency

Since the ACGME introduced the use of competency-based outcomes to define the learning experiences of residents and fellows, training programs have struggled with the implementation of these requirements in two domains: how to teach the competencies and how to determine that competency has indeed been achieved. Various methods have been used for evaluation (Table 17-4).

Epstein and Hundert[32] define competence as the "habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and reflection in daily practice for the benefit of the individual and community being served." They further state that "competence builds on a foundation of basic clinical skills, scientific knowledge, and moral development" and propose that competence is made up of several dimensions, each with a separate set of skills (Box 17-2). In one study, the authors performed a MEDLINE database search from 1966 to 2001 for articles that studied the reliability of measures of clinical or professional competence of physicians. One hundred ninety-five publications were reviewed. The most commonly used methods of assessments were (1) subjective assessment by supervisors; (2) multiple-choice examinations to evaluate factual knowledge and abstract problem solving; and (3) standardized patient assessments of physical examination and technical and communication skills. Rating the performance of trainees on standardized patients, human patient simulation, multiple-choice examinations, and objective structured clinical examinations provides important information regarding basic knowledge and the ability to perform certain skill sets, such as obtaining an accurate history and physical examination or successfully intubating the trachea. However, the evaluation of the ability to apply knowledge to patient care, the capability of working as a team member, and the development of physician-patient relationships can only be assessed by direct observation of real-life patient interactions. Epstein and Hundert[32] found that few of the assessments they reviewed evaluated trainees in terms of clinical reasoning, judgment, time management, learning strategies, and teamwork. They suggest that tools should be developed to assess competency in these domains.

Pangaro[33] writes that we need to invest in a descriptive evaluation by constructing a vocabulary that describes growing expertise that can be used from one year to the next. Such a vocabulary has been developed at the Department of Medicine at the Uniformed Services University, and it describes trainees as they develop competence while advancing from one level to the next. This vocabulary is referred to as Reporter to Interpreter to Manager-Educator (Table 17-5). Pangaro[33] summarizes the issue of assessing competence very well: "The assessment of competence requires a whole series of performances that in each moment of interaction with a patient, the competent physician must bring many qualities to bear, and what they will require varies from patient to patient."

In order to assess competency, we must understand what is being assessed. Once this has been determined, methods of evaluation should be developed. The methods of evaluation must in turn be assessed in terms of their usefulness.

Table 17–4 Methods of Evaluation to Determine Clinical Competency

Method of Evaluation	Settings
Direct observation	Objective structured clinical examination, standardized patients, human patient simulators, procedure fairs
Postrotation tests	Case-based scenarios or vignettes
Subspecialty in-training examinations	Yearly computerized examination administered by the ABP: used to evaluate level of knowledge acquisition, assesses needs of trainees and program components of education
360-degree evaluations	Evaluations from nurses and other allied health personnel and patients and their families provide a picture of the trainees' professionalism and/or communication skills
Clinical vignettes, case-based discussions	Discussion of clinical cases with review of pertinent findings and evidenced-based management points

ABP, American Board of Pediatrics.

Box 17–2 Dimensions of Professional Competence

Cognitive
- Core knowledge
- Basic communication skills
- Information management
- Applying knowledge in real-world situations
- Using tacit knowledge and personal experience
- Abstract problem solving
- Self-directed acquisition of knowledge
- Recognizing gaps in knowledge
- Generating questions
- Using resources (e.g., published evidence, colleagues)
- Learning from experience

Technical
- Physical examination skills
- Surgical/procedural skills

Integrative
- Incorporating scientific, clinical, and humanistic judgment
- Using clinical reasoning strategies appropriately
- Linking basic and clinical knowledge across disciplines
- Managing uncertainty

Context
- Clinical setting
- Use of time

Relationship
- Communication skills
- Handling conflict
- Teamwork
- Teaching others

Affective/Moral
- Tolerance of ambiguity and anxiety
- Emotional intelligence
- Respect for patients
- Responsiveness to patients and society
- Caring

Habits of Mind
- Observations of one's own thinking, emotions and techniques
- Attentiveness
- Critical curiosity
- Recognition of and response to cognitive and emotional biases
- Willingness to acknowledge and correct errors

Adapted from Epstein RM, Hundert EM: Defining and assessing professional competence, *JAMA* 287:226-235, 2002.

Table 17–5 Characteristics of a Trainee Progressing from Reporter to Manager-Educator

Category	Characteristics
Reporter	Accurately gathers and communicates information about his own patients Basic knowledge to know what to look for Being on time Following up results Distinguishes abnormal from normal Confidence to identify and label a new problem Requires sense of responsibility Consistency in achieving bedside skills
Interpreter	Must transition to the ability to prioritize and develop a list of differential diagnoses Requires higher level of knowledge More skill in selecting the clinical findings that support possible diagnoses Applies test results to specific patients Transforms from bystander to active participant in patient care
Manager-Educator	Requires even more knowledge, judgment, and confidence Decides what action needs to be taken Proposes and selects options for patients Self-directed learning: reads deeply Goes beyond the basics Shares new learning with others Has the drive to look for hard evidence on which clinical practice can be based and to determine whether the evidence will stand up to scrutiny

Modified from Pangaro LN: Investing in descriptive evaluation: a vision for the future of assessment, *Med Teach* 22:478-481, 2000.

Milestones

The ACGME Outcome Project is composed of several phases. Phase I required that training programs define objectives encompassing the six competencies. In Phase II, the competencies were integrated into the curriculum, and programs expanded the evaluations to assess performance. In Phase III, performance data will be used to make changes to the curriculum, and benchmark programs will be identified in Phase IV.

While there has been success in establishing individual evaluations of competencies such as those listed in Table 17-4, the evaluation of overall competency as trainees advance from one level to the next and their readiness for independent practice is still lacking. More recently, there have been efforts to evaluate training in terms of a developmental continuum. Carraccio et al[34] and Green et al.[26] have addressed this need by designing developmental milestones for training based on the Dreyfus model. For each of the six ACGME competencies, developmental milestones and corresponding evaluation methods are listed, with a time frame at which the trainee is expected to achieve the particular milestone. For example, under the patient care competency, the trainee is expected to achieve competence by the first six months of training. This competency will be evaluated through the use of standardized patients and direct observation. On the other hand, the ability to recognize disease presentations that deviate from common patterns and require complex decision making may take longer to achieve and may be more difficult to assess.

Education in Research, Scholarship, and Leadership

Training in the conduct of research is an integral part of pediatric critical care medicine. Meaningful scholarly activity is required by the ABP for board certification. Research activity

by faculty members and fellows is a key to accreditation of fellowship programs by the ACGME Resident Review Committee. Research in pediatric critical care is discussed in Chapter 4.

The pediatric intensivist has a central role in the education of peers and team members. Therefore, training should include the development of teaching skills that include evidence-based review of the literature, use of audiovisual aids, scientific presentations, and medical writing. In addition, pediatric intensivists are expected to manage ICUs and coordinate team members who provide multidisciplinary care to critically ill patients. As previously noted, simulation can contribute to teaching leadership skills. However, to date, training related to these skills has been lacking. Stockwell et al.[35] found that while training in leadership and management was considered an important aspect of pediatric critical care fellowship, most of the intensivists surveyed in their study felt inadequately prepared for this aspect of their work.

Mentorship

"And so it's been for me these long years. I've carried my mentor everywhere. If I get sloppy, I wonder, "What would he think of me now?" And if I'm in a tight spot clinically, he prods me back to the literature. When I'm impatient with patients, I remember his patience with me. When I'm asked to teach, I do so willingly because that is what he did. When I begin to doubt myself, I remember his belief in me. And if I am ready to quit, I can see him standing there before me in his long white coat, with stern look and stethoscope, and I go on.

What has he been for me, this mentor of mine? He's been like a father to me, but more than a father. He has been my companion in medicine, to help me through the loneliness that medicine can bring and to share with me the joy that medicine can be. My mentor has, through me and those of my students, cared decently and compassionately for countless patients. When I have cured a patient or two, why, so has he."(Michael A. LaCombe, MD, FACP, William Morgan Teaching Symposium, University of Rochester, July 20, 1989.)

Mentorship is defined as a "dynamic, reciprocal relationship in a work environment between an advanced career incumbent (mentor) and a beginner (protégé), aimed at promoting the development of both."[36] Mentorship is at the core of the training of medical students, residents, and fellows in patient care, research, and education. While the benefits to the mentee are often emphasized, it is clear that mentors benefit as well[37,38] because they tend to have greater satisfaction in their careers. Mentorship takes place at many levels. It can begin during medical school, where a mentor may guide and even inspire a student to choose a certain career path. During residency and fellowship, a mentor can be a major component in the development of the trainee's clinical knowledge and patient care skills. In addition, if the resident or fellow decides to pursue a career that includes research, the mentor can help identify a research focus and provide guidance in terms of literature search, writing a proposal, applying for institutional review, and funding sources. For junior faculty members, mentorship provides opportunities to fine-tune clinical skills and diagnostic and therapeutic acumen. Research productivity is further enhanced by guidance in manuscript writing, obtaining extramural grant support, and the conduct of basic science experiments and clinical trials. The mentor can help academic development of the junior faculty member by recommending him or her to local, state, and national committee memberships and enlisting them as co-authors for book chapters and review articles. Mentorship in teaching is important as well. The mentor can help junior faculty members develop teaching skills by example and by providing critique of lectures and audiovisual teaching tools.

While the importance of mentorship in academic development is clear, the process of finding the right mentor and developing the mentor-mentee relationship is altogether much more difficult. How does one find a mentor? First, mentees must decide where they want to be 5 or 10 years down the road. Once this is clear, they can set out to look for their mentors. Some persons recommend that new faculty members and fellows meet with everyone in the department to determine who might be the best fit. Even then, the mentee may find that no one in the department fits that role and may need to look beyond their department or institution. Perseverance is essential. For some mentees, one mentor may not meet all their needs, in which case one may have one mentor for clinical work and another for research activities. Occasionally the relationship may not work out. When that is the case, the mentee should be allowed to seek other mentors without being made to feel that it is wrong to do so. Academic departments should foster mentorship by providing support for mentors that includes faculty development courses and by providing recognition for their efforts. Junior faculty members and fellows should be provided with resources such as lists of senior faculty members who have successfully provided mentorships and what their areas of interest are. A forum should be available to junior faculty members to discuss their academic needs and concerns.

Establishing and Maintaining Competency

In reviewing ratings of performance, Williams and colleagues[39] quote the work of Kane, who defines clinical competence as embodying aspects of knowledge, skills, and judgment referable not only to the situation under observation but generalizable to similar clinical situations.[39] From this perspective, the six core competencies form a useful framework by which the practicing clinician may structure his or her self-directed education and a program to integrate reflective practice into all aspects of professional development.

Medical knowledge and patient care encompass foundational knowledge, technical facility, and professional judgment. The conventional means by which to assess knowledge is through a certification examination. Technical competence may be assessed indirectly, such as through chart reviews, resource utilization, or log books, or directly, such as through videos of patient encounters, standardized patients, or skills labs. The latter, while often used for trainees, are not practical for practicing physicians with multiple competing time demands. One straightforward approach is the establishment of a minimal number of procedures to be completed, after which the clinician is deemed competent. The number is usually set by consensus expert opinion, but it is rarely validated, and arbitrary numerical standards disregard the variability in rates of acquisition and maintenance of skills between individuals. With any method, the data used to assess competence

must meet several standards: the information must be accurate; observers and interpreters must agree on the implications of the findings; the observations must apply to a range of situations; and the tools must be feasible to use.[39] Once a skill is acquired, a number of factors influence maintenance of competency. These factors include repetition, exposure to the procedure under different clinical situations, overall technical facility, and clinical judgment. This last factor embodies both tangible and intangible qualities, including assessing when to perform a procedure and when to defer a procedure and recognizing when conditions deviate from the expected in the middle of the procedure.[39]

Medical judgment is perhaps among the most important attributes of a seasoned clinician and the most difficult to assess. Actual practice requires the application of knowledge to complex clinical situations, which rarely reflect the idealized descriptions of textbook medicine. Contemporary research in medical decision making recognizes that two major modes enter into decision making, System 1 and System 2.[40,41] Croskerry[41] describes System 1 as "intuitive, automatic, fast, frugal, and effortless." We recognize this description as pattern recognition, that is, the immediate grasp that a patient is following an expected trajectory of illness. System 2 is described by the same author as "analytical, deliberate, slower, costly, and effortful."[41] This mode describes the classic diagnostic dilemma, in which critical pieces of clinical data are not concordant with our assumptions regarding the disease process. Unfortunately, it is human nature to undervalue information that differs from our preordained conclusions and to overvalue confirmatory information. The experienced clinician is ever vigilant for misapplying the System 1 style when more cautious analysis is warranted, or vice versa.[40,41]

The core competencies of practice-based learning and systems-based practice may be conceived as a framework by which to reflect upon one's clinical experiences and refine both System 1 and System 2 thought patterns. In this construct, an effort to be "nonjudgmental" is transcended by an emphasis on developing good judgment, which includes understanding one's assumptions and biases when faced with a clinical situation.[42] The most common forum for this sort of approach is the morbidity and mortality conference. In this setting, it would be superficial to merely recount the clinical course; the context in which decisions were made is an essential part of the review. This context includes asking what clinical information was available in real time (not that which is obvious retrospectively), how that data was applied, what the conditions were in the rest of the ICU (because it would be uncommon to practice in an environment with only one critically ill patient), and how input from consultants informed our decision making.[42-45] Moreover, the expectations and understanding of our patients' families are essential elements in our clinical care and should be considered in reviewing the case.

Communication is often cited as the most important factor in both good and bad outcomes. Although communication skills often are believed to be an innate personality characteristic, they can be taught, and one's life experiences can lead to more active, sympathetic listening.[43,46] This trait is essential when dealing with the health care team, families, and patients. By promoting active listening as an essential element of communication, colleagues may find it easier to share subtle changes in patient condition that may be harbingers of a critical change. When we can both listen and provide information in a manner tailored to a family's needs, a nuanced and personalized approach is made possible. Evidence-based practice that is communicated well promotes a culture of high-quality medicine delivered as part of a multidisciplinary team.

The end of formal training as a fellow represents the beginning of a lifelong process of obtaining and refining one's knowledge and judgment, constituting the essence of professional development and maintenance of competency. While the medical profession and society at large has historically assumed proficiency on the part of medical practitioners by virtue of their continued practice, this assumption risks an inappropriate complacency and takes for granted that longevity is tantamount to expertise. Instead, the mature clinician is one who reflects upon his or her daily medical experiences to place them in a larger context of previous encounters and critically evaluates his or her own performance, acknowledging both effective and ineffective aspects of patient care.[43,47]

Critical care is practiced in an atmosphere of innate uncertainty. The available data may be incomplete, the preceding events unclear, and the outcome dependent on multiple interrelated processes. In this environment the practicing intensivist must be able to adapt "on the fly" and also, once a situation is resolved, he or she must be able to step back and pursue generalizable knowledge for the next encounter. The work of Donald Schon discusses "reflection in action," a form of creative problem solving, and "reflection on action," a looking back in an effort to inform future experiences.[48] The aspects of reflective practice that may come to bear include deliberate induction (a search for alternative explanations in addition to the one most readily assumed), deliberate deduction (a logical exploration of the consequences of alternative explanations), a testing and synthesis of these alternative proposals, and openness toward this thoughtful approach in the face of ambiguity, rather than a dogged clinging to one thesis as an anchor in the sometimes chaotic intensive care environment.[45]

Another aspect of lifelong learning is the role that teaching plays in ongoing self-directed learning. By reviewing contemporary literature and synthesizing it, whether for a formal didactic talk or for family and patient information, the seasoned intensivist creates an opportunity to address all aspects of professional development. Previous knowledge and assumptions are challenged in the face of newer scientific evidence. An objective presentation will acknowledge both areas of certainty and uncertainty. Innovations can be applied to clinical situations and compared with past experiences. The role of lifelong teacher is inextricably linked to that of lifelong learner.

The ABP has incorporated this template of professional development into its Maintenance of Certification program. Over time the framework of the six core competencies will become an integral part of ongoing professional development, including a knowledge examination, peer and family evaluations, participation in review and quality improvement activities, and evidence of ongoing clinical activity. Rather than viewing these competencies as administrative hurdles, the wise clinician may view them as reminders of the many facets of professionalism and learning that medical practice provides.

References are available online at http://www.expertconsult.com.

Chapter 18

Critical Care in Public Health Emergencies

Robert K. Kanter

PEARLS

- All-hazard, as well as incident-specific, planning and preparedness for public health emergencies make a difference in patient outcomes.
- The Hospital Emergency Incident Command System provides a leadership framework within and among organizations responding to an emergency, emphasizing flexibility and scalability, with clear lines of authority and consistent communications.
- Triage sorts patients to match their needs with available resources and evolves according to shifting needs and resources. Failures of triage may subsequently incapacitate an entire hospital.
- In order to provide essential interventions, some resource-intensive interventions, ordinarily considered standard in an intensive care unit, may have to be delayed or forgone in a mass critical care situation, because standard care would reduce the population who could receive life-saving care.
- If a public health emergency overwhelms resources despite mass critical care approaches, rationing might be considered. However, at present the public and professional consensus that would serve as the necessary foundation for rationing to be a feasible option is lacking.

Recent public health emergencies (PHEs) in North America have included the attacks of September 11, 2001, Hurricane Katrina and the subsequent flooding of New Orleans, a major nightclub fire in Rhode Island, wildfires in the West, floods in the Midwest, anthrax exposures, severe acute respiratory syndrome, and an influenza pandemic. Important lessons have been learned. All-hazard as well as incident-specific planning and preparedness make a difference. When carried out, public health preparations (including evacuation, shelter, and infection control) limited major health effects. Unavoidable illnesses and injuries were often minor, requiring outpatient treatment or first aid for the vast majority of patients. Even when critical care was necessary, existing resources were adequate to provide standard intensive care when needed. However, small differences in circumstances in any of these recent emergencies might have resulted in much larger numbers of adults and children admitted to adult or pediatric intensive care units (ICUs). It is easy to imagine disasters that would overwhelm existing ICU resources, unless we prepare to provide critical care in larger PHEs. This chapter is written for members of the pediatric critical care team facing a major PHE.

Basic Concepts

National Response Framework and Incident Command System

Responses to major public health emergencies are organized within a National Response Framework, as outlined by the federal Department of Homeland Security.[1] Emergency responses are always coordinated at the most local jurisdictional level possible, usually at the city or county level. Responses to larger disasters need support from adjacent counties, the state, and sometimes from the federal level. The Hospital Emergency Incident Command System (HEICS)[2] provides a leadership framework within and among organizations responding to an emergency. HEICS emphasizes flexibility for any type of event, scalability to the size of the event, clear lines of authority, and consistent communications. Disaster plans at every hospital incorporate HEICS principles.

Ordinary Surge and Mass Critical Care

Critical care responses to PHEs are scaled according to the size and severity of the emergency (Table 18-1).[3-5] Responses are categorized as (1) ordinary surge, (2) temporary reactive mass critical care, and (3) sustained mass critical care. For a sudden-impact event involving modest (10% to 15%) increases above usual peak hospital capacity at one or more local hospitals, ordinary surge methods would suffice to provide normal standards of critical care to all those who need it. Ordinary critical care surge needs are met by canceling elective admissions, quickly discharging all patients who can safely leave the ICU, mobilizing staff, and adding beds, as feasible. Most hospitals have occasional experience with ordinary critical care surge responses.

Mass critical care approaches would be implemented when a very large PHE threatens to overwhelm critical care resources. It is recommended that mass critical care

Table 18–1 Categories of Public Health Emergencies and Critical Care Responses

No. of Patients	Type of Event and Response	Authority to Implement Response
Modest increase (10%-20%) above usual peak capacity	"Ordinary surge" Usual standards of care	Decision making by usual clinical leaders
Up to three times usual peak capacity	Gradual onset, sustained PHE with adequate preparation, resources meet needs, usual standards of care Sudden-impact PHE, needs exceed resources, temporary "reactive" mass critical care, crisis standards of care Sustained PHE, sudden or gradual onset, needs exceed resources, sustained mass critical care, crisis standards of care	Decision making by usual clinical leaders Decision making by hospital incident commander Decision making by state public health official (varies state by state)[4]
Exceeds three times usual peak capacity	Needs overwhelm resources despite mass critical care, mass critical care, and rationing, crisis and palliative standards of care	Legal basis and liability protections are ambiguous[38]

Data from Devereaux A, Christian MD, Dichter JR, et al: Summary of suggestions from the Task Force for Mass Critical Care, *Chest* 133:1S-66S, 2008.
PHE, Public health emergency.

personnel be able to care for up to three times the usual number of critically ill patients for up to 10 days without outside help. In these circumstances, population-based goals would attempt to maximize numbers of survivors by providing immediate lifesaving interventions to all persons who need them and delaying or forgoing other interventions. Thus standards of mass critical care are not equivalent to normal circumstances and should be considered to be crisis standards of care. Sudden impact events that stress the resources of a community may require the implementation of temporary reactive mass critical care. Experience with a massive surge of critically injured patients after a major fire demonstrated the satisfactory outcomes that are possible as a result of well-organized responses that included elements of the temporary reactive mass critical care approach.[6] A sustained PHE that exceeds resources over a wide area may require the sustained implementation of mass critical care. No historical precedents exist for sustained mass critical care.

In many states existing laws would permit mass critical care to be implemented on a temporary reactive basis under the authority of an individual hospital's incident commander for a sudden impact event that threatens to overwhelm the resources of a hospital. PHE powers are defined on a state-by-state basis.[7] Where laws exist to authorize sustained mass critical care, this authority is generally at the level of a state public health official.

Mass critical care, whether temporary or sustained, should guarantee the following lifesaving interventions that can be performed immediately: (1) mechanical ventilation, (2) fluid resuscitation, (3) vasopressors, (4) antidotes and antibiotics, and (5) analgesia and sedation.

Lifesaving mass critical care interventions would be extended to much larger than usual numbers of patients by the following approaches: (1) Substitution of equivalent available interventions for scarce or unavailable treatments; (2) adapting nearly equivalent available interventions instead of other scarce or unavailable treatments; (3) conservation of resources; and (4) reuse of some single-use items. Such modifications from usual practices would be proportional to the gap between needs and resources and would be implemented in an organized way by each hospital's HEICS.

Pediatric Critical Care Needs and Resources in a Public Health Emergency

If a PHE affected persons of all ages equally, then children aged 0 to 14 years would account for 20% of the patients and children aged 0 to 19 years would account for 28% of the patients.[8] Younger patients may be more vulnerable to infections, dehydration, toxins, and trauma and are less able to protect themselves in a dangerous environment. Thus children may be overrepresented in a patient population during a PHE. Accidents involving a child-specific activity or terrorism intentionally targeting children may result in a patient population predominantly made up of children. Some planning scenarios considered by the Department of Homeland Security exceed the entire national critical care capacity.[3]

Survival rates from high-risk pediatric conditions tend to be better when children receive care at pediatric hospitals.[9-12] The younger the patient, the more age-specific are the treatment requirements. A national survey estimated a pediatric ICU (PICU) peak capacity of 54 beds per million pediatric population.[13] Because normal PICU occupancy exceeds 50%, fewer than 30 vacant PICU beds per million age-specific population are generally available in a region. Because each region may only be served by a single or a few pediatric hospitals, events that disable a pediatric hospital may disproportionately degrade regional pediatric care.

Quantitative models indicate that survival in a PHE would be better if pediatric patient surge is distributed to pediatric beds throughout a region, rather than overloading facilities near the scene of an emergency.[14] Appropriate utilization of pediatric hospitals would be promoted by clear identification of pediatric hospitals.[15,16] Unfortunately, control of patient distribution may be impossible in a PHE.[17] As a result, all hospitals must be prepared to care for some children.[18] Even if pediatric regional resources are used optimally, hospital vacancies to accommodate pediatric surges are empirically much more limited than for adult patients.[19] Whether or not patients are distributed optimally to hospitals, outcomes from a hypothetical large PHE are likely to be better with mass critical care approaches.[14,20]

When the PICU Is Notified of a Sudden-Impact Public Health Emergency

When a sudden-impact PHE is announced, PICU clinical leaders must immediately focus attention on safety of patients and staff. The hospital's HEICS is activated. Normal operations continue until other instructions are received. Staff who are already in the hospital report to their normal assigned work area, notifying their supervisor of their arrival. PICU clinical leaders review the hospital disaster plan, including job action sheets, and discuss pertinent aspects with the staff. When possible, the PICU clinical leaders will be informed about type, number, and arrival time of anticipated patients. However, such information is often unavailable and inaccurate. Scheduled admissions are reviewed for potential cancellation. Patients in the PICU are evaluated for transfer to a lower level of care or discharge.

Based on the initial assessment, ICU leaders need to determine the number of additional patients who could be accommodated with available staff, equipment, supplies, and space to provide normal standards of care. Additional needs for staff, equipment, and supplies should be communicated through appropriate channels in the HEICS. Additional staff is called in when HEICS instructs the staff present to do so. Staff already in the hospital may be reassigned by HEICS. Staff responding from outside should report to a labor pool area for assignment. Areas designated for expansion of services and overflow are prepared when instructed by HEICS.

As information about the event becomes available, PICU physician and nurse leaders provide incident-specific just-in-time teaching to staff when warranted. Just-in-time teaching is especially important when less experienced supplemental providers are assigned to the PICU.

Rapidly accommodating patients from the emergency department (ED) or operating room will be essential in allowing those areas to continue receiving new patients. At all times, clinical leaders must maintain awareness of the environment, operational problems, disaster-related communications, and reactions of staff, patients, and families.

Emergency Department Phase

To provide continuity in patient care, the PICU team must interact closely with the ED. In some cases, PICU staff may be temporarily reassigned to work in the ED. Therefore, the critical care team should be familiar with the ED perspective on disaster responses.

Triage

Triage sorts patients to match their needs with available resources. Triage is an evolving process relative to shifting needs and resources. Prehospital field triage and care is beyond the scope of this chapter, but when it is effective, patients are selected who will benefit from ED care. Some mild patients not requiring ED care may have been overtriaged, and others may arrive at the ED without prehospital assessment. The worried may well constitute a large proportion of patients arriving at an ED. Severely ill or injured patients may arrive later than those with less serious conditions in a sudden impact emergency. Triage categories are assigned in the ED by an experienced clinician whose sole role is to act as triage officer. Elements of the triage process may have to be repeated later according to evolving imbalances of patient needs and resources.

Triage at the ED is performed according to the nature of the PHE. When potential contamination of victims by toxins is involved, initial triage outside the hospital first identifies those needing immediate decontamination to protect the patient, staff, and entire hospital facility. Likewise, when a highly transmissible virulent infection is involved, triage prior to entering the ED identifies and isolates potentially infectious patients at the earliest time to avoid exposing staff and other patients. Failures of triage at the early stages of decontamination and infection control may subsequently incapacitate an entire hospital. When pertinent, the patient's medical record should clearly indicate decontamination procedures done and the patient's infection control status.

Physiologic triage identifies patients needing immediate lifesaving interventions. Physiological triage tools identify patients in five categories: (1) those needing immediate lifesaving interventions; (2) those who need significant intervention that can be delayed; (3) those needing little or no treatment: (4) those who are so severely ill or injured that survival is unlikely despite major interventions; and (5) those who have already died. Care of patients triaged to group 4, those who are so severely ill or injured that survival is unlikely, must deviate most significantly from usual approaches to intensive care. Because of overall demands on the system, scarce resources must be allocated to other patients who are more likely to survive. Group 4 patients are sometimes referred to as "expectant." Expectant patients are defined by current resource constraints as well as physiological observations. Palliative care is always provided to expectant patients. Also see the discussion of rationing at the end of this chapter.

It is beyond the scope of this chapter to advocate one triage tool in preference to others. No single tool is always rapid, completely accurate, appropriate to all ages and disorders, and already familiar to all providers.[21] Staff should be familiar with the physiological triage tool in use locally.

Decontamination

When indicated, decontamination reduces toxic effects for the victim and avoids contamination of staff and the hospital facility. The airway is monitored and maintained during decontamination. Antidotes are given after cleaning the site of administration. Age-specific issues include hypothermia in infants and behavioral limitations. Warm water may prevent hypothermia. Young children need assistance undressing, while some older children resist undressing and require encouragement and some privacy.[22,23]

Infection Control

For a public health emergency involving a highly virulent transmissible infection, infection control must begin outside the ED entrance and continue without interruption in the hospital while the patient is infectious. Infection control practices can be summarized as follows[24]:

1. Standard precautions apply to all patients, regardless of infection status (hand hygiene; use of gloves, gown, mask,

eye protection, depending on the anticipated exposure; and safe injection practices).
2. Contact precautions are used when infection may be spread by direct contact. When a single-patient room is not available, more than 3 feet separation between beds reduces sharing of items between patients. Staff should wear a gown and gloves for contact with the patient or contaminated objects.
3. Droplet precautions prevent transmission of pathogens spread through close respiratory contact. Because these pathogens do not remain infectious over long distances, special air handling is not required. When a single-patient room is not available, more than 3 feet separation with a curtain between beds reduces droplet transmission. Staff should wear a mask for close contact with the patient.
4. Airborne precautions prevent transmission of infections transmissible over long distances when suspended in the air. A negative pressure isolation room reduces airborne transmission. Staff should wear a mask or fit-tested N-95 respirator, depending on disease-specific recommendations. Infection control practices for specific clinical syndromes are detailed in standard references[24] and later in this chapter.

Keeping Families Together, Identifying and Tracking Children, Child Safety

Hospital care of children is more efficient, more effective, and less stressful when the child is accompanied by a family member or familiar caregiver. This need must be balanced against other triage considerations. Unaccompanied children must be properly identified, tracked, and reunited with their families, requiring proper identification of adult caregivers before releasing children to them. Pediatric safe areas in hospitals with appropriate staff supervision are necessary. Sample child identification and tracking documents have been designed.[18]

Intensive Care Unit Phase

For a sudden impact event in which the ED phase lasts a few hours, the ICU phase may last weeks. On admission to the PICU, a "tertiary survey" is performed to detect injuries and disorders that were overlooked in the rapid primary and secondary survey done previously. For standard interventions, template orders and an abbreviated hospital record may extend the capacity of an overloaded workforce. Every effort must be made to guarantee the essential critical care interventions: mechanical ventilation, fluid resuscitation, vasopressors, antibiotics and antidotes, and sedation and analgesia.

In order to provide essential interventions, some resource-intensive interventions that are ordinarily considered standard in an ICU may have to be delayed or forgone in a mass critical care situation, because standard care would reduce the population who could receive lifesaving care. Interventions that may have to be delayed include invasive hemodynamic monitoring, intracranial pressure monitoring, early renal replacement therapy, extracorporeal membrane oxygenation, parenteral nutrition, and frequent recording of fluid balances and vital signs.[3,25] Clinical decision making may have to be based more often on clinical judgment and less often on laboratory and imaging studies.

PICU Operations in a Gradual Onset and Sustained Public Health Emergency

Many of the same considerations pertain in sudden-impact and gradual-onset PHEs. However, a gradual onset allows event-specific preparation. Resources can be augmented and procedures can be developed and practiced. Staff can be trained. Experience in the early phase of the emergency would provide evidence to refine event-specific recommendations. Very rapid publication of such experience has provided rapid evolution of management recommendations in recent PHEs such as the spread of severe acute respiratory syndrome, the H1N1 influenza epidemic, and anthrax exposures.

Space

Patient care space may be adapted by converting single patient spaces to be used by two or three patients. After exhausting PICU space, additional space for mass critical care also may be adapted by using intermediate care units, postanesthesia care units, EDs, procedure suites, or non-ICU hospital rooms. Overflow of critically ill adolescents or young adults may be shared between PICUs and adult ICUs. Overflow of young infants or term newborns may be shared by PICUs and neonatal ICUs. Nonhospital facilities should only be used for mass critical care if hospitals become unusable.

Personnel

Supplemental providers may include physicians, nurse practitioners, physician assistants, nurses, respiratory therapists, pharmacists, and emergency medical technicians who have skills in non-ICU pediatrics or nonpediatric critical care. Rapid credentialing procedures, just-in-time education, and close supervision by experienced PICU clinicians would promote the role of supplemental providers.

Mechanical Ventilation

Mechanical ventilation is detailed in other chapters of this textbook. Most hospitals have only a small supply of standard ventilators and circuits in excess of usual ICU capacity. It may be necessary to consider temporary use of transport and anesthesia ventilators and bilevel positive pressure breathing devices.

Some pediatric hospitals use a single type of ventilator for patients of all sizes, with appropriate circuits and software algorithms. In other hospitals, ventilators usually used for adults that have high compliance circuits and adult algorithms may have to be adapted for use in infants or small children. Some difficulties may be encountered. The inspiratory flow or pressure sensor may not be sensitive to an infant's small inspiratory effort. Thus triggering of inspiration may fail for synchronized intermittent mandatory ventilation, assist control, or pressure support. Likewise, ventilator algorithms to terminate pressure support inspiration may fail in the presence of air leaks around endotracheal tubes. A substantial air leak around an uncuffed endotracheal tube may result in frequent ventilator alarms indicating low pressure or low exhaled tidal volume.

In a volume-controlled mode, adult ventilators may be unable to provide small tidal volumes and inspiratory flow appropriate for a small infant. Pressure-dependent losses of tidal volume in compressible spaces of adult ventilator circuits exaggerate breath-to-breath variation in delivered tidal volume if peak inspiratory pressure varies with patient effort or changing respiratory mechanics. Difficulties in providing small tidal volumes, as well as variation in ventilation due to leaks around uncuffed endotracheal tubes, may be alleviated by using a time-cycled, pressure-limited mode of ventilation.

Supplemental providers need considerable assistance in caring for an infant on a ventilator. Maintaining endotracheal tube patency, stabilization, and proper cuff inflation and evaluating episodes of hypoxia are challenges even for experienced PICU clinicians.

Manual Ventilation

Few hospitals stockpile enough mechanical ventilators to support three times the usual number of ICU patients. The temporary use of manual ventilation with a self inflatable bag may be essential to meet mass critical care goals. Manual ventilation is labor intensive, tiring to operators, and may expose staff to infection risks as a result of close prolonged bedside contact. However, manual ventilation has been used successfully via tracheostomy tubes for days in a polio epidemic,[26] temporarily for hours via endotracheal tubes in a power failure,[27] and during weather emergencies.[28-30] In the patient transport setting, manual ventilation provides similar gas exchange compared with mechanical ventilation.[31-33] Work to manually deliver small tidal volumes to an infant is less than that needed for an adult. Infection risks are negligible except for specific transmissible infections. Self-inflating bags can be used with ambient air or low-flow oxygen. When temporary manual ventilation is provided until mechanical ventilators are available, outcomes are likely to be superior to the outcomes in cases of untreated respiratory failure. Just-in-time training and supervision of supplemental providers may improve their performance in providing appropriate gas exchange and avoiding barotrauma.

Equipment and Supplies

Mass critical care can only be provided if essential equipment and supplies are available on site. Resupply and rental deliveries may be impossible during a PHE. Thus hospitals must balance the benefits of an adequate stockpile against costs of keeping items on site that may never be used.

The Task Force on Mass Critical Care[3] has recommended that a hospital first should target a mass critical care capacity of three times the usual maximum ICU capacity for 10 days. On-site stockpiles per mass critical care treatment space are planned accordingly (summarized in Table 18-2). Warming devices for infants are necessary to avoid cold stress.

While many interventions may be carried out by adapting nearly equivalent equipment and supplies, some adult equipment cannot be adapted to infants and small children. It is essential to stock adequate numbers of resuscitation masks, endotracheal tubes, suction catheters, chest tubes, intravenous catheters, and gastric tubes in pediatric sizes. In a crisis, resuscitation bags intended for adults can be used to manually ventilate infants. However, small resuscitation bags intended for infants cannot provide an adequate tidal volume for an adult or child.

If cuffed endotracheal tubes are used, it may be possible to cover all pediatric needs with 3.0-, 4.0-, 5.0-, and 6.0-mm cuffed tubes, reducing the need to stock uncuffed tubes in all other sizes. Guidelines for mass critical care ventilators have been provided.[3,34] Because few institutions will have enough ventilators to serve three times the usual number of ICU patients, the option to temporarily provide manual ventilation depends on having adequate numbers of self-inflatable resuscitation bags and endotracheal tubes immediately available.

Table 18–2 Equipment and Supply Stockpiles for Mass Critical Care*

Device	Minimum No. per Patient
Manual resuscitator	1.3
Closed circuit suction catheter	1.3†
Endotracheal tubes	1.6†
Yankauer suction device	1.3
Central venous catheters	1.3†
Peripheral venous catheters	6.5†
Intravenous crystalloid solution	20 L
Gastric tubes	1.3†

*Information is provided for selected items. See reference 3 for the full list.
†Numbers refer to a standard adult size. For infants and children, this number must be supplied in a range of pediatric sizes. A larger number of peripheral venous catheters would account for the greater difficulty in achieving venous access in infants.

Medications

In order to extend medication stockpiles in mass critical care, rules should be formulated ahead of time regarding appropriate substitutions, dose and frequency reductions, converting parenteral to enteral administration, restrictive indications, and shelf-life extension.[3] Experience in recent PHEs indicates that very large quantities of analgesics and sedatives are essential.[6,35] Weight-based dosing may be simplified to improve efficiency by specifying a limited number of weight range categories. When time constraints make it difficult to weigh patients, length-based estimates of weight may suffice.[36]

Critical Care in Specific Types of Public Health Emergencies

While all-hazard planning prepares for PICU operations across all types of PHEs, some responses must be event-specific. These responses are detailed extensively in standard references.[24,37] In addition to general critical care support, event-specific hospital responses and treatments are briefly outlined in Table 18-3. For any type of emergency, clinical interventions also will be necessary for illnesses and injuries that are indirectly related or unrelated to the primary event. These illnesses and injuries include patients hospitalized prior to the onset of the PHE.

Table 18–3 Specific Types of Public Health Emergencies and Event-Specific Management

Type of Event	Infrastructure	Decontamination	Infection Control	Disorders/Event-Specific Interventions
Pandemic (influenza, SARS)	Need for negative pressure isolation		Depending on organism, usually a combination of standard, droplet, airborne precautions	Pneumonia, sepsis Antibiotics/antiviral according to organism Antibiotics for bacterial coinfection
Major earthquake	Extensive damage Mass evacuation likely		Standard precautions	Multiple trauma including crush injuries requiring renal replacement therapy
Hurricane	Extensive damage Mass evacuation likely		Standard precautions	Multiple trauma
Nuclear detonation (terrorism)[40]	Extensive damage Mass evacuation likely	Radiation Contamination of body orifices, wounds, skin Treatment of life-threatening injuries is the priority	Standard precautions	Multiple trauma, burns, radiation (bone marrow, immunosuppression, gastrointestinal)
Radioactive dispersal bomb (terrorism)[41]	Local damage and contamination	Radiation Contamination of body orifices, wounds, skin Treatment of life-threatening injuries is the priority	Standard precautions	Multiple trauma, burns, radiation (bone marrow, immunosuppression, gastrointestinal)
Chemical attack Nerve agent (terrorism)		Essential, must be rapid	Standard precautions	Antidotes (atropine, pralidoxime) Anticonvulsants Bronchodilators
Chemical attack Vesicants/blister agent (terrorism)		Essential, must be rapid	Standard precautions	Chemical burns, potential airway injury
Chemical attack Pulmonary agent such as chlorine, phosgene (terrorism)		Move to fresh air Irrigate eyes, mucous membranes, skin	Standard precautions	Airway and pulmonary edema
Biologic attack Anthrax (terrorism)		If known, direct exposure to spores	Standard precautions	Ciprofloxacin Doxycycline
Biologic attack Pneumonic plague (terrorism)			Droplet precautions	Streptomycin Gentamycin
Biologic attack Smallpox (terrorism)			Standard, contact, and airborne precautions	Vaccination

Adapted from Siegel JD, Rhinehart E, Jackson M, et al: *Guideline for isolation precautions: preventing transmission of infectious gents in healthcare settings*: http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf. Accessed September 10, 2009; and Foltin GL, Schonfeld DJ, Shannon MW, editors: *Pediatric terrorism and disaster preparedness: a resource for pediatricians* (AHRQ publication No. 06-0056-EF), Rockville, MD, 2006, Agency for Healthcare Research and Quality.

Rationing

If a PHE overwhelms resources despite mass critical care approaches, rationing might be considered. Rationing might occur on a first-come first-served basis or by selecting patients most likely to survive as a result of brief lifesaving interventions. Such criteria have been suggested for selecting adults for mass critical care when needs exceed resources.[3,38] Proposed eligibility criteria include absence of severe chronic conditions, predicted mortality not exceeding an arbitrary upper limit, and improving clinical status on periodic reevaluations.

At the present time, neither evidence nor consensus of opinion nor law supports the concept of rationing, much less a particular rationing procedure. For PHE rationing to be a feasible option, public and professional consensus is a necessary foundation. Only then could states create a legal basis and liability protections.[39] Better evidence is needed to formulate eligibility criteria and operational plans for PHE rationing.

References are available online at http://www.expertconsult.com.

Structure and Function of the Heart

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PEARLS

- The basic form of the human heart and great vessels is complete 8 weeks after conception, after which the structures grow and mature. Recent data does show some limited capacity for hyperplasia that persists even into adulthood.
- The parietal pericardium is a stiff membrane that surrounds the heart loosely, separated from the heart by a small amount of lubricating pericardial fluid.
- Immediately after birth, there is a large increase in total body oxygen consumption and cardiac output to approximately twice its later values.
- Although large arteries are regarded as conduits and capillaries as vessels allowing transport of substances to and from the tissues, many substances can move across arterial walls.
- Standard echocardiographic assessments (ejection and shortening fraction) reflect myocardial performance (load-dependent measure) as opposed to true contractility. Assessments of adequacy of ventricular-vascular coupling (adequacy of contractile status with a given preload given the afterload conditions) can be assessed by noninvasive (relationship between Vcf and shortening fraction) or invasive (conductance catheter assessments of Es and Ea) methods.

Anatomic Development and Structure

Gross Anatomy

The basic form of the human heart and great vessels is complete 8 weeks after conception, after which the structures grow and mature. The ventricular mass enlarges by cellular hyperplasia and hypertrophy; hyperplasia previously assumed to cease after birth has recently been shown by carbon-14 dating to occur at an annual turnover rate of 1% at age 25 years, decreasing to half that value by age 75 years.[1] Increase of ventricular volumes is believed to depend on the increasing flow through each ventricle; diverting flow from a ventricle is believed to cause hypoplasia of that ventricle and its associated great artery. Before birth, left and right ventricles have equal wall thickness. After birth and clamping of the umbilical cord, there is a rise in systemic vascular resistance and a decrease in pulmonary vascular resistance; as a result, the left ventricle becomes thicker than the right ventricle. Left ventricular wall thickness is proportional to the logarithm of age from conception.[2] The ventricular septum is flat in the fetus. After birth, it bulges into the right ventricle and functions like part of the left ventricle. In the embryo, coronary arteries form in the embryonic epicardial tissue[3] and join the aorta to supply flow to the thickening heart muscle, which can no longer get enough blood from sinusoids from the ventricular cavity.

Muscle fibers in the ventricles form a complex helical array. Fibers in the left ventricular midwall are circumferential, parallel to the atrioventricular groove. From this position the fibers twist gradually as they move toward each surface so that at the epicardial surface they are 75 degrees and at the endocardial surface 60 degrees from the circumferential fibers.[4] Some investigators believe that the muscle fiber layers form one continuous sheet that is wrapped around itself like a turban.[5] When the ventricle is dilated, the fiber angles change and become less effective in ejecting blood.[6]

Microscopic Anatomy

The myocardium is a syncytium made of branching fibers, each consisting of bundles of myocytes in series. The myocytes are joined to adjacent myocytes by the intercalated disc, a set of mechanical junctions: adherens junctions with N-cadherin, catenins, and vinculin; desmosomes with desmin, desmoplakin, desmocollin, and desmoglein; and gap junctions with connexins and N-cadherin.[7-9] The gap junctions transmit the electrical impulse from one cell to the next.

Myocyte

The major components of the myocyte are the sarcomeres, which contain the myofibrillar contractile apparatus; the mitochondria, which contain enzymes for energy production; the sarcolemma, which contains the cell envelope and its extensions into the cytoplasm; the sarcoplasmic reticulum; and the cytosol. The numerous proteins in these structures not only play a role in normal function but, if abnormal for genetic or extraneous reasons, contribute to myocardial dysfunction.[10]

Contractile Apparatus

The functional unit is the sarcomere, defined as the structure between two transverse Z lines,[11-13] representing discs that contain proteins such as α-actinin and filamin that connect the

actin and titin filaments of adjacent myocytes. On each side of the Z line is a light zone, the I (isotropic) band, and in the center of the sarcomere are two dark zones, the A (anisotropic) bands, separated by a light H band in the middle of which is a dark thin M band (Figure 19-1). The I bands contain paired thin filaments of actin coiled in a helix and attached to the Z lines. In humans, cardiac α-actin makes up 80% of the actin in fetuses and neonates, while skeletal α-actin makes up 60% of the total in adults.[14] Two long tropomyosin filaments lie in the grooves between each pair of actin filaments (Figure 19-2).[15] Every 400 Å, near the crossover points of two actin filaments, is a troponin complex with the following three distinct troponins: (1) troponin T, which binds troponin to tropomyosin; (2) troponin I, which inhibits actin-myosin interaction; and (3) troponin C, which is a high-affinity calcium receptor. The thin actin filaments overlap with thick myosin filaments at the A bands. These myosin filaments are composed of light and heavy chains. The light chains coil around each other to

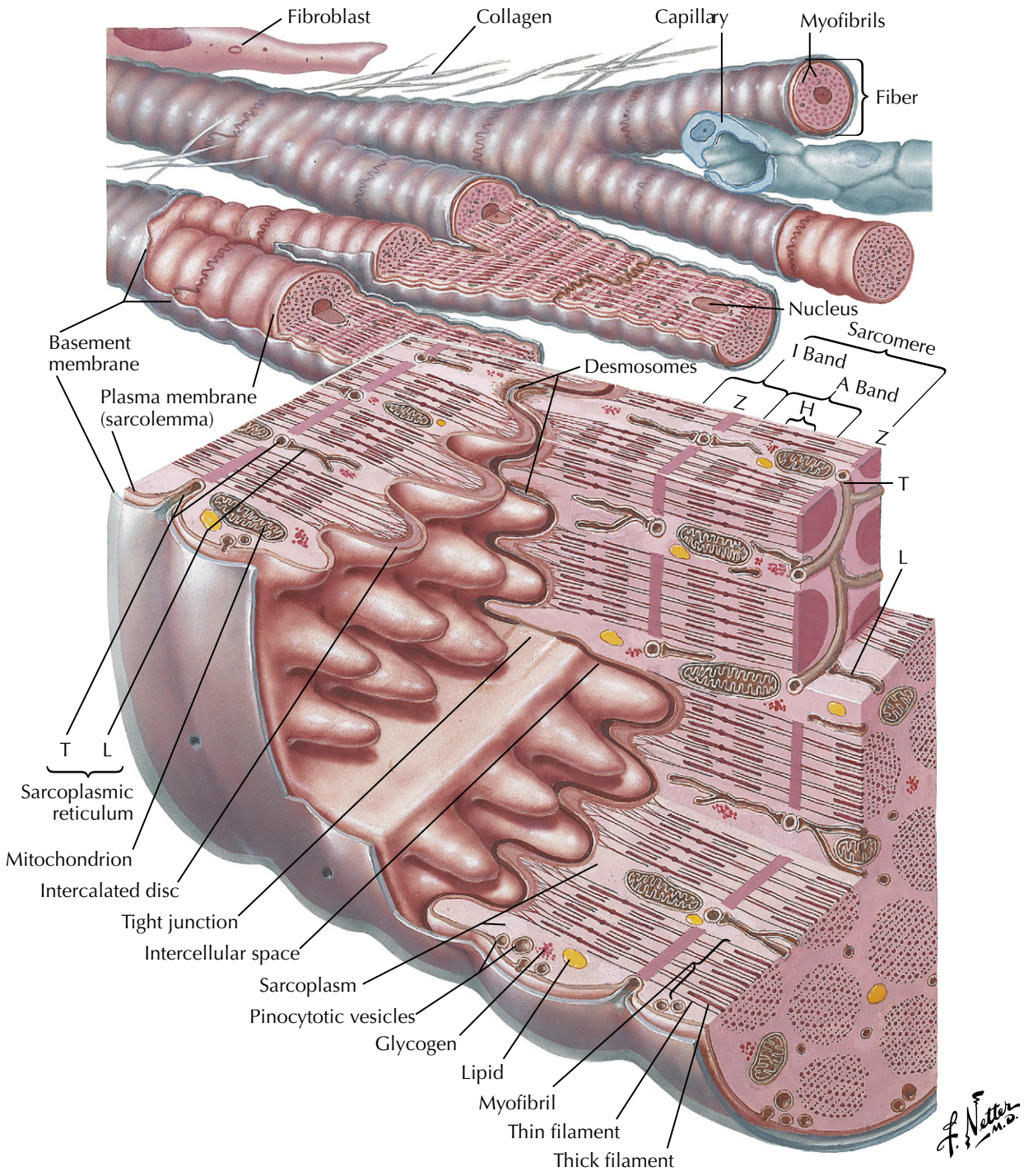

Figure 19–1. Diagram of cardiac muscle unit showing organization of structural and contractile elements. *(Netter illustration from www.netterimages.com. Elsevier Inc. All rights reserved.)*

form the long core of the myosin molecule. The heavy chains form globular myosin heads that project from the sides of the thick filament toward the actin molecules (see Figure 19-2). A collar of cardiac myosin-binding protein C encircles the thick filaments. Mutations of this protein are a common cause of hypertrophic cardiomyopathy.[16] Between two A bands there is usually a thin lighter band, the H band, which has myosin but no actin filaments.[13,15]

Titin, the largest known molecule (molecular weight 3-3.6 MDa, 1 mm long), is the third most abundant fibrillar protein. It extends from the Z band to the M band, has two isoforms, and is the main protein responsible for the elastic behavior of the myocyte.[17] It is essential for sarcomere assembly and for sensing sarcomere length[18] and, with myomesin (not shown in figure), supports the actomyosin filaments (see Figure 19-2).

Myocytes have fewer myofibrils and more water and cytoplasm before birth than after birth, and the myofibrils do not have the uniformly parallel arrays that they will have after birth.[19]

Sarcolemma and Sarcoplasmic Reticulum

The cell membrane contains receptors, ion channels, pumps, and exchangers. It has indentations overlying the Z bands, and from these indentations small tubules termed T (for transverse) tubules penetrate the cell. Abutting against the T-tubules are dilated expansions of the sarcoplasmic reticulum (junctional reticulum or cisternae), which join the free sarcoplasmic reticulum, a network of longitudinal tubules inside the cell that surround the thick (myosin) filaments. These tubular systems modulate the entry of calcium to, or its exclusion from, the cytoplasm.[11,19]

The cisternae contain the calcium-binding protein calsequestrin, whereas the longitudinal tubules contain phospholamban and the adenosine triphosphate (ATP)-dependent calcium pump.[19,20] Phospholamban inhibits the affinity of the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump for calcium, and phospholamban phosphorylation relieves the inhibition and increases calcium entry with a resulting increase in inotropy.[21-24] In heart failure, phospholamban phosphorylation is decreased by an increase in unphosphorylated calcineurin,[25] leading to decreased SERCA activity.[26,27] A similar decrease in SERCA has been found in sepsis[28] and in some forms of dilated cardiomyopathy.[29] Cisternae store and release activator calcium, whereas longitudinal tubules remove calcium from the cytosol. Calcium release is primarily via the calcium-activated calcium release channel termed the ryanodine receptor. Both T-tubules and sarcoplasmic reticulum are sparse, undifferentiated, and disorganized early in gestation but increase and differentiate markedly late in gestation and after birth in mammals. Therefore the immature heart depends mainly on extracellular sources for activator calcium,[15,19] partly explaining its marked calcium sensitivity.

Cytoplasm

During development, the proportion of mitochondria in the myocyte increases, particularly at the time of birth, and mitochondria become larger and develop more complex cristae.[19]

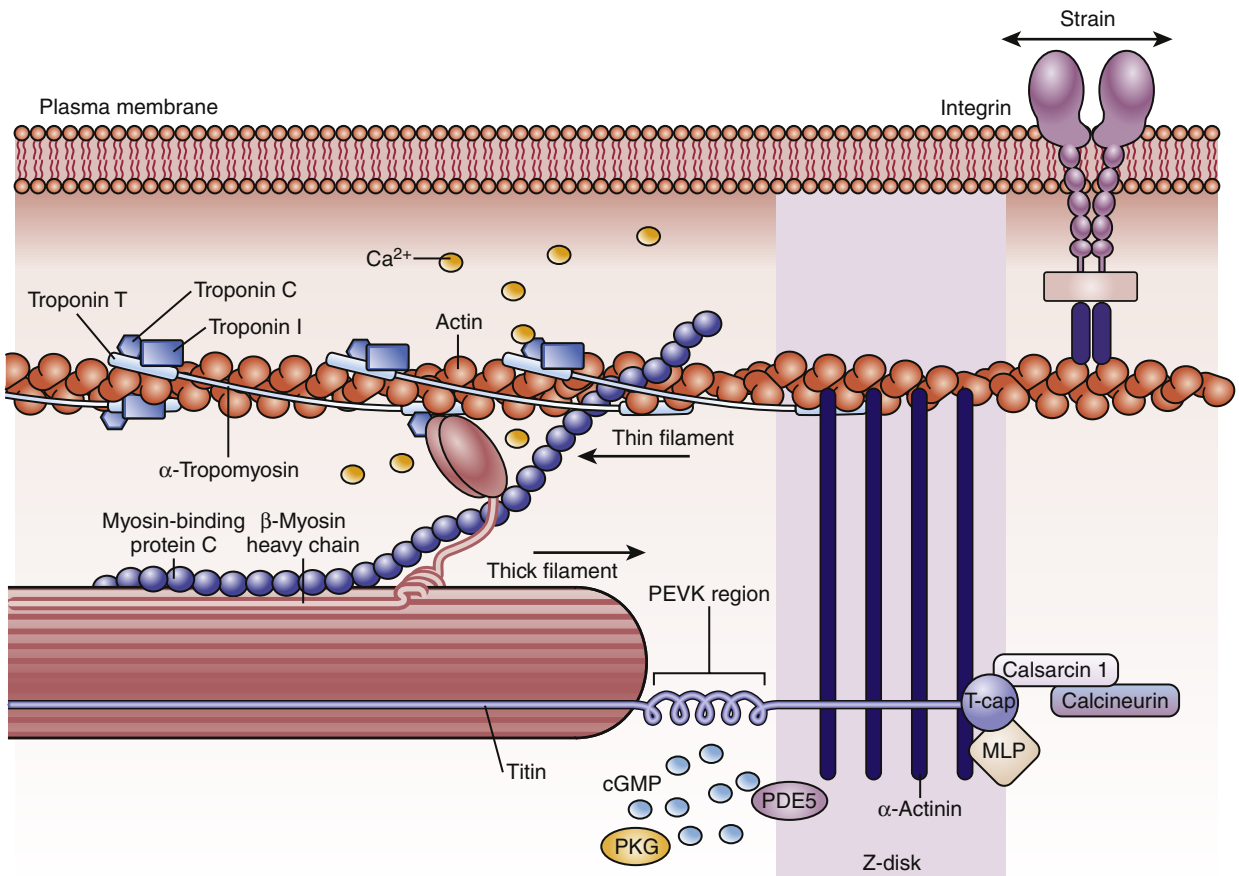

Figure 19–2. Diagram showing the integration of myofibril contraction (actin-myosin complex formation) to attachments to the Z-lines and cytoskeleton via various ultrastructural proteins. *(Modified from Mudd JO, Kass DA: Tackling heart failure in the twenty-first century,* Nature *451:919-928, 2008.)*

In the adult, approximately 30% to 40% of the muscle mass is made up of mitochondria. The cytosol contains other calcium-binding proteins[19,30] and other major proteins such as tubulin and desmin.

Cytoskeleton and Extracellular Matrix

For contractile proteins to shorten the whole myocyte, they must be linked to both the cell membrane and the extracellular matrix. Longitudinal connections are made via the Z lines, representing discs that contain proteins such as α-actinin and filamin which connect the actin and titin filaments of adjacent myocytes.[31,32] More lateral connections are made by the extrasarcomeric skeleton. There is an intermyofibrillar cytoskeleton with intermediate filaments, microfilaments, and microtubules.[31,33-35] Desmin intermediate filaments provide a three-dimensional scaffold throughout the extrasarcomeric cytoskeleton and connect longitudinally to adjacent Z discs and laterally to subsarcolemmal costameres.[33,35] Costameres are subsarcolemmal domains located in a periodic pattern, flanking the Z lines and overlying the I bands on the cytoplasmic side of the sarcolemma.[36-40] They contain the focal adhesion-type complex, the spectrin-based complex, and the dystrophin/dystrophin-associated protein complex. The focal adhesion-type complex, made up of cytoplasmic proteins such as vinculin, ankyrin, and talin, connects with cytoskeletal actin filaments with transmembrane proteins such as the dystroglycans and the sarcoglycans.[41-43] Dystrophin is linked to dystroglycan, laminin, and actin. These proteins help to fix sarcomeres to the lateral sarcolemma, stabilize the T-tubular system, and connect the sarcolemma to the extracellular matrix. Voltage-gated sodium channels colocalize with dystrophin, spectrin, ankyrin, and syntrophins. Potassium channels interact with the Z line and intercalated discs. In many of the genetic dilated cardiomyopathies, these proteins are abnormal,[44-46] thereby explaining the abnormal muscle function.

Extracellular collagen plays a major role in cell-cell and cell-vessel interactions and in ventricular stiffness.[47-50] With maturation, more collagen is type III and less is type I.[51] The relationship between sarcomeres and cytoskeleton changes with maturation, perhaps accounting for maturational differences in the resting sarcomere's mean length in myocytes.[52] In addition, cell adhesion proteins stimulated by growth factors from the myocyte are in greatest amount in the neonate, decrease with postnatal age, but increase again during hypertrophy.[53,54] Other elements in the extracellular matrix (e.g., laminin, fibronectin, and tenascin) play a major role during morphogenesis and during contraction[55] and are important mediators in hypertrophy.

Nerves and Receptors

Adrenergic, muscarinic, and other receptors appear early and are functional even before innervation. Parasympathetic innervation precedes sympathetic innervation in all species.[19,56,57] Innervation is present in the earliest viable human premature infants but may not be fully mature. Innervation is most advanced in species that are most independent immediately after birth.

Cardiac sympathetic nerve fibers come from cervical sympathetic and stellate ganglia. Right sympathetic nerves innervate the right and anterior surfaces of the heart. Left sympathetic nerves innervate the left and posterior surfaces. Vagal nerve fibers descending from medullary centers supply both atria and ventricles and the proximal portion of the bundle of His; the distal part of the bundle of His has only sympathetic nerve supply. Sympathetic and vagal afferents leave the heart and carry information from baroreceptors that respond to high pressures in the ventricles and to lower pressures in the atria, cavae, and pulmonary veins and from chemoreceptors that respond to locally produced substances such as bradykinin and prostaglandin.[58]

Ductus Arteriosus

The ductus arteriosus forms from the embryonic left sixth aortic arch and joins the main pulmonary artery that separates from the truncus arteriosus. The ductus is kept open by a balance between prostaglandin E2 (PGE2) and endothelin-1 (ET-1), both of which are formed in its wall and circulate from other sites. Initially, the ductus is very sensitive to the dilating action of PGE2, but later in gestation it becomes less sensitive to dilator and more sensitive to constrictor prostaglandins.[59-61] After birth, oxygen reacts with a cytochrome P-450 and causes release of ET-1 (the most powerful ductus constrictor).[62] A switch from dilator to constrictor prostaglandins occurs. In addition, oxygen modulates the function of mitochondrial electron chain transport by increasing the generation of H_2O_2, inhibiting voltage-gated potassium channels in ductus smooth muscle, thereby opening voltage-gated L-type Ca^{2+} channels to cause influx of calcium and ductus constriction.[63-65] These constrictor effects overpower the dilating effect of nitric oxide, which is released from the ductus when oxygen tension rises.[66] The ductus constricts, usually within the first 24 hours and almost invariably within 3 weeks. The lumen then becomes permanently occluded by fibrosis.[61,67]

Physiologic Development and Function

Myocardial Mechanics—Cardiac Sarcomere Function

Excitation-Contraction Coupling

When an electrical impulse reaches cardiac muscle, myocyte membranes depolarize. Extracellular calcium in high concentration at the sarcolemmal membrane and the T-tubules enters the cell rapidly. Spread of electrical excitation into the myocyte via the T-tubules also causes release of intracellular calcium from the sarcoplasmic reticulum.[11,68,69]

Cytosolic calcium increases from a concentration of 10^{-7} M in diastole to 10^{-5} M in systole. When the calcium that entered the cytosol binds to troponin C, the inhibitory effect of troponin I is antagonized, and a conformational change of troponin and tropomyosin exposes the actin-myosin binding sites.[11,15,68,69] These sites interact with the myosin heads to form the cross-bridges (Figure 19-3). The myosin heads rotate, generate force, and move the actin filaments, just as oars move a boat through the water. Interaction between actin and myosin pulls the two Z lines toward each other, shortening the muscle and generating force. Increasing intracellular calcium results in greater cross-bridge formation and a greater generated force. Isoforms of the troponins and tropomyosin change during development, but the functional effects of these changes are unknown.[19,70] However, troponin I is less sensitive to a fall in pH in the fetus than in the adult, which could be protective in perinatal acidosis.

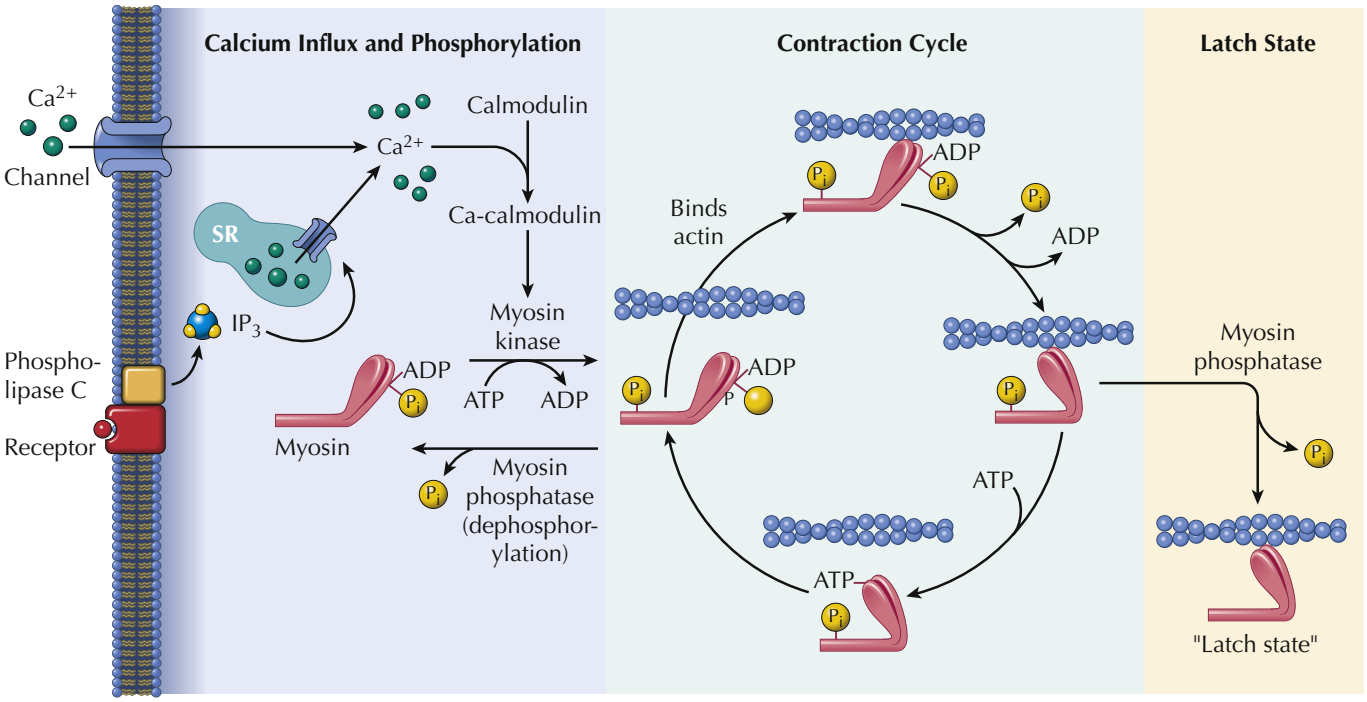

Figure 19–3. Diagram of cardiomyocyte calcium cycling and adenosine-triphosphate (ATP) utilization during actin-myosin complex formation. *(Netter illustration from www.netterimages.com. Elsevier Inc. All rights reserved.)*

The myosin head contains an ATPase that liberates energy from ATP. The activity of the ATPase determines the velocity of shortening of unloaded muscle by affecting the rate of attachment and detachment of the cross-bridges.[19,71] In most mammalian species, fetal myocardium contains V_3 myosin isoform (having two β heavy chains) with a high ATPase activity rate. In humans and most of the larger mammals, however, almost all ventricular myocardial myosin is V_3 isoform at any age, although human atria contain V_1 myosin isoform.[19]

Sarcomere Length-Tension Relationships

Sarcomere length-tension relationships have been investigated in isolated cardiac muscle strips, usually papillary muscle with its nearly parallel fibers. The muscle strip is placed in a water bath. One end is tied to a lever and the other to a force transducer (Figure 19-4, *A*). Weights attached to the other end of the lever extend the muscle to any desired length before contraction (preload); excessive stretching is prevented by a stop. Other weights added to the lever after initial length is set affect the muscle only after contraction has started and so are termed the afterload. The muscle can be stimulated to contract by an electrical impulse. Instruments for measuring muscle length, sarcomere length by laser diffraction, calcium entry by various fluorescence methods, and a host of other specialized functions can be added.[69,72,73]

Stretching relaxed muscle produces an exponential-like increase in passive tension (Figure 19-4, B). This elasticity results mainly from titin.[17,73-75] At very low sarcomere lengths, the actin filaments from each Z line overlap each other. As the sarcomere lengthens, the Z lines move farther apart and a gap appears between the two sets of actin filaments. When the sarcomere reaches a length of approximately 2.2 μm, there is a maximal overlap between actin and myosin filaments.[13,69,71] (Figure 19-4, *C*). At longer muscle and sarcomere lengths, actin and myosin filaments overlap less. The maximal sarcomere length is 3.0 μm. Further elongation of the muscle occurs by slippage of fibers and not by further sarcomere lengthening.[13,69,71]

Active contraction is studied in two ways[72] (Figure 19-4, *D*). First, muscle is stimulated to contract at different initial muscle lengths but is not allowed to shorten (isometric contraction). At the shortest lengths no force is generated; the muscle remains slack. As sarcomere lengths increase, force is generated and increases to reach a maximum at sarcomere lengths of approximately 2.2 μm. At longer sarcomere lengths, there may even be a decrease in force.[71]

If, at any length, passive tension is subtracted from the tension generated during isometric contraction, the resulting curve demonstrates active tension as a function of length (Figure 19-4, *B*).

Second, if afterload is small, the contracting muscle generates an appropriate force and then shortens while force remains constant (isotonic contraction). The rate of shortening is fastest at the onset of shortening, and from it, the velocity of shortening is measured (Figure 19-4, *D*). The shortening velocity ranges from zero when the load is so heavy that it prevents shortening to a maximum when the external load is zero[69]; however, true zero loading is impossible because of internal viscosity and elastic forces.[19,71] Increases in cytosolic calcium increase the force generated during contraction but have little influence on the maximal velocity of shortening.

In fetal lambs, the passive tension of muscle strips is abnormally high. Active tension per mm^2 cross-sectional myocyte area at any given afterload is below adult values but is

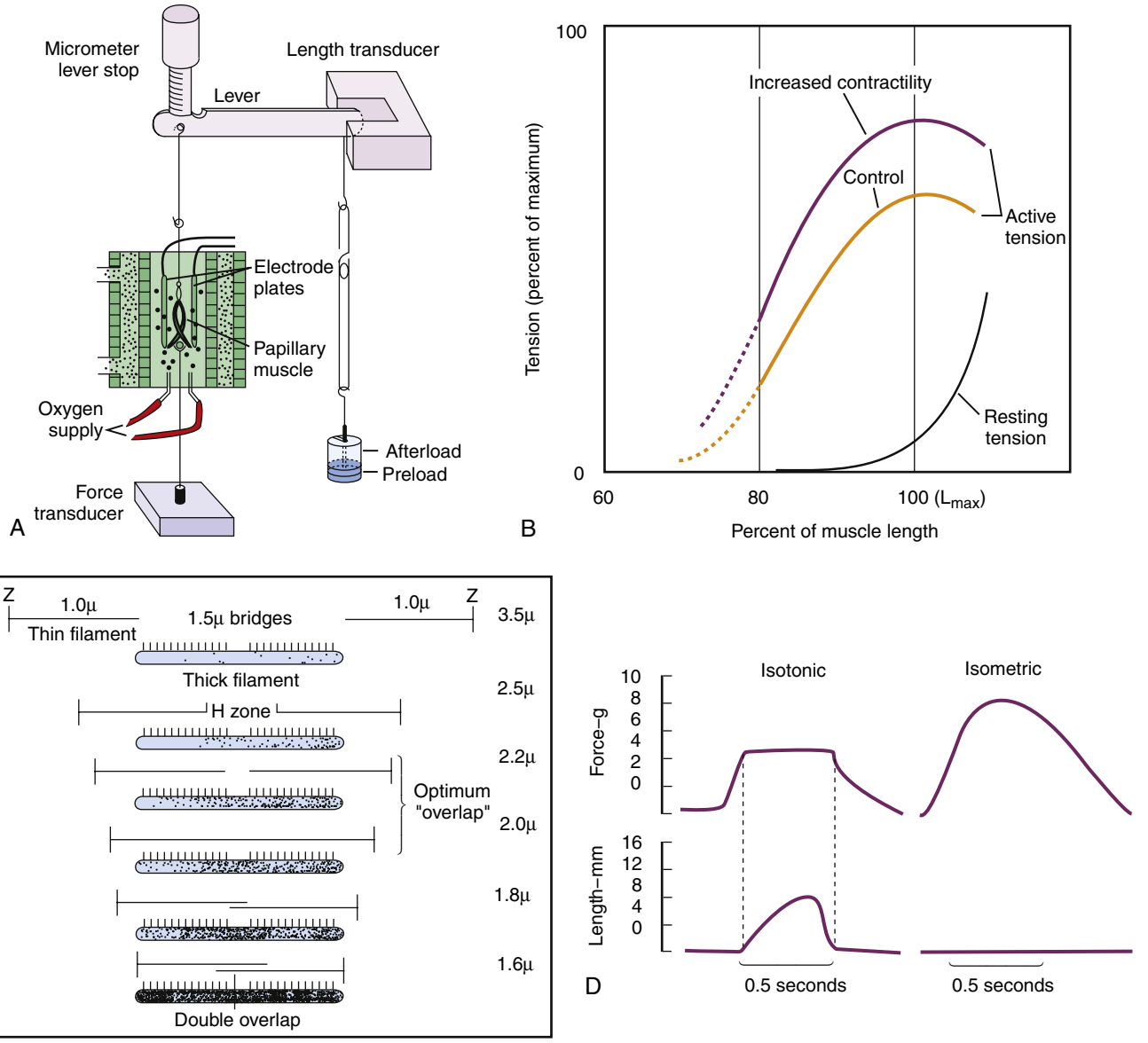

Figure 19–4. **A,** Diagram of isolated muscle strip in a water bath and attached to transducers for measuring force and length. Preload is set by the lever stop. (From Parmley WW, Tyberg JV: Determinants of myocardial oxygen consumption. In Yu PN, Goodwin JF, editors: *Progress in cardiology,* Philadelphia, 1976, Lea & Febiger.) **B,** Relationship between muscle length and resting tension or active tension at three different contractile levels. (Original drawing by Albert Miller. Redrawn from Sonnenblick EH: Myocardial ultrastructure in the normal and failing heart. In Braunwald E, editor: *The myocardium: failure and infarction,* New York, 1974, HP Publishing.) **C,** Diagram showing relationships of sarcomere length, positions of the actin and myosin filaments, and contractile force. (Original drawing by Albert Miller. Redrawn from Sonnenblick EH: Myocardial ultrastructure in the normal and failing heart. In Braunwald E, editor: *The myocardium: failure and infarction,* New York, 1974, HP Publishing.) **D,** Typical length tracings for isotonic *(left)* and isometric *(right)* contractions. The *dashed vertical lines* in the left tracing indicate the portion of contraction in which the muscle shortens against a constant force. *(Adapted from Parmley WW, Tyberg JV: Determinants of myocardial oxygen consumption. In Yu PN, Goodwin JF, editors:* Progress in cardiology, *Philadelphia, 1976, Lea & Febiger.)*

proportional to the reduced number of myofibrils.[19,30,57] Contractile material accounts for approximately 60% of cardiac muscle in adults, but only 30% in fetuses. The extent and velocity of shortening are reduced in fetal heart muscle, but correcting for the amount of contractile machinery suggests the intrinsic performance of fetal and adult actin-myosin filaments is similar.[19] The change from fetal to adult performance seems to occur fairly soon after birth, when the myofibrillar array becomes regular and when the T-tubules and the sarcoplasmic reticulum develop into their adult form.[19] For this reason, prematurely born infants (and, to a lesser extent, full-term infants) have a much-reduced ability to tolerate an increase in afterload and are exquisitely sensitive to reductions in serum calcium concentrations.

Myocardial Mechanics—Myocardial Receptors and Responses to Drugs

α_1-adrenoceptors appear early in gestation and in many species reach their highest density in the neonate.[19,56,76] These developmental changes may be associated with the normal cell hypertrophy that occurs during development. By contrast, β-adrenoreceptors increase progressively with age. Both β_1 and β_2 are present on myocytes.[77,78] In addition, histamine H_2,

vasoactive intestinal polypeptide (VIP), adenosine A_1, acetylcholine M_2, and somatostatin receptors have been identified. They act on the myocyte's contractile apparatus through one of two main pathways.

The major pathway involves the membrane-bound receptor–G protein–adenylate cyclase complexes. G proteins include the Gs (stimulatory) and Gi (inhibitory) proteins.[79] In their inactive state, these G proteins include α, β, and γ subunits and guanine diphosphate (GDP). When agonists stimulate β-adrenergic, histamine, or VIP receptors, the G proteins undergo a conformational change. The changes induce the Gs protein to exchange its GDP for guanine triphosphate (GTP) and release the β and γ subunits. The Gs-α-GTP complex interacts with adenylate cyclase to convert ATP to cyclic adenine monophosphate (cAMP), which activates a variety of protein kinases to phosphorylate proteins including voltage-dependent calcium channels, phospholambin, and troponin I. Consequently, calcium entry during depolarization and during uptake of calcium into the sarcoplasmic reticulum storage pool is increased, thus increasing contractility. The Gs-α-GTP complex has intrinsic GTPase activity that converts GTP to GDP. The β and γ subunits rejoin the complex, which now is available for further activation by the receptor. In this way, as long as receptors are occupied by the agonist, the Gs cycle produces increasingly more cAMP, thereby amplifying the stimulatory signal. The Gi protein complex undergoes a similar cycle when adenosine, acetylcholine, or somatostatin receptors are stimulated; however, activating Gi protein reduces cAMP formation and decreases contractility. β_2 adrenergic receptors also couple to Gi in addition to Gs.[80] Gi in this context is thought to oppose the effects of Gs to some degree, including limitation of the acute positive inotropic response to adrenergic stimulation and offering some protection from apoptosis.[81-83]

Another signal-transducing system in the human heart is the phospholipase C-diacylglycerol-inositol triphosphate pathway, activated by α_1-adrenergic and M_2-muscarinic receptors.[84-86] Occupation of the receptors activates phospholipase C, which cleaves phosphatidylinositol triphosphate in the cell membrane to produce diacylglycerol and inositol triphosphate. The former activates protein C kinase in the membrane, which may hinder the effects of cAMP. The latter facilitates calcium release from the sarcoplasmic reticulum. This pathway is important in smooth muscle contraction but is of less importance in heart muscle.

In heart failure, the number of β_1-adrenergic and VIP receptors are down-regulated, and β_2-adrenergic receptors are uncoupled from G proteins.[21,77,78,87,88] These changes make the myocardium less responsive to circulating or locally released catecholamines or VIP and play a role in the reduced contractility observed in heart failure. Treating heart failure with β-adrenergic blocking agents not only has reversed the receptor changes, but has also been associated with improved function of muscle strips in adult patients.[89-92]

Coupling of β-adrenoreceptors is incomplete at birth. Milrinone is an agent that stimulates contractility by inhibiting phosphodiesterases; it bypasses the adenylate cyclase system. Although previously thought to be ineffective in the newborn,[93] a multicenter randomized trial[94] and subsequent widespread use has confirmed its efficacy in the neonatal population.[95,96] Since contractile mechanisms are almost fully developed at birth, the majority of mechanisms controlling contractility (except for changes in the source of calcium) are in place at birth.

Myocardial Mechanics—Integrated Muscle Function

Relationship Between Muscle Strips and Intact Ventricles

Preload stretching a muscle strip is equivalent to end-diastolic fiber length of the intact ventricle. This length can be measured by various devices in animals, but in the intact human ventricle it is best related to end-diastolic diameter or volume. Frequently, end-diastolic pressure has been used interchangeably with end-diastolic volume as an index of preload, but this usage can be misleading if the distensibility of the ventricle changes or if pressure outside the heart (pericardial or intrathoracic) rises.[97-100]

Afterload is more complicated in the intact ventricle. Commonly, aortic systolic pressure is equated with afterload. However, in the muscle strip, afterload represents the force exerted by the muscle during contraction, and pressure and force are not the same.[75,101,102] It is preferable to calculate circumferential wall stress, which at the midwall is a function of ventricular pressure, diameter, and wall thickness. Both peak systolic and end-systolic wall stress can be used to assess ventricular function.

Calculations of wall stress are based on the Laplace relationship:

$$\text{Wall Stress} = \frac{Pr}{2h}$$

where P is pressure, r is radius of curvature, and h is wall thickness. Because the left ventricle is not a regular sphere, particularly in systole, the Laplace formula is an oversimplification.[103] A fairly simple and accurate formula was developed by Grossman and colleagues[104]:

$$\text{Wall stress} = \frac{1.35PD}{4h(^{1h}/_{D})}$$

where P is pressure, D is left ventricular minor axis dimension, and h is wall thickness at the level of the minor axis. This equation can be written as:

$$\text{Wall stress} = \frac{Pr}{2h}\left(\frac{1.35}{1+\frac{h}{r}}\right)$$

that is, as the Laplace equation modified by the expression in parentheses. Note that if the left ventricle dilates acutely, wall stress rises markedly because r gets bigger and h gets smaller.

The major findings from studies of muscle strips have been confirmed in intact ventricles. Increasing preload increases the pressure generated by an isolated ventricle that is not allowed to eject, as observed in the last century by Otto Frank. If the ventricle is allowed to eject, then increased preload allows the heart to eject the same stroke volume against an increased afterload or else to eject a greater stroke volume against a constant afterload. This is the Starling component of the Frank-Starling law.[105,106] The mechanism of this response is twofold: (1) lengthening the sarcomere narrows it and places the myosin and actin fibrils closer together for stronger interaction, and (2) increased calcium sensitivity is mediated in some way

by titin stretching.[18] If an inotropic drug is given, then contractility increases and from a given fiber length greater force of contraction is achieved. This is a phenomenon seen every day in the intensive care unit.

The force-frequency relationship can be determined in intact hearts[107,108] by examining the response of the maximal rate of change of pressure (dP/dt max) in the ventricles after premature beats. The results in intact ventricles and muscle strips are similar. Subsequently, Seed and colleagues[109] applied this technique to humans with normal or abnormal left ventricular function and found an optimal R-R interval of 800 ms. They also examined dP/dt max for two beats given at optimum intervals after the premature stimulus. As expected, the first normal beat after the premature beat was potentiated because the extra calcium introduced into the cytosol by the premature beat was available to potentiate the first beat after the premature stimulus. The second postpremature beat also was potentiated, but less so. They used the ratio of the potentiation of these two beats to calculate the fraction of calcium recirculating from one beat to the next. This amount was constant in any one patient but was much less in those with left ventricular dysfunction.

Pressure-Volume Loops

If left ventricular pressure and volume are measured simultaneously, the resulting pressure-volume loop gives information about ventricular function and can be used to assess myocardial contractility in the intact heart.

The modern approach to analyzing these loops is based on the elastance concept of Suga and Sagawa.[110-112] Elastance is the ratio of pressure change to volume change. Consider an isolated ventricle containing a balloon that can be inflated to different volumes. At each volume the ventricle is stimulated to contract and generates a peak systolic pressure (Figure 19-5, *A*). As volumes increase, so do the peak systolic pressures generated, and the relationship is linear (Frank's law). The line joining the peak pressures intercepts the volume axis at a positive value, termed V_0, that indicates the unstressed volume of the ventricle. The equation for this line is as follows:

$$P_{es} = E_{es}(V_{es} - V_0)$$

where P_{es} is end-systolic pressure, E_{es} is slope of the line, V_{es} is end-systolic volume, and V_0 is unstressed volume. If contractility increases (more calcium enters the cells), the ventricle can generate greater pressures at any given volume, thereby generating a steeper pressure-volume line (higher value of E_{es}; dashed line I in Figure 19-5, *A*). If contractility decreases, the ventricle generates lower pressures at any given volume, and the pressure-volume line is less steep (lower value of E_{es}; dotted line D in Figure 19-5, *A*). E_{es} is also termed E_{max}.

If the ventricle is allowed to eject, the typical pressure-volume loop shown in Figure 19-5, *B,* is seen. During diastolic filling, volume increases and diastolic pressure rises slightly because of the increase in passive tension. At the end of diastole, isovolumic systole occurs, and ventricular pressure rises with no change in volume. When ventricular pressure exceeds aortic pressure, the aortic valve opens, blood is ejected, and ventricular volume decreases. Ejection ends, and pressure falls to diastolic levels as isovolumic relaxation occurs. The pressure and volume reached at the end of systole are those that would have been attained by the isolated ventricle at that same end-systolic volume. In other words, at a given volume,

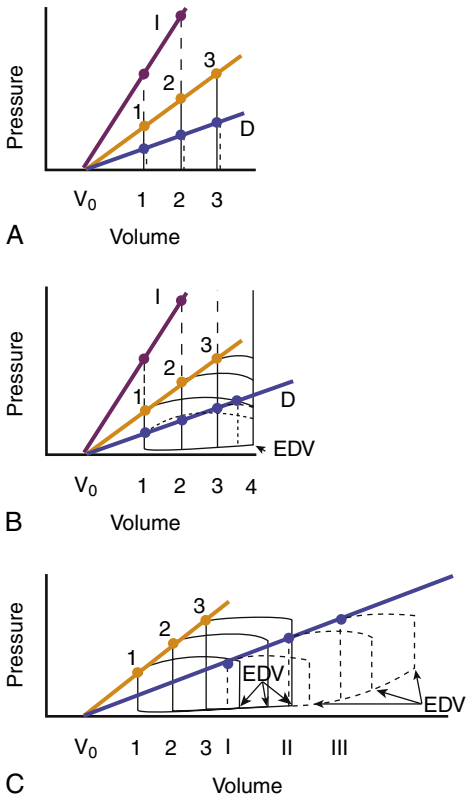

Figure 19–5. Diagrams illustrating the concept of ventricular elastance. **A,** Isolated ventricle contracting at volumes 1, 2, and 3, generating corresponding pressures. *Purple line I* indicates results at increased contractility. *Blue line D* indicates results at decreased contractility. *V_0,* resting (unstressed) volume. **B,** Ventricular pressure-volume loops achieving end-systolic pressures of 1, 2, and 3 at corresponding volumes. *Purple line I* indicates results at increased contractility, with greater end-systolic pressures at each volume. *Blue line D* indicates results at decreased contractility. From a given end-diastolic volume, either the same ejection fraction is delivered at a lower end-systolic pressure *(dotted line 1)* or the same end-systolic pressure is achieved but at a much smaller stroke volume and ejection fraction *(line 4).* **C,** When the ventricular end-diastolic volumes *(EDV)* increase as afterload increases, as is normal, then stroke volume can be maintained, even though ejection fraction decreases. If contractility is decreased *(blue line),* then stroke volume can be maintained only with increasing end-diastolic pressures. *1, 2, 3,* End-systolic volumes and pressures at normal contractility. *I, II, III,* End-systolic volumes at decreased contractility.

no higher pressure can be generated (loop 1; Figure 19-5, *B*). The decrease in volume during ejection is the stroke volume which, divided by the end-diastolic volume, gives the ejection fraction; normally, ejection fraction is greater than 65%.

If afterload is suddenly increased by raising aortic pressure, the normal heart responds as shown in Figure 19-5, *B*. In the first beat after the increase, the ventricle has to generate a higher pressure before the aortic valve opens (loop 2). It then ejects but cannot eject a normal stroke volume because that would require higher pressure from the same end-diastolic length (preload). In fact, the end-systolic volume is that which is appropriate for the higher pressure (compare Figure 19-5, *A* and *B*). If different afterloads are used, the end-systolic pressure-volume points define a sloping line that is the same as the line obtained in the isolated heart at those same volumes; this is the maximal ventricular elastance (E_{es}) or end-systolic elastance (E_{es}) line. If ventricular contractility increases, then the ventricle can attain higher ejection pressures at any given

volume, and the end-systolic pressure-volume points lie on a steeper line that lies above and to the left of the normal line (purple line I in Figure 19-5, *B*). If ventricular contractility decreases, then the ventricle cannot generate normal pressures at any given end-diastolic volume, and the end-systolic pressure-volume line lies below and to the right of the normal line (blue line in Figure 19-5, *B*). Note from Figure 19-5, *B*, that, from a given end-diastolic volume, the ventricle with impaired contractility can either eject a normal stroke volume at much reduced pressures or eject at a normal pressure only by reducing its stroke volume drastically (loop 4).

In beats that follow a sudden increase in afterload, the ventricles adjust. Because of the reduced stroke volume in the first beat, the end-systolic volume is larger than normal. During diastole, however, a normal stroke volume enters the ventricle so that end-diastolic volume increases (loop 2 in Figure 19-5, *C*). In normal ventricles, the increased end-diastolic fiber length causes little increase in diastolic pressure. The pressures during ejection and the end-systolic pressure-volume point are unchanged, but stroke volume and ejection fraction increase. After a few more cycles, a new equilibrium is established (loop 3) in which the ventricle ejects a normal stroke volume at the higher afterload. The ejection fraction, however, is subnormal because although the stroke volume is normal, the end-diastolic volume is increased. The ventricle has adapted to the higher afterload by increasing end-diastolic fiber length, a phenomenon described by Starling and discussed by Ross[101,102] under the term preload reserve. If the ventricle has decreased contractility (dashed loops), the same pattern of response occurs, but with some important differences. With decreased contractility, the ventricle cannot eject a normal stroke volume from a normal end-diastolic volume. Compensation results in a larger than normal increase in end-diastolic volume, even at normal afterloads. Any increase in afterload causes a further increase in end-diastolic volume, and this increase causes diastolic pressures to rise to high values that cause pulmonary congestion. The normal preload reserve has been used up in the attempt to eject a reasonable stroke volume against a modestly increased afterload. In more depressed hearts, even normal afterloads cannot be handled by the ventricle without a pathologically raised diastolic pressure in the ventricles or a drastic decrease in stroke volume. Note that in these hearts, because of the relatively flat slope of the maximal ventricular elastance line, a slight reduction of afterload produces a relatively large increase in stroke volume and a relatively large decrease in ventricular end-diastolic volume and pressure. This is one of the mechanisms for cardiac improvement with afterload reduction.

The normal right ventricular (RV) pressure-volume curve is triangular in shape, unlike the more rectangular left ventricular (LV) pressure-volume curve.[113] This difference is accounted for by a relative lack of isovolumic contraction and relaxation times in the RV. The normally low afterload of the RV and the high compliance of the outflow portion of the ventricle allow ejection to begin almost instantaneously after the onset of contraction and proceed through pressure decline so that there is near complete emptying of the ventricle by the end of systole and the ejection time of the RV thus spans the entire period of systole. An important consequence of this relationship is that even small increases in RV afterload begin to make the RV pressure-volume curve begin to resemble the normal LV pressure-volume curve, with isovolumic contraction and relaxation times becoming more prominent.[114] Ejection fraction is reduced, although stroke volume may be maintained due to RV dilation,[115] and the thin-walled RV may handle this new physiology quite poorly.

Assessing Myocardial Contractility

An index of contractility must reflect the ability of the ventricle to perform work independent of changes in preload and afterload. Contractility can perhaps best be defined as the alterations in cardiac function that occur secondary to changes in cytosolic calcium availability or sarcomere sensitivity to calcium. Thus, β-adrenergic agonists or phosphodiesterase inhibitors, which increase cytosolic calcium, and thyroxine, which alters myosin ATPase sensitivity to calcium in some species by altering the dominant isoform, are positive inotropic agents. However, quantifying contractility in the intact heart or assessing contractile effects of an intervention is difficult[72] because all indices of contractility are indices of overall performance and are not independent of the other determinants of performance. For example, cardiac output is an excellent index of the systolic performance of the intact ventricle, but it is not a useful index of contractility because of its high sensitivity to preload, afterload, and heart rate. It is convenient to divide methods of assessing contractility into those based on early events in the cardiac cycle (isovolumic phase indices) and those that occur later (ejection phase indices).

Isovolumic Phase Indices. The concept of maximal velocity of contraction against zero load (V_{max}) once was popular, but the complexity of the mechanics of cardiac muscle made it difficult to assess what would have been the true index, namely, V_{max} of the contractile element alone.[116] In practice, too, it is not possible to abolish internal loading of the muscle fiber. Applying this concept to the intact heart was even more difficult.[117]

As a substitute for V_{max}, investigators used dP/dt max (maximal rate of change of ventricular pressure) or dP/dt at a developed ventricular pressure of 40 mm Hg. These values usually are achieved before the aortic valve opens and are relatively unaffected by changes in preload. The index is, however, affected markedly by changes in afterload and so must be used with care when afterloads are very different. This method is more useful for measuring acute changes in contractility than for assessing absolute contractility.

Ejection Phase Indices. The index of contractility most commonly used today is the maximal (end-systolic) ventricular elastance of Suga and Sagawa, which is independent of changes in preload (see previous text). Several different afterloads must be obtained, and either ventricular volumes must be measured or echocardiographic dimensions must be used as substitutes for volumes. The most clear-cut results have been obtained when reflex changes in contractility are prevented, which may explain why the relationship is less well established in conscious than in anesthetized animals.[75,118] Several studies have shown that the maximal elastance line often is alinear and gives a negative intercept on the pressure axis, that is, a negative resting volume.[119,120] To deal with this simply, some investigators use the values of E_{max} in the mid-range of pressures.[120]

Ejection fraction and velocity of shortening also provide information about ventricular function. Because these two variables depend on afterload (see Figure 19-5), it is necessary to adjust for changes in afterload. This adjustment has been

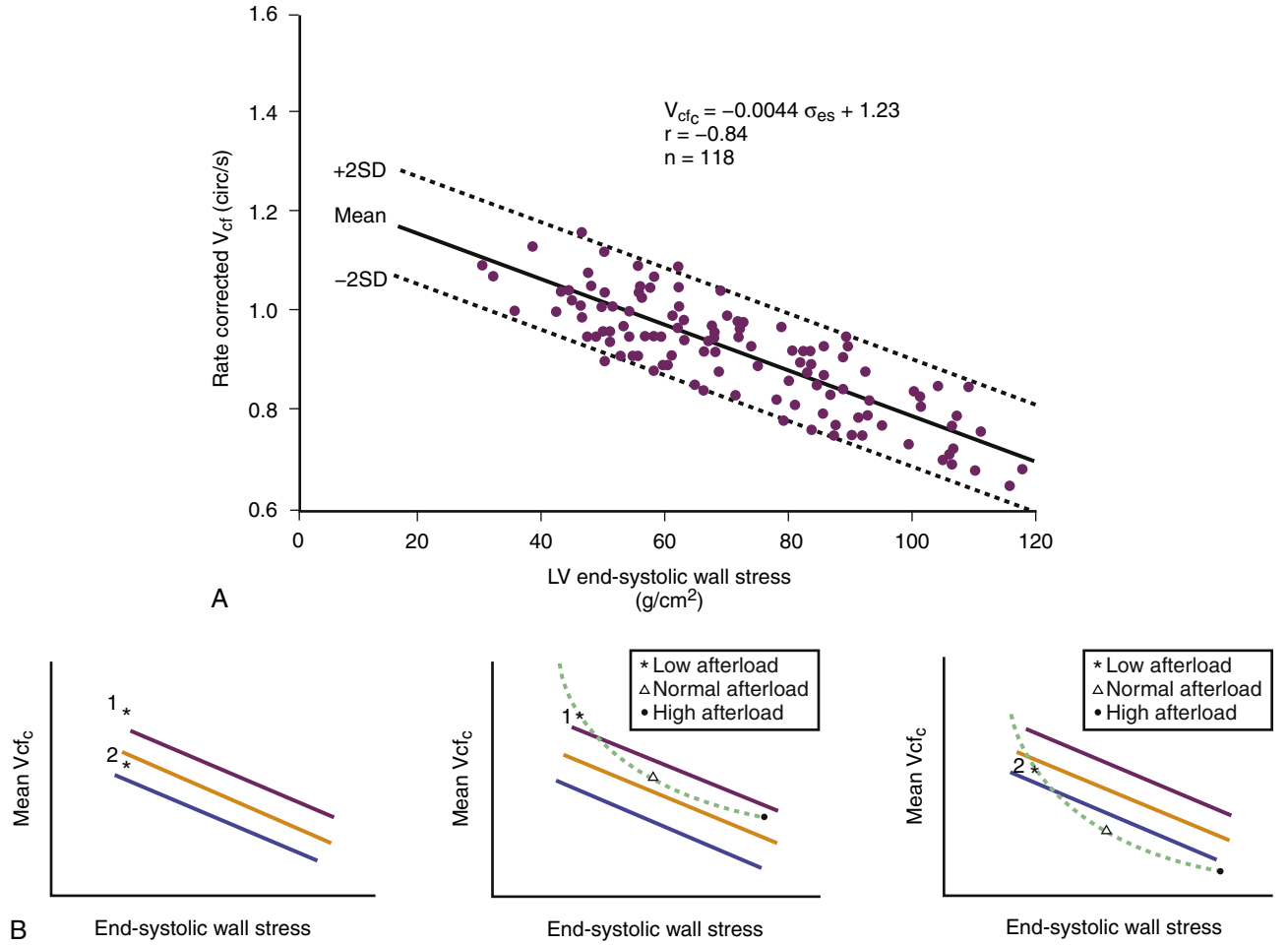

Figure 19–6. **A,** Relationship between rate-corrected mean velocity of fiber shortening *(Vcf)* and left ventricular *(LV)* end-systolic wall stress. *(From Colan SD, Borow KM, Neumann A:* J Am Coll Cardiol *4:715, 1984.)* **B,** Possibility of misinterpreting the relationship between mean velocity of fiber shortening and end-systolic wall stress. *Left,* Data point 1 is more than two standard deviations *(SD)* above normal relation (taken from left panel), suggesting increased contractility. Data point 2 is within the normal range, suggesting normal contractility. *Middle,* Alternative explanation for point 1 is that contractile state is normal, but points obtained at very low afterloads follow a hyperbolic, not a linear, relationship. *Right,* Alternative explanation for point 2 is that contractility is decreased, but because of the hyperbolic relationship and the low afterload it appears within the "normal" linear range. *(Adapted from Banerjee A, et al:* J Am Coll Cardiol *23:514, 1994.)*

made in adults and children[121-126] by providing normal data for the relationship between end-systolic wall stress and either velocity of shortening or ejection fraction (Figure 19-6). However, the relationship is not linear,[127] so single-point determinations are of little use.

Ventricular Function Curves

Sarnoff and Mitchell[128] introduced the ventricular function curve. They measured LV diastolic pressure and stroke work, then infused fluids and examined the relationship between the two variables (Figure 19-7, *A*). If contractility increased, the curve shifted up and to the left; at any end-diastolic pressure, a greater stroke work was achieved. If contractility decreased, the curve shifted down and to the right. One problem with this technique, recognized by Sarnoff, was that curvilinearity of the diastolic length-pressure relationship produced an S-shaped curve when relating stroke work to end-diastolic pressure and that techniques for measuring fiber length or ventricular volume were inadequate. In addition, using pressure instead of fiber length or volume may lead to misinterpretations if pericardial or pleural pressures change substantially. Several groups of investigators adapted this function curve to examine the stroke volume to end-diastolic pressure relationship, but this is even less satisfactory because stroke volume is affected by the resulting increases of afterload.

More recently, the relationship of stroke work to end-diastolic fiber length or ventricular volume has been examined in conscious dogs with autonomic blockade.[105] This relationship, termed preload recruitable stroke work, was linear and independent of changes in afterload (Figure 19-7, *B*). The line intercepted the length or volume axis at values close to the unstressed length or volume, that is, at the length or volume that the ventricle has at zero transmural pressure. Calcium infusion increased the slope of the line without changing the intercept on the length axis. Subsequently, the same group extended this analysis to ischemic ventricles.[129] Depression of ventricular function shifted the stroke work to end-diastolic segment length relationship to the right (increased intercept) and decreased the slope. This concept and the ventricular elastance concept have much in common. Both require measurements of wall force, stroke work, ventricular volume, or minor

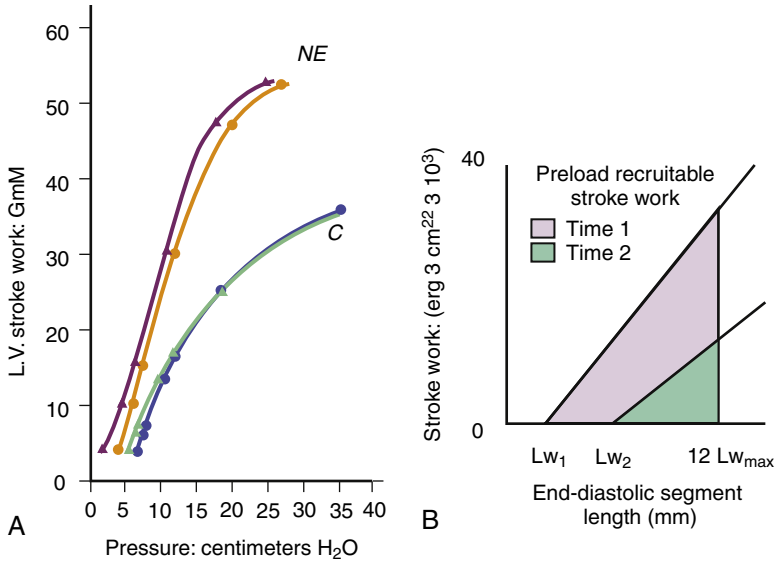

Figure 19–7. Ventricular function curves. **A,** Typical function curve relating left ventricular diastolic pressure to left ventricular (external) stroke work. *C,* Control state; *NE,* increased contractility resulting from norepinephrine infusion. *Pairs of lines* indicate repeatability of the measurement. *(Redrawn from Sarnoff SJ, Mitchell JH: The control of the function of the heart. In Hamilton WF, Dow P, editors:* Handbook of physiology, section 2: circulation, vol 1, *Washington, DC, American Physiological Society, 1962.*) **B,** Preload recruitable stroke work area, in which the area under the curve relating end-diastolic segment length to stroke work is indicated for two different contractile states of the ventricle. Lw_1, Lw_2, Intercepts on the x axis; Lw_{max}, maximal value of *Lw* for the whole experiment. For details, see reference. *(Adapted from Glower DD, et al:* Am J Physiol *255:H85, 1988.)*

axis diameter and changing them over a range so that the lines or areas defining these indexes can be obtained.

Pericardial Function

The parietal pericardium is a stiff membrane that surrounds the heart loosely, separated from it by a small amount of lubricating pericardial fluid. Intrapericardial pressure is negative, reflecting the negative intrapleural pressure. On the other hand, the pericardium exerts a surface pressure on the heart that would exist even if all fluid were removed. If the pericardium had holes in it, fluid would leak out and there would be no fluid pressure, but the heart still could be compressed. This surface pressure varies in different regions but, in general, is similar to right atrial pressure.[99,130] As a result, in the usual situation transmural diastolic pressure across the wall of the left ventricle is not the same as left ventricular diastolic ventricular pressure. It can be estimated by subtracting right atrial pressure from LV pressure. The pericardium can restrict dilatation of the LV if there is a tense pericardial effusion (tamponade)[131] and if the ventricles dilate acutely. Thus if the ventricles enlarge because of sudden volume load or sudden myocardial depression, the pericardium becomes tense and restrains further enlargement of the ventricles.[99,100]

In some patients with acute myocardial ischemia, left ventricular diastolic pressure can be greatly increased without much change in ventricular volume because of tension in the pericardium. This mechanism makes it difficult to interpret changes in diastolic pressure-volume relations only in terms of myocardial stiffness.[97,98,130,132,133]

Ventricular Interaction

A closely related mechanism is ventricular interaction.[132] For example, if right ventricular output decreases, a series interaction reduces left ventricular filling and, therefore, LV output. Second, a direct interaction occurs because the left and right ventricles share the ventricular septum and are contained within the same relatively rigid pericardium. Consequently, RV distension, as in acute pulmonary embolism or congestive heart failure, pushes the septum to the left, thereby decreasing LV volume and preload. The resulting decrease in cardiac output should not be taken to indicate LV dysfunction.[99,134,135] Additionally, the LV generates a substantial portion of RV contractility[136] and the decrease in cardiac output that occurs with acute RV failure with an intact pericardium is at least partially attributable to a decrease in LV performance.[137] Cardiac output can be improved in this situation by opening the pericardium.

The effects of pericardial restraint and ventricular interaction come into play during positive-pressure ventilation.[138] With a normal circulation, an increase in intrathoracic pressure will decrease transmural pressures, end-diastolic volumes, and stroke work of both ventricles. However, in the context of the normal circulation, these changes have no observable clinical effects. In congestive heart failure, however, where pericardial restraint regulates total cardiac volume, increased intrathoracic pressure decreases RV transmural pressure, filling, and volume, resulting in increased LV transmural pressure, end-diastolic volume, and stroke work via the Frank-Starling relationship. The ultimate effect of increased intrathoracic pressure in congestive heart failure (from a common intervention such as positive-pressure ventilation) is highly dependent on intravascular volume status. In volume-depleted patients, the effects on the right heart will predominate, resulting in further reductions in cardiac output. Adequate volume status, however, will allow the beneficial effects of increased intrathoracic pressure on the LV to dominate, resulting in an increase in cardiac output.

Diastolic Ventricular Function

Diastolic function concerns the rate and extent of ventricular relaxation.[98,139] Many forms of heart disease manifest abnormalities of both systolic and diastolic function, but one or the other form of dysfunction may predominate and determine the type of therapy needed.

Diastolic dysfunction is manifested mainly by increased ventricular diastolic pressure at normal or even low ventricular volume.[139] This can result from increased passive stiffness of the ventricles because of chronic infiltrates (e.g., amyloid), myocardial scars, constrictive pericarditis, or diffuse myocardial fibrosis. It also can result from impaired relaxation. Normally, relaxation of ventricular muscle in diastole is rapid and associated with rapid release of calcium bound to troponin and its subsequent uptake by the sarcoplasmic reticulum. Removal of calcium allows actin-myosin cross-bridges to dissociate and the sarcomeres to lengthen, thereby permitting the ventricle to dilate. Any decrease in calcium removal because of abnormalities in major contractile proteins or transport processes decreases the rate and extent of relaxation.[73,140,141] Ischemia is one major factor that impairs calcium metabolism and diastolic ventricular function, but many other forms of heart disease have similar effects.[26,29,108,142] Clinically, diastolic function is assessed by relating end-diastolic pressure and volume, by observing the rate of ventricular filling by angiography or by Doppler studies of the mitral valve inflow, by measuring the peak rate of fall of ventricular pressure (−dP/dt max), or by calculating the time constant of the fall in ventricular pressure.

Neural Control of the Heart

The heart can function without any cardiac nerves, for example, after cardiac transplantation. However, the response to exercise in these denervated hearts is slow and due to increases in circulating catecholamines and the rise in body temperature. In intact animals and humans, β-adrenoreceptor blockade blunts the heart rate increase with exercise and abolishes inotropic response, as judged by the increase in dP/dt max.[143]

Studies of the neural control of the heart must consider the basal level of sympathetic and parasympathetic tone.[143] In conscious animals, resting sympathetic tone is low, and resting parasympathetic tone is high. Therefore sympathetic blockade has little effect on heart rate and myocardial contractility, but parasympathetic blockade causes marked tachycardia. On the other hand, many anesthetics depress the sympathetic nervous system, leading to impaired contractility and bradycardia. Postoperatively, patients often have high circulating catecholamine concentrations, and the effects on myocardial function depend on the balance of catecholamine concentrations, stimulation of the sympathetic nervous system by pain, and the extent of myocardial depression caused by the drugs used for sedation.

The carotid and aortic baroreceptors respond to changes in arterial blood pressure. If basal sympathetic tone is low, as is normal, then inhibiting sympathetic tone by raising aortic pressure has little effect on myocardial contractility. On the other hand, lowering arterial pressure causes a reflex increase in sympathetic tone, with increases in heart rate and contractility. Baroreceptor sensitivity increases throughout gestation in fetal lambs[144] but may decrease after birth.[145] Also in fetal lambs, denervating the baroreceptors did not alter mean arterial blood pressure or heart rate, but did increase the variability of pressure and heart rate. Similar increased variability of pressures but not of heart rate occurred in adult sheep.[146] Denervation in the fetuses in the same study also decreased peripheral resistance.

Carotid and aortic chemoreceptors are stimulated by low P_{O_2}, high P_{CO_2}, and low pH, but the changes have to be marked, and even then the increase in myocardial contractility is modest. The fetus seems to be less sensitive than the adult to chemoreceptor stimulation.[147] The bradycardia that accompanies severe hypoxemia results from vagal stimulation. During exercise or hemorrhage, plasma catecholamines increase markedly, but the inotropic responses are different. With exercise, dP/dt max increases by as much as fourfold, the peripheral vascular bed is dilated, and cardiac output increases, whereas with hemorrhage, dP/dt max increases by only 30% to 50%, cardiac output falls, and most vascular beds vasoconstrict. Thus, the pattern of sympathetic neural stimulation rather than the circulating catecholamine concentrations determines how the heart responds to these stimuli.

Vagal effects on the heart are shown most prominently by changes in heart rate, but their effects on myocardial contractility depend on the existing level of sympathetic tone. Vagal stimulation has little effect on myocardial contractility given little sympathetic tone, but markedly reduces the inotropic effects of increases in circulating catecholamines or sympathetic nerve stimulation. Conversely, blockade of muscarinic receptors can intensify the myocardial contractile response to sympathetic stimulation.

Cardiac Output

Cardiac output in the fetus is determined mainly by heart rate because of a limited capacity to increase stroke volume. This limitation results partly from decreased diastolic distensibility and partly from positive extracardiac pressures.[148] Consequently, fetal bradycardia is detrimental to blood flow and oxygen delivery. The fetal heart, however, can respond to increased preload (Starling's law) with increased stroke volume, provided there is no concomitant increase in afterload.[149] Usually, infusion of fluid into an animal causes arterial pressure to rise, and the increased afterload tends to inhibit the increase in stroke volume that would otherwise occur.[149-151] Immediately after birth, there is a large increase in total body oxygen consumption and cardiac output to about twice its later values (per unit body size).[152]

This increase has been related to an increase in adrenergic receptors stimulated by fetal thyroid hormones.[153] In addition, because at birth approximately 80% of the infant's hemoglobin is in the form of fetal hemoglobin, the reduced ability of this hemoglobin to unload oxygen at the tissue level compels the infant to have a higher cardiac output than the infant will have 4 to 6 weeks later.[152] Therefore the neonate has limited cardiac output reserve and the heart has near-maximal contractility.[154,155] These features make the neonate unusually susceptible to diseases that impair cardiac function. The Frank-Starling mechanism, however, is intact at this time.[156] Evidence indicates β-adrenoreceptor stimulation helps the neonatal ventricle adapt to volume loads.[157] Thus β-adrenoreceptor blockade might be expected to be much more harmful in the neonate than in the older person with minimal sympathetic tone.

Myocardial Metabolism: Normal Myocardial Energy Metabolism

Basic Metabolic Processes

Basal metabolic processes can be studied by measuring oxygen uptake, production of heat, or utilization of high-energy phosphates. In isolated papillary muscle, most of the oxygen consumed is used in generating force (internal work), approximately 15% is used in shortening (external work), approximately 20% is used for basal metabolic processes (protein synthesis, sarcolemmal Na-K transport) and approximately 10% is used for the activity of Na/K-ATPase and Ca-ATPase.[158-160] Similar conclusions can be drawn from studies of whole hearts.[161]

The myocardium has a brisk rate of metabolism, consuming approximately 8 to 10 mL oxygen/100 g muscle/min under basal conditions. Potassium-induced cardioplegia can reduce myocardial oxygen consumption, but "resting" cardiac muscle still consumes more than five times as much oxygen as does resting skeletal muscle. During maximal exercise, the myocardium may consume as much as 60 to 80 mL oxygen/100 g muscle/min.[162]

Cardiac energy is generated by oxidizing substrates to carbon dioxide and water. During this process, energy is both used and stored, and most of the stored energy is in the form of ATP. When needed, ATP breaks down to adenosine diphosphate (ADP) or adenosine monophosphate (AMP) and releases energy for contractile or transport processes.[163] The substrates for energy production can be glucose, lactate, or fatty acids.[164] In a mixture, the fatty acids are preferred over the others, and an increase in plasma fatty acid concentrations, as in fasting or sympathetic stimulation, suppresses oxidation of carbohydrates by the heart.[55,164] Therefore lactate consumption or extraction cannot be used as an accurate guide to cardiac metabolism unless the concentration of the fatty acids is evaluated at the same time.[165] ATP is usually generated by oxidative phosphorylation. Various transport systems move the substrates into the mitochondria for oxidation by the tricarboxylic cycle. Other transport systems move the ATP out of mitochondria into the cytosol, where they can break down and supply energy. The ATP is replenished by transfer of a high-energy phosphate moiety from creatine phosphate to ADP, mediated by the enzyme creatine kinase.[163,166] When oxygen supply is restricted, ATP can be generated by anaerobic glycolysis, an inefficient but useful temporary pathway. Furthermore, products of glycolysis, if they accumulate, inhibit key enzymes and interfere with further ATP production. Therefore the myocardium is unable to build an oxygen debt without further depressing energy production and, hence, contractility. Oxidative metabolism is so important to the heart that more than 30% of the mass of the myocardium is mitochondria.[158]

Fetal lamb ventricles have the same oxygen consumption per unit mass as the adult left ventricle. Because fetal oxygen content is lower than that in the adult, however, myocardial blood flow per unit mass is about twice as high in the fetus as in the adult.[167,168] Oxidative capacity is relatively lower, and glycogen stores and glycolytic flux are relatively higher in the fetal heart. This condition may explain why the immature heart is more resistant to hypoxemia than is the adult heart, provided an adequate supply of glucose is available for glycolysis. The main substrates used by the fetal heart are glucose, lactate, and pyruvate, although ketones, amino acids, and short- and medium-chain fatty acids also can provide energy.[169] After birth, long-chain fatty acids become the predominant substrates. For these reasons, prolonged severe hypoglycemia can seriously depress cardiac function in the neonate but is unlikely to do so in the older person.

L-Carnitine is essential for fatty acid transport across the mitochondrial membrane. Most of the body's carnitine is produced endogenously when protein degradation releases trimethyl-lysine, which is transformed into carnitine. Carnitine is present in red meats and dairy products (including breast milk), but only small amounts are present in vegetable products. It can be absorbed by the intestine, is not broken down in the body, and is excreted by the kidney.

In all except young infants, the preferential source of energy for myocardial function comes from the β-oxidation of long-chain fatty acids. After fatty acids enter the cell, they are activated to fatty acid (or acyl) coenzyme A (CoA) compounds by palmitoyl-CoA synthetase, then linked by carnitine palmitoyl transferase I to carnitine to form acylcarnitines, thus releasing CoA. The acylcarnitines cross the mitochondrial membrane, and at the inner surface of the membrane another enzyme, carnitine palmitoyl transferase II, transfers the fatty acids back to CoA. The fatty acids can now undergo β-oxidation with the production of ATP. These enzymes also help transport acylcarnitine esters of CoA out of the mitochondria. These esters are toxic in high concentrations. Fetuses and neonates have decreased activity of carnitine palmitoyl transferase and palmitoyl-CoA synthetase, so glucose, lactate, and short-chain fatty acids are the preferred myocardial energy substrates at this age.[19,170]

Endogenous carnitine production usually is sufficient for growth, but plasma (and tissue) carnitine concentrations may decrease after 1 month of parenteral nutrition without carnitine supplements. Energy demands increase when renal excretion of carnitine increases in conditions of burns, sepsis, starvation, or after surgery; with excess excretion in Fanconi syndrome; with drugs such as valproic acid, pivampicillin, and pivmecillinam, which bind to carnitine and are excreted; with decreased production during chronic hemodialysis; and with cirrhosis of the liver.[171,172] Carnitine concentrations may be low in very premature infants.[173] Ischemia of heart or skeletal muscle depletes carnitine in the affected tissues, as does chronic congestive heart failure.[174,175] Most cases of severe carnitine deficiency in children, however, result from inherited defects in intermediary metabolism.[176]

Carnitine deficiency may produce acute or chronic syndromes, including a Reye-syndrome–like encephalopathy, hypoglycemia, myopathy, cardiomyopathy, and failure to thrive. Once the diagnosis is established, treatment is with a diet high in carbohydrates and short-chain fatty acids, plus carnitine supplements by mouth (25-300 mg/kg/day) or even intravenously if needed. Patients with congestive heart failure who do not show overt evidence of carnitine deficiency may improve after taking carnitine supplements.[175]

Determinants of Myocardial Oxygen Consumption

In 1958, Sarnoff and Mitchell[128] reported that pressure work by the heart consumed more oxygen than did volume work and found a good correlation between the area under the LV

pressure curve in systole (termed the tension-time index) and left ventricular oxygen consumption. Subsequently, others found that peak wall tension (or stress) was a better predictor of left ventricular oxygen consumption.[177-180] It is important to take account of wall thickness and ventricular dimensions in estimating myocardial oxygen consumption, which is why the tension-time index, which ignores wall stress, is not a good predictor. Increases of contractility or heart rate also increase myocardial oxygen consumption, but because they decrease ventricular size and thus wall stress, increased oxygen consumption is not as great as would be expected from studies in muscle strips.[181]

Stroke volume is an added predictor of myocardial oxygen consumption.[12,182-185] The approaches used include examining the area within the pressure-flow loop. This approach has been extended by Suga and colleagues,[112,186-191] who concluded that the best predictor of LV oxygen consumption was the area in the pressure-volume loop plus the area representing end-systolic pressure energy (Figure 19-8). By subtracting the contributions of basal myocardial metabolism, they were able to show that the oxygen consumption–pressure-volume area (PVA) relationship was independent of contractile state. Further studies by these investigators showed that PVA-independent oxygen consumption was a function of contractility, defined by E_{max}. Certain interventions, for example, acidosis, made the slope of this relation between PVA-independent V_{O_2} to E_{max} steeper, that is, they decreased the efficiency of the system.

Because oxidizing fats uses up more oxygen than does oxidizing carbohydrates, theoretically more oxygen should be used per unit of work when burning fatty acids. Though not consistently demonstrated, there are a few good studies of this phenomenon.[166]

Myocardial Oxygen Demand-Supply Relationship

One way of assessing myocardial oxygen demand is to note that it is roughly proportional to the ventricular systolic pressure generated and the duration of systole, that is, to the area under the real-time pressure curve of the ventricle in systole: the systolic pressure-time index (SPTI).[192,193] SPTI is dramatically influenced by cardiac afterload; for instance, aortic stenosis raises SPTI (at constant stroke volume). The correlation between SPTI and myocardial oxygen demand is imperfect because it does not take into account wall stress, which involves radius and wall thickness, or contractility.[194]

Because left ventricular myocardial perfusion is restricted to diastole (see Chapter 20), myocardial oxygen supply is proportional to both duration of diastole and myocardial perfusion pressure in diastole. In general, diastolic myocardial perfusion pressure can be represented graphically as the difference between superimposed aortic and left ventricular pressure curves. The area between these curves, from the instant of aortic valve closure in diastole to reopening of the aortic valve in systole, has been termed the diastolic pressure-time index (DPTI) and is proportional to

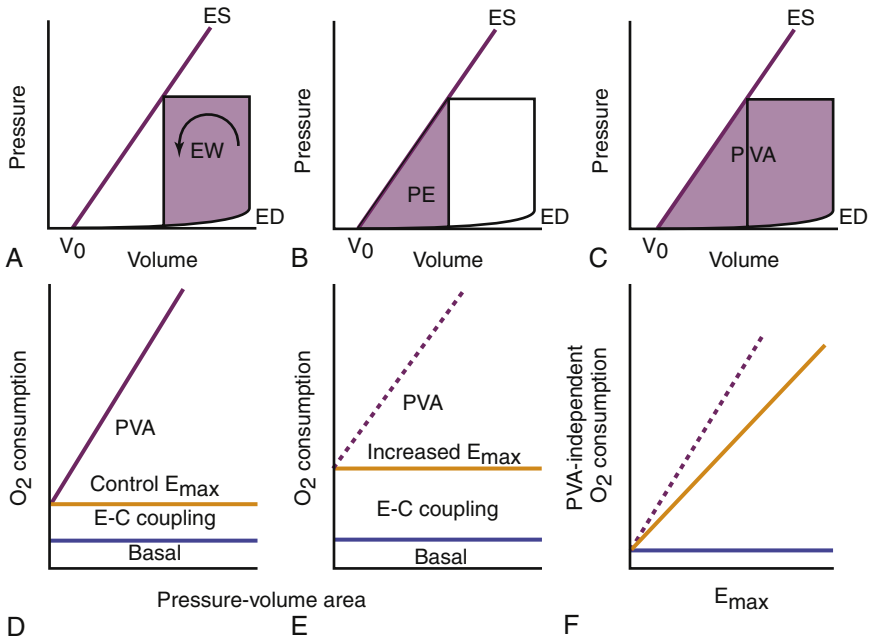

Figure 19–8. Relationship of myocardial oxygen consumption to the pressure volume area (PVA). **A,** Ventricular pressure-volume loop with pressure plotted on the ordinate and volume on the abscissa. *Arrow* shows the direction of inscription of the loop. *ED,* End-diastolic pressure-volume line; *ES,* line of end-systolic pressure-volume points (end-systolic elastance); *EW,* area representing external mechanical work; V_0, unstressed ventricular volume. **B,** *Shaded area* to the left of the pressure-volume loop in the pressure-volume diagram represents potential energy (PE). **C,** Total area (PVA) is the sum of the external mechanical work area (EW) and the potential energy area (PE). **D,** PVA is linearly proportional to oxygen consumption, but some oxygen consumption is independent of PVA. The PVA-independent oxygen consumption shown below the *upper horizontal line* results from excitation-contraction (E-C) coupling and basal oxygen consumption. **E,** When contractility is increased, as indicated by the increased value for E_{max}, the relationship between PVA and oxygen consumption is unchanged, but PVA-independent oxygen consumption increases. **F,** Relationship between E_{max} and PVA-independent oxygen consumption is linear. With myocardial depression, the slope of this relationship is steeper *(dashed line).* Thus for any value of E_{max}, PVA-independent oxygen consumption is increased so that myocardial efficiency is reduced. *(Data from references 61, 62, 125-127.)*

subendocardial blood flow. When multiplied by arterial oxygen content, this index correlates with subendocardial oxygen supply.[195]

The ratio DPTI × Arterial oxygen content/SPTI (Figure 19-9) is a fair indicator of myocardial oxygen balance. At critical levels, subendocardial ischemia occurs.[192,193] This ratio is worsened by tachycardia, which shortens diastole and the duration of myocardial perfusion; by elevation of end-diastolic pressures in the ventricles; or by elevation of coronary sinus pressure. It is adversely affected by low aortic diastolic pressure (as in shock, aortic valve insufficiency, or other large diastolic runoff lesions) and by elevated ventricular systolic pressure (as in aortic stenosis, systemic hypertension, or pulmonary hypertension). The ratio is favorably affected by balloon aortic counterpulsation, which elevates aortic diastolic pressure and reduces systolic afterload. Given the imperfect nature of this ratio, too much emphasis should not be placed on any given value, but two points are clear: (1) a fall in the ratio in any patient moves that patient toward a supply:demand imbalance and (2) any ratio less than the 8.9 that typifies normal subjects likely indicates myocardial ischemia.[196]

Effects of Myocardial Ischemia on Cardiac Function and Metabolism

Ischemia indicates a flow that is inadequate to supply the demand for oxygen by an organ or tissue; it also implies reduced clearance of metabolites.[197,198] The second part of the definition is what distinguishes ischemia from hypoxemia, in which there is a normal flow with a decreased oxygen delivery. Because the heart cannot sustain an oxygen debt, inadequate oxygen supply rapidly decreases the energy supply to the muscle cells, which cease to contract normally. If a branch of the left coronary artery is severely narrowed or occluded acutely, within 5 to 15 seconds the myocardium supplied by that branch stops contracting, turns blue, and bulges and thins during each systole. If the acute ischemia is global, that is, all coronary arteries have similar reductions in oxygen supply, then the subendocardial muscle becomes ischemic first because this muscle has the lowest coronary flow reserve.

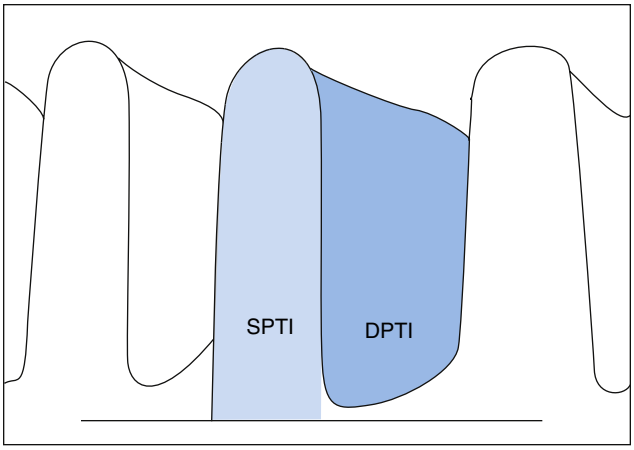

Figure 19–9. Systolic pressure time index (SPTI) reflects myocardial work and oxygen demand. Diastolic pressure time index (DPTI) reflects myocardial blood flow. *(Adapted from Fuhrman BP: Regional circulation. In Fuhrman BP, Shoemaker WC (eds):* Critical care: state of the art, vol 10, *Fullerton, CA, Society of Critical Care Medicine, 1989.)*

Subendocardial function is selectively decreased.[199-201] Global cardiac contractility decreases. Cardiac pump function is impaired, but survival is possible. More extensive global ischemia leads to death. Chronic imbalance of oxygen supply and demand leads to death of the affected muscle cells, producing either a localized infarct or diffuse, perhaps patchy, subendocardial fibrosis as occurs commonly with severe aortic stenosis, cyanotic heart disease, or dilated cardiomyopathy (see Chapter 20).

Temporary imbalance of supply and demand leads to two patterns of response, depending on the duration of the ischemia. If a branch coronary artery is occluded for 15 to 30 minutes and then the occlusion is removed, flow returns to normal rapidly, but the muscle may not contract normally for many hours. Some biochemical changes that occurred take many hours to reverse. This phenomenon is known as reperfusion injury or stunning.[202-205] It should be distinguished from the "no reflow" phenomenon in which, after a longer occlusion, release of the occlusion is followed by incomplete restoration of flow because of myocardial edema, cell swelling, plugging by neutrophils, and endothelial damage. Stunning may occur after prolonged cardiopulmonary bypass surgery and may account for some of the cardiac depression that often is observed in the early recovery period.[206,207]

Chronic ischemia of moderate severity causes myocardial hibernation, an adaptive response that leads to metabolic down-regulation and reduction of flow without extensive cell death.[208-211] Regional function is reduced, but restoration of flow leads to functional recovery. This phenomenon is best known from studies of coronary artery disease but can be present in some children with normal coronary arteries and subendocardial ischemia.

Many biochemical changes occur when the heart becomes ischemic, and which are the primary causes of the dysfunction is not always clear. As soon as oxygen supply is cut off, all components of the mitochondrial electron chain become reduced because of the absence of the final electron acceptor. Nicotinamide adenine dinucleotide (NAD) is reduced to NADH within 2 seconds after the onset of sudden ischemia.[212] Glycogenolysis increases rapidly, thereby helping to supply ATP, but then is progressively inhibited by increasing concentrations of hydrogen ion, NADH, and lactate. (This inhibition is less marked with pure hypoxemia because the associated high flows help to wash out these inhibitory metabolites.) The stores of high-energy phosphates become depleted. First creatine phosphate decreases, then ATP concentrations fall. For example, after sudden arterial occlusion, creatine phosphate is almost completely depleted within 3 minutes, and ATP is reduced to 35% of control concentration within 15 minutes. ATP is degraded to ADP and AMP, which then is deaminated to adenosine. Adenosine in turn is rapidly broken down to inosine and hypoxanthine. Because of these changes, the nucleotide pool of cardiac muscle is depleted so that even after flow is restored, a long time is required before normal high-energy stores are replenished. Furthermore, during ischemia, xanthine dehydrogenase in the tissues is converted to xanthine oxidase, which catalyzes the conversion of hypoxanthine to xanthine and superoxide radicals. These in turn can be converted by superoxide dismutase into hydrogen peroxide, which can be converted by catalase to produce highly reactive hydroxyl radicals. These free radicals can react with lipids in the cell membranes and cause lipid peroxidation,

which produces several toxic and arrhythmogenic substances and impairs the functions of the cell membrane.[213] Oxygen-derived free radicals can be introduced by activation of neutrophils by the damaged endothelium and by the formation of peroxynitriles from nitric oxide.

Accompanying these changes are accumulations of hydrogen ions, lactate, and many other catabolites. These entities create an osmotic load within the cells, with resultant swelling of the cells and the mitochondria. The cell and mitochondrial membranes become impaired, and myoglobin and enzymes such as creatine kinase leak out of the cell, as do essential ions such as magnesium and potassium. Free calcium may accumulate in the cytosol (because of loss of chelating agents) and the mitochondria, particularly during reperfusion, and this calcium load may be highly detrimental to cell function. Finally, ischemia is associated with decreased myocardial carnitine concentrations, defective transport of long-chain fatty acids into the mitochondria, and accumulation of toxic acylcarnitine esters of CoA. These changes further delay the recovery of energy production and muscle contraction.

Systemic Vasculature

General Anatomy

The large arteries are elastic. Their media contain concentric lamellae of perforated elastic tubes cross-linked by transverse collagen (type III) and smooth muscle.[47,214] When smooth muscle contracts, the wall becomes stiffer. Smaller arteries have fewer lamellae. The media is bounded by the external and internal elastic laminae, beyond which are the adventitia with nerves and vasa vasorum and the intima with sparse fibrous tissue and a metabolically active endothelium, respectively. Arterioles have no lamellae and only a thin media with circular or spiral smooth muscle; the only elastic tissue is in the inner and outer elastic laminae. Capillaries are thin-walled and nonmuscular, ideal for transport of materials into and from the tissues; however, they contain pericytes that have myosin, actin, and tropomyosin and so might have some contractile function. Veins have medial muscle but thinner walls relative to lumen diameter than do arteries. Their endothelium may have different properties. The numerous extracellular matrix components are reviewed by Buga and Ignarro.[215] The developmental aspects of blood vessels are reviewed by Stenmark and Weisen.[216]

Physiologic Mechanisms

General features. Although large arteries are regarded as conduits and capillaries as vessels allowing transport of substances to and from the tissues, many substances can move across arterial walls. Oxygen and carbon dioxide can diffuse across arteriolar walls, and lipoproteins can penetrate the walls of large arteries. Whether atheromatous deposits form in arteries depends on the balance of the amount of lipoprotein that enters and leaves the arterial wall. This balance depends on the concentration and chemical nature of lipoproteins and the action of components of the wall, such as glycosaminoglycans, in binding altered lipoprotein molecules and preventing their transit through the wall.

Arteriolar tone controls peripheral resistance and, with cardiac output, determines blood pressure and regional flow. Regions of the circulation may differ markedly in their patterns of vascular regulation. A potent stimulus for increased vascular resistance in one region of the circulation may have a different effect in another. For example, during hemorrhagic shock, flow is maintained to heart and brain but is reduced to muscle, kidneys, and gut. Venous and venular tone, together with diuretic and antidiuretic factors, determine blood volume and venous pressure.

The two active components of the systemic circulation are the medial smooth muscle and the endothelium. They both have receptors for innumerable agonists and antagonists that diffuse from autonomic nerve endings, circulate from remote regions, or are produced locally. The smooth muscle is responsible for vasoconstriction or vasodilatation. The vascular endothelium is one of the metabolic powerhouses of the body, and has several major functions:

1. Endothelial cells play important roles in the response to injury by causing leukocyte adhesion and extravasation, mediated by cell adhesion molecules such as selectins, cadherins, and integrins.[215,217]
2. They are intimately bound up with coagulation[215,218] by virtue of the production of procoagulant (e.g., platelet-activating factor [PAF], von Willebrand factor, fibronectin, and factors V and X) and anticoagulant factors (e.g., heparan, dermatan sulfate, thrombomodulin, and ectonucleotidase) and by the production of nitric oxide and PGI_2, which inhibit platelet aggregation and degranulation.
3. They regulate capillary permeability by producing ET-1 (increase) or PGE1 (decrease) and respond with increased plasma leakage to substances such as bradykinin, histamine, thrombin, oxygen radicals, and PAF.
4. They regulate smooth muscle contraction in response to shear stress, in keeping with an overriding principle that shear rate must be kept constant within narrow limits to prevent endothelial damage.[219,220] In general, most of the vascular resistance resides in microvessels smaller than 150 μm in diameter,[221] which are subject to the controls discussed here.

Any increase in local organ flow resulting from a decrease in resistance in these microvessels increases shear stress in the larger upstream arteries. This increase is sensed by endothelial integrins,[222] which set off a cascade of responses that relax smooth muscle by activating Ca^{2+}-sensitive K^+ channels and hyperpolarizing the endothelial cell membrane and by releasing acetylcholine, nitric oxide, PGI_2, ATP, and substance P.[215,222] A chronic increase in shear stress activates the nuclear factor-Kβ transcription complex and induces a number of early response genes.[215,222]

Control of vascular tone**.** In general, regional circulations regulate their flow so that they obtain required amounts of oxygen and nutrients. Any or all of the mechanisms discussed may be invoked. Vasomotor tone is strongly influenced by several mechanisms: (1) innervation and neural processes, (2) circulating endocrine and neuroendocrine mediators, (3) blood gas composition, (4) local metabolic products, (5) endothelial-derived factors, and (6) myogenic processes.

Receptors responsive to neural products (norepinephrine, acetylcholine, neuropeptides) are found throughout the circulation. Nevertheless, innervation and receptor distributions are organ specific, which allows rapid, patterned, coordinated redistribution of blood flow and an orchestrated response to hypoxia, changes in posture, and hemorrhage. Although these receptors respond to circulating agonists

(including angiotensin II and adrenal epinephrine) and to those liberated locally, they are generally associated with innervation by autonomic nerves. In general, presynaptic α-adrenergic stimulation causes norepinephrine release and vasoconstriction. β-adrenergic stimulation generally causes vasodilatation. Cholinergic stimulation (whether sympathetic or parasympathetic) generally causes vasodilatation (see Chapter 31).

In all organs, sensory and efferent nerve endings contain nonadrenergic, noncholinergic (NANC) peptides, for example, neuropeptide Y, VIP, calcitonin gene-related peptide (CGRP), and substance P.[116,223-234] Neuropeptide Y is colocalized and released with norepinephrine[235] and VIP is colocalized with acetylcholine and released upon stimulation of vagal nerve endings. Most of these peptides except neuropeptide Y are vasodilatory, and they help modulate blood pressure and regional flows. Substance P and CGRP are released when sensory nerves are stimulated by capsaicin, thus accounting for the flushing that accompanies the eating of hot peppers. (Many neuropeptides also occur throughout the central nervous system, where they may play roles in cardiovascular regulation.)

Humoral regulators of vascular tone and blood volume include angiotensin, adrenomedullin, aldosterone, arginine vasopressin (AVP), bradykinin, histamine, serotonin, thyroxine, natriuretic peptides, and various reproductive hormones. Most of these regulators have both direct effects and secondary effects, which tend to be organ-specific or regional. They tend to have altered concentrations in hypertension, congestive heart failure, or shock, and their antagonists are used in therapy. Some agents, such as histamine, serotonin, and thyroxine, probably affect peripheral resistance only in abnormal states and are not physiologic regulators.

Angiotensin plays a special role in the homeostasis of blood pressure. Its concentration increases in hemorrhagic or hypovolemic shock, following increased renal production of renin that produces angiotensin I from angiotensinogen. Angiotensin I is converted to active angiotensin II by angiotensin-converting enzyme (ACE) in the endothelium, especially in the pulmonary vessels. However, angiotensin II also is produced locally in the heart and vessel walls by renin that enters from the blood and perhaps by other local proteases.[236,237] It causes generalized vasoconstriction in both systemic and pulmonary circulations, but locally it stimulates the release of vasodilating prostaglandins in lung and kidney. Angiotensin II, via angiotensin I receptors, plays a role in cardiac and smooth muscle cell hypertrophy. In excess, it results in cardiac inflammation, fibrosis, and apoptosis.[238-241]

Adrenomedullin, originally found in pheochromocytomas, is produced in many normal cell types, including endothelium. Among its many actions are long-lasting vasodilatation and diuresis.[242,243] It shares homologous sequences with CGRP, calcitonin, and amylin.[244] Its release may be stimulated by ET-1. It may play a role in treating heart failure.[245]

Aldosterone, known primarily for its effect on sodium excretion and potassium retention, has indirect central effects on blood pressure.[246-248] Its concentration increases when renin release is stimulated. In patients with congestive heart failure, its decreased breakdown in the liver accounts for very high blood concentrations, which are harmful to the heart and blood vessels. Inhibition of aldosterone by spironolactone may have great clinical value.[247,249,250]

AVP, which is released from the axonal terminals of magnocellular neurons in the hypothalamus, causes vasoconstriction by stimulating VP_1 receptors. However, at low concentrations, AVP dilates coronary, cerebral, and pulmonary vessels. It is an antidiuretic hormone that acts on VP_2 receptors in the renal collecting ducts.[251] Its concentration is low in septic shock,[119] with ventricular arrhythmias, and after cardiac surgery,[252] but is increased in myocardial and hemorrhagic shock, congestive heart failure, and cirrhosis of the liver.[106,251,253] Selective AVP antagonists promote free water excretion without concomitant electrolyte excretion[253-256] and are useful in treating fluid overload in patients with congestive heart failure, cirrhosis of the liver, and the syndrome of inappropriate antidiuretic hormone secretion without causing electrolyte imbalance.

Bradykinin is a potent pulmonary and systemic vasodilator released locally by the action of proteolytic enzymes on kallikrein after tissue injury.[257-260] Bradykinin is metabolized by kininase II, which is the same as ACE, so ACE inhibitors not only reduce angiotensin II production but increase bradykinin concentrations. Bradykinin also causes endothelial cell release of tissue-type plasminogen activator.[261]

Histamine, released by mast cells in response to injury, is a potent vasodilator in most regions of the circulation but causes vasoconstriction in the lung. It also increases endothelial permeability.[262] No evidence indicates histamine plays a part in normal vasoregulation.

The natriuretic peptides are released from the heart when it is distended in congestive heart failure. They cause vasodilatation and increased diuresis. A-natriopeptide (mainly from atria) and B-natriopeptide (from ventricles) are released from myocardial cells, and C-natriopeptide is released from cardiac endothelium.[262-266] A recombinant B-natriopeptide (nesiritide) was initially shown to be safe and potentially more effective than dobutamine in treating acute severe congestive heart failure.[263-266] This is currently being tested in a large multinational randomized controlled trial (ASCEND-HF).[267] These natriopeptides and the kinins are broken down by neutral endopeptidase. Inhibition of this breakdown combined with inhibition of ACE by vasopeptidase inhibitors (e.g., omapatrilat) greatly augments vasodilatation.[268-273]

Serotonin probably acts mainly in the central nervous system, but peripherally it can act on S_1 receptors to produce vasodilatation and on S_2 receptors to cause vasoconstriction. It also augments the action of other vasoconstrictors.[271,272]

Tissue levels of oxygen and carbon dioxide reflect adequacy of perfusion and oxygen delivery. These blood gases are potent determinants of regional blood flow and have effects that differ among regions of the circulation. They also have a more general effect mediated by carotid chemoreceptors.

Local metabolic regulation of vasomotor tone provides an ideal homeostatic mechanism whereby metabolic demand can directly influence perfusion. For instance, adenosine, which accumulates locally when tissue metabolism is high and tissue oxygenation is marginal, causes pronounced vasodilatation in the coronary, striated muscle, splanchnic, and cerebral circulations. Cerebral autoregulation has been suggested to take advantage of local metabolite production as an indicator of adequacy of blood flow. According to the argument, when perfusion pressure falls, cerebral blood flow might decline but for local accumulation of vasodilating metabolites. The perivascular concentration of these metabolites is restored to normal as flow rises, washing out the metabolites. Potassium is

released from muscle in response to increased work, ischemia, and hypoxia.[273] Hypokalemia causes vasoconstriction.[274,275] Hyperkalemia, within the physiological range, causes vasodilatation by stimulating K_{ir} channels.[276-278] Many of the agents previously discussed are produced locally and are effective as circulating hormones. At least four different types of potassium channels are present on arterial smooth muscle cells[278]: voltage-activated channels (K_v), calcium-activated channels (BK_{Ca}), inward rectifiers (K_{ir}), and ATP-dependent channels (K_{ATP}). These channels are activated by vasodilators. As a result, the cells hyperpolarize, voltage-dependent calcium channels close, intracellular calcium concentrations decrease, and vasodilatation results.[279] Pharmacological vasodilators, such as cromakalim, pinacidil, and diazoxide, directly activate K_{ATP} channels, as do endogenous vasodilators such as CGRP, VIP, prostacyclin, and adenosine.[279] Inhibitors of K_{ATP} channels, such as glibenclamide, cause vasoconstriction.

The endothelial lining of blood vessels plays a prominent role in the regulation of vascular tone.[280] In addition to its roles in the elaboration of vasoactive eicosanoids[281] and in the metabolism of angiotensin, the endothelium secretes several other categories of vasoactive substances, including adrenomedullin (discussed previously), nitric oxide, endothelial cell hyperpolarizing factor, and endothelins.

Endothelium-derived relaxing factor (EDRF) has been identified as nitric oxide.[282] Nitric oxide is a potent vasodilator released from endothelium after stimulation and accounts for some or all of the activity generally ascribed to other agonists. For instance, acetylcholine causes constriction of vessels stripped of their intima and causes dilatation only in the presence of the vascular endothelium.[280] Adenosine, prostacyclin, and epinephrine dilate vessels stripped of their endothelium. Bradykinin, substance P, thrombin, and potassium cause only endothelium-dependent relaxation. Nitric oxide also is released from endothelium when flow increases, an example of positive feedback. Nitric oxide increases smooth muscle soluble guanylate cyclase activity, raises muscle cyclic GMP, and thereby relaxes vascular smooth muscle (see Chapter 48). In addition to EDRF, endothelial-derived hyperpolarizing factors, which are probably epoxyeicosatrienoic acids and hydrogen peroxide, are now thought to play major roles. The hydrogen peroxide is produced by the action of superoxide dismutase on superoxide anions that are generated by the metabolism of ATP.[283]

The vascular endothelium elaborates the endothelins (ET-1, ET-2, ET-3), a family of compounds that are vasoactive, structurally related peptides. ET-1 is the most potent vasoconstrictor known. It also promotes mitogenesis and stimulates the renin-angiotensin-aldosterone system and the release of vasopressin and atrial natriuretic peptide.[247,284-287] These peptides act on one of two receptor subtypes: ET_A and ET_B. ET_A is located mainly on vascular smooth muscle cells and is responsible for mediating vasoconstriction and cell proliferation. ET_B is present predominantly on endothelial cells and mediates vasorelaxation, as well as ET-1 clearance. Endothelins cause local vasoconstriction or vasodilatation, depending on dose and location in the circulation.[288] Individual endothelins occur in low levels in the plasma, generally below their vasoactive thresholds. This finding suggests they are primarily effective at the local site of release. Even at these levels, however, they may potentiate the effects of other vasoconstrictors such as norepinephrine and serotonin.[289] Endothelin antagonists, such as bosentan, now are being used, specifically in the setting of pulmonary arterial hypertension.[290,291]

Myogenic responses of vessels are changes in smooth muscle tone in response to stretch or increased transmural pressure. An increase in inflow pressure causes a rise in vessel wall tension and transmural pressure[292] that causes localized vasoconstriction. The reverse occurs when inflow pressure falls. The mechanisms of this response are complex. There probably is initial sensing by surface integrins,[293] followed by activation of cation channels with calcium entry.[294] In some way, protein kinase C, MAP kinases, and Rho kinase are also involved.[295-297]

As expected, a complex interplay exists among myogenic, flow-mediated, and metabolic regulation of vessel tone.[298] The relative importance of these mechanisms likely varies in different vascular beds.

Autoregulation

In all organs, when inflow pressure is suddenly raised or lowered while oxygen consumption remains constant, flow rises or falls transiently but then returns to the earlier value. The phenomenon is termed *autoregulation*. Myogenic tonic response is partly responsible for this phenomenon, but it is not the only mechanism. Some investigators believe tissues have oxygen sensors that respond to transient increases or decreases in oxygen supply.[299-301] Others believe the process is mediated by greater or lesser release of nitric oxide carried to the tissues by hemoglobin in the form of S-nitrosohemoglobin or by ATP release by the red blood cell.[301-306] Carbon monoxide produced by the action of hemoxygenase in endothelium and smooth muscle may play a regulatory role.[307-310]

References are available online at http://www.expertconsult.com.

Regional Circulation

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PEARLS

- When delivering critical care, one must understand the specific properties that characterize the various regional circulations because therapies that benefit one region may be detrimental to another.
- Vascular tone is influenced by (1) innervation and neural processes, (2) circulating endocrine and neuroendocrine mediators, (3) local metabolic products, (4) blood gas composition, (5) endothelial-derived factors, and (6) myogenic processes.
- The transition from the fetal pulmonary circulation to the postnatal pulmonary circulation is marked by a dramatic fall in pulmonary vascular resistance and rise in pulmonary blood flow. The failure to successfully make this transition is integral to a number of neonatal and infant diseases.
- An important feature unique to the cerebral circulation is the presence of a blood-brain barrier. As a result, the cerebral vasculature responds differently than other vascular beds to humoral stimuli.
- Regulation of myocardial perfusion is tailored to match regional myocardial oxygen supply to demand over the widest possible range of cardiac workload. Increases in myocardial oxygen demand must be met by increases in myocardial blood flow.
- Critically ill patients are at risk for impaired splanchnic blood flow that can impair the two chief functions of the gastrointestinal system: (1) digestion and absorption of nutrients, and (2) maintenance of a barrier to the translocation of enteric antigens. Splanchnic ischemia is associated with an increased incidence of morbidity and mortality in critically ill patients.
- Although renal blood flow remains constant over a wide range of renal artery perfusion pressures, urinary flow rate varies as a function of renal perfusion pressure.

General Features

General Anatomy

Vascular anatomy is generally described in terms of distinct layers. Moving from the innermost layer outward are the metabolically active endothelium, the intima (with nerves and vasa vasorum), the media, and the adventitia. The composition of these layers differs among vessel types (some vessels have fewer layers), depending on the position and function of the vessel within the circulation.

The large arteries are elastic. Their media contain concentric lamellae of perforated elastic tubes cross-linked by transverse collagen and smooth muscle. The wall becomes stiffer when its smooth muscle contracts. Smaller arteries have fewer lamellae. The media are bounded by the internal and external elastic laminae. Arterioles are less elastic, have no lamellae, and have thin media with circular or spiral smooth muscle and inner and outer elastic laminae. Capillaries have thin walls and are nonmuscular, which is ideal for transport of materials into and from the tissues. Veins have medial muscle but have thinner walls relative to lumen diameter than do arteries. The vascular endothelium has important metabolic characteristics that may differ between vessel types (i.e., arteries vs. veins) and in different regions.[1,2]

Basic Physiology

Blood flow to a regional vascular bed is primarily determined by inflow pressure, vascular resistance, and outflow pressure. Inflow pressure is usually systemic arterial pressure. Outflow pressure approximates venous pressure but at times may exceed venous pressure if vascular tone is great enough to close the circulation above venous pressure or if external pressure impinges on the vasculature.

In a model to explain the relation of arterial pressure to flow, the circulation is represented by two capacitance vessels separated by a resistance. A standpipe full of blood is allowed to discharge its contents into the arterial vasculature (the proximal capacitance). Blood flows across the resistance site (the arterioles), traverses the venous vasculature (the distal capacitance), and drains to a reservoir at some outflow pressure (P_o), taken for this example to be atmospheric (Figure 20-1).

The pressure head of the system (P_i) is generated by the weight of the column of blood in the standpipe and is proportional to its height (P_i = blood column height in cm H_2O). As the standpipe discharges, the height decreases and P_i decreases. This, in turn, decreases the rate of flow (Q) through the vasculature. Q decreases almost linearly with P_i until the column is quite low. Ultimately, flow will cease while there is still pressure in the standpipe. The pressure at which flow ceases is the critical closing pressure of the circulation (P_{cc}).[3] Lower P_i is insufficient to maintain vessel patency and to permit continued flow (Figure 20-2).

Incremental resistance to flow is generally defined as the change in pressure per unit change in flow (dP_i/dQ). At pressures well above critical closing pressure, this is nearly identical to the vascular resistance (R), defined clinically as:

$$R = (P_i - P_0) / Q$$

When P_i does not greatly exceed P_{cc} but P_{cc} does greatly exceed P_o, however, incremental resistance can differ substantially from this clinical estimate. Thus an increase in P_{cc} can be confused with a true increase in incremental resistance. For example, a diagnosis of intrinsic pulmonary vascular disease (e.g., pulmonary arterial hypertension) based on measured pulmonary artery pressures in a patient receiving mechanical ventilation with high airway pressures (that raise P_{cc}) may be spurious.

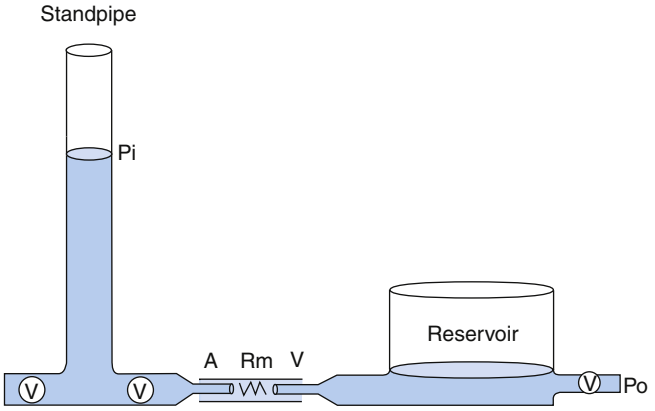

Figure 20–1. Model for facilitating interpretation of vascular pressure-flow relations. When valves (V) are properly positioned, fluid filling the standpipe to height Pi discharges across the circulation to the reservoir at outflow pressure Po. *A,* Artery; *Rm,* microvascular resistance; *V,* vein.

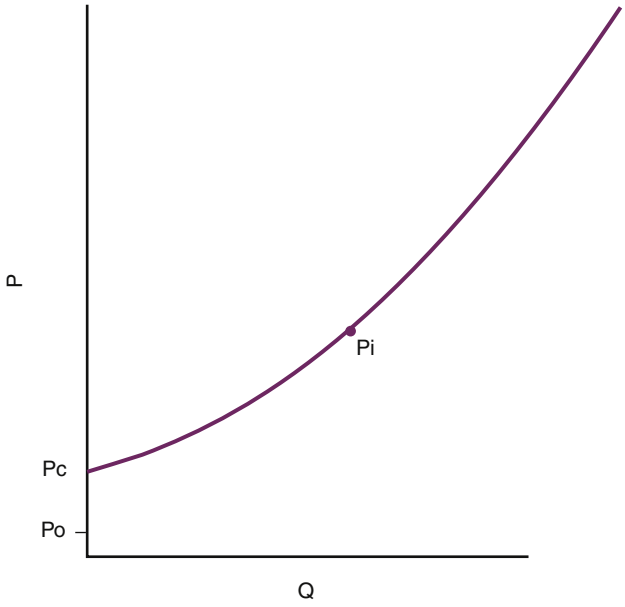

Figure 20–2. As the standpipe in Figure 20-1 discharges, Pi falls. Flow consequently slows and ultimately stops when Pi = Pc, the critical closing pressure of the circulation. Pi only reaches outflow pressure Po if Po ≥ Pc. *P,* Pressure; *Q,* rate of flow.

Venous Return and Cardiac Output

A second model illustrates the relationship of cardiac output to intrinsic mechanical properties of the systemic vasculature. In this model, the heart acts as a roller pump, creating a circulation much like that achieved during extracorporeal membrane oxygenation (Figure 20-3).

The roller pump displaces blood from the veins to the arteries, where some builds up before the resistive barrier of the arterioles. The higher the Q, the more blood resides in the arteries and the less in the veins. This complex partitioning of the blood volume depends on arterial capacitance (C_a), venous capacitance (C_v), and arteriolar incremental resistance to flow. At maximal Q, P_i is high and arterial blood volume ($P_i \times C_a$) is high, so much of the vascular blood volume is displaced to the arteries, and venous pressure (P_v) approaches P_{cc}. No further increase in roller pump speed can be sustained because any further increase in P_i would drive venous pressure substantially below venous critical closing pressure, causing vessel collapse and preventing venous return.

As Q is reduced, by turning down the roller pump, P_i falls and the volume of blood that resides in the arterial circuit also declines. This phenomenon allows more blood to reside in the veins, and venous pressure rises. As Q approaches zero, venous pressure approaches the mean circulatory pressure (P_m) (Figure 20-4). The importance of this model is that it can be used to illustrate the role of venous return as an independent determinant of cardiac output.

In its simplest form, cardiac output and central venous pressure of the intact circulation can be assumed to behave as illustrated in Figure 20-5. An increase in venous pressure distends the heart and elevates cardiac output. This behavior of the heart (see Chapter 19) can be superimposed on pressure flow characteristics of the vasculature. Venous return and cardiac output achieve equilibrium at one theoretical point for any given state of cardiac function (Starling curve) and simultaneous set of vascular characteristics (venous return curve).

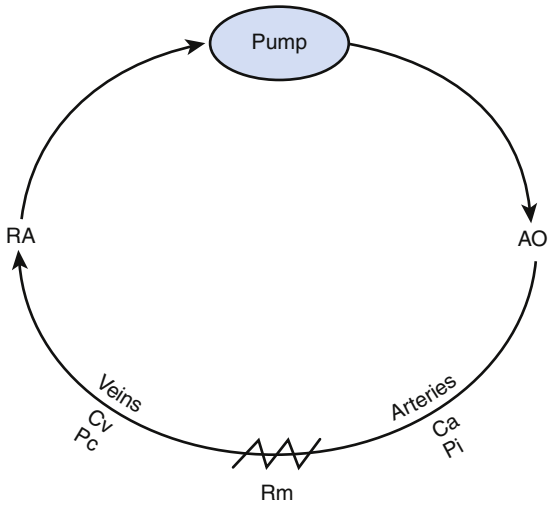

Figure 20–3. Model for facilitating interpretation of the relation of venous return to right atrial pressure. The heart is replaced by a mechanical roller pump. The right atrium (*RA*) is drained by the pump, and blood is infused into the aorta (*AO*). Blood then traverses the arteries, which have a capacitance (*Ca*) at an inflow pressure (*Pi*) determined by flow rate and microvascular resistance (*Rm*). Blood then returns through veins having capacitance (*Cv*) and critical closing pressure (*Pc*) to the right atrium.

This imaginary point defines a unique equilibrium relation of cardiac output to venous pressure. This venous return curve is dramatically influenced by changes in blood volume, vascular capacitance, and vascular resistance.

Transfusion elevates the maximal venous return that can be achieved without venous closure. Phlebotomy has the opposite effect. Because neither transfusion nor phlebotomy directly alters resistance or capacitance, the slope of the curve is not altered (Figure 20-6). Both interventions alter mean circulatory pressure because both interventions change blood volume.

Acute alterations in vascular capacitance can be expected to have effects similar to transfusion or phlebotomy, but any disparity between the change in C_a and the change in C_v will change the slope of the venous return curve.

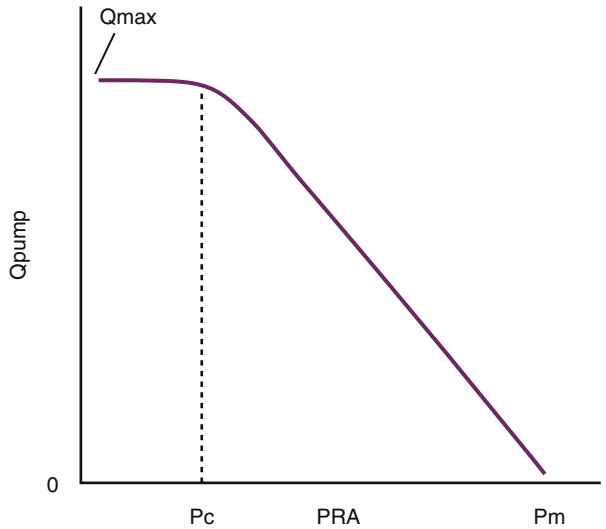

Figure 20–4. Venous return curve. As pump flow (*Qpump*) varies, right atrial pressure (*PRA*) is altered by redistribution of blood between arteries and veins. Qpump cannot be increased above Qmax because PRA would fall below critical closing pressure (*Pc*) of the venous circulation. *Pm*, Mean circulatory pressure of the vasculature at no flow; *Qmax,* Maximal flow.

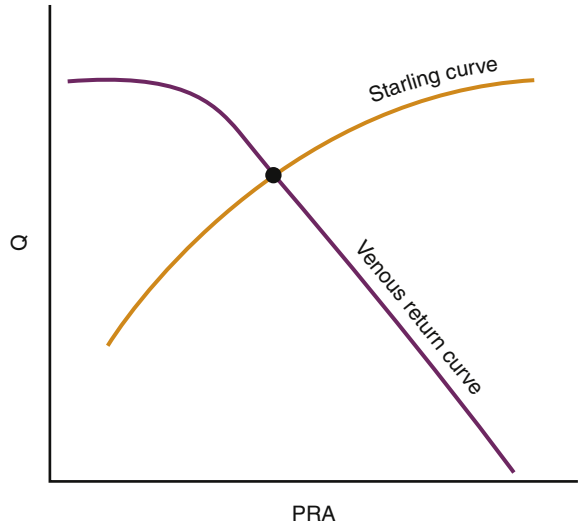

Figure 20–5. Theoretical superimposition of venous return and Starling curves. For any state of the heart and vasculature, these curves intersect at a point that characterizes right atrial pressure (*PRA*) and cardiac output (*Q*).

Isolated manipulation of incremental resistance would alter the maximum venous return attainable without venous collapse, yet it would not alter mean circulatory pressure. Changes in incremental resistance thus change the slope of the venous return curve (see Figure 20-6).

In clinical practice, it is unusual for any of these changes in vascular mechanics to occur in isolation. For instance, arteriolar dilation and dilation of other capacitance vessels often occur together. Arteriolar dilation and dilation of capacitance vessels have opposite effects on the venous return curve and, consequently, different effects on cardiac output. For this reason vascular volume expansion often is required in combination with nitroprusside or milrinone infusions to ensure adequacy of cardiac output despite successful reduction in cardiac afterload.

In patients with sepsis, toxic vasodilation may cause either high or low cardiac output, depending on associated changes in venous capacitance. Adequacy of vascular volume expansion, venous capacitance, vascular resistance, and the inotropic state of the heart can all profoundly influence cardiac output in patients with sepsis. Patients in septic shock are warm only if the circulation is adequately filled, cardiac function is sufficient, and incremental resistance is low.

Critical Closing Pressure

In many organs, as inflow pressure is lowered Q decreases, and it ceases at a pressure—the critical closing pressure (P_{cc})—that is higher than venous pressure. The probable mechanism

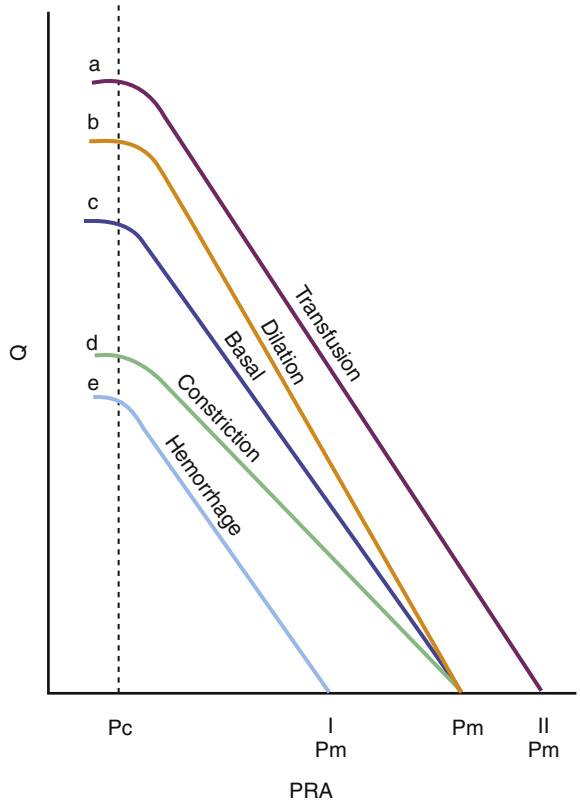

Figure 20–6. Effects of changing blood volume and microvascular resistance on the venous return curve. Curves *a*, *c*, and *e* are parallel but have different mean circulatory pressure (*Pm*) at zero flow. Curves *b*, *c*, and *d* are nonparallel but have the same Pm. *Pc*, Critical closing pressure; *PRA*, right atrial pressure; *Q,* flow.

is the vascular waterfall or Starling resistor. In 1910 Jerusalem and Starling described a device that was designed to control afterload to the left ventricle and that made possible the study of cardiac contractility.[4] The device consisted of a collapsible rubber tube traversing a pressurized glass chamber (Figure 20-7). When pressure surrounding the rubber tube exceeded the outflow pressure set by the reservoir, surrounding pressure opposed the flow of blood and became the true outflow pressure of the device. The physiologic counterpart of this phenomenon occurs in small vessels surrounded by tissue pressure. In the heart, for example, a Starling resistor effect occurs in extramyocardial coronary veins, although evidence also exists for critical closure of small arterioles. No one has yet demonstrated vessel closure directly, but this might not be necessary because as small vessels narrow when they are compressed, the wall becomes convoluted, and blood cells might become obstructed by the folds even when externally the vessel does not appear to be closed.

Autoregulation

In all organs, when inflow pressure is suddenly raised or lowered while oxygen consumption remains constant, flow rises or falls transiently but then returns to its former value; this phenomenon is termed *autoregulation*. Myogenic tonic response is in part responsible for this phenomenon, but it is not the only mechanism. Some investigators have shown that tissues have oxygen sensors that respond to transient increases or decreases in oxygen supply, and other studies indicate that the process is mediated by greater or lesser release of nitric oxide carried to the tissues by hemoglobin in the form of S-nitrosohemoglobin.[5-7] Other locally produced gases such as hydrogen sulfide[8] and carbon monoxide also may play a role.[9,10] Evidence indicates that some autoregulatory mechanisms are specific to individual microcirculations (e.g., macula densa signaling in the renal circulation).

Distensibility and Compliance

The distensibility of a vessel is defined as the change in volume as a proportion of the initial volume for a given change in pressure:

$$\text{Distensibility} = (\Delta V / \Delta P) / V$$

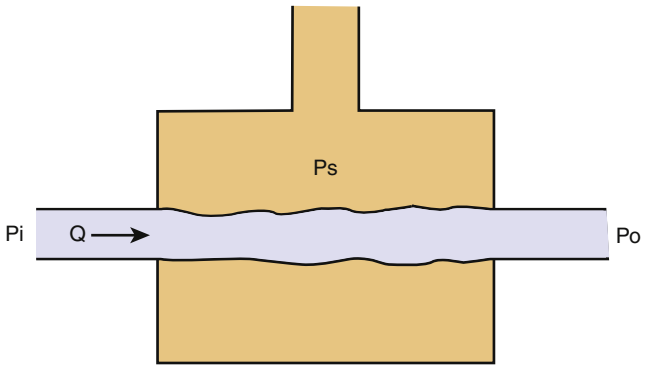

Figure 20–7. Starling resistor is a compressible conduit exposed to surrounding pressure (*Ps*). When Ps is less than outflow pressure (*Po*), Ps does not oppose blood flow. When Ps is between inflow (*Pi*) and outflow pressures, it opposes blood flow. No flow is possible when Ps exceeds Pi. *Q*, flow.

where V is volume and P is pressure. Veins are much thinner than arteries and are about eight times more distensible. Multiplying distensibility by volume yields $\Delta V/\Delta P$, which is the definition of compliance. Because venous volume is usually more than three times arterial volume, venous compliance is about 20-fold to 30-fold greater than arterial compliance. As a result, whenever fluids are infused, the bulk of the fluid volume is accommodated in the veins.

Vascular Resistance

Under normal circumstances, vascular resistance is the major control of organ flow and can be understood by considering the resistance of a Newtonian liquid passing through a rigid tube as defined by the Hagen-Poiseuille equation:

$$R = (8/\pi)(1/r^4)\eta$$

where R is resistance, l is tube length, r is the internal radius of the tube, and η is the fluid viscosity. Blood is not a Newtonian fluid, but this fact does not affect the accuracy of calculated vascular resistance much. However, vascular beds do contain many "tubes" in parallel. Thus for vascular systems a factor k is added that represents the number of vessels. The equation thus becomes:

$$R = (8/\pi)(1/kr^4)\eta$$

Because the length and number of vessels and blood viscosity are relatively constant at any one time, change in vessel radius is the major factor responsible for a dynamic change in vascular resistance. Because of the fourth power factor, small changes in radius cause large changes in resistance. Vessel radius is influenced by vascular elasticity and transmural pressure but is mainly regulated by changes in vessel wall smooth muscle tone.

Vascular Impedance

Resistance is strictly a steady-state concept. In a pulsatile system the factors affecting the relationship of pressure dissipation to flow are resistance resulting from friction and viscosity, fluid inertia, and vessel wall compliance that combine to produce an *impedance* to flow that varies with frequency. At zero frequency, steady-state resistance is approximated by the change in mean pressure over flow, but substantial contributions are made by the first three harmonics that are ignored by this calculation.

Local Regulatory Mechanisms

Regions of the circulation may differ markedly in their patterns of vascular regulation. A regulatory stimulus can have multiple effects that differ from one location to another. An agent that potently regulates vascular resistance in one region of the circulation may have no effect in another. For example, during hemorrhagic shock, flow is maintained to the heart and brain but is reduced to muscles, the kidneys, and the gut.

Vascular tone is strongly influenced by several mechanisms: (1) innervation and neural processes, (2) circulating endocrine and neuroendocrine mediators, (3) local metabolic products, (4) blood gas composition, (5) endothelial derived factors, and (6) myogenic processes.

Innervation and Neural Processes

Receptors responsive to neural products (e.g., norepinephrine and acetylcholine) are found throughout the circulation. Nevertheless, innervation and receptor distribution are organ specific, allowing rapid, patterned, coordinated redistribution of blood flow and an orchestrated response to events such as hypoxia, changes in posture, and hemorrhage. Although these receptors respond to circulating agonists (including adrenal epinephrine) as well as to those liberated locally, they generally are associated with innervation by autonomic nerves. In general, presynaptic α-adrenergic stimulation causes norepinephrine reuptake, whereas postsynaptic α-adrenergic stimulation causes norepinephrine release and vasoconstriction. β-Adrenergic stimulation generally causes vasodilation. Cholinergic stimulation (whether sympathetic or parasympathetic) generally causes vasodilation (see Chapters 25 and 117).

Circulating Endocrine and Neuroendocrine Mediators

Humoral regulators of vascular tone include angiotensin, arginine vasopressin, bradykinin, histamine, and serotonin. Of less certain significance are aldosterone, thyroxine, antinatriuretic peptide, and various reproductive hormones. Most of these regulators have both direct effects and secondary effects, which tend to be organ specific or regional in nature. Angiotensin plays a special role in the homeostasis of blood pressure and is produced in persons with hemorrhagic or hypovolemic shock. It causes generalized vasoconstriction in both systemic and pulmonary circulations, but locally it stimulates the release of vasodilating prostaglandins in the lung and kidney. Bradykinin is a potent pulmonary and systemic vasodilator released locally by the action of proteolytic enzymes on kallikrein after tissue injury. Histamine is released by mast cells in response to injury and is a potent vasodilator in most regions of the circulation but causes vasoconstriction in the lung.

Local Metabolic Products

Local metabolic regulation of vasomotor tone provides an ideal homeostatic mechanism whereby metabolic demand can directly influence perfusion. The precise mechanisms underlying the coupling of blood flow with metabolic activity remain unclear. One theory holds that as the metabolic rate increases, so too does the formation of some vasodilating substance. Thus the regional vasculature relaxes, allowing more oxygen to be delivered in support of this work. As flow rises, the metabolites are washed out, restoring their concentration to normal. Adenosine, for instance, which accumulates locally when tissue metabolism is high and tissue oxygenation is marginal, causes pronounced vasodilation in the coronary, striated muscle, splanchnic, and cerebral circulations. Another example is potassium, which is released from muscle in response to increased work, ischemia, and hypoxia.[11] Hypokalemia causes vasoconstriction, and hyperkalemia, within the physiological range, causes vasodilation.[12,13]

An increasing amount of data demonstrate the importance of the local redox state on the regulation of blood flow through the microcirculation. Reactive oxygen species such as superoxide, hydrogen peroxide, and peroxynitrite have been shown to influence normal regulatory processes and to participate in the pathophysiology of a wide array of cardiovascular disorders. For example, the rapid reaction of nitric oxide (NO) with the superoxide anion results in the formation of peroxynitrite, a potent oxidant. While peroxynitrite is known to have cytotoxic properties, under normal conditions peroxynitrite inhibits leukocyte adherence and platelet aggregation without evidence of cellular injury.[14,15] In disease states, however, peroxynitrite can lead to protein nitration and deoxyribonucleic (DNA) damage. In addition, elevated levels of superoxide may decrease the bioavailability of NO, leading to abnormal vasomotion.[16]

Blood Gas Composition

Tissue levels of oxygen and carbon dioxide have been shown to reflect adequacy of perfusion and oxygen delivery.[17] These blood gases are potent determinants of regional blood flow and have effects that differ from one region of the circulation to another. They also have a more general effect mediated by carotid chemoreceptors.

Endothelial-Derived Factors

The vascular endothelial cells are capable of producing a variety of vasoactive substances that participate in the regulation of normal vascular tone. These substances, such as NO, carbon monoxide (CO), hydrogen sulfide, and endothelin-1 (ET-1) are capable of producing vascular relaxation and/or constriction, modulating the propensity of the blood to clot, and inducing and/or inhibiting smooth muscle migration and replication (Figure 20-8).[18,19] The understanding of the role of the vascular endothelium and the factors it produces in regulating blood flow in health and disease has resulted in several treatment strategies that target, mimic, or augment endothelial processes. Examples include inhaled NO for pulmonary hypertension, L-arginine supplementation for coronary artery disease and the pulmonary vasculopathy of sickle cell disease, phosphodiesterase inhibitors (i.e., sildenafil, which prevents the breakdown of cyclic guanosine 3′5′-monophosphate [cGMP]) for pulmonary hypertensive disorders, endothelin receptor antagonists for pulmonary hypertensive disorders and vasospasm following subarachnoid hemorrhage, and NO inhibitors for refractory hypotension resulting from sepsis.[20-25] Indeed, many older therapies used to promote vascular relaxation, such as nitrovasodilators, affect endothelial function, a fact that until relatively recently was not appreciated.

NO is a labile humoral factor produced by NO synthase from L-arginine in the vascular endothelial cell. NO diffuses into the smooth muscle cell and produces vascular relaxation by increasing concentrations of cGMP via the activation of soluble guanylate cyclase. NO is released in response to a variety of factors, including shear stress (flow) and the binding of certain endothelium-dependent vasodilators (such as acetylcholine, adenosine triphosphate [ATP], and bradykinin) to receptors on the endothelial cell. Basal NO release is an important mediator of both resting pulmonary and systemic vascular tone in the fetus, newborn, and adult, as well as a mediator of the fall in pulmonary vascular resistance normally occurring at the time of birth.[26-29] Dynamic changes in NO release are fundamental to the regulation of all vascular beds.

CO is a labile humoral factor produced by the action of hemoxygenase on heme in many tissues, including endothelial cells. Hemoxygenase-1 is constitutive and hemoxygenase-2 is inducible. CO interacts with NO, is an independent stimulator of cGMP, relaxes smooth muscle, inhibits its replication, and

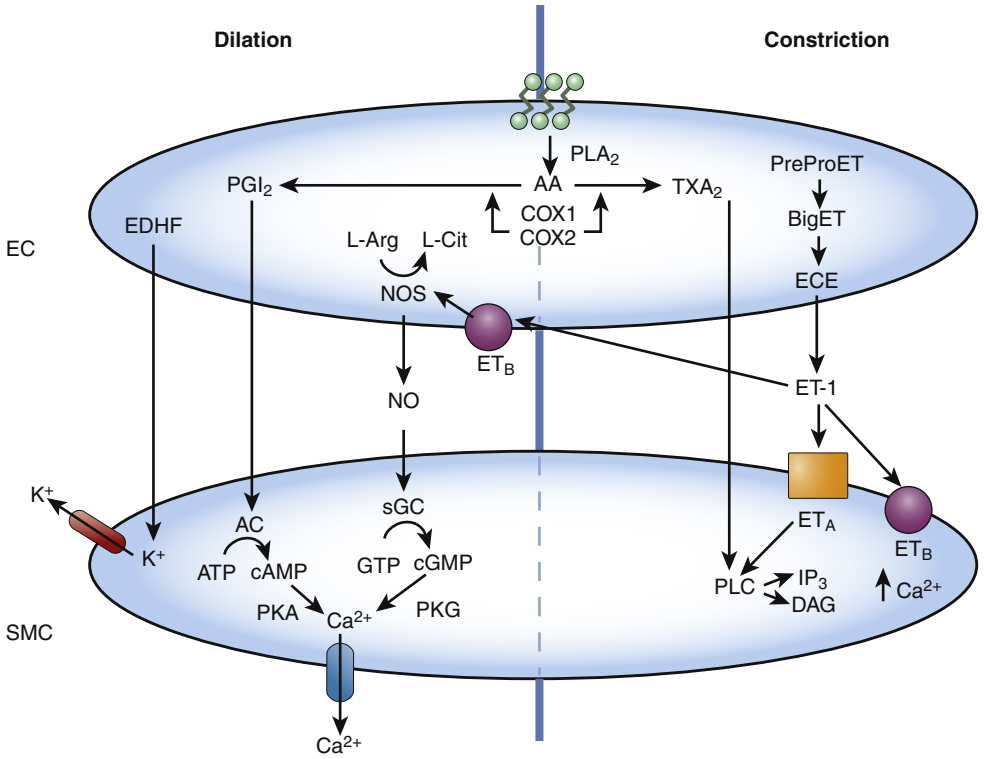

Figure 20–8. Schematic of some endogenous vasoactive agents produced by the vascular endothelium. *AA,* Arachidonic acid; *AC,* adenylate cyclase; *ATP,* adenosine triphosphate; *BigET,* big endothelin; *cAMP,* cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate; *COX,* cyclooxygenase; *DAG,* diacylglycerol; *EC,* endothelial cell; *ECE,* endothelin converting enzyme; *EDHF,* endothelial-derived hyperpolarizing factor; *ET-1,* endothelin-1; *GTP,* guanosine triphosphate; *IP_3,* inositol 1,4,5-triphosphate; *L-Arg,* L-arginine; *L-Cit,* L-citrulline; *NO,* nitric oxide; *NOS,* nitric oxide synthase; *PGI_2,* prostacyclin; *PKA,* protein kinase A; *PKC,* protein kinase C; *PLA_2,* phospholipase A_2; *sGC,* soluble guanylate cyclase; *SMC,* smooth muscle cell; *TXA_2,* thromboxane A_2.

has powerful antithrombotic and antiinflammatory effects. It is beginning to enter the field of clinical medicine.[10,30]

Hydrogen sulfide is produced in most tissues by a variety of mechanisms and may be the ultimate sensor that is stimulated by oxygen deficit or excess.[8] Hydrogen peroxide may be even more important.

ET-1 is a 21-amino-acid polypeptide also produced by vascular endothelial cells.[31] The vasoactive properties of ET-1 are complex, and studies have shown varying hemodynamic effects on different vascular beds. However, its most striking property is its sustained hypertensive action. In fact, ET-1 is the most potent vasoconstricting agent discovered, with a potency 10 times that of angiotensin II. The hemodynamic effects of ET-1 are mediated by at least two distinctive receptor populations, ET_A and ET_B. The ET_A receptors are located on vascular smooth muscle cells and mediate vasoconstriction, whereas the ET_B receptors may be located on endothelial cells and mediate both vasodilation and vasoconstriction. Individual endothelins occur in low levels in the plasma, generally below their vasoactive thresholds, which suggests that they are primarily effective at the local site of release. Even at these levels, they may potentiate the effects of other vasoconstrictors such as norepinephrine and serotonin.[32] The role of endogenous ET-1 in the regulation of normal vascular tone is presently unclear.[33] Nevertheless, alterations in ET-1 have been implicated in the pathophysiology of a number of disease states.[34]

Endothelial-derived hyperpolarizing factor (EDHF), a diffusible substance that causes vascular relaxation by hyperpolarizing the smooth muscle cell, is another important endothelial factor. EDHF has not yet been identified, although it is likely an epoxyeicosatrienoic acid, but current evidence suggests that the action of EDHF is dependent on K^+ channels (Figure 20-8).[35] Activation of potassium channels in the vascular smooth muscle results in cell membrane hyperpolarization, closure of voltage-dependent calcium channels, and ultimately vasodilation. Potassium channels are also present in endothelial cells. Activation within the endothelium results in changes in calcium flux and may be important in the release of NO, prostacyclin, and EDHF. Potassium channel subtypes include ATP-sensitive K^+ channels, Ca^{2+}-dependent K^+ channels, voltage-dependent K^+ channels, and inward-rectifier K^+ channels.[35]

The breakdown of phospholipids within vascular endothelial cells results in the production of important byproducts of arachidonic acid, including prostacyclin (PGI_2) and thromboxane. PGI_2 activates adenylate cyclase, resulting in increased cyclic adenylate monophosphate production and subsequent vasodilation, whereas thromboxane results in vasoconstriction via phospholipase C signaling (Figure 20-8). Other prostaglandins and leukotrienes also have potent vasoactive properties.

Myogenic Processes

In 1902, Bayliss[36] described an intrinsic increase in vascular tone in response to elevated intravascular pressure. This myogenic response results in alterations in vascular tone following changes in transmural pressure or stretch.[37] This response is especially important at the arteriolar level and is thought to participate in regional autoregulation. Increases

in intravascular pressure and/or stretch result in an increase in arteriolar smooth muscle tone, while decreasing pressures have the reverse effect. The precise mechanisms mediating this response are unclear, but a role for dynamic changes in intracellular Ca^{2+} and myosin light chain phosphorylation has been documented.[38] More recent work has focused on the role of tyrosine phosphorylation pathways, ENaC, transient receptor potential channels, potassium channels, and alterations in Ca^{2+} sensitivity in this response.[39-43] Moreover, the myogenic response varies between the regional circulations and between vessels within a given circulation.

Regional Circulations

Pulmonary Circulation

Maldevelopment and/or maladaptation of the pulmonary vascular bed are important components of several neonatal and infant disease states (e.g., chronic lung disease, persistent pulmonary hypertension of the newborn, and congenital heart disease). Because strategies aimed at altering postnatal pulmonary vascular resistance are commonly used in the management of these cases, an understanding of the regulation of postnatal pulmonary vascular tone is important.

The morphologic development of the pulmonary circulation affects the physiologic changes that occur in the perinatal period. In the fetus and neonate, small pulmonary arteries have thicker muscular coats than similarly located arteries in the adult. This muscularity is, in large part, responsible for the pulmonary vascular reactivity and high resistance found in the fetus. In fetal lamb lungs fixed at normal in utero perfusion pressures, the medial smooth muscle coat is most prominent in the smallest arteries (fifth- and sixth-generation arteries; external diameter 20-50 μm). During the latter half of gestation, the medial smooth muscle thickness remains constant in relationship to the external diameter of the artery.[44] Similar observations utilizing slightly different techniques have been made in human lungs.[45,46] Within the first several weeks after birth, the medial smooth muscle involutes and the thickness of the media of the small pulmonary arteries decreases rapidly and progressively.[47]

Following this perinatal transition, the medial layers of the proximal pulmonary vascular bed are completely encircled by smooth muscle. Moving distally, muscularization becomes incomplete (arranged in a spiral or helix) and disappears completely from the most peripheral arterioles.[46] In these arterioles, an incomplete pericyte layer is found within the endothelial basement membrane. Smooth muscle precursor cells reside in the nonmuscular portions of the partially muscular pulmonary arteries.[48] Under certain conditions, such as hypoxia, these cells may rapidly differentiate into mature smooth muscle cells.[48]

Subsequently, from infancy to adolescence, the arteries undergo progressive peripheral muscularization. In the adult, complete circumferential muscularization extends peripherally such that the majority of small pulmonary arteries are completely muscularized.

Normal Fetal Circulation

In the fetus, normal gas exchange occurs in the placenta and pulmonary blood flow is low, supplying only nutritional requirements for lung growth and performing some metabolic functions. Pulmonary blood flow in near-term lambs is about 100 mL/100 g wet lung weight, representing between 8% and 10% of the total output of the heart.[49] Pulmonary blood flow is low despite the dominance of the right ventricle, which in the fetus ejects about two thirds of the total cardiac output. Most of the right ventricular output is diverted away from the lungs through the widely patent ductus arteriosus to the descending thoracic aorta, from which a large proportion reaches the placenta through the umbilical circulation for oxygenation. In young fetuses (at about halfway through gestation), pulmonary blood flow is approximately 3% to 4% of the total combined left and right ventricular outputs of the heart (fetal cardiac output). This value increases to about 6% at about four fifths through gestation, corresponding temporally with the onset of the release of surface active material into lung fluid. This step is followed by another progressive slow rise in pulmonary blood flow, reaching about 8% to 10% near term.[49] Fetal pulmonary arterial pressure increases with advancing gestation. At term, mean pulmonary arterial pressure is about 50 mm Hg, generally exceeding mean descending aortic pressure by 1 to 2 mm Hg.[50] Pulmonary vascular resistance early in gestation is extremely high relative to that in the infant and adult, probably because of the low number of small arteries. Pulmonary vascular resistance falls progressively during the last half of gestation, new arteries develop, and cross-sectional area increases; however, baseline pulmonary vascular resistance is still much higher than after birth.[50,51]

Changes in the Pulmonary Circulation at Birth

After birth, with initiation of ventilation by the lungs and the subsequent increase in pulmonary and systemic arterial blood O_2 tensions, pulmonary vascular resistance decreases and pulmonary blood flow increases by eightfold to tenfold to match systemic blood flow (300 to 400 mL/min/kg body weight). This large increase in pulmonary blood flow increases pulmonary venous return to the left atrium, increasing left atrial pressure. Then the valve of the foramen ovale closes, preventing any significant atrial right-to-left shunting of blood. In addition, the ductus arteriosus constricts and closes functionally within several hours after birth, effectively separating the pulmonary and systemic circulations. Mean pulmonary arterial pressure decreases, and by 24 hours of age, it is approximately 50% of mean systemic arterial pressure. Adult values are reached 2 to 6 weeks after birth (Figure 20-9).[52,53]

The decrease in pulmonary vascular resistance with ventilation and oxygenation at birth is regulated by a complex and incompletely understood interplay between metabolic and mechanical factors, which in turn are triggered by the ventilatory and circulatory changes that occur at birth. Physical expansion of the fetal lamb lung without changing O_2 tension increases fetal pulmonary blood flow and decreases pulmonary vascular resistance, but not to newborn values.[54] A very small proportion of this decrease relates to replacement of fluid in the alveoli with gas, which allows unkinking of the small pulmonary arteries, and to the changes in alveolar surface tension, which exert a negative dilating pressure on the small pulmonary arteries, maintaining their patency.[55] Physical expansion of the lung also releases vasoactive substances such as PGI_2, which increases pulmonary blood flow and decreases pulmonary vascular resistance in the fetal goat and lamb.[56] There also is net production of PGI_2 by the lung with the initiation of ventilation at birth.[56] In addition, inhibitors

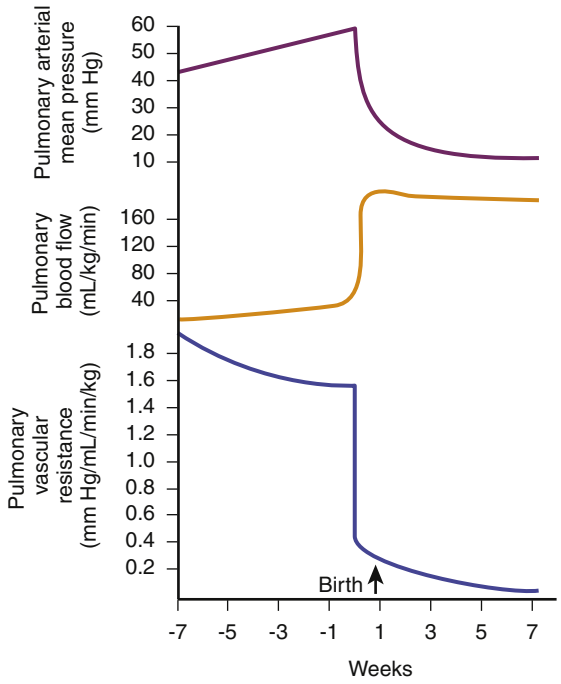

Figure 20–9. Changes in mean pulmonary arterial pressure, pulmonary blood flow, and pulmonary vascular resistance at birth. *(Data from Morin FC III, Egan E: Pulmonary hemodynamics in fetal lambs during development at normal and increased oxygen tension,* J Appl Physiol *73:213-218, 1993;* and *Soifer SJ, Morin FC III, Kaslow DC et al: The developmental effects of prostaglandin D2 on the pulmonary and systemic circulations in the newborn lamb,* J Dev Physiol *5:237-250, 1983.)*

of prostaglandin synthesis (such as indomethacin or meclofenamic acid) not only block PGI_2 production but also attenuate the increase in pulmonary blood flow and decrease in pulmonary vascular resistance that occur with physical expansion of the fetal lung, although not the changes that occur with oxygenation.[57] Therefore PGI_2 (or perhaps, but less likely, another metabolite of arachidonic acid) plays an important role in the increase in pulmonary blood flow and decrease in pulmonary vascular resistance that occur in association with the mechanical component (stretch) of ventilation at birth.

Ventilation of the fetus without oxygenation produces partial pulmonary vasodilatation, whereas ventilation with air or oxygen produces complete pulmonary vasodilatation. The exact mechanisms of oxygen-induced pulmonary vasodilation during the transitional circulation remain unclear. The increase in alveolar or arterial O_2 tension may decrease pulmonary vascular resistance either directly by dilating the small pulmonary arteries or indirectly by stimulating the production of vasodilator substances such as PGI_2 or NO. In particular, NO has been implicated as an important mediator of the decrease in pulmonary vascular resistance at birth associated with increased oxygenation.[58-63] However, the immediate decrease in pulmonary vascular resistance minutes after birth is not attenuated by NO inhibition. Therefore the decrease in pulmonary vascular resistance with initiation of ventilation and oxygenation consists of at least two components. First is partial pulmonary vasodilatation caused by physical expansion of the lung and the production of prostaglandins (PGI_2 and PGD_2). This process probably is independent of fetal oxygenation and results in a modest increase in pulmonary blood flow and a decrease in pulmonary vascular resistance. Second is a further maximal pulmonary vasodilatation associated with fetal oxygenation, which is not necessarily dependent on prostaglandin production. This process results in an increase in pulmonary blood flow and a decrease in pulmonary vascular resistance to newborn values. This latter pulmonary vasodilatation is likely caused by the synthesis of NO. Both components are necessary for the successful transition to extrauterine life. An additional mechanism by which vasodilatation occurs is related to the stimulation by increased shear forces of endothelial cells to produce both NO and PGI_2. It is possible that after the initial fall in pulmonary vascular resistance because of another mechanism, this particular mechanism acts to maintain pulmonary vasodilatation.

Control of the perinatal pulmonary circulation therefore probably reflects a balance between factors producing pulmonary vasoconstriction (low O_2, leukotrienes, other vasoconstricting substances) and those producing pulmonary vasodilatation (high O_2, PGI_2, NO, other vasodilating substances). The dramatic increase in pulmonary blood flow with the initiation of ventilation and oxygenation at birth reflects a shift from active pulmonary vasoconstriction in the fetus to active pulmonary vasodilatation in the newborn.

Failure of the pulmonary circulation to undergo this normal fall in pulmonary vascular resistance at birth (persistent pulmonary hypertension of the newborn) is associated with a variety of conditions, including aspiration syndromes, sepsis, in-utero stress events, and certain congenital heart defects (e.g., obstruction of pulmonary venous drainage and a single ventricle with restrictive atrial septum).

Regulation of Postnatal Pulmonary Vascular Resistance

After the immediate postnatal state, the pulmonary circulation is maintained in a dilated, low-resistance state. Because the inflow pressure of the pulmonary circulation is quite low, a vertical gradation to the distribution of blood flow in the lung occurs. Hydrostatic pressure must be adjusted for vertical height above the left atrium, both at the inflow and at the outflow of every alveolar capillary unit. For example, given a pulmonary artery mean pressure of 20 cm H_2O (zeroed at the level of the left atrium), an alveolar-capillary unit 12 cm above the left atrium will face an inflow pressure of only 8 cm H_2O. A left atrial pressure of 5 cm H_2O would generate no opposing outflow pressure to alveolar capillary units more than 5 cm above the left atrium. Critical closing pressure of postcapillary vessels therefore would set outflow pressure for a unit 10 cm above the left atrium. Were intrinsic vascular resistance identical throughout the lung, flow at any vertical height would be determined by hydrostatic driving pressure (inflow-outflow) and would be greatest at the base and least at the apex of the lung. West, Dollery, and Naimark[64] reported that this phenomenon partitions the lung into three vertical regions (Figure 20-10). Zone I vessels are higher above the left atrium than pulmonary artery pressure (expressed in cm H_2O) and are not perfused by the pulmonary artery. Zone II vessels lie above the height defined by the hydrostatic left atrial pressure but below the height of pulmonary artery pressure. These units are perfused in proportion to the driving pressure across them, which is approximately pulmonary artery pressure less vertical height (or critical closing pressure, whichever is higher). Zone III vessels lie at a vertical height less than outflow pressure expressed in cm H_2O. Driving pressure across these units

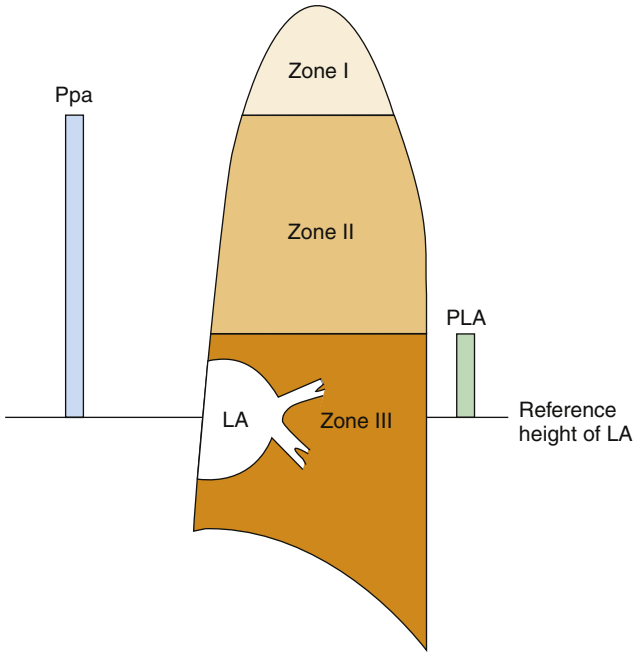

Figure 20–10. The lung is divided vertically into three regions. Zone I alveolar capillary units are unperfused because they see no functional inflow pressure. Zone II units are perfused in proportion to their height above the left atrium (*LA*). Zone III vasculature is more uniformly perfused because gravity has comparable effects on inflow and outflow pressures. *Ppa,* pulmonary artery pressure; *PLA,* left atrial pressure. *(Modified from Fuhrman BP: Regional circulation. In Fuhrman BP, Shoemaker WC, editors:* Critical care: state of the art, vol 10, *Fullerton,* CA, *1989, Society of Critical Care Medicine.)*

is independent of height because inflow and outflow pressures are comparably influenced by gravity. Zone I likely does not exist in a supine neonate.

Because small pulmonary arteries course along with the branching airways and small pulmonary vessels are intimately related with alveoli, airway pressure can directly modulate pulmonary blood flow.[65] Alveolar pressure can be loosely translated into surrounding pressure for alveolar vessels. Positive airway pressure applied to the lung can impinge on alveolar vessels whenever alveolar pressure exceeds the other determinants of outflow pressure. During positive pressure ventilation, outflow pressure of the pulmonary circulation may be determined predominantly by the mechanics of ventilation. The lung is partitioned into zones, but the distribution of flow becomes a complex function of alveolar pressure as well as left atrial and critical closing pressures.

To further complicate this view of the pulmonary circulation, lung volume and alveolar pressure both change during positive pressure ventilation. During inspiration, extraalveolar and corner vessels are dilated by radial traction, reducing their resistance to flow, whereas alveolar vessels narrow and elongate.[66] During lung inflation, alveolar surface tension rises, diminishing the transmission of alveolar pressure to alveolar vessels.[67] Evidence also indicates that, in the infant lamb, lung stretch may directly augment pulmonary vascular tone in a manner that is dependent on calcium flux and subject to calcium channel blockade using verapamil.[68] In fact, it is clear that mechanical ventilation can have profound direct effects on the intact pulmonary circulation that depend on the waveform of airway pressure applied and not on mean airway pressure alone.[69,70]

In heterogeneous lung disease, the application of positive airway pressure can modulate and redistribute blood flow away from ventilated regions and toward unventilated regions of the lung by directly increasing the pulmonary vascular resistance of lung segments exposed to elevated airway pressure, that is, segments not protected by consolidation or airway obstruction.[44]

Evidence suggests that basal release of NO and the subsequent increase in smooth muscle cell concentrations of cGMP partly mediate the low resting pulmonary vascular resistance of the newborn.[28,71] Other vasoactive substances—including histamine, 5-hydroxytryptamine, bradykinin, and metabolites of arachidonic acid by the cyclooxygenase and lipoxygenase pathways—have been implicated in mediating postnatal pulmonary vascular tone. However, their precise roles are not well elucidated.

Two of the most important factors affecting pulmonary vascular resistance in the postnatal period are oxygen concentration and pH. Decreasing oxygen tension or pH elicit pulmonary vasoconstriction of the resting pulmonary circulation.[72] Alveolar hypoxia constricts pulmonary arterioles, diverting blood flow away from hypoxic lung segments and toward well-oxygenated segments.[73] This process enhances ventilation-perfusion matching and is a unique pulmonary vascular response to hypoxia, which is probably greater in the younger animal than in the adult.[74] The mechanism of alveolar hypoxic pulmonary vasoconstriction, which remains to be defined, is the subject of several extensive reviews.[75] Acidosis potentiates hypoxic pulmonary vasoconstriction, and alkalosis reduces it.[72] The exact mechanism of pH-mediated pulmonary vasoactive responses is incompletely understood but appears to be independent of $Paco_2$.[76] Alveolar hyperoxia and alkalosis often are used to relax pulmonary vascular tone because they generally relieve pulmonary vasoconstriction while having little apparent effect on the systemic circulation as a whole. However, detrimental effects of hypocarbia or respiratory alkalosis on cerebral and myocardial blood flow may occur.[77]

The lung is innervated, but neural effects on pulmonary vascular resistance appear to be of little consequence to basal tone. However, pulmonary neurohumoral receptors are sensitive to α-adrenergic, β-adrenergic, and dopaminergic agonists. Therefore vasoactive agents that stimulate these receptors will affect the vascular tone of both the pulmonary and systemic circulations. The degree of pulmonary versus systemic alterations induced by these agents is variable and often dictated by the relative tone of each vascular bed at a given time. Therefore the response of these agents is difficult to predict in an individual critically ill patient.

A selective pulmonary vasodilator was long sought for treatment of pulmonary hypertension because (with the exception of oxygen) the response of the pulmonary circulation to humoral vasoactive agents is generally similar to that of the systemic circulation. To date, inhaled NO is the most commonly used agent for selective pulmonary vascular dilation. It is worth noting that its selectivity is not based on a differential effect in the pulmonary and systemic circulations. Rather, when delivered as an inhaled gas, NO is rapidly bound to hemoglobin and inactivated, thus limiting its effects to the pulmonary circulation. Other agents with rapid metabolism (i.e., inhaled prostacyclin) also are being studied via inhalational delivery routes to take advantage of this pharmacologic selectivity.[78]

Cerebral Circulation

Although the general principles governing the circulation certainly hold true for the cerebral circulation, blood flow to the brain is specially regulated to facilitate the myriad of complex functions that the brain oversees.

In adults, the brain (which makes up 2% of body mass) receives approximately 14% of the cardiac output and accounts for close to 20% of the body's O_2 consumption. In neonates, the brain receives up to 30% of cardiac output and accounts for 50% or more of total oxygen consumption and up to 98% of produced hepatic glucose consumption. Other organ systems receive a larger percentage of the total cardiac output (e.g., the lung) and utilize greater amounts of oxygen (e.g., skeletal muscle), but the brain is unique in its intolerance for diminished blood flow. In fact, although some favorable outcomes have been reported, severe if not irreversible damage often occurs after just minutes of circulatory arrest under normal conditions.[79-82]

Blood is supplied to the brain by the carotid and vertebral arteries. The common carotid artery bifurcates, forming the internal carotid artery (ICA) and external carotid artery. The ICA gives rise to its major branches—the posterior communicating, anterior cerebral, middle cerebral, and anterior choroidal arteries—which comprise the anterior circulation. The vertebral arteries give rise to the anterior spinal and posterior inferior cerebellar arteries before merging to form the basilar artery, which in turn gives rise to the anterior inferior cerebellar, superior cerebellar, and posterior cerebral arteries. These vessels comprise the posterior circulation. Venous drainage from the superficial and deep cerebral veins enters the dural sinuses and exits the cranium mostly via the internal jugular vein, although the vertebral veins are important secondary pathways available for venous outflow.[83]

The cranium has three compartments: tissue, cerebrospinal fluid (CSF), and blood. The Monro-Kellie doctrine states that these compartments occupy a relatively fixed space and that an increase in one compartment can only occur at the expense of another. For example, when brain swelling occurs, CSF and cerebral venous blood must be displaced if intracranial pressure (ICP) is to remain unchanged. As the limits of CSF and blood evacuation are approached, ICP rises. Raised ICP and/or venous obstruction can impede cerebral blood flow (CBF). Cerebral perfusion pressure (CPP), generally defined as the difference between the mean arterial pressure and the ICP, is thus a more accurate descriptor of cerebral inflow pressure. CBF will decline when the CPP falls below the lower limit of the autoregulatory curve. In the setting of raised ICP or venous hypertension, this process occurs even in the face of elevated systemic arterial pressures.

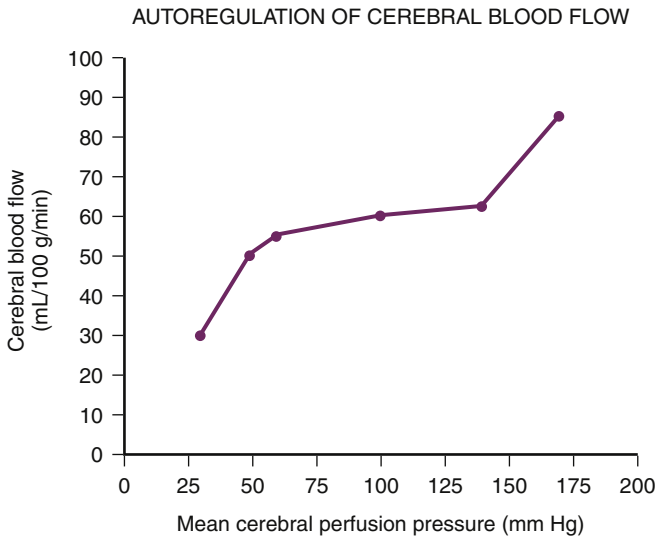

Figure 20–11. Cerebral blood flow (*CBF*) autoregulates at perfusion pressures between 50 and 160 mm Hg. Below 50 mm Hg, CBF falls. Above 160 mm Hg, CBF rises. *(Modified from Fuhrman BP: Regional circulation. In Fuhrman BP, Shoemaker WC, editors:* Critical care: state of the art, vol 10, *Fullerton, CA, 1989, Society of Critical Care Medicine.)*

At rest, CBF is approximately 50 mL/100 g tissue/min.[84] Cerebral oxygen consumption is surprisingly high, averaging 3.2 mL/100 g tissue/min. Glucose is the primary energy substrate, although ketones can be utilized during periods of starvation. The brain has no functional capacity to store energy and thus is completely dependent on a steady supply of O_2 because up to 92% of its ATP production results from the oxidative metabolism of glucose.[79-82]

An important feature unique to the cerebral circulation is the presence of a blood-brain barrier (BBB). The vascular endothelium of brain capillaries forms a continuous sheet, with adjacent cells joined by tight junctions. Unlike the endothelium of nonneural capillaries, vascular endothelium does not contain intercellular clefts through which water-soluble particles can traverse, and pinocytosis is markedly diminished. However, the lipid-soluble substances CO_2 and O_2 can freely diffuse across the endothelium. Metabolically important components such as glucose, lactate, and amino acids depend upon specific carrier proteins to facilitate their diffusion into the brain. Furthermore, the BBB has a biochemical component, with high levels of degradative enzymes that protect the vascular smooth muscle and extracellular fluid from the effects of circulating vasoactive substances, such as catecholamines.[85] Thus, as a result of the BBB, the cerebral vasculature responds differently than other vascular beds to humoral stimuli. However, humoral stimuli can significantly alter the vascular tone of large cerebral arteries and can affect blood flow to parts of the brain that lack a complete BBB such as the choroid plexus, the median eminence, and the area postrema.[86,87]

For more than 60 years it has been recognized that CBF remains constant over a wide range of mean systemic arterial pressures[88] (Figure 20-11). Constant CBF is maintained in the face of increasing inflow pressures by compensatory vasoconstriction. Conversely, in the setting of low systemic arterial pressures (i.e., low inflow pressures), the cerebral vasculature dilates to maintain steady CBF. At systemic arterial pressures outside the autoregulatory range, further dilation or constriction can no longer maintain blood flow. At high pressures, disruption of the BBB ensues, with subsequent edema and even hemorrhage from ruptured cerebral vessels. At low pressures CBF begins to fall, with continued decreases leading to ischemia and ultimately brain death.[80,89-91] Importantly, normal cerebral autoregulation can be impaired in the setting of disease. Traumatic brain injury, subarachnoid hemorrhage, and stroke, for example, all can abolish or impair the normal autoregulatory response.[92-95]

Although the brain's ability to autoregulate flow is well established, the mechanisms underlying it are not completely understood.[91] A myogenic response appears to be especially

important in the setting of raised CPP. Large- and medium-sized cerebral arteries, including the ICA, have been shown to constrict both in vitro and in vivo in response to elevated transmural pressures. While small arteries and arterioles primarily modulate cerebral resistance during normotension, at higher pressures (greater than 110 mm Hg), the large cranial vessels dominate. Thus at high perfusion pressures, smaller more delicate vessels are protected by changes in upstream resistance.[91,96]

In marked contrast to other vascular beds, neural stimuli have relatively little effect on basal CBF. Cerebral vessels display extensive perivascular innervation, especially by the sympathetic nerves arising from the superior cervical sympathetic ganglia, but the brain is well protected from circulating catecholamines by the BBB. Thus many of the vasoactive agents used in the critical care setting (α- and β-adrenergic agonists) have minimal effects on resting cerebral vascular tone. Mild to moderate electrical stimulation, as well as surgical resection of both the sympathetic and parasympathetic nervous system, does not alter cerebral vascular tone under resting conditions. However, vigorous sympathetic stimulation, as would occur with strenuous exercise or hypertension, does result in vasoconstriction of large- and medium-sized cerebral vessels.[82] Thus while a neurogenic mechanism may not mediate cerebral vascular resistance under normal conditions, it does provide protection during times of stress.[96-98] Indeed, patients with chronic hypertension have been shown to have a rightward shift of the autoregulatory curve.[82,91]

With the advent of sophisticated methods of detecting and measuring CBF, such as radioactive xenon, positron emission tomography scanning, and functional magnetic resonance imaging (MRI), intracerebral regional circulatory variations could be mapped and were found to correlate with local central nervous system activation.[84,99,100] Blood flow to the occipital cortex increases with visual stimulation.[101] Motor activity augments flow to the motor strip and speech enhances flow to Broca's area.[102,103] CBF decreases during deep sleep but returns to normal awake levels during rapid eye movement sleep.[104]

As in other vascular beds, it appears that CBF is linked or "coupled" to changes in metabolism.[105-107] For example, hypothermia decreases the cerebral metabolic rate of oxygen , and therefore CBF, in both animal and human studies.[108-111] Seizure activity and fever both increase the cerebral metabolic rate of oxygen and CBF, which explains the deleterious consequences of both conditions for patients with raised ICP.[112] The mechanisms underlying this coupling of blood flow and metabolism are still unclear. A number of substances have been shown to affect cerebrovascular tone, including carbon dioxide, oxygen, hydrogen ions, lactic acid, histamine, potassium ions, prostaglandin, ET-1, NO, and adenosine.[80,82]

Carbon dioxide plays a critical role in the regulation of CBF. In fact, a linear increase in CBF is seen with increasing $Paco_2$, making CO_2 one of the most potent known cerebral vasodilators.[113,114] Carbon dioxide exerts its effect via a reduction of the perivascular pH. Whereas arterial H^+ cannot cross the BBB, CO_2 can easily diffuse into the brain. Carbonic anhydrase facilitates the reaction between CO_2 and H_2O, forming carbonic acid with subsequent dissociation producing H^+ ions. Perivascular acidosis dilates the cerebral vasculature, while alkalosis leads to vasoconstriction.[115,116] In this way the cerebral vasculature is distinct in that respiratory acidosis and alkalosis alter tone and CBF, while metabolic acidosis and alkalosis do not.[114,117] Interestingly, abnormal CO_2 reactivity has been associated with several disease processes, including traumatic brain injury, subarachnoid hemorrhage, stroke, carotid stenosis, and congestive heart failure.[92-94] Indeed, abnormal CO_2 vasoreactivity has been used as a means to prognosticate in some disease states.[94,95]

Several studies have demonstrated that the cerebral vasculature adapts in the setting of chronically elevated $Paco_2$, with changes in the pH of the brain extracellular fluid.[118] This finding has obvious implications for the clinician attempting to treat raised ICP with chronic hyperventilation.

Arterial oxygen tension (Pao_2) also participates in the regulation of CBF. Arterial hypoxia dilates cerebral vessels at Pao_2 below 40 to 50 mm Hg (Figure 20-12).[113] The relation between CBF and arterial oxygen content is almost linear, and cerebral oxygen delivery can be maintained unless arterial oxygen content falls below 4 vol%. Hyperoxia does not appear to be a very potent stimulus for vasoconstriction, however.[113,119] Hypoxic vasodilation is not limited to the cerebral circulation. Efforts to fully elucidate this phenomenon continue, but it is known that adenosine and both $Ca2^+$-activated and ATP-activated potassium channels are particularly important. Adenosine, which leads to vasodilation through an increase in cyclic adenylate monophosphate, has been found to increase more than fivefold with hypoxia.[120-123] Adenosine also is critical in autoregulation, with experimental data revealing a sixfold rise in brain adenosine levels as mean arterial pressure falls from 135 mm Hg to 45 mm Hg.[124]

A large body of evidence, both in animals and humans, implicates NO in a number of important processes within the cerebral circulation.[119,125-130] Nitric oxide antagonists have been shown to mitigate the normal increase in CBF brought on by neuronal activation.[127,131,132] Multiple lines of evidence suggest that NO has a role in the maintenance of basal cerebrovascular tone.[133] Exogenously administered inhibitors of

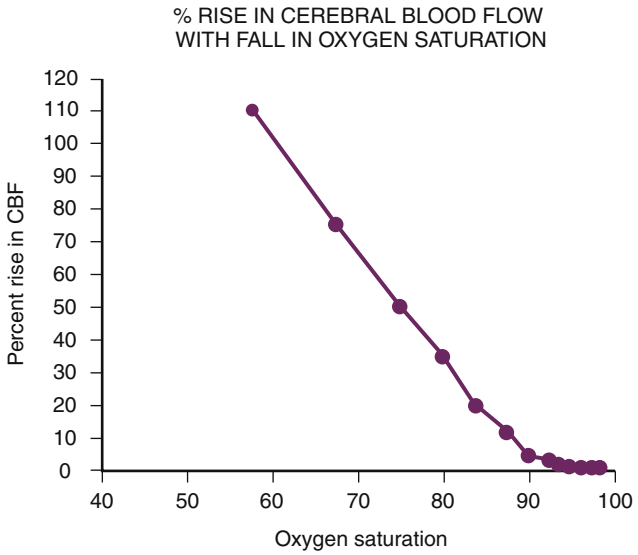

Figure 20–12. Arterial hypoxia dilates cerebral vessels and maintains cerebral oxygen delivery. *CBF,* Cerebral blood flow. *(Modified from Fuhrman BP: Regional circulation. In Fuhrman BP, Shoemaker WC, editors:* Critical care: state of the art, vol 10, *Fullerton, CA, 1989, Society of Critical Care Medicine.)*

nitric oxide synthetase (NOS) constrict cerebral vessels and decrease CBF in the basal state of several species, including humans.[132,134-137] Interestingly, asymmetric dimethylarginine, an endogenous and potent inhibitor of NOS that has been implicated in a number of vascular disorders, is produced in the brain, but its precise role in regulating CBF has not yet been clarified.[138,139] Vascular reactivity to CO_2 also is strongly influenced by NO.[140] One human study found decreased major coronary artery flow in response to hypercapnia following NOS inhibition.[119] Similar results have since been confirmed by others and have been documented in animal work as well.[126,136,140] CO_2 reactivity is not completely ablated, however, suggesting that other factors also contribute. Further, in a neuronal-NOS-knockout mouse model, CO_2 reactivity remained intact, again suggesting redundant systems underlying the response.[140-142] Clinically, it is noteworthy that nitroprusside and other NO donor compounds can dilate cerebral vessels.[143] This process greatly complicates the management of hypertension in patients with increased ICP. In that setting, nitroprusside, for example, may reduce arterial pressure but raise CBF and blood volume, thereby causing herniation to occur.

Vasodilation in response to acetylcholine, oxytocin, substance P, histamine, ET-1, adenosine diphosphate, ATP, and prostaglandin have all been shown to be NO dependent.[35] In some studies NOS inhibition was found to blunt the increase in blood flow in response to hypoxia.[125] A role for NO in other disease states also has been demonstrated recently. Treatment with L-arginine, the substrate for NOS, and tetrahydrobiopterin, an important cofactor for NOS, reverse impaired endothelial function caused by acute hypertension, hypercholesterolemia, and atherosclerosis.[144-146] In addition, impaired NO signaling is important in the pathophysiology of subarachnoid hemorrhage in which endothelial dysfunction has been well documented. Dysfunctional NO signaling may be an important cause of vasospasm in that setting. A number of mechanisms have been proposed, including decreased endothelial NOS activity, alterations in soluble guanylate cyclase activation and cGMP production, inactivation of NO by hemoglobin, and increased superoxide anion production.[147-151] Furthermore, alterations in vascular tone in response to shear force are mediated, at least in part, by NO.[35]

Prostacyclin, a metabolite of arachidonic acid, is another important dilator of the cerebral vasculature. The cyclooxygenase enzymes COX-1 and COX-2 both appear to be involved in basal cerebral vascular tone and in the vasodilation associated with various stimuli, such as inflammation and hypoxia, depending on the species investigated.[35,81,82]

ET-1 is another important mediator of cerebrovascular tone.[152] Both ET_A and ET_B receptors have been identified in the cerebral vasculature.[153] When given in high concentrations, ET-1 constricts cerebral vessels, probably via ET_A receptor activation.[154] In low concentrations, however, ET-1 relaxes cerebral vessels via endothelial cell ET_B receptor activation, a response that is NO dependent. Sarafotoxin 6c (a selective ET_B agonist) causes cerebral vasodilation.[153] However, ET_A and combined receptor antagonists do not alter basal cerebrovascular tone.[35] Recently, ET-1 has been identified as an important mediator of vasospasm following subarachnoid hemorrhage.[154,155] ET-1 levels are increased following subarachnoid hemorrhage. Associated with this increase, ET_A receptor levels, smooth muscle cell ET_B receptor levels (which mediate vasoconstriction), and endothelin-converting enzyme activity are increased.[156] The potential clinical use of endothelial receptor antagonists following subarachnoid hemorrhage is under investigation, with promising preliminary results.[21]

Reactive oxygen species, especially superoxide, have been shown to participate in the regulation of cerebral vascular tone. Production of superoxide anion has been associated with acute hypertension, seizures, head injury, meningitis, and cerebral ischemia.[157-161]

Coronary Circulation

Right and left coronary arteries arise from sinuses of Valsalva and course over the surface of the heart. Nutrient branches penetrate the myocardium to supply both superficial (epicardial) and deep (subendocardial) layers of the muscle. Venous blood drains primarily to the coronary sinus, although some returns by way of anterior coronary veins to the right atrium or via sinusoids directly to the ventricles.

Myocardial workload (which sets myocardial oxygen demand) is determined not only by the needs of the heart but by the demands of the body as well. Furthermore, the heart is required to generate its own perfusion pressure. Accordingly, regulation of myocardial perfusion is tailored to match regional myocardial oxygen supply to demand over the widest possible range of cardiac workload and under conditions fashioned not so much for maximal cardiac efficiency but rather for benefit of the body.

Normally over a cardiac cycle myocardial perfusion is approximately the same per gram of tissue in the outer (subepicardial), mid, and inner (subendocardial) layers of the left ventricle, but the dynamics during the cardiac cycle are complicated.[11] At the end of diastole, when the ventricle is relaxed and tissue pressures are probably under 10 mm Hg in any layer of the left ventricle, pressures in the intramural arteries are probably similar to each other and to aortic pressure. At the beginning of systole, tissue pressure rises to equal intracavitary pressure in the subendocardium but then falls off linearly across the wall to about 10 mm Hg in the subepicardium.[162] These pressures are for an instant added to those inside the vessels because the vessels walls are not rigid, and as a result, intravascular pressures in subendocardial arteries exceed aortic pressures, but aortic pressures are higher than pressures in subepicardial arteries.[163] These pressure gradients and the greater shortening of subendocardial versus subepicardial muscle fibers during systole compress the subendocardial vessels and squeeze blood out of them both forward into the coronary sinus and backward toward the epicardium.[164-166] In fact, narrowing of the subendocardial vessels facilitates thickening and shortening of the myocytes.[167] This backflow enters the subepicardial arteries to supply their systolic flow.[163] In systole, some forward flow does indeed occur into the orifices of the coronary arteries but does not perfuse the myocardium; it merely fills the extramyocardial arteries.[11,163,168] In fact, often reverse flow occurs in the epicardial coronary arteries.[169] In early diastole, blood flows first into the subepicardial vessels that have not been compressed but takes longer to refill the narrowed subendocardial vessels. Given enough time and perfusing pressure, all the myocardium will be perfused, but if diastole is too short or perfusion pressure is too low, subendocardial ischemia occurs. Right ventricular myocardium, on the other hand,

normally is perfused both in systole and in diastole (Figure 20-13) because of lower tissue pressures.[170,171] We would expect perfusion of the hypertrophied right ventricle of a persons with severe pulmonic stenosis or tetralogy of Fallot to resemble that of the left ventricle.[172]

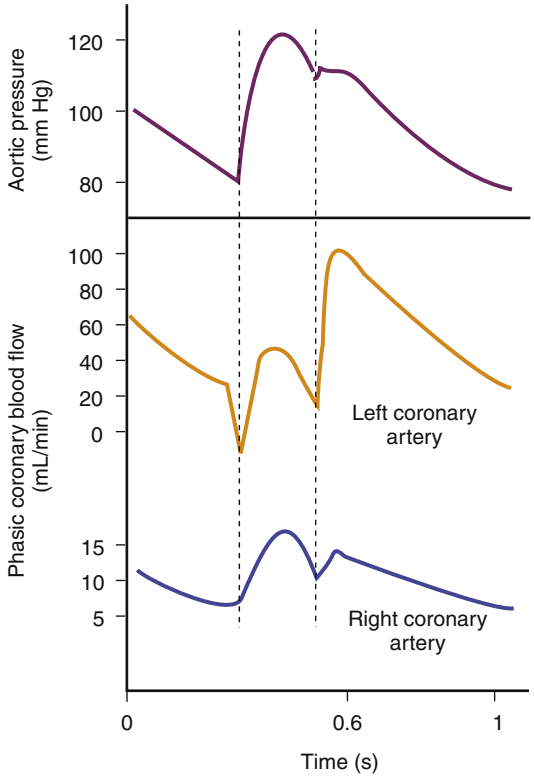

Figure 20–13. Myocardial blood flow is modulated by ventricular wall tension. Most of the perfusion of the left ventricular myocardium occurs in diastole. *(Modified from Berne RM, Levy MN:* Cardiovascular physiology, *ed 7, St Louis, 1997, Mosby.)*

Myocardial Oxygen Demand-Supply Relationship

The left ventricle extracts most of the oxygen from the blood passing through the myocardium; coronary sinus oxygen saturation is normally about 30%. Therefore increases in myocardial oxygen demand have to be met by increases in myocardial blood flow. At rest, left ventricular myocardial blood flow is about 80 to 100 mL/100 g/min, and with maximal exertion, left ventricular oxygen consumption increases about fourfold, as does left ventricular blood flow in normal people and animals.[173] If coronary perfusion pressure does not change during exertion, the increased flow has to be achieved by a decrease in coronary vascular resistance; the response is termed *metabolic regulation*.

Coronary vascular resistance has three components: a basal low resistance in the arrested heart with maximally dilated vessels, an added resistance when vessels have tone, and a phasic resistance added whenever the ventricle contracts.[174,175] In the beating heart with vessels maximally dilated by a pharmacologic dilator, the second of these resistances is absent. Perfusion of the left ventricular myocardium then produces a steep pressure-flow relation that is linear at higher flows but usually curvilinear at low pressures and flows (Figure 20-14, *A*). Because the vessels are maximally dilated, flow is uncoupled from metabolism and depends only on driving pressure and resistance. If heart rate is increased, maximal flow at any perfusion pressure decreases because the heart is in a relaxed state for a smaller proportion of each minute.

If tone is allowed to return to the coronary vessels, then the pressure-flow relationship can be assessed at different perfusion pressures after cannulating the left coronary artery. It is necessary to do this because when cardiac metabolism and blood flow are coupled, increasing aortic blood pressure will increase coronary flow not only by increasing perfusion pressure but also by increasing myocardial oxygen demand. Under normal conditions coronary blood flow is autoregulated, such

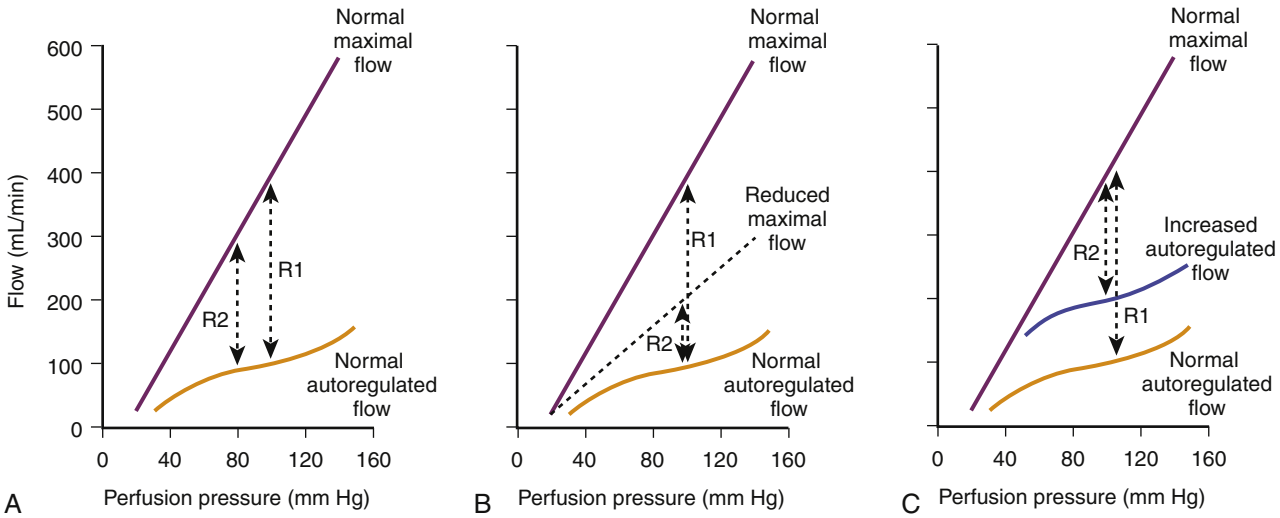

Figure 20–14. **A,** Normal pressure-flow relations in the left coronary artery during normal autoregulated flow and during maximal vasodilation. Values are appropriate for a left ventricle weighing approximately 100 g. *R1, R2,* Coronary flow reserve measurements at two different coronary perfusing pressures. **B,** Effect on coronary flow reserve of a reduced maximal flow. At the same coronary perfusing pressure, flow reserve is reduced from the normal R1 to R2. **C,** Effect on coronary flow reserve of an increased autoregulated flow. Reserve is reduced from R1 to R2.

that if perfusion pressure is raised or lowered from its normal value, there is a range over which almost no change in flow occurs; a rise in pressure has caused vasoconstriction, and a fall in pressure has caused vasodilatation.[176] At perfusion pressures above some upper limit, flow increases, probably because the pressure overcomes the constriction. More importantly, at pressures below about 40 mm Hg (but varying, as discussed later), flow decreases predominantly in the deep subendocardial muscle (see Fig. 20-14, *A*), indicating that some vessels have reached maximal vasodilatation and can no longer decrease resistance to compensate for the decreased perfusion pressure. In these vessels, flow and pressure are directly related. If this pressure dependency occurs, then further decrease in perfusion pressure decreases local blood flow below the required amount, or if myocardial oxygen demands increase at the same low perfusion pressure (as will occur if the ventricle becomes dilated), the requisite increase in flow will not occur. These two conditions cause subendocardial ischemia.

At any given pressure, the difference between autoregulated and maximal flows is termed *coronary flow reserve*.[177-179] (Coronary flow reserve can be measured in units of mL/min, but also can be assessed by a dimensionless flow reserve ratio derived by dividing maximal flow by resting flow.) Flow reserve depends on perfusion pressure because of the steepness of the pressure-flow relation in maximally dilated vessels. Coronary flow reserve indicates how much extra flow the myocardium can get at a given pressure to meet increased demands for oxygen; if reserve is much reduced, then flow cannot increase sufficiently to meet demands and myocardial ischemia will occur. What the figure does not show is that coronary flow reserve is normally lower in the subendocardium than in the subepicardium and that decreases in coronary flow reserve are always more profound in the subendocardium than in the subepicardium.

If autoregulated flow is normal but maximal flow is decreased, as indicated by the decreased slope of the pressure-flow relation during maximal dilatation (Figure 20-14, *B*), then coronary flow reserve will be reduced. Such a change can occur with marked tachycardia; a decrease in the number of coronary vessels because of small vessel disease, as in some collagen vascular diseases, especially systemic lupus erythematosus; increased resistance to flow in one or more large coronary vessels because of embolism, thrombosis, atheroma, or spasm; impaired myocardial relaxation because of ischemia; myocardial edema; a marked increase in left ventricular diastolic pressure; marked increase in left ventricular systolic pressure if coronary perfusion pressure is not also increased, as in aortic stenosis or incompetence; and an increase in blood viscosity, most commonly seen with hematocrits greater than 65%.

Coronary flow reserve also can be reduced if maximal flows are normal but autoregulated flows increase (Figure 20-14, *C*). Increased myocardial flows above normal values can occur with exercise, tachycardia, anemia, carbon monoxide poisoning, leftward shift of the hemoglobin oxygen dissociation curve (as in infants with a high proportion of fetal hemoglobin), hypoxemia, thyrotoxicosis, acute ventricular dilatation (because of increased wall stress), inotropic stimulation by catecholamines, and acquired ventricular hypertrophy. Ventricular muscle mass increases without a concomitant increase in conducting coronary blood vessels if hypertrophy develops a few months after birth. Ventricular hypertrophy returns wall stress to normal, and myocardial flow per minute per gram of muscle is approximately normal. Therefore total left ventricular flow is increased in proportion to ventricular mass, but because maximal flow per ventricle is usually unchanged, the coronary flow reserve is diminished. Often autoregulated flow is increased and maximal flows are reduced at the same time, for example, with severe tachycardia or cyanotic heart disease with hypoxemia, ventricular hypertrophy, and polycythemia. Under these circumstances, coronary flow reserve can be drastically reduced. A third mechanism that reduces coronary flow reserve is a shift to the right of the pressure-flow line. If with maximally dilated vessels diastolic coronary flow is measured at different mean diastolic perfusion pressures, a pressure-flow line is obtained that is linear at higher pressures but curved in the low pressure-flow region.[180,181] Zero flow occurs at a pressure of about 8 to 12 mm Hg; this is the critical closing pressure that is above right atrial pressure.[182,183] The whole pressure-flow line can be shifted to the right by several factors, the most important of which are pericardial tamponade, a rise in right or left ventricular diastolic pressures, and α-adrenergic stimulation. Such a rightward shift decreases flow reserve. It is important to note that because the line of maximal pressure-flow relations slopes up and to the right, any decrease in that slope (Figure 20-14, *B*), any increase in autoregulated flow (Figure 20-14, *C*), or any rightward shift of the slope raises the pressure at which autoregulation fails to compensate for decreased perfusing pressure. It also is important to reemphasize that any decrease in coronary flow reserve affects the subendocardium predominantly, so that autoregulation will fail first and ischemia will occur in the subendocardium before these changes occur in the subepicardium.[184] The predominant reduction in subendocardial flow and reserve is particularly marked when left ventricular diastolic pressure is very high.

The interactions between myocardial blood flow and ventricular function are of particular importance when ventricular hypertrophy is present. Myocardial wall stress is regulated within a fairly narrow range, with or without myocardial hypertrophy. Consequently, myocardial blood flow per unit mass is fairly constant at about 1 mL/min/g of the left ventricle at rest.[185-190] Strauer and colleagues[186,188,191,192] have shown a close relationship between peak wall stress in systole and the ratio of left ventricular mass to volume. If no hypertrophy is present, coronary flow reserve is normal, but it is reduced if the left ventricular mass is increased. Should the heart dilate acutely, then the mass-to-volume ratio decreases, wall stress and myocardial oxygen consumption increase, and coronary flow reserve falls. If ventricular dilatation is marked, subendocardial ischemia can be present. Decreasing ventricular dilatation by afterload and preload reduction reverses these unfavorable events and is another reason for the resulting improvement in ventricular function.

Right ventricular myocardial blood flow follows the general principles regarding coronary blood flow, but differences exist that are related to the low right ventricular systolic pressure and the fact that alterations in aortic pressure change coronary perfusing pressure without altering right ventricular pressure work. If the normal right ventricle is acutely distended, for example, by pulmonary embolism, right ventricular failure eventually occurs; the increased wall stress increases its oxygen consumption, but the raised systolic pressure reduces the

coronary flow, so that when supply cannot match demand, right ventricular myocardial ischemia occurs.[193] Raising aortic perfusing pressure mechanically or with α-adrenergic agonists increases right ventricular myocardial blood flow, relieves ischemia, and restores right ventricular function to normal. Improved coronary flow is not the only mechanism of this improvement; the increased left ventricular afterload moves the ventricular septum toward the right ventricle and improves left ventricular performance.[194] If right ventricular pressure is chronically elevated so that right ventricular hypertrophy occurs, as in persons with pulmonic stenosis, many forms of cyanotic congenital heart disease, and some chronic lung diseases, then right ventricular myocardial blood flow behaves in the same way as left ventricular blood flow, with one exception.[195-197] If aortic pressure is lowered, left ventricular pressure also decreases, as does left ventricular work and oxygen consumption. In the right ventricle, however, the workload may not be reduced (if there is no ventricular septal defect), and thus an imbalance between myocardial oxygen supply and demand may occur. The worst imbalance occurs when aortic systolic pressure is maintained but coronary perfusing pressure decreases, which can occur in a child with tetralogy of Fallot who has too large an aortopulmonary anastomosis. The high aortic and left ventricular systolic pressures mandate an equally high right ventricular systolic pressure, but the low diastolic aortic pressure reduces coronary perfusion pressure in diastole and can cause both left and right ventricular ischemia and failure.[198]

Gastrointestinal Circulation

The maintenance of adequate splanchnic blood flow in critically ill patients is important. In a globally compromised circulation, the gastrointestinal system is particularly prone to injury, impairing its two chief functions: the digestion and absorption of nutrients and the maintenance of a barrier to the translocation of enteric antigens.[199-204] Moreover, splanchnic ischemia has been associated with multiple organ failure and an increased incidence of morbidity and mortality in these patients.[205-208]

The three major arteries supplying blood to the gastrointestinal circulation arise directly from the aorta. The celiac artery supplies blood to the stomach, liver, and spleen. The superior mesenteric artery supplies the small intestine, the pancreas, and the proximal colon, while the inferior mesenteric artery supplies the remaining middle and distal colon. There is extensive collateral blood flow.[83] Total flow accounts for 20% to 25% of the cardiac output in the resting unfed state.[209]

The gastrointestinal circulation has multiple levels of regulation that can be broadly divided into intrinsic and extrinsic mechanisms. Intrinsic mechanisms include local metabolic processes, locally produced vasoactive substances, and myogenic reflexes. Extrinsic factors include circulating vasoactive substances, neural innervation, and general hemodynamic forces.[209-211] Neural input arising from the medulla oblongata through preganglionic fibers of the intermediolateral area of the spinal cord participates in the regulation of large blood vessels (>50 μm), largely through sympathetic α-adrenergic control.[212,213] Blood flow to the intestinal circulation, like other vascular beds, is autoregulated such that oxygen delivery remains fairly constant, with inflow pressures varying from 30 to 120 mm Hg.[211,214-216] Oxygen, carbon dioxide, H^+ ions, and adenosine are important local metabolic mediators of this process.[217-223] Other important vasoactive mediators of intestinal blood flow include serotonin, histamine, bradykinin, and prostaglandin, although their role in autoregulation is unclear.[224-228] Finally, various gastrointestinal hormones and peptides released from the intestinal mucosa and intestinal glands including gastrin, vasoactive intestinal polypeptide, cholecystokinin, secretin, glucagon, enkephalins, somatostatin, and kallidin are known to have vasoactive properties.[209,229]

A phenomenon unique to the gastrointestinal circulation is the increase in flow following the consumption of nutrients.[230] This postprandial intestinal hyperemia appears to involve multiple factors. However, the composition of the chyme is particularly important.[231] In fact, luminal distention, mechanical stimulation, and extrinsic neural stimulation are not necessary for the response to occur.[209,232-234] Lipids in combination with bile salts are the most potent triggers for postprandial hyperemia.[235-237] Glucose is the most potent single stimulus for this response.[238] Blood flow to skin and skeletal muscle decreases and cardiac output increases during postprandial hyperemia.[230] Furthermore, nutrients that induce the largest increase in blood flow elicit the largest oxygen debt within the intestinal villi.[239-244]

Interestingly, this postprandial hyperemia may be protective in some instances of low blood flow to the intestinal mucosa. Glucose has been shown to ameliorate mucosal ischemia in models of septic and hemorrhagic shock, and early enteral feeding has been advocated in human studies as well.[245-247] Conversely, enteral feeding also has been associated with bowel ischemia and injury in some patients, such as premature infants, thus complicating decisions around enteral feeding during or following low-flow states.[248-250]

Increasing data demonstrate a large role for NO in the regulation of gastrointestinal blood flow. Endothelial NOS is expressed throughout the gastrointestinal vasculature, including the liver and pancreas.[251] A number of stimuli such as shear stress, adenosine, bradykinin, and serotonin activate endothelial NOS production of NO.[252] NO, at least in part, mediates basal mesenteric and hepatic blood flow. Inhibitors of NOS decrease splanchnic blood flow and increase hepatic pressure.[253,254] Indeed, a number of studies implicate endothelial dysfunction—and aberrations in nitric oxide signaling in particular—in portal hypertension and cirrhosis.[255-257] NO also participates in the maintenance of the mucosal barrier function and is further protective by virtue of its inhibitory effect on platelet and leukocyte adhesion.[258] Furthermore, postprandial hyperemia has been shown to involve adenosine-mediated NO release.[259,260] Finally, neuronal nitric oxide synthase and inducible nitric oxide synthase are important in both normal and abnormal gastrointestinal motility and gastrointestinal inflammatory disorders, respectively.[261-266]

While NO is integral to gastrointestinal health and disease, therapies for gastrointestinal disorders that utilize the NO signaling cascade are sparse. Inhibition and potentiation of NOS activity have been studied for the treatment of portal hypertension with mixed results.[258,267,268] NO donor agents have been investigated as therapy for diseases with impaired mucosal barrier function, such as gastric ulcerative disease. These therapies also have had limited success.[269,270]

ET-1 is another important mediator of intestinal blood flow. The intestinal vasculature displays increased vasoconstriction in response to ET-1 compared with other vascular beds.[271-273]

This finding has particular importance for gastrointestinal blood flow in critically ill patients because ET-1 levels have been found to be elevated following surgery and in association with a number of disease states, including hypoxia, pancreatitis, and sepsis.[274-280] Endothelial-receptor antagonism ameliorates ischemic injury to the bowel in several models of low-flow states.[281,282] Interestingly, as in the pulmonary circulation, developmental changes appear to occur in the activity of ET-1.[283] Infusion of ET-1, however, results in sustained vasoconstriction of intestinal vessels across age groups.[216]

Finally, it should be remembered that drugs used to augment systolic blood pressure and/or to enhance cardiac output could have various effects on the gastrointestinal circulation. Fenoldopam, a dopamine-1 receptor agonist, has been shown to improve intestinal perfusion during hemorrhage.[284] However, findings on more common agents such as norepinephrine, dopamine, and vasopressin have had mixed results depending on the doses used and the models or clinical situations studied.[285-289] Thus investigations continue to be aimed at determining the optimum strategy to improve overall cardiac output and oxygen delivery without compromising flow to specific organs, such as the bowel.

Renal Circulation

Blood flow to the kidneys greatly exceeds the metabolic needs of the organs themselves. In an adult weighing 70 kg, combined renal blood flow is approximately 1200 mL/min, accounting for more than 20% of the total cardiac output supplying organs that represent under 0.5% of total body weight.[290] This high renal blood flow is necessary to support glomerular filtration so that solute and fluid homeostasis can be maintained.

Blood is supplied to the kidneys by the renal arteries, which branch to form the interlobar, arcuate, and interlobular arteries. Interlobular arteries progress to form the afferent arterioles, which lead to the glomerular capillaries within the glomerulus, the site of fluid and solute filtration. The distal glomerular capillaries reform into the efferent arterioles, which then lead to a second capillary system, the peritubular capillaries. An elevated hydrostatic pressure within the glomerular capillaries supports filtration, whereas a much lower pressure within the peritubular capillary system supports absorption.[290] Alterations in the resistances of the afferent and efferent arterioles regulate these pressures and allow for dynamic changes in renal function in response to overall fluid and solute needs.[291] The venous system branches in a fashion similar to the arterial supply, and blood eventually enters the inferior vena cava from the renal veins.

Renal blood flow is proportional to the difference between renal artery pressure (which is generally equivalent to systemic arterial pressure) and renal vein pressure, and it is inversely proportional to the renal vascular resistance. In general, three vascular segments make up the renal vascular resistance: the interlobular arteries, afferent arterioles, and efferent arterioles.[292-294] Regulation of renal vascular resistance can be broadly divided into extrinsic mechanisms and intrinsic mechanisms. Extrinsic mechanisms, which include the sympathoadrenal system, atrial natriuretic system, and renin-angiotensin-aldosterone axis, modulate renal blood flow by alterations in intrarenal vascular tone, mesangial tone, intravascular volume, and systemic vascular resistance.[290] Intrinsic mechanisms, which primarily alter afferent arteriolar resistance, are responsible for the autoregulation of renal blood flow in response to changes in renal perfusion pressure.[295]

The juxtaglomerular apparatus, which is comprised of the afferent and efferent arterioles, the macula densa, and the glomerular mesangium, is an important site in the regulation of renal perfusion and glomerular filtration. Glomerular filtration is largely a function of glomerular filtration pressure, which in turn is dependent upon renal perfusion pressure and, importantly, the balance between afferent arteriolar and efferent arteriolar tone. Increased efferent arteriolar tone increases glomerular filtration by increasing glomerular pressure, whereas increased afferent arteriolar tone has the opposite effect.

Endogenous epinephrine and norepinephrine derived from sympathetic neural input has various effects on renal perfusion and glomerular filtration. Mild sympathetic output preferentially constricts the efferent arterioles, thereby increasing glomerular pressure and filtration.[296] However, intense sympathetic discharge results in afferent arteriolar constriction, which decreases glomerular filtration.[297] Furthermore, sympathetic stimulation of afferent arterioles results in renin release, which leads to increased sodium reabsorption and fluid retention. Sympathetic stimulation can affect renal blood flow more generally by alterations in systemic arterial pressure. Clinically, norepinephrine has been shown to increase renal perfusion and renal function (measured by changes in creatinine clearance) in patients with septic shock.[298]

Angiotensin II, produced by cleavage of angiotensin I by the enzyme angiotensin-converting enzyme, also has important effects on renal perfusion. Like catecholamine stimulation, the effects of angiotensin II are dose related. At low levels, angiotensin II results in efferent arteriolar constriction, whereas at high levels both the afferent and efferent arterioles are constricted.[296,299] Angiotensin II alters renal blood flow further by alterations in intravascular volume through aldosterone and arginine vasopressin and by increasing systemic vascular resistance.

Arginine vasopressin (AVP) is synthesized in the anterior hypothalamus and released from the posterior pituitary gland. It plays a critical role in maintaining serum osmolality within a narrow range. Both V_1 and V_2 receptors have been identified.[300,301] V_2 receptors are located on the renal collecting ducts, and stimulation results in increased reabsorption of water.[302,303] Activation of V_1 receptors on systemic vessels results in vasoconstriction. Interestingly, V_1 receptor activation in the pulmonary vasculature results in vasodilation, at least in part via NO production.[304] Triggers for AVP release include changes in serum osmolality, hypovolemia, and hypotension. Patients with septic shock have been shown to have decreased levels of AVP, which has led to the use of AVP supplementation clinically.[305] Unlike catecholamines and angiotensin II, high levels of AVP appear to preferentially constrict efferent arterioles, which preserves glomerular filtration.[306]

ET-1 has diverse effects on the kidney.[307] In general, endothelin results in vasoconstriction, decreased renal perfusion, and decreased glomerular filtration. ET-1 constricts both the afferent and efferent arterioles.[308] ET-1 also has been shown to stimulate cell proliferation within the kidney. Conversely, ET-1 also may promote natriuresis through ET_B-receptor activation.[309] Furthermore, alterations in ET-1 signaling have been implicated in a host of renal diseases, including acute and chronic renal failure, essential hypertension, glomerulonephritis, renal fibrosis, and renal transplant rejection.[307,310-315]

Important vasodilators within the renal circulation include prostaglandins and atrial natriuretic peptide (ANP). The vasodilating prostaglandins (D_2, E_2, and I_2) are synthesized from arachidonic acid by the enzyme phospholipase A_2.[316-318] Most of the important vasoconstricting factors, such as catecholamines, angiotensin II, and AVP, stimulate the release of prostaglandins, promoting increased renal perfusion and glomerular filtration.[319] ANP is produced within the atrial myocytes and is released in response to increased atrial stretch. Through cGMP signaling, ANP results in afferent arteriolar dilation and increased renal perfusion and glomerular filtration. ANP also antagonizes the actions of endogenous catecholamines, angiotensin II, and AVP.

Like other organ systems, renal blood flow is autoregulated via mechanisms intrinsic to the renal vasculature.[290] Early studies demonstrate that renal blood flow and glomerular filtration remain constant at renal artery perfusion pressures of between 80 and 180 mm Hg.[295,320] Importantly, urinary flow rate is not constant within the autoregulatory range, but rather changes as a function of renal perfusion pressure. The precise mechanisms underpinning this autoregulation are unclear. However, recent evidence indicates that the mechanisms are likely complex, involving interactions between tubuloglomerular feedback and myogenic processes that protect the kidney from damage in the setting of hypertension and also regulate renal function.[321-323]

An increasing amount of data suggest that NO plays an important role in normal renal function and that alterations in NO signaling may mediate renal pathophysiology.[324-328] Techniques that utilize intrarenal NO antagonism decrease renal blood flow and increase systemic arterial pressure. Intramedullary administration of NO inhibitors increases afferent arteriolar tone with lesser effects on the efferent arterioles.[324] Various experiments demonstrate that NO signaling modulates angiotensin II–mediated vasoconstriction. Furthermore, NO appears to modulate salt and water reabsorption within the nephron independent of changes in glomerular filtration or renal blood flow.[326] Chronic NO antagonism was found to increase systemic arterial pressure, decrease medullary blood flow, and result in a positive sodium balance. The administration of L-arginine, the substrate for NO production, has been shown to abrogate the development of hypertension to salt in salt-sensitive rats and to decrease blood pressure in spontaneously hypertensive rats.[325,328]

Reactive oxygen species also participate in the regulation of renal blood flow, largely by altering the bioavailability of NO.[329,330] Superoxide dismutase attenuates the development of hypertension in spontaneously hypertensive rats.[330-332] Furthermore, superoxide dismutase diminishes angiotensin II–induced vasoconstriction and increases renal medullary blood flow.[330,333]

A number of disease states that affect critically ill patients result in the loss of renal autoregulation. Acute tubular necrosis, septic shock, hepatic failure, and cardiopulmonary bypass all have been associated with renal dysfunction and a loss of renal autoregulation.[334-337]

Conflicting Needs of Regional Circulations

Individual regional circulations respond to threats to homeostasis both independently and in concert. This response is natural because individual organs have their own separate needs. Yet each region also has a responsibility to the body as a whole. At times individual need and responsibility conflict. Life-threatening illness accentuates these "conflicts of interest." An example follows.

Pulmonary vascular resistance is pathologically elevated in persistent pulmonary hypertension of the newborn and idiopathic pulmonary hypertension and in certain patients with congenital cardiac disease, chronic pulmonary disease, or acquired cardiac disease. This problem is often managed acutely by hyperventilation, which is easily induced and requires no sodium or osmotic load. However, hypocarbic alkalosis is a vasoconstrictor in brain and myocardium, while metabolic alkalosis has little acute effect on cerebral circulation. A good understanding of the regulation of regional circulations is necessary to adequately arbitrate this conflict. The treatment of elevated pulmonary vascular resistance following caval-pulmonary anastomosis for single ventricle physiology is an excellent example of this conflict. In this postoperative setting, mild elevations of pulmonary vascular resistance may decrease pulmonary blood flow and venous return. With this anatomy, pulmonary blood flow is dependent upon superior vena cava venous return. If hyperventilation is utilized to decrease pulmonary vascular resistance, hypocarbic alkalosis decreases CBF and subsequent superior vena cava return. This process may result in a net decrease in pulmonary blood flow and desaturation.

Another example occurs in the daily treatment of persons with an acute lung injury. The lung is responsible for gas exchange for the entire body. When it fails or becomes frankly inefficient as a result of disease, other organs may be subjected to hypoxia, hypercarbia, and acidosis. Positive pressure ventilation may be essential to life. Yet mechanical ventilation can impede cardiac output (see Chapter 26), and increasing ventilator pressures with high inspired oxygen concentrations may induce further lung injury. The need for positive pressure ventilation may impose a trade: good peripheral perfusion with desaturated blood for less perfusion, better arterial oxygen content, and lower risk of iatrogenic lung injury. Decisions based on optimal oxygen delivery are generally global. Bowel and brain vascular beds autoregulate to blood pressure, but cerebral vessels dilate to hypoxia, whereas mesenteric vessels constrict. The bowel might benefit from a different combination of P_{O_2}, cardiac output, and blood pressure than the brain, although any of several combinations of these parameters might be associated with the same net oxygen delivery.

It is possible that unsuccessful arbitration among regional circulations contributes to the genesis of the syndrome of multiple organ systems failure (see Chapter 104). An increasing understanding of the mechanisms that regulate regional microcirculatory blood flow will lead to new and improved treatments that optimize blood flow and allow the intensivist to successfully arbitrate the regional blood flow "conflict of interests" that will best serve the short- and long-term interests of the critically ill patient.

References are available online at http://www.expertconsult.com.

II

Chapter 21

Principles of Invasive Monitoring

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PEARLS

- Hemodynamic monitoring refers to measurement of the functional characteristics of the heart and the circulatory system that affect the perfusion of tissues with oxygenated blood.
- Hemodynamic monitoring can be performed invasively or noninvasively and can be used for diagnosis, surveillance, or titration of therapy.
- The central venous waveform is composed of three waves (a, c, and v) and two wave descents (x and y).
- The arterial waveform has three components: rapid upstroke, dicrotic notch, and runoff.
- Cardiac output can be calculated using the Fick method or measured directly via thermodilution.
- Continuous Svo_2 monitors can guide goal-directed therapy in patients who are in septic shock.
- A pulmonary artery catheter can be used to measure cardiac output and indices of oxygen delivery and extraction.

Role of Invasive Hemodynamic Monitoring

Since William Harvey's observation in the early 1600s that the heart pumps blood in a continuous circuit, the function of the circulatory system has been the subject of intense scrutiny. Hemodynamic monitoring refers to measurement of the functional characteristics of the heart and the circulatory system that affect the perfusion of tissues with oxygenated blood in order to maintain homeostasis and to remove byproducts of metabolism. Several different types of invasive hemodynamic monitoring can be used concurrently to guide management. The goal of hemodynamic monitoring is to provide more accurate diagnoses and to guide additional interventions to deliver improved care to the critically ill patient.

In his 1733 report "Statical essays: containing haemastaticks; or, an account of some hydraulick and hydrostatical experiments made on the blood and blood-vessels of animals," Hales[1] described early experiments in horses in which he was the first to measure central venous pressure (CVP). Figure 21-1 depicts Hales and an assistant in the process of these early experiments.

Clinical hemodynamic assessment at the bedside begins with noninvasive measurements such as heart rate (HR), blood pressure, urine output, and peripheral perfusion. Other noninvasive studies that may contribute to assessment of hemodynamic status include electrocardiograms, chest radiographs, and echocardiography. Frequently, in the pediatric intensive care unit (ICU) these measurements are supplemented by invasive hemodynamic measures that require entrance into the intravascular space. Such invasive hemodynamic measurements include placement of central venous catheters to assess right atrial filling pressures and to measure mixed venous oxygen saturation, arterial catheters to assess arterial blood pressure, and pulmonary artery catheters to assess left-sided pressures, cardiac output (CO), and vascular resistance. Although invasive hemodynamic monitoring can provide the skilled intensivist with a plethora of valuable information, it is not meant to take the place of or minimize the extensive amount of information that can be gained by less invasive techniques. Successful use of invasive hemodynamic measurements necessitates the requisite skills to obtain these measures safely and with utmost attention to the multiple potential risks imposed upon the patient. Furthermore, for invasive hemodynamic measurements to be useful, the clinician must be able to successfully interpret the information provided by the measurements. Finally, as with any technology, the use of invasive hemodynamic monitoring is in evolution, and it is incumbent upon the clinician to be familiar with developments as they arise and with current controversies regarding these procedures.

This chapter aims to be a practical guide to the use of hemodynamic monitoring in the pediatric ICU. The chapter reviews general principles of measurement and then discusses the three main types of invasive hemodynamic monitoring: central venous catheter, arterial catheter, and pulmonary artery catheter. It addresses the indications and controversies, sites of insertion, interpretation of waveforms, and potential complications. It also reviews CO monitoring and calculation of oxygen consumption and delivery. Chapter 15 discusses the specific techniques for gaining access in order to make these measurements.

Indications for Invasive Hemodynamic Measurements

The three main indications for invasive hemodynamic monitoring are diagnosis, surveillance, and titration of therapy. Diagnosis may include the differentiation of septic shock (through assessment of factors such as diminished right heart filling pressures or preload and decreased systemic vascular resistance) from cardiogenic shock (which is characterized

Figure 21–1. Clinician and an assistant measuring the blood pressure of a horse. *(From Pickering G: Systemic arterial hypertension. In Fishman AP, Dickinson WR, editors:* Circulation of the blood: men and ideas, *New York, 1964, Oxford University Press.)*

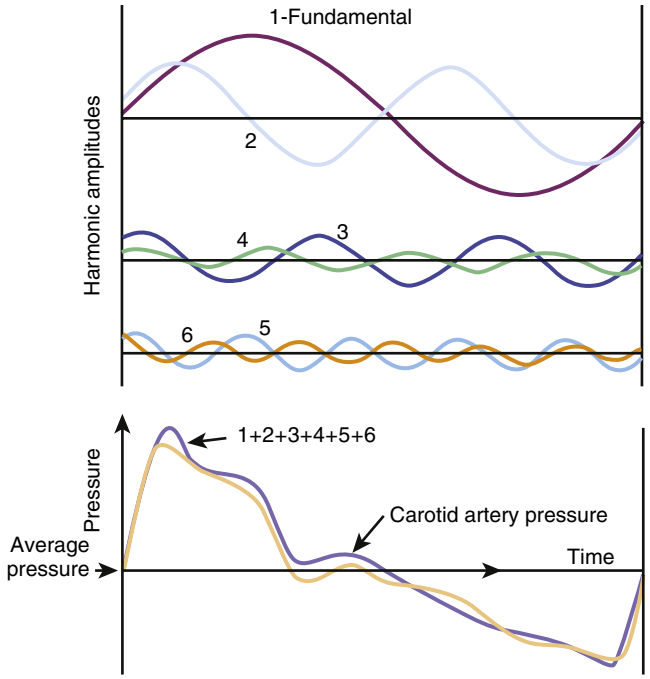

Figure 21–2. Fourier series representation of an arterial pressure tracing. **Bottom,** High-fidelity carotid artery pressure tracing and the sum of the first six harmonics of its Fourier series representation. Despite the few terms used in the synthesis, the close fit of the two curves is evident. **Top,** Individual harmonic components labeled with their harmonic number. *(Redrawn from RSC:* Transducers for biomedical measurements: principles and applications. *New York, 1974, John Wiley & Sons, from Hansen AT:* Acta Physiol Scand *19[suppl 68]:1, 1949; and Perloff WH: Invasive measurements in the PICU. In Fuhrman BP, Zimmerman JJ, editors:* Pediatric critical care, *ed 2, St. Louis, 1998, Mosby.)*

by elevated left heart pressures and afterload). Surveillance implies observation over time. The purpose of surveillance may be to assess the stability of a patient at risk for adverse changes or to determine the response to therapy. Invasive measurements performed for diagnostic purposes often are continued for surveillance purposes. Titration of therapy often is based on information gleaned from invasive measurements.

Principles of Measurement

Intensive care clinicians rely on a wide variety of measurement systems to assess patient clinical status and response to therapy. However, not all clinicians have a good understanding of how physiologic variables are measured, and some may not be able to troubleshoot monitoring systems or recognize when information obtained is inaccurate. A detailed discussion of monitoring is beyond the scope of this chapter, but a basic understanding of the principles of measurement is helpful in deciding which measurements to trust and how to assess a monitoring system for accuracy. Detailed descriptions of monitoring systems are provided elsewhere.[2-4]

Signal Analysis

Measurements generally are made directly by comparison with known standards or indirectly by use of a calibration system. Determination of length or weight usually is made by direct comparison with a standard ruler or standard mass. Most invasive measurements in the ICU are made indirectly, therefore requiring use of a calibration system. Thus understanding the basis for calibration of a system is important to determine the validity of the measurement.

Measurement systems detect and transform signals so that they can be presented in an interpretable way to the user. Signals can be characterized as static or dynamic. Slowly changing signals, such as body temperature, can be thought of as static. Hemodynamic measurements change from moment to moment and thus are dynamic. Physiologic signals may be periodic; for example, arterial pressure is periodic because it varies with the cardiac cycle.

Complex periodic signals, such as an arterial pressure waveform, can be described mathematically as the sum of a series of simpler waveforms called a Fourier series. Alternatively, the arterial tracing can be thought of as a sum of simpler waveforms, sine waves, and cosine waves. Figure 21-2 depicts an arterial pressure waveform as the sum of the first six terms in the Fourier series. The sum of the first six terms in the series forms a waveform similar to the original tracing. Adding additional terms from the Fourier series, or higher harmonics, results in an increasingly better representation of the actual

waveform. In general, to reproduce a pressure tracing without loss of significant characteristics for clinical use, the measurement system must have an accurate frequency response to approximately 10 times the fundamental frequency (first 10 harmonics).

The sampling rate of a measurement system determines how often a physiologic value is measured. For body temperature, sampling every few minutes might be sufficient, but for arterial pressure measurement, a higher rate is needed. This principle may seem obvious, but as an example of the importance of sampling rate, consider the number of points needed to define a circle. If we place three equidistant points on a circle, we describe a triangle, not a circle. Similarly, four points describe a square. If we increase the number of points (sampling rate), we can describe the circle more completely. For a sine wave, the minimum frequency of sampling needed to preserve the waveform is twice the frequency. This mathematical minimum is known as the Nyquist frequency.[2] For complex waveforms such as arterial pressure tracings, the sampling rate must be at least twice the highest frequency component in the waveform.

Measurement Systems

Hemodynamic monitoring in the clinical setting usually uses a fluid-coupled system where changes in pressure are transmitted via a column of (uncompressible) fluid in a (ideally incompressible) tube to a mechanical transducer. The mechanical transducer, usually a displaceable screen diaphragm, converts a change in pressure to an electrical signal, which can be processed and displayed. In laboratory settings, vascular pressures can be measured by a transducer at the point of interest rather than remotely as in the clinical setting. Measuring pressure at the point of interest—directly in the aorta, for example—decreases loss of signal integrity because of the measurement system. Most clinical pressure measuring systems have sufficient fidelity for clinical purposes. However, compliance, resistance, or impedance in the pressure tubing can result in damping or alteration of the recorded signal. The presence of bubbles in the fluid can further damp the recorded signal.

Errors in Measurement

The ideal measurement system determines the actual or "true" value for the measured variable. However, determination of a true value may be difficult. Every measurement system is subject to various errors. Errors in measurement can be classified as either systematic or random. Systematic errors occur in a predictable manner and are reproduced with repeated measures. Bias in a measurement system—for example, a baseline offset—results in a systematic error. Random errors are unpredictable and do not recur predictably with repeated measures.

Accuracy of a measurement is defined by the difference between the measured and true values, divided by the true value. Precision is defined by the reproducibility of the measurement; thus a more precise system yields more similar values for repeated measures under the same conditions than does a less precise system. Imprecision can be thought of as a representation of random errors, whereas bias can be thought of as a representation of systematic errors.

Calibration

Many measurement systems are linear, that is, based upon an assumption that the relationship between the inputs and outputs from a measurement device can be fitted to a straight line. This assumption allows a system to be calibrated under two conditions, with the rest of the values falling on the line defined by those two points. Actual nonlinearity of the system adversely affects the measurements.

Calibration is a process in which the reading, or output of a device, is adjusted to match a known input value. For example, an electronic pressure transducer may be calibrated against a mercury manometer. If the input to the device is zero, the output should be adjusted so that the reading also is set to zero. This "zeroing" reduces any baseline offset, thus reducing systematic errors in subsequent readings. The system then is calibrated to a nonzero value, for example, 100 mm Hg pressure, and the system gain is adjusted to read this value as well.

Frequency Response

The ability of a measurement system to accurately measure an oscillating signal, such as arterial blood pressure, is dependent upon the system's frequency response. The system can either overestimate or underestimate the true amplitude of a signal. If the system is overdamped, the value reported underestimates the amplitude, and waveform characteristics may be lost. Resonance in the system may result in overestimation of the amplitude. Measurement of arterial systolic pressure—the amplitude of the arterial waveform—may be inaccurate because of overdamping, and important waveform characteristics may be lost if the frequency response of the measurement system is poor. Figure 21-3 illustrates the effects of dampening on measurement of blood pressure.

Impedance

Impedance is the ratio of the change in blood flow along a vessel to the change in the pressure in the vessel. Impedance has both resistive and reactive components. In a pulsatile system such as the cardiovascular system, resistance alone does not fully describe the impediment or impedance to forward flow of blood. The caliber, length, and arrangement of the blood vessels and the mechanical properties of the blood determine resistance in the blood vessels. Reactance includes compliance of the vessels and inertia of the blood and thus is a dynamic component of impedance. This is important because the pulsatile nature of the cardiovascular system is dynamic.

When blood is propelled through a vessel at a branch point, a reflected pressure wave back toward the heart increases the impedance of the system. The major sites of wave reflection from vessel branching are from vessels approximately 1 mm in diameter.[3] Thus these small vessels contribute significantly to overall impedance. Figure 21-4 shows the relationships between pressure and flow velocity with distance along the length of the aorta. Because blood pressure increases with distance from the heart and flow velocity decreases with distance, the impedance increases toward the peripheral vasculature. Hemodynamic measuring systems are essentially physical extensions of the vascular system; thus the configuration and characteristics of the tubing and transducer system can alter the overall effect of impedance.

Invasive Techniques

Central Venous Pressure Catheters

Indications

Indications for CVP catheter placement in pediatric patients include assessment of right heart filling pressure (CVP), monitoring of large fluid shifts between the intravascular and the extravascular space, infusion of vasoactive substances, monitoring mixed venous oxygen saturation for goal directed therapy of sepsis, and infusion of hyperosmolar fluids and/or irritants.[5-7]

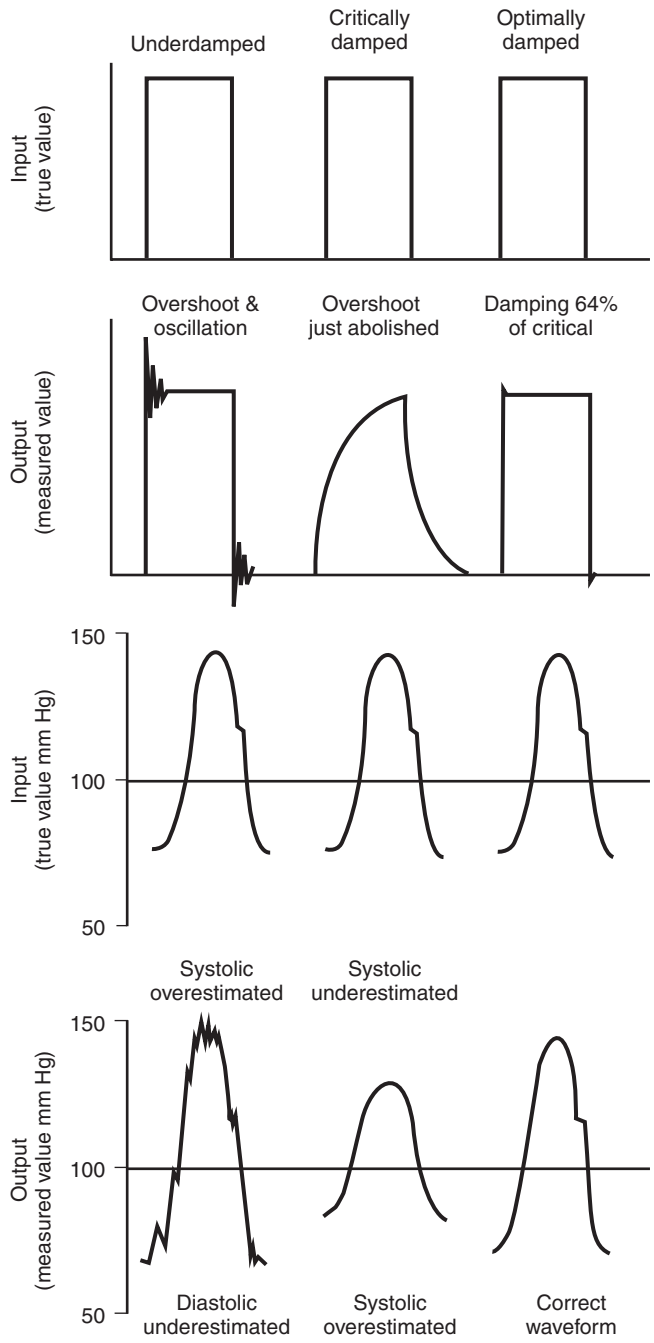

Figure 21–3. Effects of dampening on blood pressure measurement. **Upper two graphs** depict the response to a square-wave input from three different blood pressure transducers with different dampening. **Lower two graphs** show the effect of dampening on blood pressure measurement. *(From Chatburn RL: Principles of measurement. In Tobin MJ, editor:* Principles and practice of intensive care monitoring, *New York, 1998, McGraw-Hill.)*

Interpretation of Waveforms

CVP is a measure of right atrial pressure, although it may be measured in the inferior or superior vena cava (SVC). It is a measure of preload—the force or load on the right ventricle during relaxation or filling. CVP is measured at the end of diastole, just prior to ejection. Final filling of the right ventricle occurs at the end of atrial contraction. When the tricuspid valve is open during diastole, the right atrium and right ventricle form a continuous column; therefore right atrial pressure reflects right ventricular end-diastolic pressure. CVP is used to measure filling pressure or preload and as such is an indicator of volume status. It is commonly used in patients with hypovolemic or septic shock in whom volume resuscitation is desirable prior to institution of vasopressor therapy. In patients with decreased right ventricular function or pulmonary hypertension, an increased CVP well beyond normal limits may be observed, and further fluid resuscitation may promote the development of congestive heart failure. Increases in the positive end-expiratory pressure can decrease preload despite a paradoxically increased CVP. Finally, increases in extrathoracic pressure, such as that caused by increased abdominal distension, can increase CVP.

The CVP waveform is divided into three components: *a*, *c*, and *v* waves (Figure 21-5). Each component can be correlated with a specific portion of the electrocardiogram (ECG) tracing. The a wave occurs with atrial contraction and is seen after the P wave of the electrocardiogram during the PR interval. Thus the mean value of the a wave approximates right ventricular end-diastolic pressure. Canon a waves (Figure 21-6), which are enlarged a waves seen when the right atrium is ejecting against a closed tricuspid valve, may be seen when atrioventricular discordance occurs (i.e., during junctional ectopic tachycardia, ventricular tachycardia, or heart block).

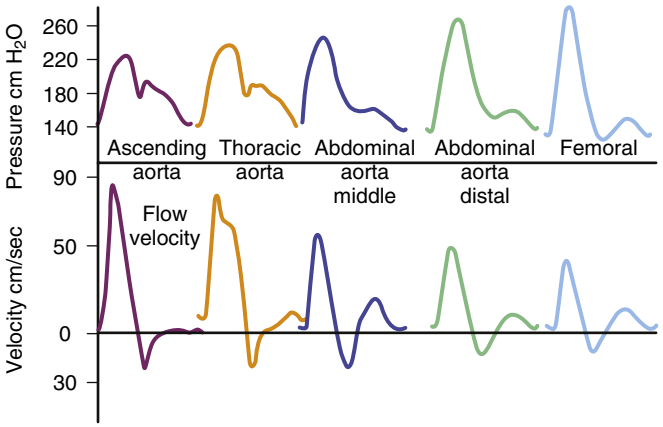

Figure 21–4. Pressure pulses and flow velocity at various points in the systemic arterial circulation. Data were obtained from dogs and are similar to measurements made in humans. The data indicate that both peak and pulse pressure increase with distance from the heart, whereas oscillation in flow velocity shows a progressive decrease. Consequently *impedance* (discussed in the text) must increase toward the periphery. *(From Perloff WH: Invasive measurements in the PICU. In Fuhrman BP, Zimmerman JJ, editors:* Pediatric critical care, *ed 2, St Louis, 1998, Mosby.)*

The c wave occurs in early systole with closure of the tricuspid valve and is seen at the end of the QRS complex in the RST junction. The v wave occurs during filling of the right atrium in late systole prior to opening of the tricuspid valve and is seen between the T and P waves of the ECG. The v wave is increased in the setting of tricuspid regurgitation. The x descent is the decrease in pressure after the a wave, reflecting atrial relaxation. The y descent is the decrease in pressure that occurs after the v wave as the tricuspid valve opens and passive filling of the right ventricle occurs.

Continuous Mixed Venous Oxygen Saturation

Mixed venous oxygen saturation (Svo_2) can be measured continuously by using a specially designed central venous catheter. These catheters have two to three lumens and have the same capabilities of the catheters previously described. The Svo_2 catheters use reflection spectrophotometry and are able to read hemoglobin oxygen saturation continuously. The reflected light is dependent on the oxygenated and deoxygenated hemoglobin concentration in the circulating blood.[8]

Svo_2 is another parameter used to monitor the relationship between oxygen delivery and demand and is often used as a surrogate for cardiac index. Rivers et al.[9] showed that when continuous Svo_2 monitoring was used to guide resuscitation and hemodynamic support in patients with severe sepsis and septic shock, survival rates improved. Recent guidelines set forth by the American College of Critical Care Medicine/Pediatric Advanced Life Support have recommended goal-directed therapy with a target Svo_2 of ≥70% in children and adolescents who are in septic shock.[7] A randomized controlled trial conducted by Oliveira and colleagues[10] supported the use of these guidelines in children and adolescents with severe sepsis or fluid-refractory septic shock.

Ideally, the catheter should be placed in the right internal jugular, with the tip taking measurements in the SVC. Svo_2 measurements obtained from the inferior vena cava exhibit greater variability because of fluctuations in splanchnic oxygen utilization and thus are less reliable. Svo_2 measurements from the right atrium contain coronary sinus blood and are more desaturated because of the high oxygen extraction rate of the myocardium. Studies in critically ill children have evaluated Svo_2 measurements obtained in the pulmonary artery and the SVC. Concordance analysis showed appropriate agreement in the measurements between these two sampling sites.[11] This finding has clinical importance because the use of pulmonary artery catheters (PACs) has declined, while central venous line use has increased.[12] Continuous Svo_2 monitoring can alert the intensivist to early changes in hemodynamic status and allows for less frequent opening of the central line for blood sampling and thus less risk of infection. Percutaneously placed Svo_2 central lines have even been used to monitor patients undergoing complex cardiac surgery, thus avoiding the risks associated with transthoracic lines following surgery.[13]

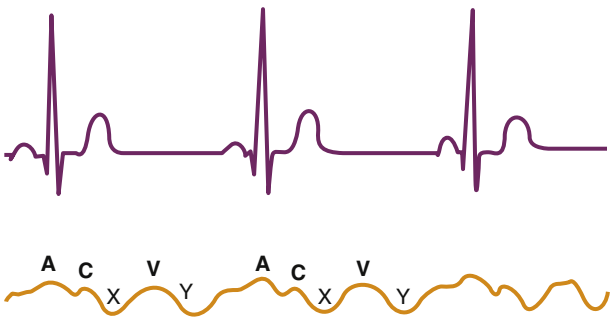

Figure 21–5. Central venous pressure (*A*) tracing with corresponding electrocardiogram (ECG). The a wave is produced by atrial contraction and occurs after the P wave of the ECG during the PR interval. The c wave (*C*) is produced by closure of the tricuspid valve and takes place early in systole at the end of the QRS complex in the RST junction. The v wave (*V*) is caused by rapid filling of the right atrium late in systole prior to opening of the tricuspid valve and is seen between the T and P waves of the ECG. The x descent (*X*) reflects the decrease in pressure in the right atrium after the *a wave* as the tricuspid valve is pulled away from the right atrium by the right ventricle as it contracts during systole. The y descent (*Y*) is the decrease in right atrial pressure that occurs after the *v wave* as the tricuspid valve opens and blood moves from the right atrium into the right ventricle. *(From O'Rourke RA: The measurement of systemic blood pressure: normal and abnormal pulsations of the arteries and veins. In Hurst JW, editor:* The heart, *New York, 1990, McGraw-Hill.)*

Arterial Pressure Catheters

Indications

The transition to direct monitoring of arterial blood pressure dates back to the mid 1950s when two separate studies compared invasive arterial measurements and noninvasive or cuff measurements in healthy adults.[14,15] Van Bergen and colleagues[15] noted a frequent difference between direct and indirect measurements, with indirect measurements increasingly lower than direct measurements as the systemic blood pressure increased. The greatest disparity was found in young hypertensive patients. Similarly, Cohn and Luria[16] observed that invasive arterial pressures were significantly greater than cuff pressures and emphasized the importance of direct measurements of systemic arterial pressure when caring for patients

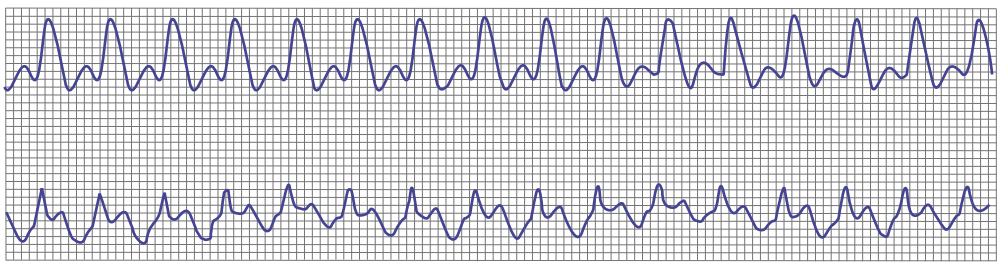

Figure 21–6. Canon a waves are enlarged a waves seen when the right atrium is ejecting against a closed tricuspid valve. These waves are typically seen when atrioventricular discordance occurs, such as during junctional ectopic or ventricular tachycardia or heart block.

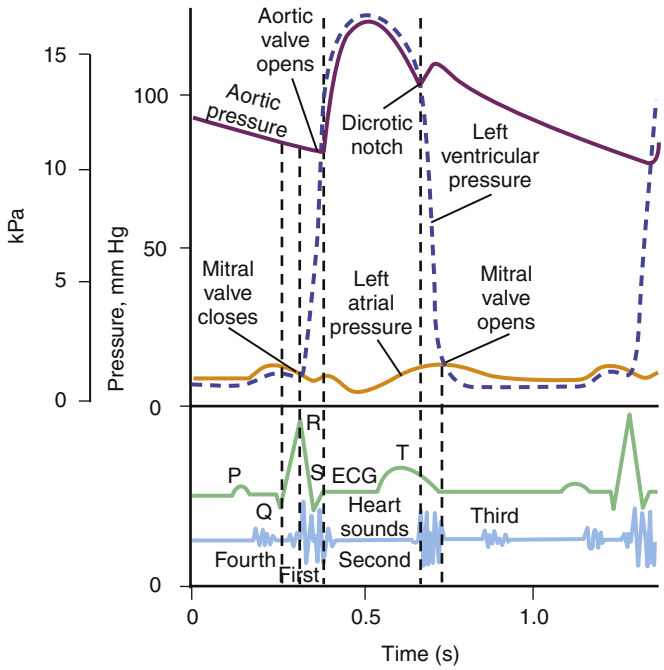

Figure 21–7. Aortic, left ventricular, and left atrial pressure waveforms as they correspond to the electrocardiogram (ECG), opening and closing of the aortic and mitral valves, and heart sounds. Note the presence of the dicrotic notch on the descending limb of the aortic waveform. *(From Peura RA: Blood pressure and sound. In Webster JG, editor:* Medical instrumentation: application and design, *Boston, 1978, Houghton Mifflin.)*

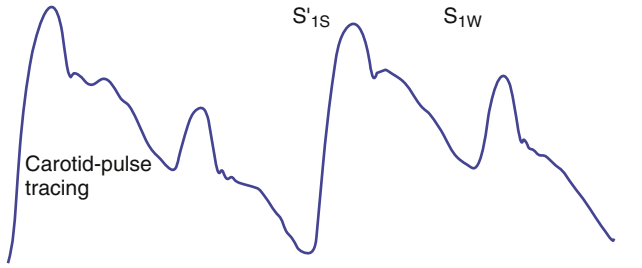

Figure 21-8. Pulsus alternans occurs with left ventricular failure and is characterized by regular variations in the peak amplitude of systolic pressure during sinus rhythm. *(Adapted from Cha K, Falk RH: Images in medicine: pulsus alternans,* N Engl J Med *334:834, 1996.)*

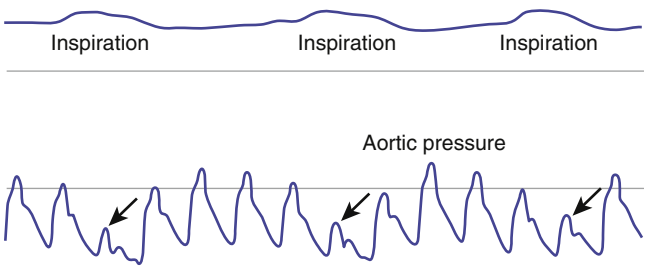

Figure 21–9. Pulsus paradoxus is characterized by an exaggerated decrease in the systolic blood pressure during inhalation. It is commonly seen in conditions marked by great swings in intrathoracic pressure, such as in status asthmaticus, or when there are changes in cardiac function as in pericarditis. In severe hypovolemia pulsus paradoxus also can be observed as a result of a decrease in preload. *(Adapted from Wu LA, Nishimura RA: Images in clinical medicine: pulsus paradoxus,* N Engl J Med *349:7, 2003.)*

with hypotension and shock. Continuous direct monitoring of arterial blood pressure should be considered when treating patients who require more than minimal vasopressor therapy.

Indications for arterial catheterization include continuous monitoring of systemic arterial blood pressure, frequent blood sampling, and withdrawal of blood during exchange transfusions.[17] In addition to the value of the measurements themselves, these measurements provide components of derived measures of CO and oxygen delivery.

Interpretation of Waveforms

Systolic blood pressure (SBP) in children varies greatly with age and gender. As with the CVP waveform, the arterial waveform can be correlated with specific parts of the cardiac cycle. The arterial waveform has three main components (Figure 21-7): (1) a rapid upstroke and downslope that correlates with systolic ejection, (2) a dicrotic notch that correlates with closure of the aortic valve, and (3) a smooth runoff that correlates with diastole. The dicrotic notch or incisura is decreased in situations of hyperdynamic CO in which left ventricular output and stroke volume (SV) are increased, pulse pressure is widened, and diastolic blood pressure (DBP) is increased (e.g., surgical systemic-to-pulmonary shunts, patent ductus arteriosus, aortic regurgitation, anemia, fever, sepsis, hypovolemia, and exercise).[18] Conversely, cardiac tamponade and severe aortic stenosis can narrow the pulse pressure and are associated with a deflection (anacrotic notch) on the ascending limb of the waveform.[18]

Systolic pressures measured in the periphery typically are greater than those measured more centrally because of pulse amplification of pressure waves reflected back from arterial branch points[18,19] (see Figure 21-4). More peripheral sites, such as the radial artery, have greater SBP and lower DBP than more central sites and thus taller and narrower waveforms with greater pulse pressures (difference between SBP and DBP). Important to note is that the mean arterial pressure (MAP in Equation 1) represents the area under the waveform curve, and the overall magnitude of the reading remains the same regardless of the location of the tracing.

$$MAP = DBP + (SBP - DBP)/3 \quad (1)$$

The appearance of the arterial waveform also provides clinical information to the observer. Pulsus alternans (Figure 21-8) is observed when regular variations occur in the amplitude of the peak systolic pressure during sinus rhythm. This phenomenon can be seen in patients with severe left ventricular failure. Pulsus paradoxus (Figure 21-9) demonstrates an exaggerated decrease in the systolic pressure (>10 mm Hg) during the inspiratory phase of the respiratory cycle. This phenomenon can be observed in patients with pericarditis, pulmonary hyperinflation, and decreased intravascular volume.

Pulmonary Artery Catheters

History and Controversy

In 1847, Claude Bernard, a French researcher with widespread interests in experimentation, described a method for recording intracardiac pressures in animals by inserting a glass tube in the heart.[20] However, the true pioneers of cardiac catheterization were two other Frenchmen: Jean Baptiste Auguste

Chaveau, at that time a veterinarian interested in the relationship between the dynamic motion of the heart and heart sounds, and Etienne-Jules Marey, a physician interested in the physiology of the circulation. In the early 1860s, using techniques adapted from Bernard's work, Chaveau and Marey inserted a double-lumen catheter into the right atrium of a horse to record phasic changes in intracardiac pressures as they simultaneously recorded the apical impulse.[20-23]

Right heart catheterization was not considered a safe practice in humans until the early twentieth century. In 1929, Werner Forssman, a German surgeon, secretly performed a right heart catheterization on himself. Forssman had been interested in the work of Bernard, Chaveau, and Marey and wanted to advance their techniques in order to apply them to humans. In direct contradiction to his supervisor's instructions, Forssman inserted a urinary catheter into his own left antecubital vein and then advanced it approximately 1 foot to the head of his humerus. He then went to the radiology department and asked a nurse to hold up a mirror while he advanced the catheter the remainder of the way to his right atrium under fluoroscopic guidance. Forssman performed right heart catheterizations on himself a total of nine additional times without adverse consequences and expanded his findings by demonstrating the feasibility of injecting contrast dye during the procedure.[24,25]

In the early 1940s, Andres Cournand and Dickinson Richards, working at Bellevue Hospital in New York City, continued Forssman's work. They performed right heart catheterization in healthy humans and in those with cardiac failure.[25-28] In 1956, Forssman, Cournand, and Richards won the Nobel Prize in Physiology or Medicine for their discoveries relating to heart catheterization and pathologic changes in the circulatory system. They were the first investigators to measure pulmonary capillary wedge pressures using cardiac catheterization.[29,30]

In 1953, Michael Lategola and Hermann Rahn,[31] two pulmonary physiologists from Rochester, New York, performed experiments in dogs in which they were the first to use a self-guiding balloon-tipped catheter to measure pressures in the pulmonary circulation. Seventeen years later, Swan et al[32] at the University of California, Los Angeles, used this technique to assess right heart pressures in humans and in doing so brought this methodology to the bedside, where it is still used today.

During the past 3 decades, much debate has occurred regarding the safety and efficacy of PACs in critically ill adults,[33-42] with multiple calls for a moratorium on PAC usage.[43,44] One randomized, controlled clinical trial underscored the lack of evidence supporting a benefit to therapy directed by PACs compared with standard care,[38] while another showed no significant effect on morbidity and mortality when PACs were used early in patients with sepsis, acute respiratory distress syndrome, or both.[39] An evidence-based review of PAC use reported no added benefit to its routine use, unless it is associated with a defined clinical protocol.[40] Shah and collegues[41] performed a meta-analysis of 13 randomized clinical trials of the impact of PAC use in critically ill patients and found that it conferred no added benefit, nor did it cause an increase in mortality or hospital days. They concluded that use of evidence-based protocols in combination with PACs may prove to be beneficial. Studies have revealed a significant lack of knowledge and expertise on the part of physicians using PACs, suggesting the tool itself may not be the cause of the problems often associated with the PAC.[45,46] An international consensus recently reviewed the available literature on the use of hemodynamic monitoring in patients with shock. They concluded that the routine use of PACs was not indicated.[47] Notably, Friese and colleagues[42] reviewed more than 53,000 patients from the National Trauma Data Bank and found that PACs were used in the management of more severely injured trauma patients. They found that patients who arrived in severe shock and those aged 60 years or older had an associated survival benefit when a PAC was used.[42]

With regard to pediatric patients, the Pulmonary Artery Catheter Consensus Conference, based on a consensus of expert opinions, concluded that the PAC was useful for clarifying cardiopulmonary physiology in critically ill infants and children with pulmonary hypertension, shock refractory to fluid resuscitation and/or low-to-moderate doses of vasoactive medications, severe respiratory failure requiring high mean airway pressures, and on rare occasions multiple organ failure.[48] They found no data indicating that PAC use increases mortality in children; however, they also failed to find any controlled trials that proved a benefit of PAC use. The panel recommended PAC use for selected patients and called for randomized, controlled trials, a registry of PAC use, and studies to assess the impact of PAC use on cost and duration of ICU/hospital stay.[48]

Indications

Although still controversial, current indications for PAC use in children include septic shock unresponsive to fluid resuscitation and vasopressor support,[49-51] refractory shock following severe burn injuries,[52] congenital heart disease (CHD),[51] multiple organ failure,[53] and respiratory failure requiring high mean airway pressures.[51,54]

Capabilities of PACs include determination of CVP, pulmonary artery pressure (PAP), and pulmonary artery occlusion pressure (PAOP), also referred to as pulmonary capillary wedge pressure (Pw). PAOP is a measurement of left atrial pressure and left ventricular end-diastolic pressure (when the mitral valve is open). PACs also are used to assess CO, Svo_2, oxygen delivery (Do_2) and consumption (Vo_2), and pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). A fundamental application of the PAC is to examine the function of the right and left ventricles separately. PACs are used to establish diagnoses, guide response to therapy, and assess the determinants of oxygen delivery. PACs are especially helpful in cases of discordant ventricular function.

One of the most common uses of the PAC in infants and children is monitoring pulmonary pressures during and after repair of CHD. In addition to flow-directed balloon-tipped PACs, transthoracic left atrial catheters often are used in these patients.[55] Use of PACs has altered the management of children with CHD by identifying residual anatomic defects and diagnosing pulmonary hypertensive crisis.[56,57] The ability to monitor PAP provides the means to titrate response to inhaled nitric oxide and other pulmonary vasodilators.[58,59] The lack of response to inhaled nitric oxide may suggest a residual structural anomaly in postoperative patients and indicate the need for repeat cardiac catheterization and/or repair.[59] In addition to monitoring for pulmonary hypertensive crisis, PACs can be used to assess the effects of changes in concentration of inspired CO_2 on mean pulmonary artery pressure (MPAP), pulmonary vascular resistance index (PVRI), and cardiac index (CI).[60]

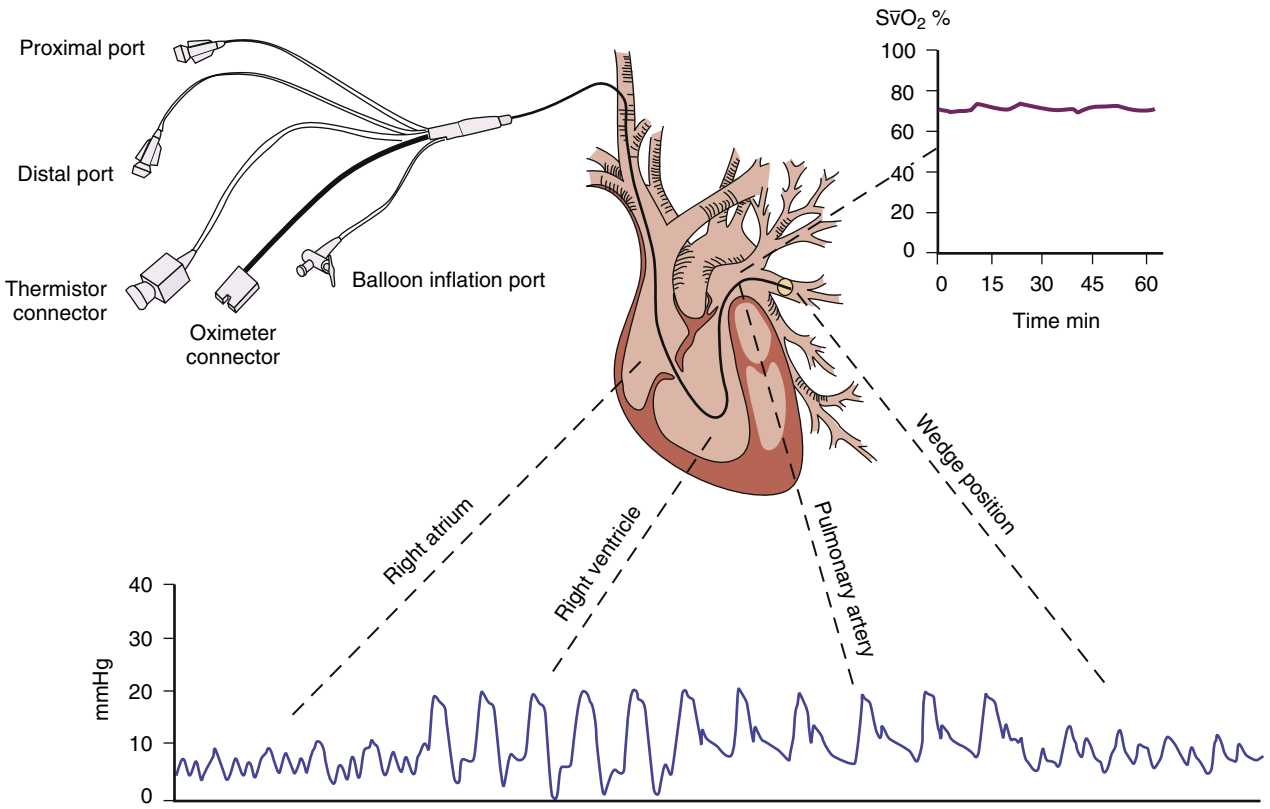

Figure 21–10. Components and functional features of a thermodilution flow-directed pulmonary artery catheter. The flexible multilumen catheter with the balloon at the distal tip inflated is in the wedge position. The proximal ends of the five lumens are labeled. The distal port is connected to a pressure measurement system for catheter insertion and subsequent monitoring. When the distal tip is within the central venous circulation, the balloon is inflated to enhance flow direction of the tip through the right atrium into the right ventricle and then to the pulmonary artery. Recorded pressures (*lower panel*) correspond to these locations, confirming the course of the catheter. The *last tracing on the right* corresponds to the "wedge" position, commonly reflecting pressure transmitted from the left atrium via the pulmonary veins and capillaries. *Upper right panel* shows an example of a continuous Svo_2 (venous oxygen saturation) tracing from the fiberoptic monitor available on adult-size catheters. *(Modified from Daily EK, Tilkian AG: Hemodynamic monitoring. In Tilkian AG, Daily EK, editors:* Cardiovascular procedures, diagnostic techniques and therapeutic procedures, *St. Louis, 1986, Mosby.)*

Catheter Ports

PACs contain the following ports (Figure 21-10). The proximal port is located 15 cm from the tip in 5F catheters and 30 cm from the tip in larger catheters. It opens into or near the right atrium. The proximal port provides access for infusion of fluid or drugs, injection of cold saline solution as indicator (thermodilution method), CVP monitoring, and blood sampling. In infants or small children, PAC placement via the internal jugular or subclavian vein may result in the improper location of the proximal port before the right atrium such that the port lies inside the sheath or outside the body. Therefore it is essential to verify not only the placement of the distal tip in the pulmonary artery but also the location of the proximal port in the right atrium.

The distal port opens at the tip of the catheter. It is used for monitoring PAP and PAOP, for blood sampling of mixed venous blood gases, and for infusion of fluids. By monitoring pressure continuously through this port during catheter placement, the location of the tip can be determined from the characteristic pressure tracings shown in Figure 21-10. After placement, PAP should be monitored continuously in order to identify inadvertent migration into the pulmonary capillary bed or "wedged" position. It is important to allow the catheter tip to "float" into the wedged position only when actively measuring PAOP in order to minimize risk of pulmonary artery infarct or rupture.

The balloon inflation port inflates the balloon, which is located 1 cm proximal to the catheter tip. The balloon is inflated for flow-directed catheter placement and for PAOP monitoring.

The thermistor is located just proximal to the balloon and connects to a bedside computer to measure changes in the temperature of pulmonary artery blood.

The oximeter uses a fiberoptic-based sensor to continuously measure the Svo_2.

Larger catheters also may have cardiac pacing ports. An adult-sized catheter is available for "continuous" CO determination when coupled with an appropriate bedside computer (see Figure 21-10).

Measurement of Cardiac Output

CO is the volume of blood pumped by the heart each minute, or SV multiplied by the number of ejections per minute or HR (CO = HR × SV) and often is expressed as CI, which is CO divided by the body surface area (BSA) in m^2. The normal range for infants and children is approximately 3.3 to 6 L/min/m^2.[61,62] Two methods for calculating CO are discussed here: the Fick method and thermodilution.

Fick Method

In 1870, Adolph Fick, a brilliant mathematician, was the first to study the relationship between blood flow and gas exchange in the lungs using a mathematical model.[63] Fick hypothesized that the amount of oxygen extracted by the body from the blood must equal the amount of oxygen taken up by the lungs during breathing. Fick also reasoned that the flow of blood through the lungs must equal the CO to the remainder of the body in the absence of a shunt. If the amount of oxygen consumed by the body and the amount of oxygen extracted by the body from the blood can be determined, then the CO can be determined. In Fick's time, oxygen consumption was measured using a basal metabolism spirometer, and the oxygen content in arterial and venous blood was measured using a rudimentary method. In his *Compendium der Physiologie des Menschen,* Fick reported that the CO of the resting adult was 4.6 L/min.[63] This value is consistent with values obtained from healthy patients using modern methods. Although Fick's method remains the gold standard, it is rarely used in the ICU because it is less practical than the more commonly used thermodilution method described in the next section. However, Fick's method is commonly used in the cardiac catheterization laboratory because the required data are readily available in this setting, although oxygen consumption typically is estimated.

As noted previously, Fick's equation is based on the assumption that the amount of oxygen extracted by the body from the blood equals the amount of oxygen taken up from the lungs during breathing.

The amount of oxygen extracted by the body from the blood equals the difference in oxygen content of arterial (Ca_{O_2}) and venous blood (Cv_{O_2}) in mL/L, also referred to as arterial-mixed venous oxygen content difference (avD_{O_2}), multiplied by the total amount of blood pumped through the lungs or body (CO).

The oxygen content of the blood is a function of the hemoglobin (Hb) concentration of blood in g/dl, the arterial or venous oxygen saturation (Sa_{O_2} or Sv_{O_2}) expressed in decimal form, and the arterial or venous partial pressure of arterial oxygen (Pa_{O_2} or Pv_{O_2}) in mm Hg. The oxygen-carrying capacity of adult Hb is 1.34 ml O_2 per gram Hb, and the Bunsen solubility coefficient of O_2 in plasma at 37° C equals 0.003. A true Sv_{O_2} is measured in the pulmonary artery; however, in the presence of an intracardiac shunt, Sv_{O_2} should be measured in the SVC.

$$Ca_{O_2} = 10 \times [(1.34 \times Hb \times Sa_{O_2}) + (Pa_{O_2} \times 0.003)] \quad (2)$$

$$Cv_{O_2} = 10 \times [(1.34 \times Hb \times Sv_{O_2}) + (Pv_{O_2} \times 0.003)] \quad (3)$$

Note that the units for oxygen content in this chapter are milliliters of oxygen per liter of blood rather than milliliters of oxygen per deciliter of blood, as is in many other sources. (Thus the values for Ca_{O_2} and Cv_{O_2} must be converted to mL/L by multiplying in a correction factor of 10 dL/L.) Expressing oxygen content in these units allows for easy computation of CO, which is expressed as liters per minute.

The avD_{O_2} is the difference between Ca_{O_2} and Cv_{O_2} and normally ranges from 20 to 78 mL/L.[62]

$$avD_{O_2} = Ca_{O_2} - CV_{O_2} \quad (4)$$

As noted earlier, the amount of oxygen extracted (consumed) by the body from the blood equals avD_{O_2} multiplied by the amount of blood that flows through the lungs (Q_P). Assuming Q_P equals the flow of blood through the systemic circulation (Q_S), then Q_P is a measure of CO. (Note that pulmonary and systemic blood flows cannot be assumed to be identical in children with CHD with single-ventricle physiology or with shunts).

$$O_2 \text{ extraction} = (Ca_{O_2} - Cv_{O_2}) \times CO \quad (5)$$

The amount of oxygen taken up by the lungs equals the amount of oxygen consumed by the body. According to Fick, the amount of oxygen extracted by the body from the blood (Equation 5) equals oxygen consumption (V_{O_2}).

$$(Ca_{O_2} - Cv_{O_2}) \times CO = V_{O_2} \quad (6)$$

CO can be calculated by rearranging Equation 6:

$$CO = V_{O_2} / (Ca_{O_2} - Cv_{O_2}) \quad (7)$$

As noted in Equations 2 and 3, the amount of dissolved oxygen in blood (Pa_{O_2} or Pv_{O_2}) contributes an almost negligible amount to the oxygen content and can be left out for ease of computation. By rearranging Equation 7, a rough estimate of CO can be calculated rather easily at the bedside without use of a PAC:

$$CO = V_{O_2} / (1.34 \times Hb \times (Sa_{O_2} - Sv_{O_2}) \times 10) \quad (8)$$

Oxygen consumption can be measured using the metabolic cart or taken from standardized tables.[11] Hb concentration can be measured directly. Sa_{O_2} can be taken from the pulse oximeter. Sv_{O_2} can be measured by the oximeter at the distal end of the PAC or determined from a venous blood gas sample from a catheter in the internal jugular or subclavian vein.

These data also can be used to calculate the intrapulmonary shunt fraction, which is the fraction of blood that passes through unventilated areas of lung:

$$Qs / Qt = (Cpv_{O_2} - Ca_{O_2}) / (Cpv_{O_2} - Cv_{O_2}) \quad (9)$$

where Ca_{O_2} is systemic arterial oxygen content and Cv_{O_2} is mixed venous oxygen content.

Cpv_{O_2} is the theoretical oxygen content in a normal pulmonary vein and can be calculated using the alveolar gas equation:

$$Cpv_{O_2} = 10 \times [1.34 \times Hb \times Spv_{O_2} + Ppv_{O_2} \times 0.003] \quad (10)$$

where Spv_{O_2} is pulmonary vein O_2 saturation and Ppv_{O_2} is pulmonary vein p_{O_2}.

For the normal lung, Ppv_{O_2} can be estimated from the alveolar air equation, and Spv_{O_2} is presumed to be 1.0:

$$Ppv_{O_2} = P_{AO_2} = (Pi_{O_2} - P_{wp}) - Pa_{CO_2} / R \quad (11)$$

where P_{AO_2} is alveolar partial pressure of oxygen, Pi_{O_2} is inspiratory p_{O_2}, P_{wp} is vapor pressure of water (47 mm Hg at 37° C), Pa_{CO_2} is arterial CO_2, and R is respiratory quotient, which is normally assumed to be 0.8.

The normal shunt fraction is 3% to 7%.

Thermodilution Method

In 1921, Stewart[64] first described an indicator-dilution method for measuring CO. Flow was calculated by measuring the change in concentration of an indicator over time. The "ideal" indicator is "stable, nontoxic, uniformly distributed,

and [does] not leave the system between sites of injection and detection. However, it should be rapidly cleared in a single circulation time to prevent recirculation interfering with measurement."[65] Initially indocyanine green was used as an indicator, but recirculation was problematic because the dye is unstable and accumulates.

In 1953, Fegler[66,67] demonstrated that a change in the heat content of blood could be used as an indicator for CO measurement. A bolus of cold liquid of a known temperature is injected into or proximal to the right atrium. A thermistor near the PAC tip in the pulmonary artery or a pulmonary artery branch measures a change in the temperature of the blood as the bolus passes by the end of the catheter. A computer calculates the flow by integrating the change in temperature at the thermistor.

The first law of thermodynamics, the conservation of heat, is the fundamental principle underlying thermodilution. Thermodilution makes several assumptions: physiologic conditions must remain constant during the period of observation, all heat exchange occurs between the indicator and the blood without heat loss to the surrounding tissues, mixing of the injectate and blood is complete upstream of the temperature measurement, and the temperature sensor is sufficiently sensitive, accurate, and rapidly responsive to depict accurately the change in temperature over time.

Measurement of CO using the thermodilution method can be understood by examining a modified version of the Stewart-Hamilton equation.[65] V_1 is injectate volume (in mL), Tb is temperature of the pulmonary artery at baseline (in degrees Celsius), Ti is temperature of the injectate (in degrees Celsius), K^1 is density factor that equals the specific heat of the injectate multiplied by the specific gravity of the injectate, divided by the product of the specific heat and specific gravity of blood, and K^2 is constant that figures in the dead space of the catheter and the loss of heat from the injectate as it moves through the catheter. The denominator of the equation is the integral of the change in the temperature of the blood (Tb) over time (t) (adapted from reference 65):

$$CO = V_1(Tb - Ti)\, K^1K^2 / \int \Delta Tb(t)dt \qquad (12)$$

The computer generates a CO curve with the area under the curve inversely related to the magnitude of the CO. In settings of low CO, less warm blood flows with the injectate, and the injectate stays cooler. The difference between the injectate temperature and that of the blood remains large, and the CO curve has a high domed shape, with a slow return to baseline temperature (Figure 21-11, *A*). In situations of high CO, more pulmonary artery blood flows with the injectate and the temperature of the injectate approaches or equals that of the blood more rapidly. In these situations, because the difference between the final temperature of the injectate and that of the blood is small, the CO curve rapidly returns to baseline following a sharp spike from the cold injectate (Figure 21-11, *B*). In extreme low-flow states, the change in temperature of the injectate resulting from handling alone, before the injectate even enters the catheter from the proximal port, may be greater than the change caused by warming of the injectate by the flow of blood.

A correction factor is added to the equation to account for warming of the injectate because of handling alone; however, the correction factor may be inaccurate if the injection is too slow or the syringe is held in the injector's hands for too long. Therefore CO readings should be made as quickly as possible and should be repeated until three successive readings are within 15% of each other. Other sources of error include a falsely elevated CO because of inadvertent warming of the thermistor when it is up against the wall of the pulmonary artery. The thermodilution method generally should not be used in patients with an intracardiac shunt; however, if the shunt fraction is less than 10%, the error likely is negligible.[18]

Calculation of Oxygen Delivery and Consumption

Metabolic derangements, such as fever, sepsis, and shock, interfere with oxygen delivery (Do_2) to and consumption by (Vo_2) the tissues. The Svo_2 is a measure of the oxygenation of blood returning to the heart. Svo_2 is measured continuously by the fiberoptic oximeter (see description of PAC ports in the catheter ports section) and normally ranges from 65% to 75%. The oxygen extraction ratio (ERo_2) is $avDo_2$ (see Equation 4) divided by Cao_2 (Equation 2) and usually is approximately 25%[61,62]:

$$ERo_2 = avDo_2 / Cao_2 \qquad (13)$$

Do_2 also can be expressed as the product of CI and Cao_2 and Vo_2 as the product of CI and $avDo_2$. The normal value for Do_2 is 620 ± 50 mL/min/m^2, whereas Vo_2 typically ranges from 120 to 200 mL/min/m^2.[61,62]

$$Do_2 = CI \times Cao_2 \qquad (14)$$

$$Vo_2 = CI \times avDo_2 \qquad (15)$$

Refer to Table 21-1 for a summary of the hemodynamic parameters that can be derived from a PAC.

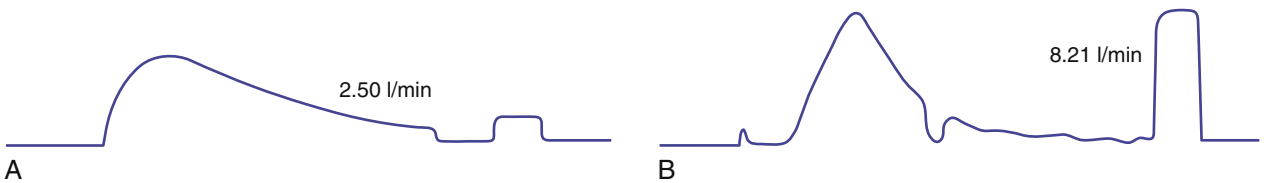

Figure 21–11. A, In the thermodilution method for calculation of cardiac output, a known amount of solution with a known temperature is injected rapidly in a proximal port. This solution mixes with the surrounding blood and cools. The temperature is then measured downstream by thermistor bead in the pulmonary catheter tip. When cardiac output is low, more time is needed for the temperature to return to the known baseline, and the area under the curve is inversely proportional to the cardiac output. **B,** When cardiac output is increased, the cool solution is carried faster through the heart, and a smaller area under the curve is produced. *(Adapted from Headley JM:* Invasive hemodynamic monitoring: physiological principles and clinical applications, *Irvine, CA, 2002, Edward Lifesciences.)*

Table 21–1 Hemodynamic Parameters

Parameter	Formula	Normal Range	Units
Cardiac index	CI = CO/BSA	3.5 – 5.5	L/min/m^2
Stroke index	SI = CI/heart rate × 1000	30 – 60	mL/m^2
Arterial-mixed venous O_2 content difference	$avDo_2 = CaO_2 - Cvo_2$	30 – 55	mL/L
O_2 delivery	$Do_2 = CI \times O_2$	620 ± 50	mL/min/m^2
O_2 consumption	$Vo_2 = CI \times avDo_2$	120 – 200	mL/min/m^2
O_2 extraction ratio	$ERo_2 = avDo_2/Cao_2$	0.26 ± 0.02	
Arterial oxygen content	$(1.34 \times Hb \times Sao_2) + (Pao_2 \times 0.003)$		mL/L
Venous oxygen content	$(1.34 \times Hb \times Svo_2) + (Pvo_2 \times 0.003)$		mL/L
Fick principle	$Vo_2 = CO \times (Cao_2 - Cvo_2)$		
Systemic vascular resistance index	SVRI = 80 × (MAP – CVP)/CI	800 – 1600	dyne–sec/cm^5/m^2
Pulmonary vascular resistance index	PVRI = 80 × (MPAP – PAOP)/CI	80 – 200	dyne–sec/cm^5/m^2
LV stroke work index	LVSWI = SI × MAP × 0.0136	56 ± 6	gm-m/m^2
RV stroke work index	RVSWI = SI × MPAP × 0.0136	0.5 ± 0.06	gm-m/m^2

$avDO_2$, Arterial-mixed venous content difference; *BSA,* body surface area in m^2; *CaO_2*, O_2 content of systemic arterial blood in ml/L;*CI,* cardiac index; *CO,* cardiac output; *CvO_2*, O_2 content of mixed venous blood in ml/L; *CVP*, central venous pressure in mm Hg; *DO_2,* oxygen delivery; *ERo_2,* O_2 extraction ratio*; Hb,* hemoglobin; *LVSWI*, left ventricular stroke index; *MAP*, mean systemic arterial pressure in mm Hg; 80 is the conversion factor used for the units in the table; *MPAP*, mean pulmonary arterial pressure in mm Hg; *PAWP*, pulmonary artery wedge pressure in mm Hg, which is approximately equal to the left atrial pressure under many circumstances; *Pvo_2,* partial oxygen pressure in mixed venous blood; *PVRI*, pulmonary vascular resistance index; *RVSWI*, right ventricular stroke work index; *SI,* stroke index; *Svo_2,* venous oxygen saturation; *SVRI*, systemic vascular resistance index;*Vo_2*, oxygen consumption. (Modified from Katz RW, Pollack MM, Weibley RE: Pulmonary artery catheterization in pediatric intensive care. In *Advances in Pediatrics*, Chicago, 1984, Year Book Medical Publishers.)

Interpretation of Waveforms

The waveforms corresponding to the right atrium and the systemic arterial blood pressure were discussed in previous sections. The pressure in the right atrium ranges from approximately 3 to 12 mm Hg. As the PAC passes into the right ventricle, the diastolic pressure drops to 0 to 10 mm Hg and the systolic pressure increases to 13 to 42 mm Hg.[18] As the catheter enters the pulmonary artery, the diastolic pressure increases to 3 to 21 mm Hg while the systolic pressure remains relatively similar to that of the right ventricle, 11 to 36 mm Hg.[18] Once the catheter tip advances into the pulmonary capillary bed and the pulmonary artery is occluded by the inflated balloon, the measured pressure decreases to 2 to 14 mm Hg.[18] By recognizing the changes in the various tracings, the movement of the catheter tip can be followed through the chambers of the right heart and into the pulmonary circulation, without simultaneous imaging.

The waveforms are affected by the components of the respiratory cycle. As expected, the effects of respiration differ during spontaneous breathing (negative pressure) versus mechanical ventilation (positive pressure). During spontaneous ventilation, PAPs decrease during inhalation and increase during exhalation. In contrast, during mechanical ventilation, PAP increases during inhalation and decreases during exhalation. The cyclical changes induced by the respiratory cycle cause the tracings to take on a sinusoidal pattern once the tip of the catheter enters the thorax. The effects of respiration on PAC determinations can be minimized by measuring pressures at the end of expiration, when pleural pressures are closest to zero.

Because CVP is a measure of preload or filling of the right ventricle, it reflects changes in volume status, right ventricular function, and pulmonary vascular tone. Similarly, PAOP measures filling pressures of the left atrium and ventricle. When the pulmonary artery is occluded, the pressure from the left atrium is transmitted back to the catheter tip. During diastole, when the mitral valve is open and the aortic valve is closed, a continuous fluid-filled column is formed from the catheter tip to the left ventricle, and PAOP is equivalent to the left ventricular end-diastolic pressure. In patients with cardiogenic shock, an elevated PAOP may reflect decreased function of the left ventricle. Rather than provide further fluid resuscitation or preload, increasing contractility or decreasing afterload may be preferable. Afterload is the load that the heart must eject blood against and is inversely related to SV (volume of blood ejected by the heart with each beat) and CO. It is determined by the impedance of the vasculature, ejection pressure, preload, and ventricular wall stress.

According to Laplace's law, ventricular wall stress (T) is proportional to ventricular transluminal pressure (P) (Intraluminal pressure – Extraluminal pressure) and radius (r) and is inversely related to twice the wall thickness (t):

$$T = P \times r/2t \quad (16)$$

For a given pressure, wall stress is increased by an increase in radius (ventricular dilation); therefore volume administration may increase ventricular diameter and consequently wall stress. Thus afterload is preload dependent. Similarly, during spontaneous breathing the transluminal pressure and consequently the wall stress increase, whereas during mechanical ventilation (positive pressure) the transluminal pressure and wall stress both decrease. Ventricular hypertrophy increases wall thickness and therefore decreases wall stress.

Resistance

To understand resistance, returning to Ohm's law is helpful: voltage (V) varies directly with resistance (R) and current (I):

$$V = IR \quad (17)$$

Rearranging Equation 17 by substituting pressure for voltage and flow for current gives Equation 18:

$$R = (Pin - Pout)/Q \quad (18)$$

where *R* is resistance, *Pin* is pressure going into a vessel, *Pout* is pressure exiting the vessel, and *Q* is flow. According to Poiseuille's law, the resistance of flow through a tube varies directly with the viscosity of the fluid and the length of the tube and is inversely proportional to the radius to the fourth power multiplied by pi (π):

$$R = 8\eta l/\pi r^4 \quad (19)$$

where η is viscosity, *l* is length, and *r* is radius. Unfortunately, Poiseuille's law assumes uniform viscosity, length, and radius, none of which holds true in the case of the pulmonary or systemic circulation; however, the principles behind the law are valuable in understanding the major determinants of resistance.

By substituting the appropriate values into Equation 16, the formulas for SVR and PVR can be derived. CO is substituted for Qs and Qp in the absence of a right-to-left or left-to-right shunt or single-ventricle physiology. In the case of the equation for PVR (Equation 21), PAOP is substituted for pulmonary vein pressure in determining Pout:

$$SVR = (MAP - CVP)/CO \quad (20)$$

$$PVR = (MPAP - PAOP)/CO \quad (21)$$

SVR and PVR are measured in mm Hg × minute × L^{-1} (or mm Hg/L per min). These units also are referred to as hybrid resistance units or Wood units after the cardiologist Paul Wood.[18] By multiplying by 80, hybrid resistance units or Wood units can be converted to the centimeter-gram-seconds (cgs) system, where resistance is measured as dynes sec/m^2/cm^5 also known as absolute resistance units.

PVR and SVR often are indexed for BSA (in square meters). The systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) are measured as dynes sec/m^2/cm^5:

$$SVRI = 80 \times (MAP - CVP)/CI \quad (22)$$

$$PVRI = 80 \times (MPAP - PAOP)/CI \quad (23)$$

SVRI usually is 800 to 1600 dynes sec/m^2/cm^5 in children[62,63] and 2180 ± 210 in adults.[68]

Calculation of Intracardiac Shunt

If the oxygen saturations throughout the cardiopulmonary circulation are known, derivation of the values for the ratio of pulmonary to systemic blood flow or intracardiac shunt (Qp/Qs) is possible:

$$Qp = Vo_2/(1.34 \times 10 \times Hb\,(Spvo_2 - Spao_2)) \quad (24)$$

$$Qs = Vo_2/(1.34 \times 10 \times Hb\,(Sao_2 - Svo_2)) \quad (25)$$

$$Qp/Qs = (Sao_2 - Svo_2)/(Spvo_2 - Spao_2) \quad (26)$$

where $Spvo_2$ is oxygen saturation in the pulmonary vein and $Spao_2$ is oxygen saturation in the pulmonary artery. In the absence of severe intrapulmonary shunt, $Spvo_2$ approaches 98% to 100%. In a complete mixing lesion, $Spao_2$ and Sao_2 should be equal by definition, enabling Sao_2 to be substituted for $Spao_2$.

Directly and Indirectly Measured Variables

Measurements from PACs include directly and indirectly measured or derived variables. Directly measured variables include CVP, MAP, MPAP, PAOP, CO, Sao_2, and Svo_2. Derived parameters include CI, PVR, SVR, PVRI, and SVRI (as noted earlier), as well as SV (in mL/beat) and stroke volume index (SVI; in mL/beat/m^2). Stroke index (SI) normally is 30 to 60 mL/m^2.[61,62]

$$SV = CO/HR \quad (27)$$

$$SVI = SV/BSA \quad (28)$$

Left ventricular stroke work index (LVSWI) and right ventricular stroke work index (RVSWI) normally are 56 ± 6 and 0.5 ± 0.06 gm-m/m^2, respectively.[61,62] Note all values are for pediatric patients unless otherwise indicated.

$$LVSWI = SI \times MAP \times 0.0136 \quad (29)$$

$$RVSWI = SI \times MPAP \times 0.0136 \quad (30)$$

Conclusions

Invasive hemodynamic monitoring provides the intensivist with valuable information regarding the condition of critically ill children. Correct interpretation of this information is necessary to optimally aid in the management of these patients whose condition is often complex. New noninvasive monitoring modalities are emerging that may eventually replace the need for these invasive measurements, but thus far invasive monitoring remains a cornerstone of pediatric critical care medicine.

References are available online at http://www.expertconsult.com.

II

Chapter 22

Assessment of Cardiovascular Function

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PEARLS

- Cardiovascular assessment and monitoring in the pediatric intensive care unit requires careful integration of physical findings, laboratory studies, and electronic data to make appropriate therapeutic decisions.
- Noninvasive monitoring includes physical examination, chest radiography, echocardiography, blood pressure monitoring, and pulse oximetry. Invasive monitoring includes intravascular and intracardiac monitoring, cardiac output measurements (thermodilution or Fick method), and laboratory studies.
- Appreciating the quantity of therapy required to achieve and sustain adequate systemic oxygen delivery and perfusion pressure is useful for the clinician to understand the patient's overall condition, discern the patient's trajectory, and anticipate associated consequences of current management choices.
- Management of patients with single-ventricle physiology (such as the neonate with hypoplastic left heart syndrome) poses several unique challenges to the cardiac intensivist, including optimization of pulmonary-to-systemic blood flow ratios for best systemic oxygen delivery.

Pediatric patients undergoing surgical treatment for congenital heart disease (CHD) or those with severe systemic illnesses such as sepsis and other causes of multiple organ system failure commonly have impaired cardiovascular function.[1,2] In addition to treating the primary disease process, the pediatric intensivist should use strategies to reliably assess and monitor cardiovascular function, which specifically involves assessing adequacy of oxygen delivery (DO_2) and systemic perfusion pressure, the primary determinants of tissue oxygenation.

Cardiovascular Function

The function of the heart and vasculature is to deliver oxygen (O_2) and other nutrients to various tissues in order to meet the metabolic demands of the organism. Mild to moderate depression of DO_2 normally is compensated by augmented O_2 extraction at the tissue level, thereby maintaining a stable level of oxygen consumption (VO_2). When DO_2 falls below some critical level, this compensatory mechanism fails and a state of O_2 supply dependency exists[3] such that any further drop in DO_2 leads to a parallel fall in VO_2.[4-6] Under a state of supply-dependent O_2 consumption, affected tissues and organs attempt to maintain homeostasis partly through anaerobic metabolism. Several studies suggest the initial metabolic response to hypoxemia or decreased DO_2 differs between the newborn and older ages and varies among different vascular beds. In adults at rest, DO_2 is in great excess of VO_2. This "O_2 surplus" means moderate reductions of O_2 transport are generally well tolerated without compromise of VO_2. In contrast to the adult, the metabolism of the newborn may be particularly susceptible to modest alterations in O_2 transport because of the high resting demands for O_2, the ease with which these demands can be increased by small environmental changes, and the apparently limited reserve for augmenting cardiac output (CO) or O_2 extraction acutely.[7,8] Thus it is crucial that cardiovascular assessment and monitoring in the pediatric intensive care unit (ICU) involve continuous and reliable evaluation of the adequacy of systemic perfusion and DO_2 in order to select appropriate hemodynamic support strategies.

Quantity of Therapy

If one considers hemodynamic monitoring not only in terms of DO_2 and perfusion pressure but also in terms of what therapy is required to produce a given level of tissue oxygenation, one gains a much better understanding of the overall "condition" of the patient. It is therefore important to monitor not only DO_2 and perfusion pressure but also the "quantity of therapy" (QOT) needed to procure and maintain adequate tissue oxygenation. Consider two hypothetical 6-month-old infants, Destiny and Dakota, 2 hours after repair of tetralogy of Fallot. They have identical (and adequate) DO_2 and perfusion pressure, but Destiny has a left atrial (LA) pressure of 6 mm Hg and a right atrial (RA) pressure of 8 mm Hg, whereas Dakota has received volume infusion to achieve an LA pressure of 6 mm Hg and an RA pressure of 15 mm Hg. Assuming that the levels of intravascular volume provided are exactly those needed to achieve the (identical) DO_2 values and perfusion pressures, it is clear that the physiologies of these two patients are different. The clinician who has learned what to expect relative to the QOT in any given set of circumstances will find Dakota's sufficient tissue oxygenation only mildly

reassuring and asks: Is there substantial residual right ventricular (RV) outflow tract obstruction or other problem(s) that I need to know about? Will Dakota have sufficient DO_2 in 10 hours when post-bypass myocardial depression is at its worst? Might additional therapy secure adequate DO_2 at a lower filling pressure, thereby minimizing adverse effects of systemic venous hypertension? As this example illustrates, the QOT concept is useful for three reasons:

1. The QOT is, in part, a function of the patient's overall "condition" and can reflect anatomic or physiologic problems that require further exploration.
2. Physiologic trajectory is key, especially early in the course of certain illnesses or after cardiopulmonary bypass, when DO_2 predictably declines over the first 12 hours.[2] Taking into account the QOT relative to tissue oxygenation at any point in time helps one better estimate the likelihood of the need for augmented support (e.g., mechanical support of the circulation) as time passes.
3. Some therapies (e.g., fluid infusion to obtain high filling pressure, or high airway pressure) while helpful at a point in time, can be pernicious over the longer run: High venous pressure, especially in infants, causes third spacing of fluid, and the effect of ventilator-associated lung injury on lung function can be devastating. By using high central venous or airway pressures, the intensivist is, in effect, incurring a debt to secure short-term perfusion that will have to be repaid later. Experienced clinicians always take the QOT into account in their work, thus influencing their level of concern about a patient and guiding subsequent timing and choice in adjusting therapy.

Almost any form of therapy might be included in the QOT concept, but we will focus on medical therapies that have the most important effect on hemodynamics, including DO_2 and perfusion pressure. These therapies include inotropic/vasoactive agents, volume infusion, and airway pressures used during mechanical ventilation. The amount of inotropic and vasoactive drugs administered, assuming that they are used appropriately, seems to be a crude indicator of patient illness.[2] Volume infusion to achieve adequate filling pressure is required even for the normal heart, but the QOT concept applies when higher than normal filling pressure is needed to maintain adequate CO. The consequences of high filling pressures are body edema (especially in infants), pleural and other cavity space effusions, and pulmonary edema. If high venous pressure is coupled with systemic hypotension (e.g., with a "failing" Fontan circulation), there may be critically reduced trans-tissue perfusion pressure with a potentially negative impact on cerebral and splanchnic perfusion.

With respect to mechanical ventilation, the need for high mean airway pressure (P_{aw}) is most commonly a reflection of lung disease, but pulmonary edema on a hydrodynamic basis may occasion the use of high P_{aw} for optimal lung recruitment. High P_{aw} can reduce venous return to the heart, increase pulmonary vascular resistance (PVR), and contribute to ventilator-associated lung injury.

Variables that Determine Tissue Oxygenation

Tissue oxygenation is directly related to both DO_2 and systemic arterial blood pressure (SAP). DO_2, the quantity of O_2 delivered to the tissues per minute, is the product of systemic blood flow (SBF), which equals CO except in patients with certain cardiac malformations, and arterial O_2 content:

$$DO_2\ (\text{mL/min}) = 10 \times CO\ (\text{L/min}) \times CaO_2\ (\text{mL/100 mL blood}),$$

where *CO* is cardiac output or SBF in L/min or L/min/m^2 and Cao_2 is quantity of O_2 bound to hemoglobin plus the quantity of O_2 dissolved in the plasma in arterial blood. The O_2 content of arterial blood (mL O_2/dl blood) equals:

$$CaO_2 = (SaO_2 \times Hgb \times 1.36) + (PaO_2 \times 0.003)$$

where Sao_2 is arterial O_2 saturation, *Hgb* is hemoglobin concentration (g/dL), *1.36* (constant) is the amount of O_2 bound per gram of hemoglobin (mL) at 1 atm of pressure, Pao_2 is arterial partial pressure of O_2, and *0.003* (constant) multiplied by the PaO_2 equals amount of O_2 dissolved in plasma at 1 atm. The quantity of dissolved O_2 is generally considered to be negligible in the normal range of Pao_2. Hypoxia, because of poor gas exchange within the lungs (i.e., intrapulmonary shunt), or in the setting of CHD with right-to-left shunting, is an important determinant of blood O_2 content.

CO is the product of stroke volume (quantity of blood ejected per beat) and heart rate, and SAP is determined by CO and systemic vascular resistance (SVR). The four primary determinants of cardiac function are preload (which determines the precontractile lengths of the myofibrils), end-systolic wall stress (function of systemic blood pressure and physical characteristics of the arterial system, ventricular wall thickness, and chamber dimension), myocardial contractility, and heart rate. These determinants of ventricular function can be altered by many factors in the intensive care setting. Preload, or end-diastolic volume, is affected by ventricular compliance (rate and extent of cardiomyocyte relaxation and cardiac connective tissue), intravascular volume, and intrathoracic pressure. Expansion of the heart resulting from transmural filling pressure, rather than the LA pressure per se, determines the force of contraction. Therefore, intrathoracic (or intrapericardial) pressure is a key determinant of preload. Ventricular hypertrophy, vasodilator and diuretic therapies, and positive pressure mechanical ventilation all adversely affect preload. Similarly, cardiac function is inversely related to afterload, or end-systolic wall stress. Anatomic obstructions and systemic or pulmonary hypertension may negatively affect ventricular systolic and diastolic function. Excessively fast or slow heart rates and inappropriately timed atrial contraction (relative to ventricular systole) may negatively affect ventricular function. Finally, myocardial contractility often is negatively affected by the following factors: hypoxemia, acidosis, hypomagnesemia, hypocalcemia, hypoglycemia, hyperkalemia, cardiac surgery, sepsis, and cardiomyopathies.

Monitoring Tissue Oxygenation

CO can be assessed qualitatively by physical examination and other modalities and quantitatively by a variety of techniques using invasive and noninvasive devices, laboratory data, and other clinical indicators. DO_2 is easily derived if systemic blood flow can be measured, but it is only indirectly inferred if this information is lacking.

Qualitative Assessment of Cardiac Output

Physical Examination

The physical examination often is the initial and the most common technique used to assess and monitor cardiovascular function. Significantly diminished CO may manifest as diminished peripheral pulses, cool or mottled extremities, and delayed capillary refill. However, certain clinical signs of low CO may be unreliable depending on the particular diagnosis. For example, in the context of cardiac lesions associated with a large arterial pulse pressure (e.g., severe aortic insufficiency and aortopulmonary shunts), peripheral pulses may be increased despite low CO and reduced systemic DO_2. Patients in septic shock often are peripherally vasodilated and warm despite hypotension and reduced tissue DO_2. Impaired oxygenation may present as cyanosis of the skin, lips, and/or nail beds. Central cyanosis from either cardiac or respiratory causes results from arterial O_2 desaturation. In contrast, peripheral cyanosis results from vasoconstriction and low blood flow at the microcirculatory level. In some patients, cyanosis is a relatively subtle physical finding, particularly if the patient is anemic or has a dark complexion. Hydration status can be assessed by skin turgor, dryness of mucous membranes, and fullness of the anterior fontanel (in infants), but these manifestations of hydration status relate mostly to interstitial fluid and may poorly reflect intravascular volume, which must be directly measured.

Cardiac auscultation for abnormal heart sounds, including valve clicks, rubs, gallops, and murmurs, may provide the first indication of a significant functional or structural cardiac abnormality, although these sounds do not directly reflect DO_2. Unfortunately, the lack of a heart murmur, especially in low CO states, does not necessarily rule out a significant residual cardiac lesion. The presence of crackles on pulmonary auscultation, particularly in the older pediatric patient, may signify pulmonary edema. However, crackles are nonspecific and may be caused by lung disease or fluid overload, in addition to disorders of cardiac structure or function. Finally, jugular venous distension and hepatomegaly often are indicative of high right-sided filling pressures often associated with RV dysfunction.

Chest Radiography

Although the chest radiograph is of little value in assessing a patient's hemodynamic profile per se, it may be helpful for assessing certain aspects related to cardiovascular status. Provided the chest radiograph is technically adequate, the clinician can assess heart size, contour and configuration, pulmonary vascularity, pleural effusions, lung parenchyma, and abdominal situs. Some of these findings, when abnormal, may help determine the etiology of cardiovascular dysfunction. Increased pulmonary arterial vasculature may be indicated by enlarged pulmonary arteries in the hila that radiate toward the periphery of the lung. Conditions that increase pulmonary blood flow (PBF, or Q_p) at least twice normal also increase the size of the pulmonary arteries. Increased pulmonary capillary pressure may be inferred by the presence of pulmonary edema. The edema may present as a "fluffy" hilum but may have a more diffuse granular appearance in neonates. Pleural effusions may accompany pulmonary edema, particularly in conditions associated with poorly compensated congestive heart failure. Increased pulmonary venous markings are indicative of elevated pulmonary venous pressures of any cause, although usually from decreased left ventricular compliance or obstruction in the pulmonary veins or left atrium.

In the early postoperative period, the most important information obtained from the chest radiograph is (1) the positions of the endotracheal tube, chest tubes, and intracardiac lines; (2) the presence of extrapulmonary fluid or air; and (3) the presence of pulmonary edema. The cardiothoracic ratio gives a quantitative estimate of cardiac size, which is obtained by dividing the transverse measurement of the cardiac shadow in the posteroanterior view by the width of the thoracic cavity. Cardiomegaly is present if this value is greater than 0.5 in adults and 0.6 in infants. Although useful for assessing left ventricular (LV) enlargement, the cardiothoracic ratio is not as sensitive to RV enlargement. RV enlargement results in lateral and upward displacement of the cardiac apex on the posteroanterior view and filling of the retrosternal space on the lateral view. It is perhaps more important to know what the chest x-ray may not reveal; significant cardiac problems, such as constrictive pericarditis, acute fulminant myocarditis, and even acute pericardial tamponade often are associated with a normal-sized heart on a chest radiograph.

Quantitative Assessment of Cardiac Output

Quantitative measures of CO in the ICU can be obtained by a variety of techniques, including the Fick method, thermodilution, the dye dilution techniques, and Doppler echocardiography. Each of the first three methods applies a similar principle of dilution of an indicator: O_2, cold, or indocyanine green dye, respectively. The change in concentration of a substance is proportional to the volume of blood in which it is being diluted. In general, thermodilution is the method most widely used in the intensive care setting. However, for conditions of low CO, the Fick method is more reliable than the thermodilution or dye dilution techniques. Conversely, the Fick method is less accurate in conditions of high systemic blood flow because of difficulty in measuring narrow arteriovenous O_2 differences in the blood.

Thermodilution Technique

The thermodilution technique requires use of a specialized pulmonary artery (PA) catheter. CO is calculated by injecting a known volume of iced water or saline solution into the right atrium (proximal catheter port) and measuring the temperature change at the catheter tip in the PA. CO is calculated by the following equation:

$$CO = 1.08 \times V_i\,(T_b - T_i) / e_0 T_b(t)dt$$

where V_i is injectate volume (mL), T_b is temperature of blood, T_i is injectate temperature, and $T_b(t)dt$ is area under the curve. In general, thermodilution CO measures are performed using a completely automated system, and the calculations are performed by a computer. This method (as with any indicator dilution method) requires complete mixing and thus is most accurate in situations where a mixing chamber is located proximal to the thermistor. It is generally used only in patients who do not have intracardiac or great vessel–level shunts or an insufficient valve between the injection site and the sampling site. The injection must be made rapidly because a slow injection will give a falsely elevated CO. Possible sources of

error with this method include inaccurate measurement of the volume of injectate or of the temperature of the blood or injectate, close approximation of the thermistor to a vessel wall, and inadequate mixing, as is sometimes seen in venous systems with low flow.

Fick Method

According to the Fick principle, CO equals O_2 consumption divided by the arteriovenous O_2 content difference:

$$CO = VO_2 / (CaO_2 - CvO_2)$$

where VO_2 is O_2 consumption (mL/min) and CaO_2 and CvO_2 are arterial and venous O_2 content (mL O_2/100 mL blood), respectively. Care must be taken to select the appropriate sampling site for a true mixed venous blood sample. With a normal heart, the best site to obtain a mixed venous sample is within the PA. If a left-to-right shunt is present, however, the mixed venous site should be the cardiac chamber proximal to the site of the shunt. When a site other than the PA is used for the mixed venous site, the resultant value for arteriovenous O_2 difference is a less reliable reflection of the absolute CO, but it can be used for serial observations and for monitoring response to therapy over time.

Because measuring VO_2 in the intensive care setting requires special equipment and is somewhat cumbersome, the arteriovenous O_2 difference is often used as an indirect measure of CO. A wide arteriovenous O_2 difference generally reflects a low CO and indicates a large O_2 extraction by the tissues, whereas a narrow arteriovenous O_2 difference usually reflects a high CO. Unfortunately, studies suggest VO_2 is quite variable for any individual patient in an intensive care setting.[9] Furthermore, mixed venous O_2 saturation (and, hence, arteriovenous O_2 difference) may be misleading in patients with decreased tissue O_2 extraction.[10,11]

Doppler Echocardiography

Doppler techniques can be used to measure CO using the mean velocity of systolic flow, the heart rate at the time of measurement, and the cross-sectional area of the artery in which measurements are being made (usually the ascending aorta):

$$CO = A \times V \times HR$$

where *A* is the area of the orifice, *V* is integrated flow velocity, and *HR* is heart rate. To determine the integrated flow velocity, the area under the Doppler curve must be measured. The area of the aortic orifice is commonly obtained by measuring the aortic diameter from the two-dimensional image, where A = 0.785 ∞ d2. This technique requires special care for accurate Doppler interrogation of blood flow and is seldom used in the critical care unit.

Pulse Oximetry

Pulse oximetry measures the quantity of hemoglobin saturated with O_2 in peripheral arterial blood. It depends on two principles: (1) oxygenated and reduced hemoglobin have different absorption spectra; and (2) at constant light intensity and hemoglobin concentration, O_2 saturation of hemoglobin is a logarithmic function of the intensity of transmitted light (Beer Lambert law). Two wavelengths of light that have different absorption spectra for reduced hemoglobin and oxyhemoglobin are transmitted from the light-emitting diodes through the arterial bed. Light absorption at the two wavelengths is compared, yielding the ratio of oxyhemoglobin to reduced hemoglobin, or the O_2 saturation. Pulse oximeters have a high potential for error at saturations below 80%.[12] Furthermore, the O_2 dissociation curve flattens out at the high range so that at saturations greater than 95%, large changes in PaO_2 accompany small changes in saturation. This phenomenon should be kept in mind when monitoring premature infants, for whom it is important to avoid hyperoxia.

Other Measures of DO_2

Acid-Base Status

When tissue hypoxia occurs and affected tissues and organs resort, in part, to anaerobic metabolism, increased production of lactate, CO_2, and hydrogen ions occurs. The anion gap, the difference in unmeasured serum anions and unmeasured serum cations, can yield information regarding the cause of metabolic acidosis. If the anion gap is normal (8 to 16 mEq/L), loss of bicarbonate has occurred, usually via the kidneys or gastrointestinal tract, or rapid dilution of the extracellular fluid has occurred.

Blood Lactate

Blood lactate concentration is a laboratory measure that indirectly reflects perfusion.[13,14] Blood lactate measurements are extensively utilized for monitoring and evaluating response to therapy. We observed that initial absolute blood lactate levels were less important than the temporal trend in lactate concentrations for predicting mortality in postoperative cardiac patients.[15] Unfortunately, the specificity of blood lactate is imperfect and may lack sensitivity for detecting supply-dependent O_2 consumption, particularly if it is only regional. In addition, blood lactate depends on hepatic metabolism and the rate of production and clearance.

Gastric Tonometry

Gastric tonometry, a technique available for clinical use in adult and some pediatric ICUs, allows indirect assessment of perfusion by measuring gut intramucosal pH or partial pressure of carbon dioxide.[16,17] It may have an advantage over blood lactate concentration in that it can uncover regional hypoxia and hypoperfusion involving the gut and can be adapted for continuous online measurement.[17] Nonetheless, this technique assumes that a critical reduction in O_2 transport manifests in the splanchnic circulation before it can be detected systemically (probably a reasonable assumption), and tonometric methods are not entirely noninvasive.

Urine Output

Urine output generally reflects CO, but oliguria may occur in the first 24 hours after open heart surgery, especially in neonates, even in the context of good CO and blood pressure. It is therefore important to consider urine output in the context of other indicators of organ perfusion, and not as an isolated variable. It should also be noted that the kidneys are quite sensitive to perfusion pressure and that good systemic blood flow coupled with low systemic arterial pressure (due to low SVR) may adversely affect urine output more than other measures of tissue perfusion.

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS), a noninvasive technique that has been applied to assess systemic and regional oxygen transport in several clinical and laboratory studies,[18-26] is gaining acceptance, particularly in patients with CHD, as a means of trending regional DO_2 or as a surrogate for mixed venous O_2 saturation or systemic DO_2.[27] Abdominal site NIRS has been shown to correlate with simultaneous intramucosal pH measurements by gastric tonometry in neonates and infants with CHD undergoing catheter-based or surgical intervention.[28] In an experimental setting in which DO_2 is controlled, NIRS has been used to correlate cytochrome *aa3* (the terminal link in the electron transport chain responsible for mitochondrial respiration), VO_2, and lactate flux.[23] Thus NIRS has the potential to identify a critical regional reduction in O_2 transport at the cellular level.

Systemic Arterial Blood Pressure

Invasive Blood Pressure Monitoring

Intravascular pressure monitoring often is essential in the management of critically ill neonates and infants in the intensive care unit. Typically, an end-hole catheter is inserted into a vessel (or cardiac chamber) and connected to a pressure transducer by a coupling system composed of fluid-filled extension tubing, a stopcock for withdrawing blood and balancing the transducer to atmospheric pressure, and a continuous infusion device to flush out blood and air. The transducer translates pressure into an electrical signal that can be processed through a preamplifier into a waveform or numerical display on a monitor. The pressure transducer must be properly calibrated, dampened, and positioned (at mid chest level). Inaccurate measurements can occur for a variety of reasons.

In the pediatric population, blood pressure is age-dependent and is a relatively insensitive marker of CO and DO_2. Because blood pressure is the product of CO and SVR, hypotension may result from diminished CO and/or decreased SVR.[29] Because the treatment options are different, distinguishing low CO from low SVR is important.

Noninvasive Blood Pressure Monitoring

The auscultatory method of blood pressure measurement with a cuff and pressure gauge is difficult if access to the patient is limited, if the patient is small or uncooperative, and when frequent recordings are required. Therefore two techniques, Doppler and oscillometric measurements, have been developed. The Doppler technique uses a Doppler ultrasound probe that is applied to the radial or brachial artery. A cuff wrapped around the upper arm is inflated until the audible Doppler signal is obliterated and then deflated until the signal first becomes audible again (systolic blood pressure). This method has been validated in low-flow states and in small children.[30] The oscillometric method has the advantage of being readily automated. The device for indirect noninvasive mean arterial pressure (Dinamap) is based on the principle that blood flow through a vessel produces oscillation of the arterial wall that may be transmitted to an inflatable cuff encircling the extremity. As cuff pressure decreases, a characteristic change occurs in the magnitude of oscillation at the levels at which systolic, diastolic, and mean pressures are registered. Accuracy of Dinamap blood pressures has been validated in children, and it correlates well with direct intravascular radial artery pressures.[31] The accuracy of these two techniques relates to the cuff size. If the cuff is too narrow, the pressure recorded may be erroneously high; if the cuff is too wide, the pressure recorded may be too low. Both techniques are unreliable and inadequate in patients with low CO, hypotension, dysrhythmias, significant edema, or systemic vasoconstriction.

Central Venous or Intracardiac Pressure Monitoring

Pressures also can be measured in the cardiac chambers or in the pulmonary vasculature. However, the necessity for intravascular or intracardiac lines should always be carefully considered, and they should be removed as soon as the clinical condition permits. The placement of relatively large catheters in small vessels for prolonged periods carries a risk of thrombosis and systemic thromboembolism.

Central venous access affords the opportunity to measure central venous pressure (CVP), deliver drugs or high osmolarity nutritional solutions, and repeatedly sample blood to monitor venous O_2 saturations and for other laboratory studies. Intraarterial lines offer the opportunity to continuously monitor arterial pressure and for intermittent blood gas analysis.

Intravascular pressures provide information about ventricular preload and afterload. RV preload is assessed by the CVP. The CVP is determined by a variety of factors, including patient age, preoperative status (i.e., a patient with RV hypertrophy and increased RA pressure), cardiac performance, intrathoracic pressure, blood volume, vasopressor therapy, and status of the pericardium. The CVP *a wave* reflects atrial contraction and the *v wave* reflects atrial filling. Serial measurements of CVP are frequently used to evaluate the response to fluid administration. RV afterload can be assessed using a PA catheter. This catheter is particularly important for monitoring pulmonary artery pressure and therapeutic response to vasodilators in patients with elevated PVR. The PA wedge pressure reflects LA pressure (in the absence of pulmonary vein stenosis). In the postoperative cardiac patient, a direct LA line can be placed to directly assess LV preload. LV afterload is assessed by measurement of SAP, provided no LV outflow tract obstruction is present.

Assessing Variables that Affect the Quantity of Therapy

If it is important to take into account the QOT needed to secure adequate tissue perfusion, it follows that one would like to assess the variables that affect the QOT. Table 22-1 summarizes the effect of abnormalities of cardiovascular and pulmonary function on QOT. What follows is a brief description of how these cardiovascular variables may be assessed in the critical care unit.

Ventricular Systolic Function

Precise measurement of ventricular systolic function is difficult,[32] especially in the critical care setting. A commonly used surrogate is the echocardiographic demonstration of ventricular wall excursion/shortening. LV shortening and ejection fractions can be measured using echocardiography with

Table 22–1 Cardiovascular Function and Quantity of Therapy

Cardiac System Variable	Impact on QOT
CARDIAC FUNCTION	
↓ Ventricular systolic function	↑ Filling pressure, ↑ inotropic/pressor support
↓ Ventricular diastolic function	↑ Filling pressure, ↑ pressor support
Abnormal rhythm	↑ Filling pressure, ↑ inotropic/pressor support
Intracardiac structural lesions (↓ efficiency)	↑ Filling pressure, ↑ inotropic/pressor support
Single ventricle with A-P shunt (↓ efficiency)	↑ Filling pressure, ↑ inotropic/pressor support
PERIPHERAL VASCULATURE	
↑ SVR	↑ Ventricular work → ↑ filling pressure, ↑ inotropic/pressor support
↓ SVR	↑ Filling pressure, ↑ inotropic/pressor support
↑ PVR Two ventricles	↑ Ventricular work → ↑ filling pressure, ↑ inotropic/pressor support
Aortopulmonary shunt	↓ PBF → ↓ O_2 → ↑ filling pressure, ↑ inotropic/pressor support
Bidirectional Glenn	↑ SVC pressure
Fontan	↑ filling pressure, ↑ inotropic/pressor support
VASCULAR FUNCTION	
"Leaky" vascular bed → edema → volume infusion → edema	↑ Filling pressure, ↑ inotropic/pressor support
PULMONARY FUNCTION	
↓ Lung compliance, ↓ gas exchange	↑ Airway pressure → ↓ venous return → ↑ systemic venous pressure, barotrauma

reasonable accuracy, but these variables are influenced by preload and afterload and by inotropic conditions. RV morphology makes echocardiographic measurement of systolic function even more problematic, despite a variety of described techniques to assess this variable.[33] For either ventricle, most often one resorts to a qualitative assessment of ventricular wall excursion as a crude estimate of systolic function. Although cardiac magnetic resonance angiography/magnetic resonance imaging can accurately measure LV and RV ejection fraction, it often is of limited practical utility in the critically ill pediatric patient.

Ventricular Diastolic Function

Ventricular diastolic function also is very difficult to measure precisely. In the critical care unit, diastolic dysfunction is usually manifested as a need for increased filling pressures for a given magnitude of ventricular output. Echocardiography sometimes will demonstrate an apparently underfilled ventricle despite adequate or high filling pressures, but most often a lack of compliance is inferred from high filling pressures alone. Echocardiographic measures of ventricular compliance exist, but many clinicians have found them to be of limited practical value. It is important to emphasize that *transmural filling pressure*, not atrial pressure per se, is what determines diastolic filling; elevated pericardial or intrathoracic pressure will reduce ventricular filling for any given atrial pressure.[34]

Rhythm Disturbance

A variety of abnormal rhythms can decrease systemic perfusion and therefore lead to increased QOT. A surface electrocardiogram may be sufficient to delineate the type and mechanism of an arrhythmia; however, especially with tachycardia, all too often one cannot clearly discriminate P waves from the T and QRS deflections. The use of atrial leads in conjunction with limb leads can be exceedingly helpful for both diagnosing and treating arrhythmias in postoperative patients. Alternatively esophageal electrodes sometimes can be helpful, although they are somewhat cumbersome to use (and cannot always effect atrial capture). It is important to frequently and carefully re-assess the rhythm, because significant changes (e.g., from sinus rhythm to junctional ectopic tachycardia) may escape casual detection.

Abnormal Systemic Vascular Resistance

Abnormal systemic vascular resistance is determined by the following equation:

$$SVR = (SAP - CVP) / CO$$

where *SAP* is mean systemic arterial pressure (mm Hg), *CVP* is mean central venous pressure (mm Hg), and *CO* is cardiac output, usually indexed to surface area (L/min/m^2).

Increased SVR can be useful when CO is insufficient for adequate systemic perfusion pressure with normal SVR. On the other hand, SVR increased beyond that needed for adequate SAP increases systemic ventricular afterload and may therefore negatively affect CO.[35] For reasons discussed in the following section on single ventricle physiology, increased SVR also may result in excess PBF in patients with an aortopulmonary shunt. Finally, increased SAP in a newly postoperative patient may contribute to excessive bleeding. In contrast, low SVR can cause systemic hypotension despite adequate or supra-normal CO. Anecdotal observations and some published information indicate that low SVR may occur after cardiac surgery, as well as with other systemic illnesses (e.g., sepsis).

As previously noted, because CO is infrequently measured in pediatric intensive care units, SVR is most commonly inferred from observation of cutaneous perfusion and SAP. Indeed, it is important to evaluate systemic hypotension in the context of cutaneous perfusion (brisk capillary refill suggests low SVR), because rational therapy for decreased SVR with adequate CO (vasopressor support) is quite different from that useful for hypotension due to inadequate CO.

Increased Pulmonary Vascular Resistance

The clinical consequences of increased PVR are directly related to the specific cardiac anatomy and physiology. With two separate ventricles, high PVR can reduce systolic and diastolic

function of the pulmonary ventricle and limit its output. In patients with a physiologically large aortopulmonary shunt, increased PVR, up to a point, can be useful because it reduces what would otherwise be excessive PBF. On the other hand, if PVR is too high, or in the setting of an excessively restrictive aortopulmonary shunt, inadequate PBF results. With a bidirectional Glenn circulation, elevated PVR may result in upper body congestion and hypoxemia. With a Fontan circulation, high systemic venous pressure, low CO, and hypoxemia (if a fenestration is present) may occur.

In patients with a structurally normal cardiovascular system, measuring PVR is analogous to measurement of SVR and is subject to the same practical difficulties. Echocardiographic estimation of RV pressure is a useful surrogate, using a tricuspid regurgitant jet, pulmonary regurgitant jet, or interventricular septal position. Unfortunately, in the absence of significant tricuspid regurgitation (or another defect that allows a pressure gradient to be measured between the right ventricle and a chamber of known pressure), echocardiographic estimation of RV pressure is crude.

For patients with an aortopulmonary shunt, PVR is rarely measured in the intensive care unit; determining PBF requires measuring VO_2 (an assumed VO_2 is questionable because it is so variable[9]), pulmonary arterial O_2 saturation, and pulmonary venous O_2 saturation. Because pulmonary venous catheters are rarely used, pulmonary venous O_2 saturations are usually assumed; however, this is a potential source of significant error, because these saturations are variable and unpredictable.[36] Most important, pulmonary artery pressure is essentially never measured in the critical care unit in patients with shunts. For these patients, even estimating PVR is problematic because many variables (e.g., PVR, systemic blood pressure, PBF and CO, hematocrit, and VO_2) influence the most obvious manifestation of increased PVR, low systemic arterial O_2 saturation. Circumstantial data may be used to infer that PVR is not elevated in hypoxemic patients with an aortopulmonary shunt; for example, echocardiographic demonstration of narrowing of the shunt suggests that increased PVR is likely not the cause of the hypoxemia. Alternatively, an increase in systemic arterial O_2 saturation with inhaled nitric oxide also would suggest that baseline PVR is increased.

Measuring PBF in patients with a cavopulmonary palliation (e.g., bidirectional Glenn, hemi-Fontan, and Fontan) also can be done using the Fick method (thermodilution cannot be used to measure PBF because of inadequate mixing of the cold indicator in the systemic venous pathway). From a practical standpoint, increased PVR in this setting often is inferred from high systemic venous pathway pressures (superior vena caval pressures in a bidirectional Glenn patient), taking into consideration possible anatomic obstruction in the superior vena cava, pulmonary arteries, or pulmonary veins or increased systemic ventricular end-diastolic pressures.

Inefficient Circulation

The most important fundamental ways that structural defects can result in an inefficient circulation in patients with cardiac structural lesions are: (1) increased ventricular afterload (e.g., RV or LV outflow tract obstruction), (2) increased ventricular volume load (e.g., ventricular septal defect and atrioventricular valve regurgitation), (3) impaired ventricular filling (e.g., atrioventricular valve stenosis), (4) reduced PBF with shunting into the systemic circulation, (5) mixing of pulmonary and systemic venous blood, and (6) D-transposition of the great arteries physiology (i.e., PVR predominantly directed to the PA and SVR predominantly directed to the aorta). Impaired coronary perfusion resulting in ventricular ischemia is perhaps not, conceptually, a problem of efficiency but a structural lesion that needs to be considered. Many patients have some combination of these lesions. It is beyond the scope of this chapter to discuss the evaluation of cardiac patients relative to structural lesions and their impact on DO_2, systemic perfusion pressure, and QOT. Suffice it to say that it is exceedingly important that the anatomy and associated physiology of patients with cardiac malformations be very well defined. Echocardiography is the single most useful modality for delineating cardiac structure (and often even physiology) in the critical care unit. Cardiac catheterization and angiography remain important diagnostic and therapeutic tools, and magnetic resonance imaging and computed tomography are sometimes helpful.

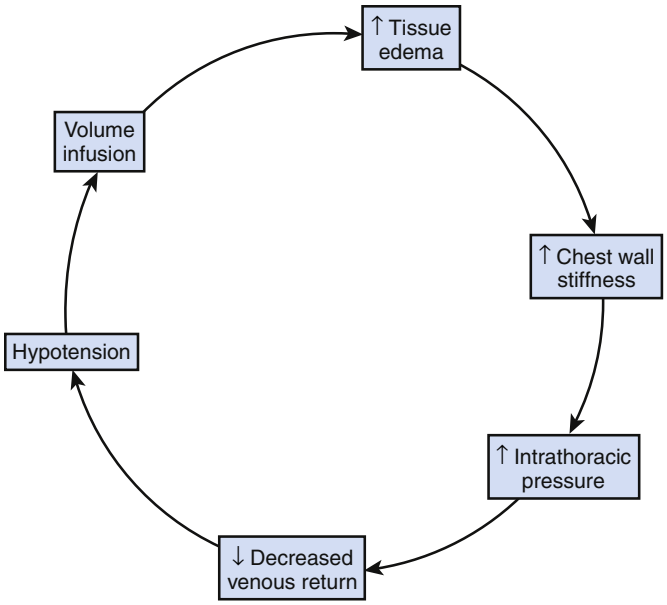

Figure 22–1. Flow diagram.

Vascular Integrity

By vascular integrity we refer to the ability of the vascular (mostly microvascular) bed to keep fluid where it mostly belongs—in the intravascular space. Leaky blood vessels result in organ, chest wall, and peripheral edema and fluid in the thoracic and abdominal cavities. This situation is exacerbated by high CVP and tends to be self-perpetuating, especially in infants (see Figure 22-1).

It is important to assess third spacing, particularly in infants, where opening the chest may help minimize the hemodynamic effects of chest wall edema in post-cardiac surgical patients. Similarly, assessment for abdominal compartment syndrome due to ascites may allow surgical or catheter-based evacuation with improved pulmonary mechanics and urine output. Also, because progressive edema, even if relatively benign early on, is likely to eventually become a significant problem, this finding should figure prominently in the clinician's overall assessment of the patient's condition.

Pulmonary Function

Pulmonary dysfunction due to edema or acute or chronic lung injury can be a major physiological liability for the obvious reasons related to impaired gas exchange. In addition, insofar as increased P_{aw} is required for adequate gas exchange, venous return to the heart may be impaired. This can be especially important in special circumstances, such as the patient after cavopulmonary palliation. Williams and colleagues[37] nicely showed the unfavorable impact of small increments of positive end-expiratory pressure in patients after Fontan palliation, which, as careful inspection of their data reveals, was mostly due to decreased venous return. Increased P_{aw}, especially if it causes overinflation of the lungs, also can increase PVR. Finally, increased P_{aw}, if applied for sufficient duration, can take a long-term toll by chronic reduction in lung function.

It is beyond the scope of this chapter to describe all available techniques for evaluating lung function. However, high P_{aw} is an important component of QOT and should lead the intensivist to consider alternatives (e.g., permissive hypercapnia or extracorporeal life support).

Physiology of the Patient with a Single Ventricle

Patients with single-ventricle physiology differ from children with two functioning ventricles in many ways. They pose several unique challenges to the pediatric intensivist. For many patients with a single ventricle, initial palliation in infancy may involve placement of an aortopulmonary (e.g., modified Blalock-Taussig) or right ventricle to PA ("Sano") connection as a source of PBF. The total output of the single-ventricle circulation is thus the sum of the pulmonary (Q_p) and systemic (Q_s) blood flows. The relative percentage of blood flow to the pulmonary and systemic circulations depends, in part, on the resistance in each vascular bed. Because PVR usually is substantially lower than SVR soon after birth, the size (diameter, length, and vessel of origin) of the aortopulmonary shunt is also a major contributor to total resistance to flow in the pulmonary circuit and hence an important determinant of Q_p/Q_s. SVR is often the single most important variable influencing Q_p[38] and the one most amenable to manipulation in the intensive care unit. In patients with a single ventricle who have complete admixture of systemic and pulmonary venous blood, arterial O_2 saturation is influenced not only by lung function (e.g., pulmonary venous O_2 saturation) but also by Q_p and myocardial function (which influences Q_s and, hence, mixed venous O_2 saturation) (Figures 22-2 and 22-3).

Computer modeling of shunt-dependent single-ventricle physiology[31] suggests that a $Q_p/Q_s \sim 1.0$ is ideal for optimizing systemic O_2 availability for a given pulmonary venous O_2 saturation, CO, and VO_2. The arterial O_2 saturation, considered in isolation, is a very poor indicator of Q_p/Q_s, because a low mixed venous O_2 saturation will depress arterial O_2 saturation, even in patients with a high Q_p/Q_s. Accurately measuring Q_p/Q_s, which equals systemic arterial O_2 saturation minus systemic venous O_2 saturation divided by pulmonary venous O_2 saturation minus pulmonary arterial O_2 saturation, requires determining O_2 saturation in blood in the proximal superior vena cava (SVC), as distinct from RA or inferior vena cava, and is subject to the previously noted variability and unpredictability of pulmonary venous O_2 saturations. That said, estimating Q_p/Q_s using the SVC O_2 saturation (as mixed venous) and the arterial O_2 saturation

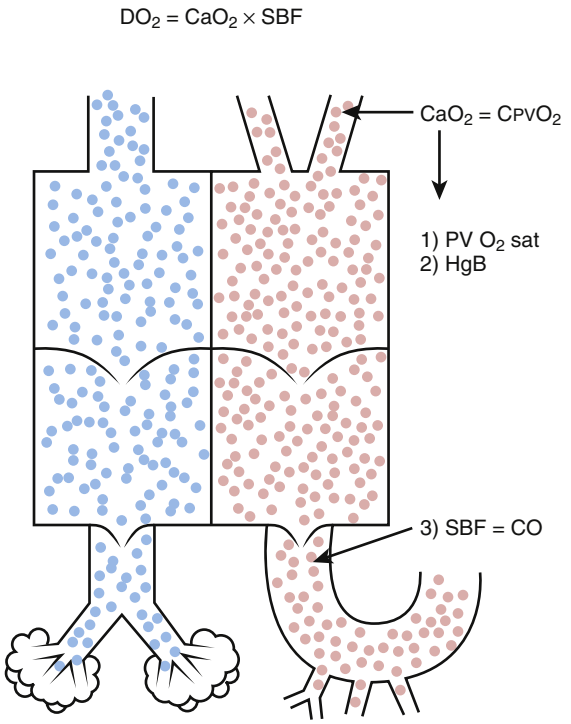

Figure 22–2. Cartoon depicting the variables that determine systemic oxygen delivery (DO_2) with a normal heart. Blue dots depict desaturated (systemic venous) blood and red dots depict fully saturated (pulmonary venous) blood. *CaO_2,* Systemic arterial blood O_2 content; *CO,* cardiac output; *$CpVO_2$,* pulmonary venous blood O_2 content; *HgB,* blood hemoglobin concentration; *PvO_2 sat,* pulmonary venous O_2 saturation; *SBF,* systemic blood flow. Dissolved O_2 in the blood is ignored.

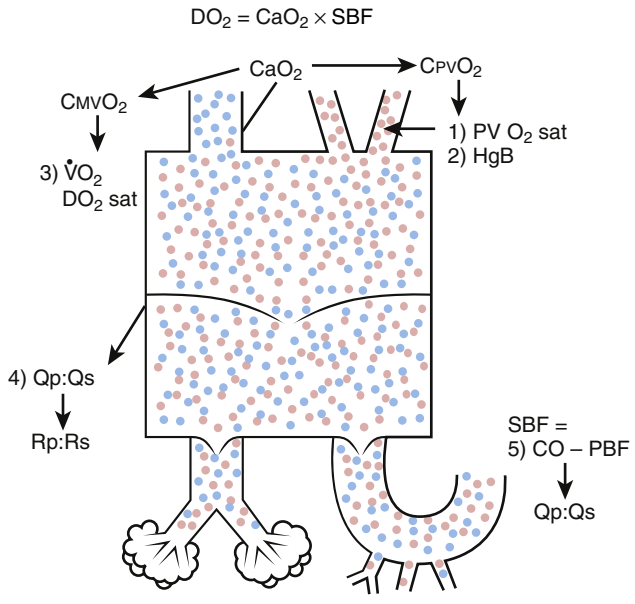

Figure 22–3. Cartoon depicting the variables that determine systemic oxygen delivery (DO_2) with a cardiac malformation resulting in complete mixing of systemic and pulmonary venous blood. Blue dots depict desaturated (systemic venous) blood and red dots depict fully saturated (pulmonary venous) blood. *CaO_2,* Systemic arterial blood O_2 content; *$CMvO_2$,* systemic venous O_2 content; *CO,* cardiac output; *$CpVO_2$,* pulmonary venous blood O_2 content; *HgB,* blood hemoglobin concentration; *PvO_2 sat,* pulmonary venous O_2 saturation; *PBF,* pulmonary blood flow; *Qp:Qs,* ratio of pulmonary to systemic blood flow; *Rp:Rs,* ratio of pulmonary to systemic vascular resistance; *SBF,* systemic blood flow; *VO_2,* total body O_2 consumption. Dissolved O_2 in the blood is ignored.

(which is also the PA O_2 saturation) and assuming the pulmonary venous O_2 saturation is very helpful in estimating whether a patient with single ventricle and an aortopulmonary shunt has appropriate (i.e., associated with optimal systemic DO_2), increased, or decreased Q_p/Q_s. However, it is important to note that Q_p/Q_s is merely a number when considered in isolation. It must be placed into the context of the patient's overall status, considering the parameters previously outlined for assessing systemic DO_2. In particular, in patients following single-ventricle palliation, a progressive decline in the serum lactate concentration (regardless of the initial postoperative concentration) is a fairly sensitive and specific marker for early survival. In contrast, rising lactate levels is generally a robust predictor of early postoperative cardiovascular collapse or need for mechanical support unless therapy can improve the hemodynamic picture.[15]

It should be noted that the physiology is somewhat different in patients with two ventricles and an aortopulmonary shunt (e.g., tetralogy of Fallot with severe RV outflow tract obstruction and a modified Blalock-Taussig shunt). Because PBF usually is made up of both systemic arterial blood and systemic venous blood, arterial O_2 saturation is higher for a given amount of PBF and cannot be calculated using systemic arterial O_2 saturation as the PAO_2 saturation.

Although the cardiopulmonary physiology of patients with bidirectional Glenn palliation differs somewhat from that of others (e.g., the apparent paradoxical relationship between alveolar ventilation and arterial O_2 saturation[39,40]), cardiovascular assessment is much the same as for other patients. Two things are worth noting, however. First, because arterial O_2 saturations often increase significantly during the first several postoperative hours after Glenn palliation, lower than desired but acceptable O_2 saturations early on do not necessarily imply inadequate palliation. Second, although some degree of upper body edema and duskiness is not unusual soon after an operation, marked upper body congestion suggests the possibility of obstruction of the SVC to PA pathway, which requires prompt evaluation. Echocardiography may be sufficient to interrogate this pathway, although angiography may be required.

Evaluation of postoperative Fontan patients is also much the same as for other postoperative cardiac patients, but because Fontan patients are particularly sensitive to factors that impede transit of blood across the lungs and into the ventricle, it is important to identify any such factors, especially remediable ones, very early on in the struggling patient. Anatomic abnormalities that might have little clinical importance in other circumstances (e.g., partial obstruction of one or more pulmonary veins) can have a marked impact on the early postoperative Fontan patient. The same goes for modestly increased PVR and mildly decreased ventricular compliance. Catheters in the central systemic veins and left atrium are useful for estimating PVR and ventricular compliance, and the previously noted measures of systemic perfusion are helpful. The sick postoperative Fontan patient may pose the perfect storm of marginal SAP, acutely elevated CVP (relative to preoperative CVP), and hypoxemia (from right-to-left shunting of highly desaturated systemic venous blood through a fenestration), all complicated by the use of inotropic agents (which increase myocardial and total body VO_2). The experienced intensivist will consider these multiple variables, including the QOT, in aggregate when evaluating the patient.

References are available online at http://www.expertconsult.com.

Echocardiography and Noninvasive Diagnosis

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PEARLS

- When congenital heart disease or myocardial dysfunction is suspected during the management of a neonate or child in the intensive care unit, echocardiography is the noninvasive diagnostic tool of choice.
- Difficulty in oxygenation may be an indication for a noninvasive study. The goals are to (1) confirm normal intracardiac anatomy, (2) assess intracardiac shunting as a cause of cyanosis, (3) assess left and right ventricular function, (4) assess right-sided heart pressures, (5) assess valve competence, and (6) look for pleural or pericardial effusion.
- In neonatal patients, it is important to assess the status of the ductus arteriosus and to measure the aorta-to-pulmonary artery pressure difference.
- In the postoperative period, information about the right ventricular pressure and pulmonary-to-systemic flow ratio facilitates manipulation of pulmonary vascular resistance.

Since the early 1980s, echocardiography (also known as ultrasonic imaging of the heart and cardiovascular system) has been at the forefront of advances in pediatric cardiology. This technology allows imaging of anatomy, assessment of ventricular function, and determination of peripheral blood flow velocities in both arteries and veins. This noninvasive technique has enhanced the assessment of fetal and neonatal congenital heart disease and facilitated the management of postoperative and other patients in the pediatric intensive care unit. Early in the history of pediatric cardiology, the electrocardiogram was the dominant tool for exploration of intracardiac anatomy, whereas chest radiography was the screening tool for signs of congestive heart failure and abnormalities of extracardiac anatomy, such as pulmonary artery size and vascularity. Now, complete anatomic and physiologic assessment can be obtained in the neonate and in the fetus at 20 weeks of gestation. Intracardiac and extracardiac anatomy can be defined in most patients, and details of the physiologic state, such as fluid balance, cardiac output, and myocardial contractility, can be determined noninvasively.

The technique of echocardiography and the practice of "echocardiology" have changed the practice of pediatric cardiology by largely replacing cardiac catheterization/angiography for the diagnosis of congenital malformations. Combined with use of prostaglandin for maintaining the patency of the ductus arteriosus, echocardiography has dramatically reduced the need for emergency cardiac catheterization in neonates. Most patients with congenital heart disease detected in the neonatal period can undergo palliative surgery without cardiac catheterization. Most definitive surgical repairs can be performed successfully without the risk of invasive studies. Pulsed, continuous-wave, color, and tissue Doppler have added important capabilities for anatomic and functional assessment. Intraoperative and postoperative management of congenital heart defects has been aided by the addition of transesophageal echocardiography (TEE). This mode can improve resolution in neonates and older patients in whom transthoracic imaging is difficult, and greatly aids the surgeon by providing immediate feedback about the quality of the repair prior to separation from the heart-lung machine. Higher-resolution imaging systems continue to evolve. Multielement transducer technology and advances in high-speed computing, three-dimensional real-time imaging, color Doppler, and tissue Doppler have facilitated the assessment of systolic and diastolic function of the myocardium.[1] This chapter focuses on the detection of congenital heart disease in pediatric patients presenting with cardiopulmonary compromise at any age and illustrates the use of TEE for physiologic assessment and management.

Diagnosis of Congenital Heart Disease

Comprehensive analysis of cardiovascular anatomy requires a step-by-step segmental approach. In certain complex congenital malformations, portions of the heart may be absent or malpositioned. Delineation of cardiac anatomy may require that data obtained from several echocardiographic windows be combined. A complete, step-by-step approach to cardiac diagnosis includes the diagnosis of atrial situs diagnosis; identification of the chambers and their interconnections; and systematic assessment of valves, septa, coronaries, systemic and pulmonary veins, and aortic anatomy. Imaging of the thymus and diaphragm is part of the detailed echocardiographic examination.

The segmental approach is based on the principle that all aspects of abnormal cardiovascular morphology can be

broken down into discrete, mutually exclusive descriptors, allowing unambiguous delineation of any complex congenital malformation. The schema must include information on the presence, position, and connection of each cardiac segment. Classically, three segments have been recognized: atria, ventricles, and great arteries. By describing the anatomic segments and indicating the normality or abnormality of each, a complete description of the cardiac anatomy is possible. It now is possible to code cardiac anatomic abnormalities by segmental analysis.[2]

Cardiac Function Assessment

Echocardiography is a tomographic anatomic tool, but it also provides dynamic information about cardiac function and structure. Observations about the cardiac walls, their movement, thickness, and degrees of shortening and thickening can be extremely useful in determining segmental and global cardiac function. In general, the shortening fraction of the left ventricle should be at least 28% (end-diastolic minus end-systolic divided by end-diastolic dimension), and the walls of the left ventricle should move inward symmetrically.

Doppler echocardiography can provide functional information that is not available by any other method. Pulsed Doppler can interrogate a site in the circulation and measure the direction and speed of blood flow in systole and diastole. For example, sampling in the aorta allows comparison of upper and lower body resistances to blood flow by revealing the direction of flow in systole and diastole. The structure and function of the cardiac valves can be determined, perhaps the most powerful application of echocardiography. For example, atrioventricular (AV) valve regurgitation can be diagnosed and its severity, which depends on many technical and physiologic factors, can be estimated. In addition to visualizing a ventricular septal defect (VSD), the jet of a left-to-right shunt can be detected by pulsed Doppler, with the pressure gradient quantified by continuous-wave Doppler (using the simplified Bernoulli equation: Pressure gradient = 4V2, where *V* is peak velocity), and the defect spatially localized by color Doppler. Using the continuity equation and the proximal isovelocity surface area (PISA) concept, flow area and volume can be calculated in left-to-right shunts, and the regurgitant volume and area can be calculated in AV valve regurgitation. Pulmonary artery pressure often can be estimated using the peak velocity of the tricuspid regurgitation jet, and the severity of semilunar stenosis or coarctation can be estimated using the peak and mean gradients. This hemodynamic information can be integrated into the segmental description using the anatomic segment as the finding and the functional aspect as the modifier. For example, the morphologic mitral valve is an anatomic site and location, for which regurgitation might be a modifier. This step-by-step approach to diagnosis answers specific questions about cardiac function and screens for congenital and acquired abnormalities.[3,4]

Structure-Oriented Approach

Adult-oriented, two-dimensional echocardiographic reports usually are based on standard views of the cardiac anatomy that are highly reproducible. The investigators describe the appearance of a given cardiac lesion as seen on a standard parasternal, apical, or subcostal scan. However, this approach can lead to diagnostic errors when applied to congenital heart disease.[5] For example, a scan of an aortopulmonary window from the right ventricular outflow tract can simulate the origin of the aorta from the right ventricle (i.e., transposition of the great arteries). In congenital heart disease, the various views must be integrated, scanning from one echocardiographic window to another to obtain a complete anatomic examination. Although the echocardiographic examiner with experience learns to identify the normal appearances of the heart without congenital defects from various echocardiographic windows, a structure-oriented or anatomic approach always is superior to an approach based on standardized views.

Achieving high sensitivity in the detection of congenital heart disease requires a compulsive approach in order to locate rare anatomic variations that may be important. For example, coronary artery anomalies, such as a coronary originating from the pulmonary artery, can be reliably detected using a standardized approach to defining the origins and courses of the coronary branches.[6]

Segmental Analysis: Situs Diagnosis

Determination of cardiac position and atrial-visceral situs is a standard portion of the echocardiographic assessment of congenital heart disease and is the foundation of the segmental approach. Atrial situs and atrial morphology are diagnosed together, and four possibilities exist: solitus (normal), inversus, and heterotaxy that may be right atrial isomerism or left atrial isomerism. For example, for situs solitus, the morphologic right atrium is on the right and the morphologic left atrium is on the left. Abnormal atrial situs and cardiac malposition, such as dextrocardia, frequently are associated. Both can be diagnosed by obtaining a short-axis scan of the abdomen, identifying the spine and the inferior vena cava and the descending aorta. The location of the cardiac apex is important for later scanning from the apex. Subcostal scanning above the diaphragm immediately shows the position of the cardiac apex. From this scan below the diaphragm, the position of the inferior vena cava and aorta can usually be identified, and their location with respect to the spine identifies the situs (Figure 23-1).

The descending aorta and inferior vena cava are oriented symmetrically with respect to one another, with the inferior vena cava to the right in situs solitus and to the left in situs inversus. In right atrial isomerism, the aorta and inferior cava run together on either side of the spine, with the cava anterior. A venous structure that courses behind the aorta and does not enter the heart suggests azygos continuation of the inferior vena cava, which is associated with left atrial isomerism. These patients usually have separate, anomalous hepatic venous connections to the heart. Occasionally, atrial appendage morphology can be identified and the diagnosis of atrial situs confirmed directly. A broad-based atrial appendage usually is a morphologic right one, and a narrow-based appendage is a morphologic left one. Symmetrical appendages suggest atrial isomerism. Situs diagnosis is important clinically for the care of the intensive care patient. Complex congenital malformations occur predictably with right and left isomerism, and asplenia (associated with right atrial isomerism) may place the child at risk for recurrent or persistent infection. Left isomerism is associated with a high rate of gastrointestinal obstruction after birth.

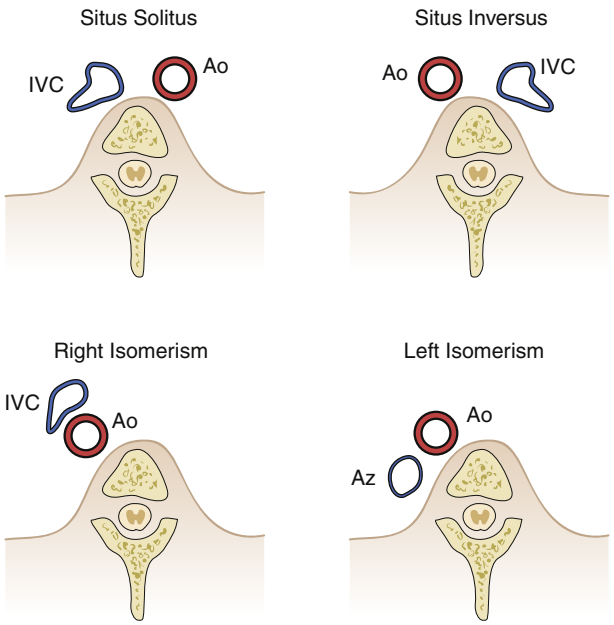

Figure 23–1. Situs by echocardiography. Situs solitus is normal, and the aorta (*Ao*) and inferior vena cava (*IVC*) are symmetrically positioned adjacent to the spine. In situs inversus, there is a mirror image relationship. In right atrial isomerism, the IVC and Ao run together on either side of the spine. In left isomerism, there is azygos continuation of the IVC (*Az*) located retroperitoneally with the Ao.

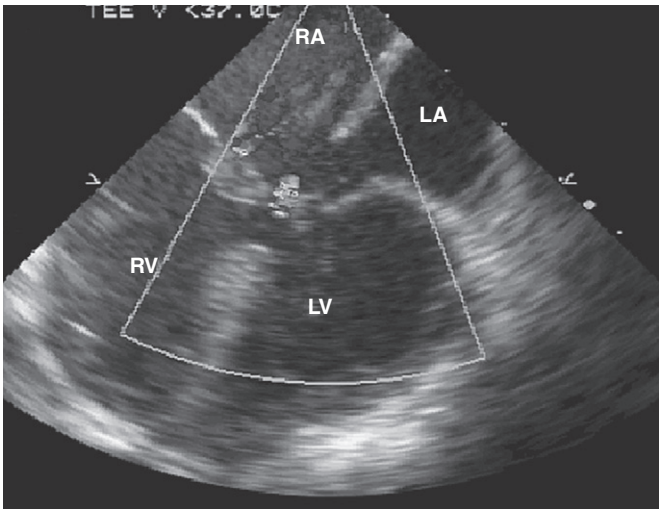

Figure 23–2. Atrioventricular canal defect with dextrocardia. A large primum atrial septal defect and ventricular septal defect are present. Note the mitral and tricuspid valves are at the same level. *LA,* Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

Segmental Analysis: Atrioventricular Connection

Description of the connection of the atria and ventricles (i.e., AV connection) requires knowledge of both atrial and ventricular morphology. The echocardiographic criteria for a morphologic left ventricle include insertion of the mitral valve at the crux of the heart farther from the cardiac apex than that of the tricuspid valve, two normally placed left ventricular papillary muscles, mitral semilunar continuity, a typical elliptical, smooth septal wall, and a fishmouth appearance of a mitral valve having two commissures. In the absence of typical offsetting of the AV valves and with cardiac malposition, the trabecular pattern of the ventricles sometimes can be recognized: the smooth wall pattern of the left ventricle and the coarser, more heavily trabeculated pattern of the right ventricle. The appearance of the ventricular outflow tracts may aid in ventricular morphologic diagnosis and should be observed as part of the segmental approach. Normally, there is continuity between the mitral valve of the left ventricle and the aortic valve, but muscle of the right ventricular outflow tract separates the tricuspid and pulmonary valves. The most reliable criterion for identifying the morphologic right ventricle is tricuspid valve chordal attachments to the septum. With an atrial septal defect of the primum type, the AV valves are at the same level (Figure 23-2).

Four patterns of AV connection exist: concordant (normal); discordant; univentricular through a single inlet (tricuspid or mitral atresia), double inlet, or common inlet; and ambiguous (two ventricles with atrial isomerism). When the morphologic right atrium connects normally to the morphologic right ventricle and the left atrium connects to the left ventricle, AV concordance is present. When this connection is reversed and the morphologic right atrium connects to the morphologic left ventricle, AV connection is discordant and sometimes is referred to as ventricular inversion. Patients with these abnormalities have "corrected transposition"; they may present with complete heart block and have a high incidence of associated congenital cardiac malformations, such as VSD and pulmonary stenosis. They usually also have ventriculoarterial discordance. AV discordance occurs rarely, and in these cases the ventriculoarterial connection is normal.

If most of the AV connection is to one ventricle, the connection is univentricular through one valve (single inlet with atresia of the other valve), double inlet (two AV valves), or common inlet (common AV valve). A common inlet ventricle is part of the spectrum of AV septal defect (AV canal) in which hypoplasia of one of the ventricular chambers occurs and the AV connection is predominant to the other.

The accuracy of echocardiographic imaging in the diagnosis of AV connection is unsurpassed by other modalities. Occasionally, an inexperienced observer confuses a common inlet with a common (four-leaflet) valve with a single inlet, but this should not be a problem after experience is gained with imaging the variations of AV septal defect. Identification of the lower atrial septum unequivocally identifies the crux of the heart and points to a single inlet with atresia of the other valve. The general consensus is that echocardiography in experienced hands is the best method for assessing AV connection and abnormalities of the cardiac valves.

Segmental Analysis: Ventriculoarterial Connection

Ventriculoarterial connection is the manner in which the great arteries and semilunar valves connect to the ventricular outflow tracts. Normally, the morphologic right ventricle connects to the pulmonary valve and the morphologic left ventricle connects to the aortic valve. Four possibilities exist: concordant (normal); discordant (right ventricle to the aorta and left ventricle to the pulmonary trunk); double outlet (usually the right ventricle); and single outlet (aortic or pulmonary atresia or truncus arteriosus).

The most common type of abnormality of ventriculoarterial connection is transposition of the great arteries, in which the morphologic right ventricle gives rise to the aorta and the morphologic left ventricle gives rise to the pulmonary trunk (ventriculoarterial discordance) (Figure 23-3). To diagnose this abnormality, the great vessels must be identified. The pulmonary artery is identified by its branching pattern into left and right pulmonary arteries and ductus arteriosus, and the aorta is identified by the coronary, carotid, and subclavian arteries. Both great vessels may originate from one ventricle (usually the morphologic right ventricle), creating a double-outlet right ventricle. If the aortic or pulmonary valve is atretic, a single-outlet ventricle is the result. Another example of a single outlet is truncus arteriosus, in which a single truncal valve originates from the ventricular mass but overrides the ventricular septum. The ventriculoarterial connection is designated as a single outlet with an overriding truncal valve. In complex malformations, including right atrial isomerism with the asplenia syndrome, the AV septal defect often is associated with a double-outlet right ventricle. In cases of tetralogy of Fallot, overriding of the aortic valve is often present so that almost half of the valve annulus appears to arise from the right ventricle. Mitral aortic continuity is present and, except for the rare circumstance in which more than 50% overriding of the aortic valve occurs, the ventriculoarterial connection in tetralogy of Fallot is concordant.

Reports of neonates with abnormalities of ventriculoarterial connection and children with transposition of the great arteries show that echocardiography can accurately detect these abnormalities. A newborn with cyanosis caused by transposition can be diagnosed without catheterization, and most neonates now undergo surgery without catheterization.

Ventricular and Atrial Septa

Atrial Septum

Before birth, the atrial septum usually bows toward the morphologic left atrium because of the significant blood flow to the left side of the heart through the fossa ovalis. After birth, aneurysmal bowing of the atrial septum may be a clue to right-to-left or left-to-right intertrial shunting. Color Doppler studies have confirmed that left-to-right shunting through a patent foramen ovale is a normal finding soon after birth, particularly if the ductus arteriosus has not closed. After the infant reaches age 6 weeks, persistent shunting at the atrial level is considered abnormal if the color diameter of the shunt is greater than 4 mm.

Results of echocardiographic imaging of atrial septal defects are good. Detailed analysis of the venous connections is needed to exclude partial anomalous pulmonary venous return, for example. The triage of patients with an atrial defect requires detailed measurements of the rims of the defect to determine whether the patient is a candidate for device closure of the defect in the catheterization laboratory. The popular Amplatzer device straddles the hole, effectively closing it permanently. Another practical application of echocardiography is evaluation of the atrial defect created by balloon atrial septostomy or blade and balloon techniques.

A thin strand of tissue in what appears to be a common atrium suggests right atrial isomerism. The upper atrial

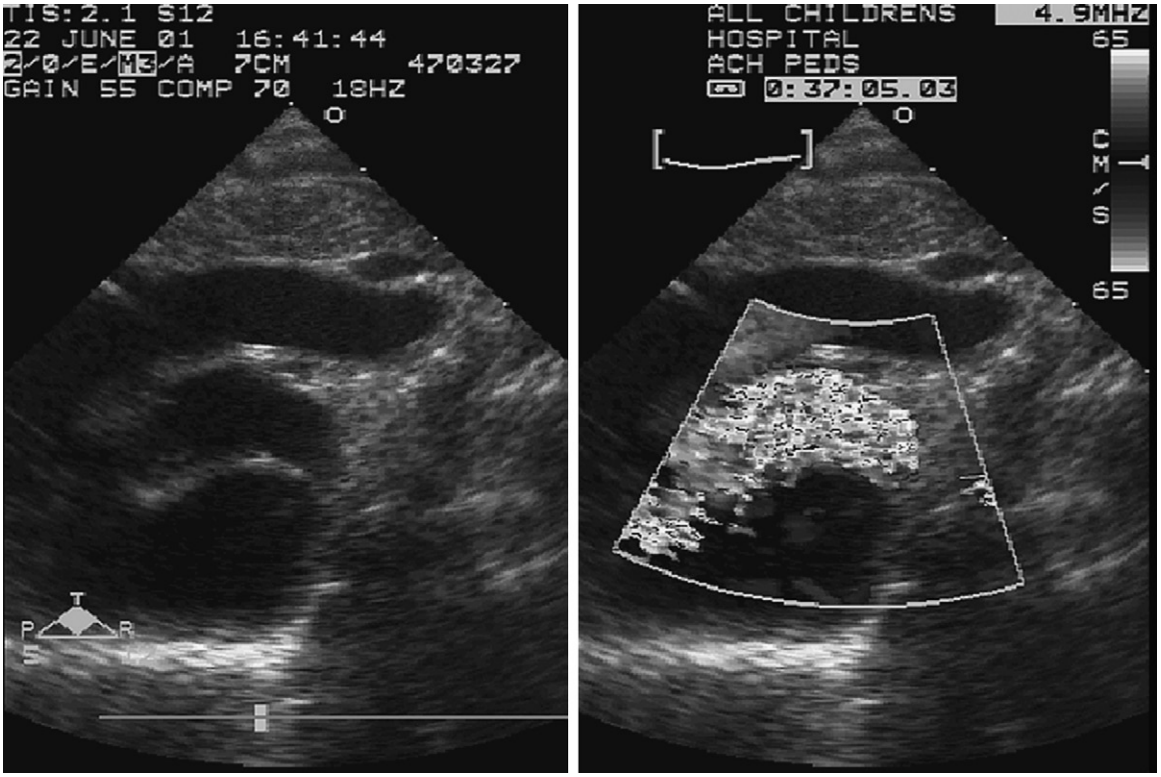

Figure 23–3. Transposition of the great arteries (discordant ventriculoarterial connection). Note the parallel exit of the anterior aorta and posterior pulmonary artery.

septum where a sinus venosus defect may occur can be difficult to evaluate in an older child, but color flow mapping has improved the accuracy of diagnosis in all forms of atrial septal defect (Figure 23-4; also see Figure 23-9).

Ventricular Septum

Defects of the ventricular septum can be analyzed using multiple tomographic imaging approaches, and defects can be separated into perimembranous, muscular, and subarterial. An inlet perimembranous defect (AV canal-type defect) can be differentiated from complete AV canal by the presence of the central fibrous body at the internal crux of the heart (Figure 23-5). Small, muscular VSDs and even a significant defect in the perimembranous region may be missed by imaging alone, but color Doppler has substantially improved the sensitivity of echocardiography in detecting muscular defects. Color may be crucial for detection of multiple VSDs. The details of complicated interventricular communications in the trabecular septum may be aided by angiography or a detailed evaluation using TEE. TEE with color Doppler appears adequate for evaluation of these patients, especially when they are older. Three-dimensional echocardiography offers the promise of improved spatial orientation and delineation of the defect(s).

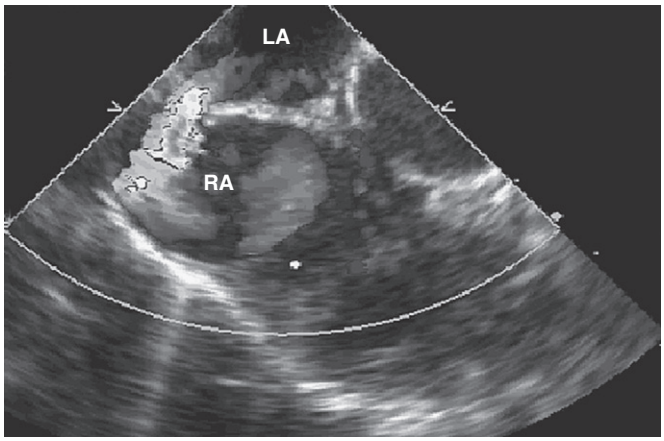

Figure 23–4. High sinus venosus atrial septal defect between the left atrium *(LA)* and right atrium *(RA)*. Left-to-right shunting is seen by color Doppler (*blue* flow away from the transducer with aliasing).

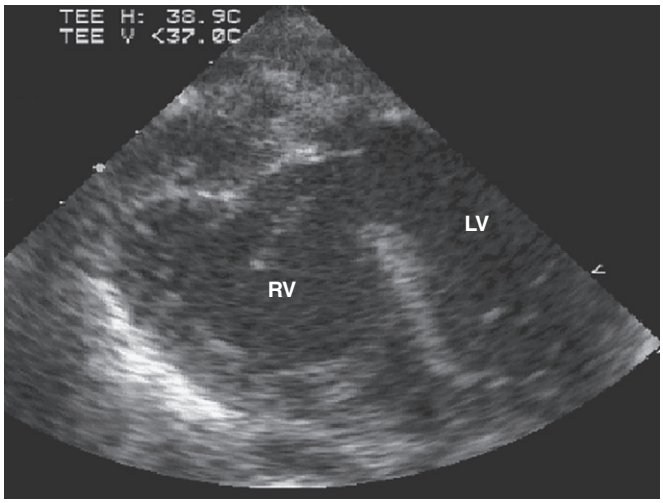

Figure 23–5. Ventricular septal defect between the left ventricle *(LV)* and right ventricle *(RV)*. The defect is in continuity with the tricuspid valve and therefore is a perimembranous defect.

Segmental Analysis: Valves

Atrioventricular Valves

A wide variety of malformations may involve the left or right AV valves. The mitral or tricuspid valve may be abnormally positioned, stenotic, regurgitant, or hypoplastic, or the valve may have a cleft or exhibit prolapse, straddling, or Ebstein malformation. The pattern of opening on real-time imaging is augmented by Doppler or M-mode functional assessment. Almost all forms of congenital abnormalities of the mitral valve can be recognized immediately by imaging alone, with the possible exception of supravalvar mitral ring, in which the ring may adhere to the valve tissue. The normal papillary muscles in this disorder differentiate it from most other congenital forms of mitral stenosis. Color flow mapping and continuous-wave Doppler more effectively evaluate the hemodynamics of AV valve stenosis than do invasive techniques. Regurgitation of AV valves can be detected with excellent sensitivity, and color Doppler can be used to grade the severity of regurgitation of the AV and semilunar valves (Figure 23-6).

Semilunar Valves

Semilunar valves (either pulmonary or aortic) are described by their age-adjusted size, cusp morphology, and pattern of opening. Because the size of a valve annulus reflects the flow through it, hypoplasia of the valve annulus is usually associated with severe stenosis. Echocardiographic imaging may detect this condition, doming of a stenotic valve, or muscular hypertrophy of infundibular stenosis. Abnormal coaptation of the semilunar valve cusps also correlates with regurgitation of the valve. Because of flow variability through a stenotic valve, a flow-independent method, known as the continuity equation, may be useful. The ratio of mean velocity at the valve to velocity below the valve is used to estimate the ratio of effective subvalvar to valvar area. As a rule of thumb, a peak velocity of stenosis that is four times the velocity below the valve is predictive of critical narrowing of functional valve area. Prosthetic valves may be present in the pediatric population and require a combination of transthoracic and transesophageal echocardiographic assessment.

Segmental Analysis: Veins

Systemic Venous Connections

Segmental diagnosis of systemic venous connection is possible by echocardiography before and after birth. Systemic venous return may be typical of the atrial situs (e.g., azygos continuation with left atrial isomerism). Systemic venous return that is abnormal in situs solitus may be normal if the situs is not solitus. Normal inferior and superior venae cavae connecting to the right atrium indicate a normal systemic venous connection to the morphologic right atrium. It is important to image the inferior vena cava connecting to the heart and its extensions into the abdomen, so that hepatic veins connecting separately to the atrium are not mistaken for it. Each of the systemic venous segments, including the right superior

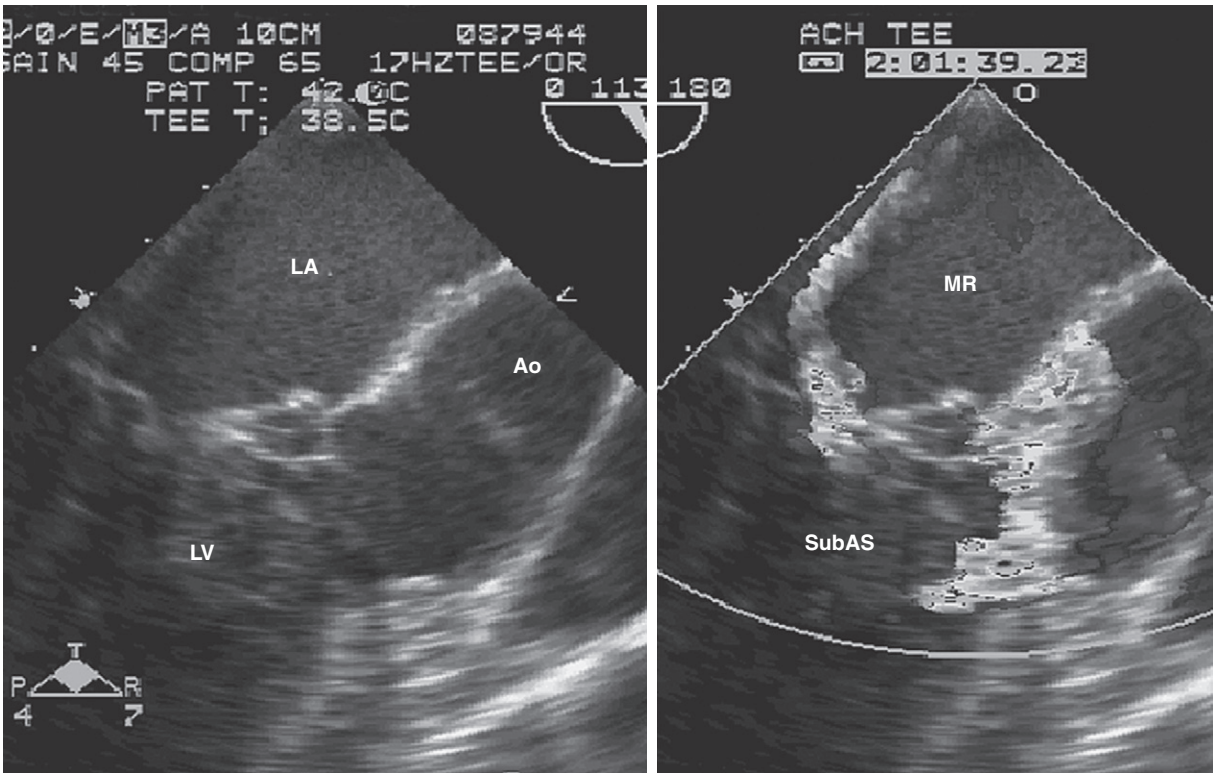

Figure 23–6. Mitral regurgitation *(MR)* between the left ventricle *(LV)* and the left atrium *(LA)* created by a subaortic membrane causing subaortic stenosis *(SubAS). Ao,* Aorta.

vena cava, left superior vena cava, inferior vena cava, coronary sinus, and hepatic veins, should be examined individually.

Systemic Venous Anomalies

A persistent left superior vena cava is present in up to 10% of patients with congenital heart disease and can be detected by echocardiography and confirmed by contrast studies. Persistent left superior vena cava is the most common venous defect, and is present in 0.5% of patients without congenital cardiac defects. Rarely does this minor defect require attention, except to document its presence in case surgical management is needed for other forms of congenital heart disease. If the persistent left superior vena cava appears to be connected to the left atrium or drains to this site because of unroofing of the coronary sinus, cyanosis results. In this case, echocardiographic contrast injection in the left arm shows immediate opacification of the left atrium. A sinus venosus atrial septal defect can direct superior vena caval drainage to the left atrium, causing mild cyanosis in an otherwise normal child.

Pulmonary Veins

Each pulmonary vein connecting to the morphologic left atrium must be imaged in a sequential fashion. A four-chamber view often reveals at least two pulmonary veins connecting to the left-sided morphologic left atrium. The suprasternal scan may demonstrate all four pulmonary veins connecting to the left atrium (the so-called "crab" view). Total anomalous pulmonary venous connection can be detected with high sensitivity, depending on the experience of the examiner. Although accurate diagnosis of isolated total anomalous pulmonary venous connection can be made in neonates and infants, the ability of any noninvasive tool to exclude an isolated partial anomalous connection of one vein has not been tested. Color Doppler can confirm pulmonary venous flow in the location where the vein is thought to be connecting. Detection of variations of pulmonary venous obstruction depends on Doppler imaging. Direct visualization of all four pulmonary veins is mandatory before corrective surgery for any defect, especially for atrial septal defect or anomalous pulmonary venous connection. Any deviation from the usual anatomy should prompt a complete angiographic study or a detailed study by magnetic resonance imaging, which in experienced hands can clarify the defect. Severely cyanotic neonates with atrial isomerism usually have abnormalities of pulmonary venous connection and may require angiography prior to palliative surgery.

Segmental Analysis: Coronary Arteries

The coronary arteries are examined in a sequential fashion to detect abnormalities. One approach is summarized in Box 23-1. The two proximal coronary arteries are identified, the proximal branching of the left is visualized, the distal course of the right and left coronaries is imaged in the AV valve grooves, and the distal anterior and posterior descending branches are imaged. If intracardiac repair is contemplated, the origin of the coronary vessels and their courses must be visualized using a segmental approach. Any coronary passing between the two semilunar valve annuli is abnormal. With the exception of aneurysm detection in Kawasaki disease or the abnormal origin of the common left or right coronary artery, the ability of ultrasonography to define abnormalities of the coronary circulation is limited. Use of TEE can significantly improve diagnosis of the intramural course of coronary arteries. In the case of fistulae, enlargement of one of the coronaries can usually

Box 23–1 Coronary Artery Segmental Analysis

- Define both proximal arteries from the aorta.
- Image the bifurcation of the left coronary.
- Exclude coronary passing between the aortic and pulmonary arteries.
- Confirm normal direction of flow in the left coronary.
- Examine the distal courses of the coronaries.

be detected, and pulmonary atresia with a significant fistula can be diagnosed. In our experience, an isolated coronary fistula can be repaired without bypass, and the entry site can be defined by color Doppler.

Anomalous origin of one or both coronaries from the pulmonary trunk can be detected with high specificity using high-frequency two-dimensional color Doppler and a low peak repetition frequency. Any electrocardiographic evidence of coronary insufficiency should prompt immediate coronary angiography if surgical intervention is contemplated. With experience, imaging studies of the coronary artery anatomy in tetralogy of Fallot and transposition should be successful. All patients with tetralogy should undergo assessment of the coronaries to define the origin of the left anterior descending branch before a right ventriculotomy is performed.

Segmental Analysis: Aorta

Segmental analysis of the aorta and congenital abnormalities that affect it includes assessment of the (1) ascending aorta, (2) aortic arch branching, (3) aortic isthmus, and (4) descending aorta. Echocardiography is highly accurate for diagnosing abnormalities of the aorta in neonates, infants, and children. Each segment of the aorta is located in a slightly different tomographic plane, requiring a sequential, segmental approach. Normal branching of the right innominate artery indicates a left aortic arch with normal branching. Branching to the left indicates a right aortic arch with mirror-image branching. A left-sided patent ductus arteriosus is the most common abnormality of the aorta. Color and continuous-wave Doppler echocardiography are indicated in every study to detect ductal shunting (Figure 23-7).

Coarctation of the aorta, which in the neonatal period has a typical appearance that includes hypoplasia of the transverse aortic arch and right ventricular enlargement, can be diagnosed by echocardiography. The typical Doppler pattern confirms the diagnosis if the ductus has closed. The presence of a posterior ledge and a transverse arch that is similar in size to the left subclavian artery makes the diagnosis. With an open ductus, the flow pattern may be mildly turbulent without gradient. In patients with a large VSD, the status of the aorta always should be investigated to exclude coarctation. In hypoplastic left heart syndrome with aortic atresia, the patent ductus arteriosus has bidirectional shunting similar to that seen in interrupted aortic arch. In hypoplastic left heart syndrome, the ascending aorta is small, with reversed flow in the arch (Figure 23-8).

In adults, the segmental analysis of the aorta is less reliable, but Doppler techniques have significantly improved the detection of aortic obstruction in cases where imaging had been poor. TEE allows identification and measurement of internal mammary branches.

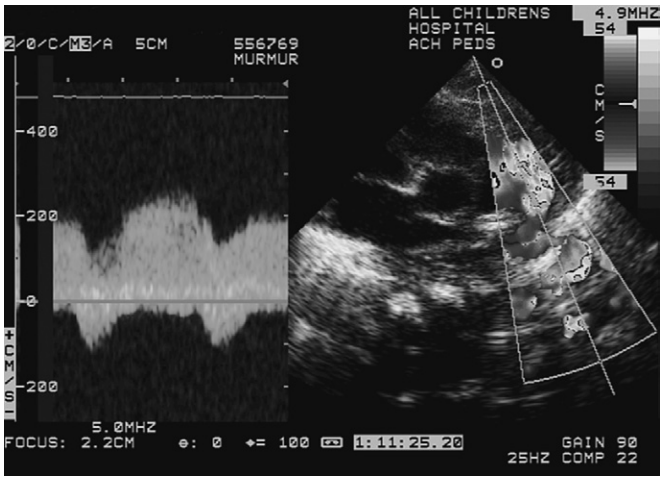

Figure 23–7. Patent ductus arteriosus in a neonate with a heart murmur. *Left,* Left-to-right shunt velocity is measured by continuous-wave Doppler as a peak of 2.3 m/s. *Right,* Left-to-right shunt into the pulmonary artery is seen by color Doppler.

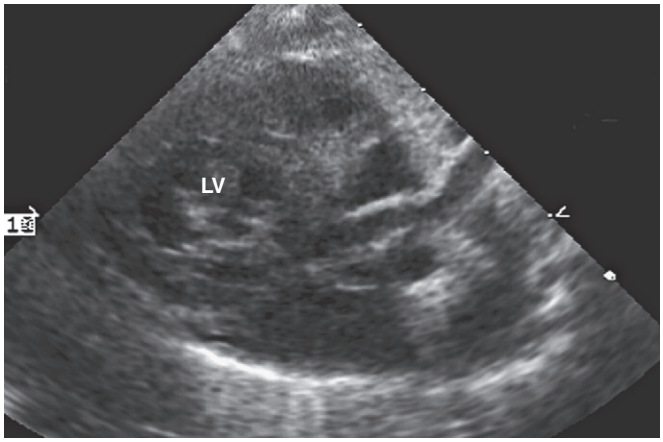

Figure 23–8. Small ascending aorta in a neonate with aortic atresia (hypoplastic left heart syndrome). Note the large remnant of left ventricle *(LV).*

Systemic Arteriovenous Fistulas

Systemic arteriovenous fistulas cause enlargement of the artery feeding the fistula and generalized enlargement of the aorta. Sequestration and hepatic and cerebral fistulas are most common. Sequestration of the lung and other fistulas causing an obligatory shunt can be detected, but require careful technique. The defect known as a *vein of Galen* malformation may simulate coarctation of aorta because of the aortic isthmus morphology created by branching of the ductal flow to the upper and lower body. Cerebral angiography is required for preoperative definition of small-vessel anatomy.

Pulmonary Arteries

The most common abnormality of the pulmonary arteries that indicates congenital heart disease is hypoplasia. The pulmonary arteries normally are confluent in the midline, and this detail of anatomy is important when planning a palliative approach to cyanotic congenital heart disease. Abnormalities of the origin or size of the pulmonary arteries may occur. In

severe right ventricular outflow tract obstruction in neonates, pulmonary artery hypoplasia is associated with a reciprocal increase in the size of the aorta, and the ratio of size of the pulmonary arteries to the aorta may be useful in diagnosing the abnormality and making surgical decisions where the ability of the pulmonary vascular bed to carry the total combined cardiac output is questionable. Assessment of the details of the distal arteries requires angiography or magnetic resonance imaging. A pulmonary arteriovenous fistula presents with cyanosis and enlargement of the pulmonary arteries and veins on echocardiography, and should be confirmed by angiography and pulmonary venous oxygen saturation measurements.

Tetralogy of Fallot with pulmonary atresia and major aortopulmonary artery collaterals may be difficult to evaluate. The neonate with this condition can be differentiated from a neonate with ductal-dependent pulmonary supply by the oxygen saturation when off prostaglandin and by imaging the ductus and poorly developed confluent pulmonary arteries. All patients with collateral arteries and multifocal pulmonary supply must undergo complete angiographic evaluation prior to surgery. Comparison of the sum of the diameters of the right and left pulmonary arteries with the diameter of the descending aorta can be useful in planning surgery.

Ventricular Function Assessment and Hemodynamics

Temporal resolution of two-dimensional echocardiography is limited by the scanning rate limits of the equipment. M-mode techniques, on the other hand, interrogate the heart at a much higher rate (800 to 1500 times per second) and allow tracking of the ventricular wall and valves at rapid rates of movement. The most useful application of M-mode echocardiography is the measurement of absolute cardiac chamber dimensions and wall thicknesses and their dynamic changes. Normal values for the systolic and diastolic dimensions of the left atrium and ventricle increase with age and body size, and comparison of right and left heart measurements to normal ranges should be part of every echocardiogram. M-mode parameters from the left ventricle can be used to estimate the wall stress of the left ventricle and its dynamic changes and the rate of relaxation. Systolic function can be estimated by measuring shortening fraction (SF): SF = (End-diastolic dimension − Systolic dimension)/End-diastolic dimension. In normovolemic patients, dimensional shortening of the left ventricular endocardial cavity can be used to estimate stroke volume.

Diastolic function can be assessed using tissue Doppler techniques and may be useful in the diagnosis of cardiac transplant rejection. Tissue Doppler is a technique by which low-velocity, high-intensity signals from the valve annuli and cardiac walls are examined to assess contraction and relaxation of the myocardium. New advances in the calculation of segmental wall strain are being studied. An easily obtained nongeometric parameter that is useful for assessment of right and left ventricular performance is the myocardial performance index. The so-called *Tei index* is the ratio of the isovolemic contraction time to the ejection time of the ventricle. This nongeometric index is useful for detecting systolic or diastolic function abnormalities when ventricular shape is not ideal, as in the morphologic right ventricle.

Valvular regurgitation allows estimation of the first derivative over time of the pressure change in the ventricle using the continuous-wave Doppler waveform. Practically, this can be calculated by measuring the time (in seconds) from the waveform at the 1 and 3 m/s points and dividing it into 32, which yields dP/dt (in millimeters of mercury per second).

Contrast Echocardiography

An ultrasonic contrast agent is a substance that stabilizes microbubbles in solution, which are large enough to reflect ultrasound but small enough that they disappear rapidly and are physiologically safe. The agent may be as simple as an injection of saline into the circulation during two-dimensional echocardiographic imaging or as complex as precision-engineered microbubbles of polysaccharide that dissolve in the circulation after injection. Advances in bubble technology allow imaging of myocardial capillary perfusion. Contrast also can be useful in defining the identity of an imaged structure. For example, a structure under the aortic arch may be confusing but can be confirmed to be the innominate vein by echocardiographic contrast injection in a left arm vein. In congenital heart disease, the major application of contrast echocardiography is in the postoperative patient with residual shunts or as a means to exclude congenital heart disease. Systemic venous injection of contrast fills the right side of the heart sequentially, and the site of residual right-to-left shunting can be defined. In the neonatal or pediatric intensive care unit, contrast injections using agitated saline can detect right-to-left interatrial shunting in cases of persistent pulmonary hypertension with difficulty oxygenating the patient.

Transesophageal Echocardiography

The indications for TEE in patients with congenital heart disease are expanding because TEE greatly aids intracardiac imaging. TEE is a technique that pediatric cardiologists cannot be without in surgical practice or in the care of the critically ill neonate or child. As with any new technique, there has been a learning curve, but the methods are now well developed and useful.[7] Use of training guidelines and frequent continuing education is desirable.[8] Biplane probes now come in many sizes so that even in neonates weighing 2.5 to 5 kg, a biplane probe can be passed safely in the operating room under general anesthesia, with minimal hemodynamic compromise. Multiplane probes for pediatric patients are improving slowly. Current technology allows use of a multiplane probe in patients weighing as little as 5 kg.

The reproducibility of quantitative measurements with TEE is good, that is, they are reproducible to within 5% for multiple examiners. TEE has special value in pediatric practice, particularly in left ventricular outflow obstruction and assessment of AV and semilunar valves. Assessment of mitral regurgitation is important after repair and re-repair of AV canal defects. TEE can identify the type and severity of mitral regurgitation and is superior to transthoracic echocardiography or cineangiography.[9,10]

Complications of TEE are more common in smaller patients. Failure to pass the probe occurs in approximately 0.8% of children with congenital heart disease, and airway obstruction occurs in approximately 1%.[11]

Echocardiography can be used during transcatheter closure for precise positioning of a device or coil. TEE also is useful

during ductal closure. Intraoperatively, ductal patency can be monitored during minimally invasive procedures.[12] For example, in neonates with critical aortic stenosis, balloon positioning can be monitored using TEE. Guidance of radiofrequency ablation catheters can be facilitated with TEE, particularly where single-ventricle anatomy is present.

Cardiac output can be estimated by TEE from the minute distance (time-velocity integral) measured in the descending aorta. Assessment of ventricular function using Doppler to estimate the first derivative of pressure in the left ventricle (dP/dt) is useful for identifying patients in need of inotropic support.[13]

The use of preoperative and postoperative TEE is increasing in the intensive care unit. Critically ill infants and children and those on assisted circulatory devices can be optimally evaluated this way. The average duration for performance of TEE includes approximately 42 minutes of technician time and 32 minutes of physician time.

Adults with congenital heart disease are best studied by TEE. Reviews of TEE use in pediatric patients suggest the technique will be increasingly utilized in the future[14,15] (Box 23-2). Combined use of TEE echocardiography and CT and MRI imaging shows comparable results in current studies.[16]

Specific Lesions

Shunts

Shunting lesions are well seen from the multiple-view possibilities offered by TEE. Shunts at the atrial level, for example, are most accurately defined by TEE. Defects at the fossa ovalis can be quantitated with regard to size and shunt. Sinus venosus defect can be readily seen, and the associated anomalies of pulmonary venous drainage detailed (Figure 23-9).

VSDs can be studied in detail, and multiple coexisting VSDs can be distinguished. The most common VSD is perimembranous VSD, which often is partially occluded by tricuspid valve tissue. The larger defects in this position may extend into either the inlet or the outlet septum. With experience, both size and position can be determined (Figure 23-10). Shunt is defined by color Doppler. Shunting through the patent ductus arteriosus can be observed from high probe positions.

Complex Heart Defects

Evaluation of complex congenital heart defects requires a segmental approach, exactly as with transthoracic imaging. For example, with a single AV valve, the situs, AV connection, and ventriculoarterial connection must be defined. With hypoplastic left heart syndrome, the function of the tricuspid valve is important, and the atrial septum should be assessed at each preoperative examination because of the possibility of late constriction. The details of AV canal defect can be defined, and the commitment of the valves and valvular function can be analyzed. With pulmonary artery atresia, a high-velocity jet from the right ventricle to right atrium is seen (Figure 23-11).

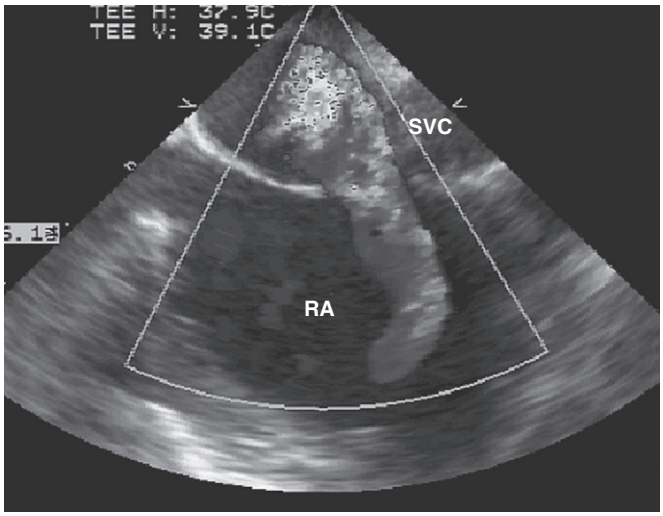

Figure 23–9. Sinus venosus atrial septal defect on sagittal scan by TEE with left-to-right shunting by color Doppler. *RA,* Right atrium; *SVC,* superior vena cava.

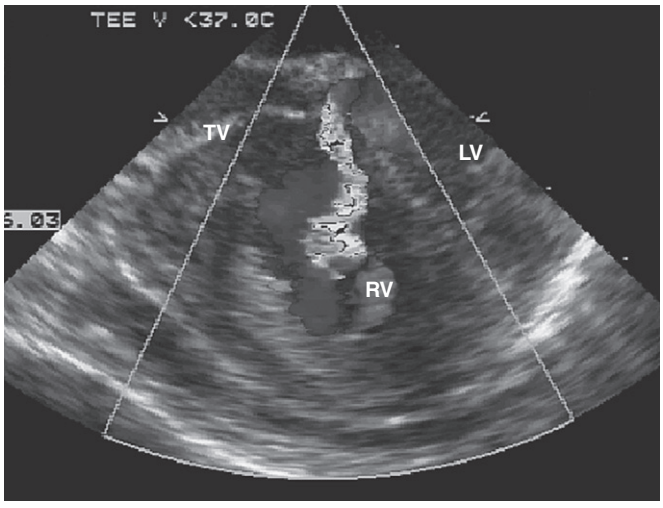

Figure 23–10. Color Doppler of shunt TEE from the left ventricle *(LV)* to the right ventricle *(RV)* through a ventricular septal defect *(VSD).* The VSD is perimembranous because of its proximity to the tricuspid valve *(TV).*

Box 23–2 Transesophageal Echocardiographic Scans and Structures Visualized

Transverse Scans

1. Inferior vena cava
2. Right atrium
3. Atrial septum
4. Right and left pulmonary veins
5. Left atrium
6. Superior vena cava
7. Ventricular inlets: tricuspid and mitral valves
8. Left ventricular outflow tract
9. Aortic valve
10. Coronary arteries

Sagittal Scans

1. Right superior vena cava
2. Right atrium and appendage
3. Atrial septum
4. Ascending aorta
5. Right ventricular outflow tract
6. Pulmonary valve
7. Pulmonary arteries
8. Aortic arch/ductus arteriosus

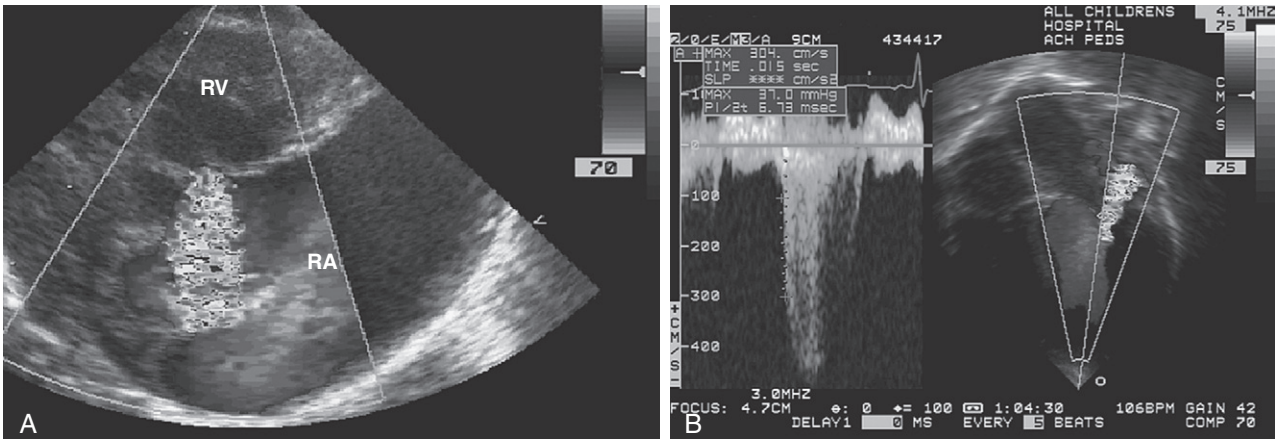

Figure 23–11. **A,** Tricuspid valve regurgitation in a neonate with pulmonary atresia with intact septum. Note enlargement of the right atrium *(RA). RV,* Right ventricle. **B,** Continuous-wave Doppler shows a very high predicted pressure in the hypoplastic right ventricle.

Left Heart Lesions

TEE can define left ventricular outflow obstruction with great accuracy. Details of the aortic valve, subvalvar region, and mitral valve can be easily seen. Three-dimensional imaging is now possible in real time, but with low resolution in the infant and child. This situation is expected to improve significantly in the future. TEE can precisely define the structure and function of the aortic valve and subaortic area. No other imaging tool performs as well in examining the fine structure of the cusps and the presence of regurgitation. After the Ross procedure, in which the pulmonary valve is transplanted into the left ventricular outflow tract, neoaortic valve function can be evaluated without difficulty.

Regurgitation of the mitral valve can be diagnosed, but assessment of the valve requires information about the mechanism of the regurgitation. A posteriorly directed jet is consistent with mitral valve prolapse. Doppler can be used to assess the hemodynamics, including dP/dt (Figure 23-12).[13]

Right Heart Lesions

In general, the right ventricular outflow tract is more difficult to evaluate by TEE because it is farther away from the transducer. Nonetheless, the details of tetralogy of Fallot can be seen and communicated to the surgeon in the operating room. The presence of complicating lesions can be defined. Accurate assessment of tetralogy of Fallot can be accomplished before and after surgery. The right ventricle to pulmonary artery gradient can be assessed using continuous-wave Doppler. The tricuspid valve can be seen well, and the details of its leaflets, chordal attachments, and function can be assessed. This observation is particularly important in infants with pulmonary atresia, intact septum, and hypoplasia of the valve. More than absolute measurements, diastolic and systolic function and structure of the valve best predict its potential for growth.

Special Considerations after Chest Trauma

Trauma to the chest can result in dissection or transection of the aorta. TEE imaging is the best technique for examining the ascending and descending portions of the aorta.

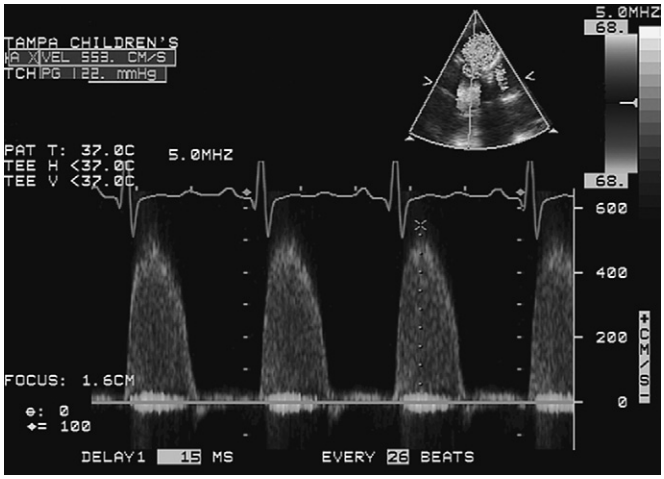

Figure 23–12. *Left,* The rate of upstroke of mitral regurgitation is quantified by measuring the time from the 1 to the 3 m/s points on the waveform, in this example 15 ms. dP/dt = 32 ∏ 15 ms ∞ 1000 = 2133 mm Hg/s, which is normal. *Right,* Mitral regurgitation from an apical view with alignment of the continuous-wave Doppler cursor.

Myocardial contusion can be recognized after edema develops in the myocardial wall, but may be suspected when cardiac enzyme elevations are disproportionate to the degree of myocardial dysfunction. Air in the chest may make transthoracic echocardiography difficult but often does not hamper a transesophageal approach.

Safety of Ultrasound

Significant adverse effects of ultrasound imaging, M-mode, or Doppler evaluation have not been reported. The potentially negative bioeffects of ultrasound can be classified as those caused by either cavitation or heating. Cavitation refers to the development of tiny, gas-filled bubbles that resonate at the ultrasonic frequency and induce neighboring particles of liquid to vibrate, potentially damaging the ultrasound-transmitting medium. Practically, the sound intensities used for echocardiography (typically 10 W/cm^2) are almost an order of magnitude less than those known to produce cavitation. Thermal effects may result from heat generated in the tissue. To

reach the thermal threshold for damage using modern ultrasonic intensities, an average intensity of 1000 W/cm^2 must be applied for hours.

Higher intensities with pulsed Doppler have the potential to cause cavitation, and concerns regarding Doppler use for first-trimester fetal assessment are being investigated.

Costs and Benefits

One major reason for the rapid proliferation of ultrasound use in pediatric practice is that the technique is noninvasive and generally painless. Ultrasound equipment is less expensive than radiographic equipment. Indications for cardiac catheterization are being reassessed. The development of echocardiography as an extension of the clinician's other assessment skills has decreased the need for catheterization, especially in neonatal patients. Echocardiography has the potential to decrease the cost of medical care for these patients.

For the most effective cardiovascular use of ultrasound, the physician should be involved in both the performance of the study and its interpretation. A more physician-intensive diagnostic process may benefit the patient but may be more expensive than comparable tests performed by technicians.

Trends

Technology is changing so rapidly that it is difficult to predict which technique will be optimal for a given lesion 5 years from now. The rapid development of nuclear magnetic resonance for imaging and spectroscopy is beginning to show potential. Rapid CT has potential to create high-quality, three-dimensional images in pediatric patients with a very short duration of exposure. These two modalities will become indispensable for assessment of extracardiac anatomy and the coronary arteries. Positron emission tomography can be used to assess myocardial perfusion, although it is rarely used in pediatric patients at this time. Emerging areas in echocardiography include the development of contrast agents, some of which allow myocardial blood flow assessment by ultrasonography; tissue characterization techniques; automated cardiac function assessment; three-dimensional real-time imaging and color Doppler display as well as stress and strain-rate assessment in three dimensions; invasive imaging probes for intracardiac imaging; transesophageal imaging in neonates for intraoperative functional assessment; and offline three-dimensional reconstruction of cardiac images from ultrasound datasets. One thing is certain, the roles of the various noninvasive diagnostic modalities used in assessing congenital heart disease will require continued reevaluation.

References are available online at http://www.expertconsult.com.

II

Chapter 24

Diagnostic and Therapeutic Cardiac Catheterization

Peter C. Laussen and Joshua Salvin

PEARLS

- The cardiac catheterization laboratory plays important diagnostic and therapeutic roles in the management of children in the pediatric intensive care unit.
- For patients with cardiac disease whose critical care course is not progressing as expected, early-exploration diagnosis of unsuspected or residual defects by cardiac catheterization often improves outcomes.
- To derive the maximum benefit from hemodynamic, angiographic, and interventional procedures, effective communication between the intensive care physician and the interventional cardiologist before, during, and after the procedure is essential.

The cardiac catheterization laboratory plays an important diagnostic and therapeutic role in the management of children in the critical care environment. Obtaining comprehensive hemodynamic data in the catheterization laboratory helps formulate and tailor management strategies. In the postoperative patient, the diagnosis of unsuspected or residual cardiac anatomic defects, using hemodynamic data and angiography obtained during cardiac catheterization, may enable therapeutic surgical or catheter-directed interventions to improve a patient's outcome. Numerous interventions can be performed during cardiac catheterization, such as balloon dilation of stenotic blood vessels, atrioventricular, and semilunar valves; device closure of intracardiac and extracardiac shunts; and radiofrequency ablation of an arrhythmic focus. The pediatric critical team must be aware of the possible benefits and limitations of catheterization procedures, and effective communication between the intensive care physician and the physician performing the procedure is crucial.

Catheterization Laboratory Environment

Cardiac catheterization laboratories usually are remote from the intensive care unit and rarely are configured to accommodate critical care personnel and equipment. Relative to patient size, the lateral and anteroposterior cameras used for imaging are in close proximity to the patient's head and neck, limiting access to the airway. A mechanical ventilator and monitors around the patient further confine the space in which the critical care team works and limit access to the patient during a procedure. In addition, the environment is darkened to facilitate viewing of images, and full monitoring, either invasive or noninvasive, must be established before the procedure begins. Because of limited access to the patient and airway, end-tidal capnography and pulse oximetry are mandatory to ensure adequate ventilation and oxygenation during the procedure and to provide immediate detection of disconnection or dislodgment of the endotracheal tube that could inadvertently occur during movement of the catheterization table and cameras. The environment is cooler because of computer and x-ray equipment, and children may become hypothermic from conductive and convective heat loss; this is a particular problem in neonates and infants. In addition, frequent flushing of the catheters and sheaths to prevent clotting or air embolism may contribute to hypothermia. Unnecessary exposure of the child must be prevented, and convective warming blankets used where possible. Care must be taken when positioning a patient on the catheterization table because of the risk to pressure areas and of nerve traction injury. In particular, brachial plexus injury may occur when the patient's arms are positioned above the head for prolonged periods to enable better exposure for the lateral camera. To facilitate femoral vein and arterial access, the pelvis is commonly elevated from the catheterization table. This position may displace abdominal contents cephalad, restricting diaphragm excursion and increasing the risk for respiratory depression in a sedated patient.

Safe transportation of a critically ill child from the intensive care unit to the catheterization laboratory can be a significant challenge but should not be a deciding factor as to whether or not the procedure should be performed. Safe transport requires planning and multidisciplinary coordination. This process includes physician and nursing staff accompanying the patient with complete monitoring and resuscitation equipment, respiratory therapy staff to assist with ventilation and establishing mechanical ventilation in the catheterization laboratory if indicated, coordinating timing with the catheter laboratory staff to prevent needless delays, assistance with establishing adequate space for equipment and patient access in the laboratory, and correct positioning on the catheterization table to enable access for both the catheterizer and intensive care staff as necessary.

Adequate sedation and anesthesia during cardiac catheterization are essential to facilitate acquisition of meaningful hemodynamic data and to assist during interventional procedures. For the most part, hemodynamic or diagnostic catheterization procedures can be performed with the patient under sedation.[1] For many interventional procedures, sedation may be appropriate; however, for procedures that are associated with significant hemodynamic compromise or are prolonged, general anesthesia is preferable. Whatever technique is used, hemodynamic data must be attained in conditions as close to normal as possible. For accurate calculation of the intracardiac shunt, reducing the inspired oxygen concentration to room air may be necessary, although this step requires close collaboration with the catheterizer because lowering Fio_2 may be inadvisable in patients with significant desaturation and lung injury.

Hemodynamic and Oxygen Saturation Data

Hemodynamic cardiac catheterization may not be necessary when echocardiographic analysis with Doppler measurements and color flow mapping is complete and unambiguous. However, in patients with complex cardiac anatomy, severe low cardiac output state, pulmonary hypertension, severe lung injury of uncertain etiology, or with concerns for important residual anatomic lesions after cardiac surgery, physiologic data from catheterization may provide important information.[2] Catheterization allows description of the direction, magnitude, and approximate location of intracardiac and intrapulmonary shunts. Intracardiac and intravascular pressures are measured to determine the presence of obstructions and whether shunt orifices are restrictive or nonrestrictive. Pressure gradients across sites of obstruction must be considered in light of estimated cardiac output, as a small pressure gradient measured at a time of low cardiac output is misleading.

Normally, no significant change in oxygen saturation from venae cavae to pulmonary artery is observed. In the child with congenital heart disease, the superior vena cava provides the simplest mixed venous oxygen saturation. A greater than 5% to 10% increase in oxygen saturation from the superior vena cava through to the pulmonary artery suggests the presence of a left-to-right shunt at the level of the right atrium with an atrial septal defect (ASD), in the right ventricle (RV) with a ventricular septal defect (VSD), and in the pulmonary artery with a patent ductus arteriosus (PDA) or aorto-pulmonary artery collateral vessels.[3] The magnitude of the left-to-right shunt can be calculated by applying the Fick equation to the pulmonary and systemic vascular beds separately (assuming O_2 uptake and consumption are equal):

$$Qp = VO_2 / (SpvO_2 - SpaO_2)\ (Hb)\ (1.36)\ (10) \quad (1)$$

$$Qs = VO_2 / (SaO_2 - SsvcO_2)\ (Hb)\ (1.36)\ (10) \quad (2)$$

where *Qp* is pulmonary blood flow, *Qs* is systemic blood flow, Vo_2 is oxygen consumption, $Spvo_2$ is pulmonary vein saturation (which can be assumed to be 0.96 in the absence of significant pulmonary disease), $Spao_2$ is pulmonary artery saturation, Sao_2 is arterial oxygen saturation, $Ssvco_2$ is superior vena cava oxygen saturation, and *Hb* is hemoglobin. (Note that saturation data in the equations is expressed as a decimal number and not as a percentage, e.g., 98% saturation = 0.98.)

In pediatric patients, the pulmonary and systemic flows usually are indexed to body surface area:

$$CI = Qs / BSA \quad (3)$$

where *CI* is cardiac index and *BSA* is body surface area.

Thermodilution can be used to calculate the cardiac output in pediatric patients, although it is confounded by the presence of intracardiac or extracardiac shunts.[4] Although measurement of oxygen consumption is preferable[5] because assumed values are unreliable in patients with critical illness and in those requiring substantial hemodynamic support, the practical reality is that the majority of catheterization laboratories tend to assume oxygen consumption.[6] The inherent error of all calculations should always be considered, particularly with respect to flow and resistance calculations.

The pulmonary to systemic blood flow ratio (Qp/Qs) can be derived simply from the measured oxygen saturation values because all other variables cancel out (from Equations 1 and 2):

$$Qp / Qs = (SaO_2 - SsvcO_2) / (SpvO_2 - SpaO_2) \quad (4)$$

The patient whose aortic blood is fully saturated can be assumed to have no significant right-to-left intracardiac shunt. However, when a right-to-left shunt is present, oxygen saturations also should be obtained from the pulmonary veins, left atrium, and left ventricle to determine the source of desaturated blood. Pulmonary venous desaturation implies a primary pulmonary source of venous admixture (e.g., pneumonia, atelectasis, or other pulmonary disease).

Vascular resistance is calculated by the change in pressure divided by the flow (Dp/Q):

Pulmonary vascular resistance (PVR) =

$$(Mean\ PAP - Mean\ LAP) / Qp \quad (5)$$

Systemic vascular resistance (SVR) =

$$(Mean\ AoP - Mean\ SVCP) / Qs \quad (6)$$

where *PAP* is pulmonary artery pressure, *LAP* is left atrial pressure, *AoP* is aortic pressure, *SVCP* is superior vena cava pressure, *Qp* is pulmonary blood flow, and *Qs* is systemic blood flow.

Once again for pediatric patients, the vascular resistance usually is indexed to body surface area and expressed as Wood units:

$$PVR = (Mean\ PAP - Mean\ LAP)(BSA) / Qp \quad (7)$$

$$SVR = (Mean\ AoP - Mean\ SVCP)(BSA) / Qs \quad (8)$$

Assessment of Critical Illness

The cardiac catheterization laboratory can be useful in a number of situations during the management of critically ill infants and children who have structurally normal hearts (Table 24-1) or congenital heart disease. Fluoroscopy can be used to assist with placing difficult central venous or pulmonary artery lines, performing pericardiocentesis and pleurocentesis, and assessing diaphragm function.

Patients with pulmonary hypertension can benefit from investigation in the catheterization laboratory. Catheterization may help diagnose or rule out structural disease involving the pulmonary arteries or pulmonary veins, as in cases of

multiple thromboembolic disease or undiagnosed pulmonary vein stenosis. Data obtained during catheterization are important for evaluation of the response of pulmonary vasculature to vasodilator treatment, for example, with increased Fio_2 or inhaled nitric oxide.[7] Such evaluation and measurement of a specific response is important for longer-term management strategies of patients with pulmonary hypertension. In the presence of a left-to-right shunt and elevated PVR, pressure and saturation measurements often are repeated with the patient breathing 100% oxygen to assess both the reactivity of the pulmonary vascular bed and any contribution of ventilation/perfusion abnormalities to hypoxemia. If breathing 100% oxygen and inhaled nitric oxide increases pulmonary blood flow and dramatically increases Qp/Qs (with a fall in PVR), potentially reversible processes such as hypoxic pulmonary vasoconstriction may be contributing to the elevated PVR. The patient with a high, unresponsive PVR and a small left-to-right shunt may have extensive pulmonary vascular damage from the underlying lung injury or irreversible obstructive pulmonary vascular disease.

The reactivity of the pulmonary vascular bed and change in PVR are important components to the assessment of patients potentially listed for cardiac transplantation. An elevated PVR or pulmonary artery pressure is a risk factor for cardiac transplantation. PVR likely is elevated in patients with heart failure associated with left atrial hypertension. However, if PVR decreases with 100% FiO_2 or inhaled nitric oxide when these patients are tested during pretransplant catheterization, they still may be suitable candidates for cardiac transplantation.

Patients who present with severe cardiac failure because of myocarditis or idiopathic dilated cardiomyopathy or intractable dysrhythmias often require cardiac catheterization, not only for hemodynamic assessment but also for endomyocardial biopsy. Biopsies in these circumstances can be associated with significant morbidity, and treatment of the baseline condition should not be delayed until catheterization is performed.[8,9] The risk of myocardial perforation is particularly increased in infants with thin-walled ventricles, and biopsy should be reconsidered in infants with a very dilated and poorly functioning left ventricle. Patients who have a low cardiac output state associated with fulminant myocarditis are at risk for dysrhythmias during catheterization, and resuscitation resources must be immediately available, including mechanical support. The catheterization study and desire for a biopsy in an effort to establish a diagnosis must not take priority over efforts to support the circulation and maintain cardiac output.

Table 24–1 Indications for Cardiac Catheterization or Management in the Catheterization Laboratory of Pediatric Intensive Care Patients with Noncongenital Heart Disease

Diagnostic	• Hemodynamic evaluation of intracardiac and intravascular pressures and oxygen saturations • Evaluation of persistent hypoxemia: Pulmonary vein desaturation Decreased pulmonary blood flow Intracardiac right to left shunt • Cardiac output measurement • Pulmonary hypertension assessment and reactivity • Fluoroscopy: Central venous catheter position Diaphragm movement • Myocardial biopsy
Therapeutic	Pericardiocentesis Pleurocentesis Radiofrequency catheter ablation of an arrhythmogenic focus

Transcatheter Radiofrequency Ablation

Pediatric patients undergoing radiofrequency catheter ablation (RFCA) vary in age and diagnosis.[10] Ablation may be necessary in newborns or infants with persistent reentrant tachycardia or ectopic atrial tachycardia[11,12] and in older children with ectopic foci but otherwise structurally normal hearts that are refractory to or poorly controlled by conventional antiarrhythmic drugs. If an incessant dysrhythmia, particularly a supraventricular tachycardia such as ectopic atrial tachycardia or permanent junctional reciprocating tachycardia, is the primary cause of a dilated poorly contracting heart at the time of presentation, electrophysiologic study and mapping of the dysrhythmia focus may be important diagnostic steps performed in the catheterization laboratory. Elective mechanical support of the circulation with extracorporeal membrane oxygenation (ECMO) may be indicated in order to preserve hemodynamic stability during ablation.[13] Successful RFCA in this circumstance may enable recovery of ventricular function.[14]

An increasing population of patients undergoing ablation consists of those with previous surgical repair of congenital heart defects. Patients with persistent volume or pressure load on the right atrium and those who required an extensive incision and suture lines within the right atrium, such as following a Mustard, Senning, or Fontan procedure, may be at increased risk for supraventricular tachyarrhythmias (SVT) such as atrial flutter and fibrillation.[15,16] Ventricular tachyarrhythmias may develop late after repair of certain congenital heart defects, such as right ventricular outflow tract reconstruction for tetralogy of Fallot.[17]

RFCA procedures can be lengthy. Because children find it difficult to lie still for prolonged procedures, endotracheal general anesthesia is usually preferred. In addition, patients must remain immobile to prevent catheter movement at the time of ablation, because sudden patient movement may result in creation of a radiofrequency lesion at an incorrect site. For instance, if the focus is close to the atrioventricular (AV) node, inadvertent movement might displace the catheter and cause permanent AV conduction blockade.

On occasion, holding ventilation in either inspiration or expiration may be necessary to ensure adequate contact of the ablation catheter with the arrhythmic focus. For the most part, RFCA procedures are well tolerated hemodynamically and blood loss is minimal. During mapping, the focus is stimulated and the tachyarrhythmia induced. This situation may result in hypotension but usually is short-lived and can be readily converted via intracardiac pacing. If hypotension is prolonged and intracardiac conversion is unsuccessful, transthoracic cardioversion may be necessary; therefore a defibrillator should be immediately available.

Congenital Heart Disease

Although most congenital heart defects can be evaluated noninvasively by echocardiography or, more recently, by magnetic resonance imaging, further preoperative evaluation by angiography is essential in some instances to assist with surgical planning.

Patients with pulmonary atresia and intact ventricular septum (PA/IVS) require careful examination of the coronary anatomy prior to decompressing the RV either surgically or with catheterization techniques, because of the possible presence of fistulas from the RV to the coronary artery circulation.[18,19] RV to coronary artery fistulas can be seen on echocardiography, but selective right ventricular angiography and aortography, or even selective coronary angiography if necessary, are important to determine any associated coronary stenoses or atresia (RV-dependent coronary circulation).[20] Myocardial ischemia can occur if the right ventricle pressure decreases after the outflow tract is opened, leading to arrhythmia and myocardial failure. At another end of this spectrum, patients with tetralogy of Fallot and pulmonary atresia often have diminutive native pulmonary arteries. Aortopulmonary collaterals may contribute greatly to pulmonary blood flow. Angiography can delineate the exact location and anatomy of these collaterals and, if indicated, may be followed by coil occlusion of aortopulmonary collaterals that provide dual supply to the native pulmonary arteries. It is important to know the extent of collateral vessels prior to surgery and cardiopulmonary bypass because of the risk for impaired systemic perfusion from excessive runoff to the pulmonary circulation.

Patients with hypoplastic left heart syndrome with mitral stenosis and aortic atresia (MS/AA) may also be at higher risk for early mortality after stage one palliation with the Norwood procedure.[21] Analogous to the PA/IVS patient population, patients with MS/AA may have left ventricle-subepicardial coronary artery fistulae, and be at risk for inadequate myocardial protection during cardiopulmonary bypass and ischemia following stage one palliation. Preoperative coronary angiography may be warranted in this subgroup prior to surgical palliation.[22] Finally, preoperative angiography may be useful in patients with obstructed total anomalous pulmonary venous connection (TAPVC). While pulmonary venous anatomy can often be determined by noninvasive methods, palliative transcatheter approaches to relief of pulmonary venous obsruction may be lifesaving in the critically ill neonate.[23,24]

Therapeutic Interventions in the Newborn

Interventional cardiac catheterization has matured. Many specific anatomic defects can be treated in the catheterization laboratory to alleviate the need for surgical intervention.

Atrial Communication Procedures

The first therapeutic procedure performed in the catheterization laboratory for congenital heart disease was balloon atrial septostomy (BAS) in newborns diagnosed with transposition of the great arteries (TGA) with intact ventricular septum.[25] A BAS usually is needed in newborns with TGA to facilitate mixing of systemic and pulmonary venous return at the atrial level prior to the arterial switch operation. This procedure can be performed by echocardiographic guidance[26] (Figure 24-1) or in the cardiac catheterization laboratory if additional diagnostic information is required or there are potential vascular

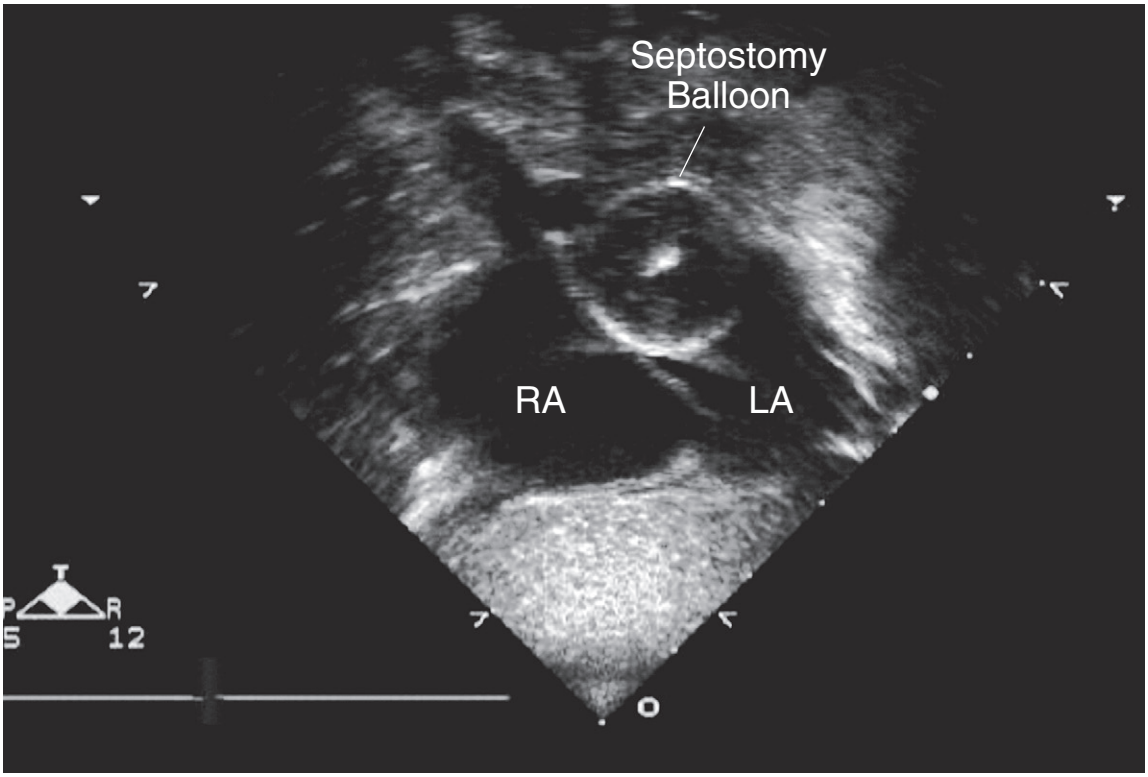

Figure 24–1. Echocardiography-guided balloon atrial septostomy. From the subcostal view, the septostomy balloon is easily seen as it inflates in the left atrium *(LA)*. ***RA,*** Right atrium.

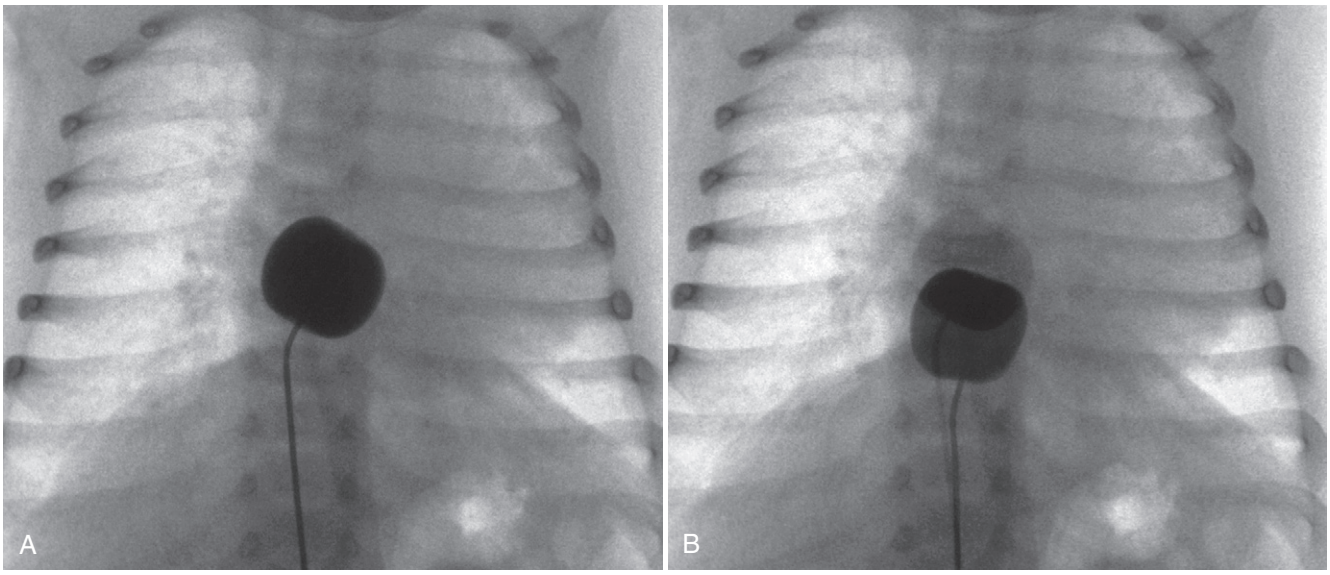

Figure 24–2. Fluoroscopy-guided balloon atrial septostomy. **A,** The balloon is inflated with diluted contrast and positioned in the left atrium. **B,** The balloon is rapidly "jerked" across the atrial septum, resulting in a tear in the septum primum and enabling complete mixing of blood in the atria.

access problems. Via either the femoral or umbilical vein, a balloon catheter is advanced across the atrial defect from right atrium to left atrium (Figure 24-2, *A*) and its position is confirmed by echocardiographic or fluoroscopic guidance. The balloon is inflated to the desired volume and jerked back to the right atrium to tear the septum primum (Figure 24-2, *B*). While it has been reported that BAS may be associated with an increased risk for embolic neurological injury, this has not been the experience at our institution and others. It is always preferable to facilitate mixing at the atrial level and reduce left atrial pressure and risk for pulmonary hypertension prior to cardiac surgery and the arterial switch procedure. The BAS can be performed under fluoroscopic or echocardiographic guidance, and whatever the mode of imaging, it is important that anticoagulation with 50 U/kg of heparin be administered prior to balloon inflation and tearing of the atrial septum.[27-29]

In some patients with a single-ventricle lesion (such as mitral atresia or hypoplastic left heart syndrome) and who also have a restrictive or near intact atrial septum, the left atrial pressure may be very high at birth, causing pulmonary edema and pulmonary artery hypertension. The physiology in this circumstance is identical to that of patients with obstructed TAPVC. Patients usually are cyanotic with a low cardiac output state, and urgent dilation of the atrial septum to lower the atrial pressure and improve mixing can be lifesaving.[30,31] It also allows the pulmonary artery pressure to decrease and pulmonary edema to resolve prior to stage 1 palliation. It is important to appreciate that the atrial septum often is thickened in these patients, which is quite different than the thin-walled restrictive foramen ovale of patients with TGA. Because of its thickness, disruption of the septum using a balloon atrial septostomy technique is usually not possible. In addition to the thickened atrial septum, the atrial cavity size usually is small, so inflating a balloon in the left atrium without causing myocardial injury or tearing a pulmonary vein may be difficult. Instead, decompression of the pulmonary atrium can be achieved with a Brockenbrough transseptal puncture (Figure 24-3, *A*), followed by an atrial septoplasty involving balloon dilation of the thickened or restrictive atrial septum and possible stent placement across the defect to maintain a gradient across the septum of 4 to 6 mm Hg (Figure 24-3, *B*). Because of the degree of cyanosis and the low cardiac output state, concurrent resuscitation with volume replacement, inotrope support, and mechanical ventilation are usually necessary during this procedure until adequate mixing is established and pulmonary veins are decompressed.

Pulmonary Balloon Valvotomy

Congenital pulmonary valve stenosis may present as a murmur heard in the newborn period. If the obstruction is mild, intervention with balloon dilation can be deferred. Newborns with critical pulmonary valve stenosis or pulmonary valve atresia have severe restriction or absence of antegrade flow across the right ventricular outflow and, as a result, have ductus arteriosus-dependent pulmonary blood flow. Balloon dilation in the catheterization laboratory is the therapeutic procedure of choice (Figure 24-4).[32,33] A balloon catheter is passed over a guidewire antegrade across the pulmonary valve, and balloon dilation, usually up to 120% size of the pulmonary valve annulus, is performed. Heart block and ventricular ectopy may occur with wire manipulation in the RV but usually are transient. Antegrade flow across the pulmonary valve may not increase significantly after balloon dilation until right ventricular compliance improves, and continuation of prostaglandin E1 (PGE1) infusion to maintain patency of the ductus arteriosus for several days following balloon dilation may be necessary. Perforation of the relatively thin right ventricular outflow tract with the guidewire is a potential complication, particularly in low-birth-weight and premature newborns.

Aortic Balloon Valvotomy

The newborn with critical valvar aortic stenosis who develops hypotension and acidosis as the ductus arteriosus closes requires resuscitation with PGE1 to restore aortic flow, plus mechanical ventilation and inotropic support to achieve stabilization before an intervention is performed. Balloon dilation

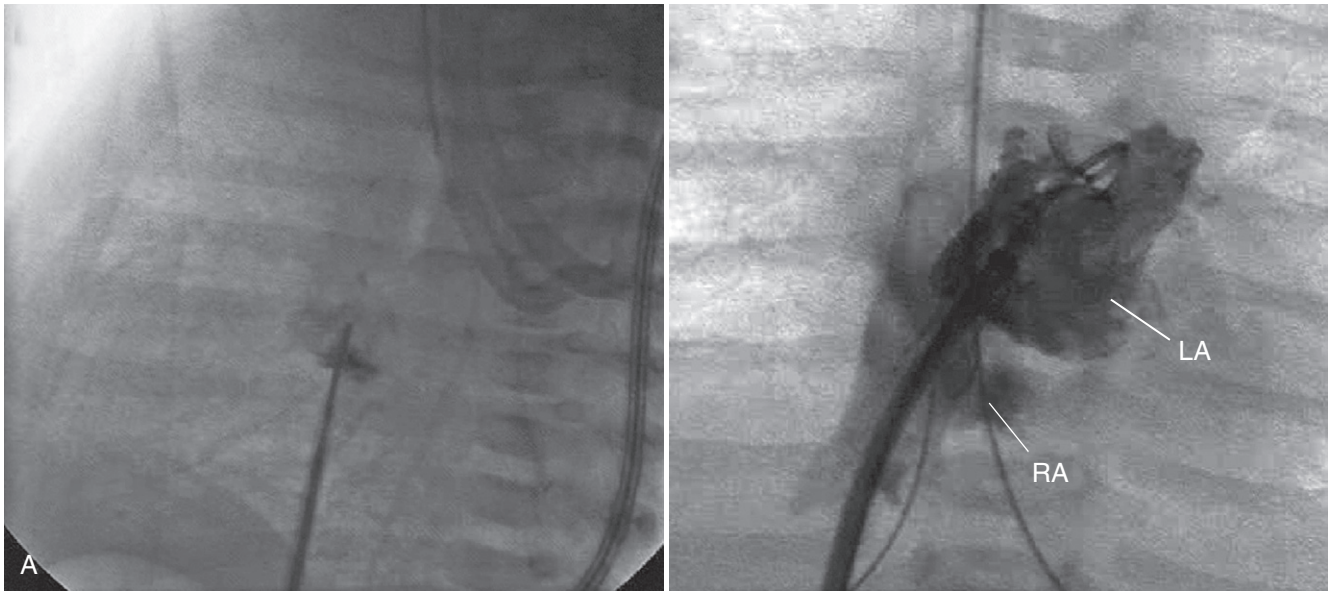

Figure 24–3. Atrial septoplasty in a newborn with restrictive atrial septum and hypoplastic left heart syndrome. **A,** Lateral view of a Brockenbrough transseptal needle introduced across the thickened atrial septum and contrast injected into the small left atrium. **B,** Anteroposterior view following stent placement across the thickened atrial septum. Contrast is seen equally in both the left atrium (*LA*) and the right atrium (*RA*).

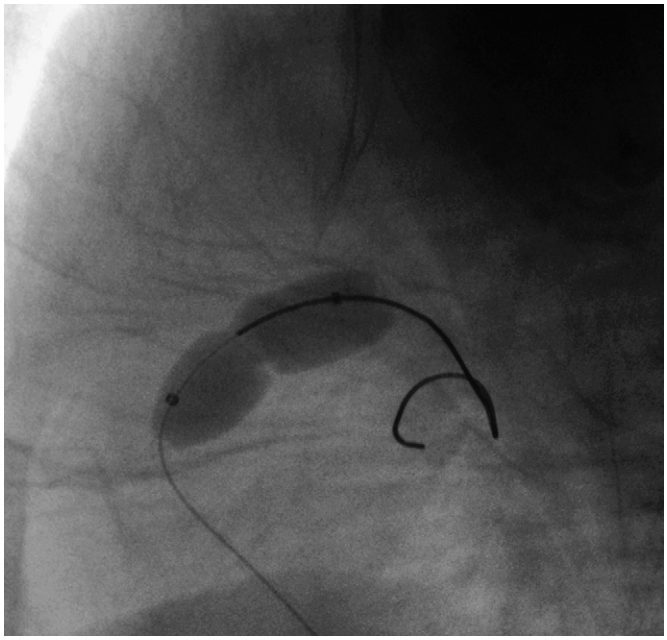

Figure 24–4. Pulmonary valvuloplasty in a newborn with severe pulmonary valve stenosis. Lateral view with balloon catheter centered across a stenotic pulmonary valve. As the balloon is inflated, a "waist" representing the stenotic valve is seen.

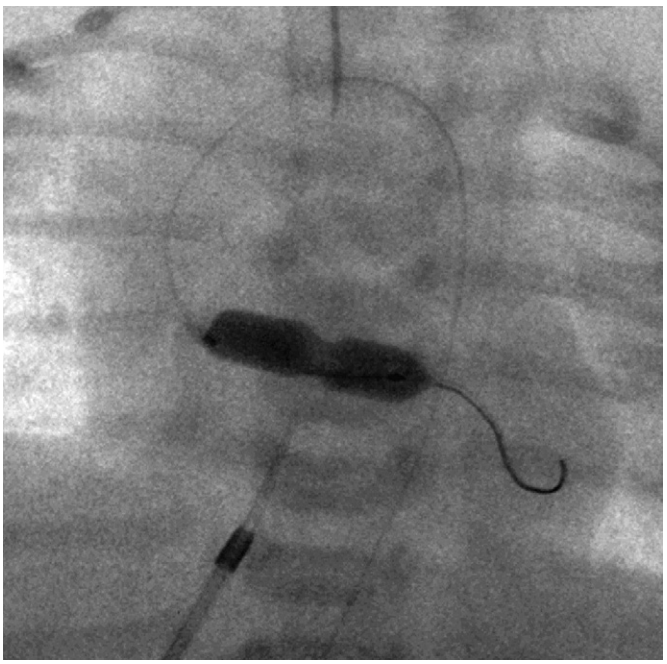

Figure 24–5. Aortic valvuloplasty in a newborn with critical aortic stenosis. Anteroposterior view with retrograde catheter course from the femoral artery. The balloon, also with the "waist" apparent, is seen being inflated across the aortic valve.

of the stenotic aortic valve during cardiac catheterization is the preferred intervention (Figure 24-5),[34] although surgical valvotomy under direct vision using cardiopulmonary bypass (CPB) is the surgical alternative. At catheterization, a guidewire is passed either retrograde (via femoral artery) or antegrade (via femoral vein) across the aortic valve. A balloon catheter is passed over the wire and serial dilations performed up to 90% to 100% size of the aortic valve annulus. The pressure gradient across the aortic valve is remeasured after each dilation, and an ascending aortogram is obtained to evaluate aortic valve regurgitation. Because of the initial minimal flow across the valve, balloon dilation of critical neonatal aortic stenosis usually is well tolerated. Despite the successful relief of obstruction, antegrade flow across the valve may not increase significantly until left ventricular compliance and function improve; therefore continuation of PGE1 infusion, mechanical ventilation, and vasoactive drugs following dilation for some days may be necessary. Until flow across the

valve increases, the residual gradient across the aortic valve will be underestimated by echocardiography, and serial studies usually are necessary to track the evolving gradient and left ventricular function. Other complications include possible mitral valve damage from a relatively stiff guidewire if an antegrade approach is used for dilation, and possibly ventricular fibrillation and an acute low cardiac output state secondary to coronary ischemia in patients with a hypertrophied ventricle.

Perioperative Interventional Procedures

A thorough understanding of the anatomy and morphology of complex congenital heart defects is essential for successful management of patients with complex congenital heart disease. This is particularly critical when establishing a diagnosis and planning surgical intervention. Important for the successful perioperative management in the intensive care unit is a thorough understanding of the pathophysiology of various defects. This understanding includes not only the preoperative pathophysiology associated with defects but also the potential alteration in pathophysiology related to surgical repair and/or development of complications in the postoperative period. As a general guide, if patients are not progressing as expected and low cardiac output persists, early cardiac catheterization should be performed to investigate and exclude the possibility of undiagnosed or residual structural defects. Despite biases to the contrary, early postoperative catheterization can be performed by an experienced catheterizer and anesthetic team with no significant increased risk of adverse events.[35,36] Transcatheter treatment of congenital cardiac defects continues to evolve and expand, and in some circumstances is effectively replacing the need for conventional intraoperative surgical procedures.[37] This experience has a significant impact on the severity and complexity of illness seen in the operating room and interventional laboratory. For example, several centers are routinely palliating hypoplastic left heart syndrome with a hybrid approach including transcatheter-based ductal and atrial septal stents along with pulmonary artery bands, with favorable intermediate stage results.[38] Transcatheter pulmonary valves have been successfully inserted in patients with right ventricular outflow tract conduit dysfunction.[39] Additional interventions now routinely performed in the catheterization laboratory include angioplasty, often combined with transcatheter placement of endovascular stents, for treatment of systemic and pulmonary arterial and venous stenoses, and device occlusion or embolization of systemic-to-pulmonary arterial communications, venous channels, fistulas, muscular VSDs, ASDs, and PDAs.

Risks and Complications

Placement of catheters in and through the heart increases the risk for dysrhythmias, perforation of the myocardium, damage to valve leaflets and chordae, cerebral vascular accidents, and air embolism. Use of radiopaque contrast material may cause an acute allergic reaction (rare in children with the use of nonionic contrast media), pulmonary hypertension, renal impairment, and myocardial depression. Blood loss may be sudden and unexpected when large-bore catheters are used or vessels are ruptured. More insidious blood loss may occur over several hours in heparinized small children or neonates because of bleeding around the catheter site or multiple aspirations and flushes of catheters. Transfusion requirements and appropriate vascular access should be continually assessed.

Arrhythmias, albeit transient, may be recurrent and even fatal if not promptly treated. Arrhythmias include catheter-induced SVTs, ventricular tachycardia, ventricular fibrillation, and occasionally complete heart block requiring temporary transvenous pacing support. On most occasions, removing the wire or catheter resolves the arrhythmia, but full resuscitation and cardioversion equipment must be available in case the arrhythmia does not resolve.

The complications of various interventional procedures are related in part to the type of procedure, but all share the risks associated with percutaneous vascular access with large catheters that course through the heart and vessels.[40-43] Table 24-2 lists the specific problems that can occur during various transcatheter procedures. Overall adverse event (AE) rates are in the range of 5% to 18%, with higher AE rates reported in interventional (20%) versus noninterventional (10%) catheterization procedures.[44] Many complications are potentially life-threatening, and successful treatment of complications depends on prompt action by critical care physicians and/or anesthesiologists cooperating closely with the interventional cardiologists who are manipulating the catheters.

Balloon Dilation of Pulmonary Arteries

Pulmonary artery balloon dilation and stent placement to relieve stenosis is a common procedure performed in the catheterization laboratory.[45] Pulmonary artery stenoses may be congenital or acquired lesions. They may be discrete, involving the main or branch pulmonary arteries, or multiple, involving distal segmental vessels. The increase in pulmonary artery pressure and fixed resistance to antegrade pulmonary blood flow may have related and deleterious consequences, which include the following:

1. An increase in the afterload on the RV, which in turn causes right ventricular hypertension. The RV can cope with a significant pressure load for some time. However, as right ventricular end-diastolic pressure increases and tricuspid regurgitation possibly develops, right atrial pressure increases and manifests as hepatomegaly, ascites, and persistent or recurrent pleural effusions.
2. Reduced antegrade flow across the pulmonary outflow, which in turn reduces preload to the left ventricle and contributes to a low cardiac output state. Further, the hypertrophy of the ventricular septum reduces the compliance of the left ventricle and increases left ventricular end-diastolic pressure.
3. An increase in right ventricular pressure and ventricular hypertrophy may compromise coronary blood flow. Hypotension or tachycardia with altered coronary filling time may cause myocardial ischemia, with the subendocardium at particular risk.
4. If the pulmonary valve is incompetent, for example, following right ventricular outflow reconstruction for repair of tetralogy of Fallot with or without pulmonary atresia, a considerable amount of pulmonary regurgitation may occur that causes an additional volume load on the RV, leading to right ventricular dilation and systolic failure. In addition, the increased pulsatility to the branch pulmonary arteries may cause extrinsic compression of the main stem bronchi.

Table 24–2 Potential Complications in the Catheterization Laboratory

Procedure	Representative Lesion	Complications
Hemodynamic evaluation	Congenital heart disease Pulmonary hypertension Postoperative course; progress not as expected, persistent low cardiac output state, inability to wean from mechanical ventilation, persistent chylous effusions; evaluate residual intracardiac shunt or outflow tract obstruction	Blood loss requiring transfusion Air embolism Vascular access; trauma, dissection, occlusion, perforation Myocardial perforation and tamponade Arrhythmias; ventricular and supraventricular tachycardia, ventricular fibrillation, complete heart block
Coil embolization	Aortopulmonary collaterals Systemic-pulmonary shunts	Fevers Excessive hypoxemia Systemic embolization
Transcatheter device closure	Patent ductus arteriosus Atrial septal defect Ventricular septal defect Baffle leak	Air or device embolization Blood loss Interference with AV value function Arrhythmias; ventricular arrhythmias, complete heart block
Balloon and stent dilations	Pulmonary artery stenosis	Pulmonary artery tear and hemorrhage Pulmonary edema: high flow False aneurysm Right ventricle ischemia
	Pulmonary valve stenosis	As above Pulmonary valve regurgitation
	Mitral valve stenosis	Mitral insufficiency Pulmonary hypertension
	Coarctation of the aorta	Aortic dissection Hypertension
	Right ventricular conduit	False aneurysms Stent embolization
Atrial septotomy	Transposition of the great arteries, mitral stenosis (atresia), and restrictive atrial septum	Perforation of the heart and tamponade

Patients with persistent signs of right ventricular failure, such as low cardiac output state, hepatomegaly, ascites, recurrent pleural effusions (particularly if chylous in nature), and inability to wean from mechanical ventilation, should be considered for catheterization. Although echocardiography may help determine a specific problem, catheterization provides quantitative data that can direct vasoactive support and enable interventions such as pulmonary artery dilation, coiling of collateral vessels, and creation of an atrial communication that allows an atrial level right-to-left shunt.

The function of the right ventricle is critical, and often the cause of complication is related to pulmonary artery dilation. At the time of balloon dilation, cardiac output may decrease significantly, causing hypotension, bradycardia, arterial oxygen desaturation, and a fall in end-tidal CO_2. Because the balloon is inflated for only a few seconds and provided preload is maintained, the procedure usually is well tolerated and the circulation usually recovers spontaneously. Patients who have a hypertrophied, poorly compliant RV with intraventricular pressures at systemic or suprasystemic levels may not tolerate the sudden increase in afterload associated with balloon dilation, even for a short period. In particular, myocardial ischemia and arrhythmias may occur, causing severe acute right ventricular failure and loss of cardiac output. General anesthesia and controlled ventilation are recommended prior to intervention in this at-risk group of patients.

Pulmonary artery disruption is signaled by local extravasation of contrast in the lung parenchyma, sudden hemodynamic deterioration from cardiac tamponade or acute hemothorax, or sudden onset of hemoptysis.[46] The tear in the pulmonary artery may be confined (Figure 24-6, *A*) and therefore controlled, or unconfined, resulting in hemodynamic collapse and the possible need for immediate surgical intervention. The potential for pulmonary artery disruption is increased because of the high pressure used to inflate the balloon and maintain tension on the vessel wall to tear the intima and media. The risk for pulmonary artery disruption may be increased in early postcardiac surgery patients if the dilation is performed across a recent pulmonary artery anastomosis. The safe time frame to wait for the anastomosis to heal before attempting balloon dilation has not been determined. If the patient is stable without signs of right ventricular failure or low cardiac output state, we prefer to wait 6 weeks after surgery before proceeding with balloon dilation. However, early balloon dilation may be necessary in the immediate postoperative period, particularly if the patient has severe right ventricular failure, low cardiac output state, or inability to wean from mechanical ventilation. Provided the dilation is performed cautiously with all resuscitation facilities immediately available, successful balloon dilation can be achieved in the immediate postcardiac surgery period.[47] Cutting balloons have been added to the options available for achieving successful balloon dilation.[48] The relative safety between a cutting balloon and high pressure dilations is unknown, but a high index of suspicion should be maintained in patients with peripheral pulmonary artery stenosis treated with a cutting balloon. In the presence of substantial hemoptysis, immediate

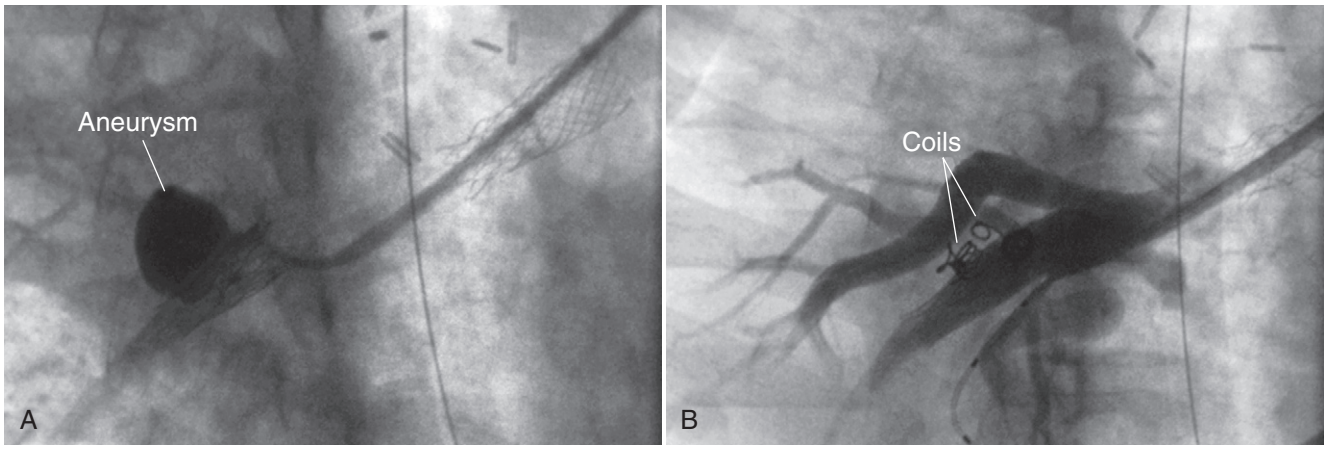

Figure 24–6. Pulmonary artery trauma in a patient with multiple peripheral pulmonary artery stenoses. **A,** Pulmonary artery aneurysm following balloon dilation. Note that a stent has been placed but the aneurysm is still present. **B,** Resolution after coils are placed in the neck of the aneurysm.

endotracheal intubation is indicated for airway control and ventilation. Hypertension and further airway stimulation should be avoided, the addition of positive end-expiratory pressure may be useful, and instillation of 1 mL of 1:100,000 epinephrine via the endotracheal tube may help reduce immediate bleeding by causing vasoconstriction of mucosal vessels. An immediate intervention by the catheterizer to tamponade the disrupted branch pulmonary artery with a balloon catheter may be lifesaving. Permanent occlusion of the vessel with a coil (Figure 24-6, *B*) or covered stent may be necessary to prevent further hemorrhage.

Transient unilateral or unilobar pulmonary edema is also seen in the setting of pulmonary artery dilation. This finding is related to sudden large increases in pulmonary blood flow and distal pulmonary artery pressure after dilation in a previously underperfused pulmonary vascular bed. Pulmonary edema after dilation usually occurs immediately following balloon dilation but can be delayed for up to 24 hours. Pulmonary edema and disruption of a pulmonary artery can occur abruptly, in isolation, or together, during pulmonary artery dilation procedures. Both can cause the appearance in the airway of frank blood or blood-tinged edema fluid in substantial quantities.

Patients who have a dilated RV secondary to a long-standing volume load, such as chronic pulmonary regurgitation, are at risk for arrhythmias and low output during catheter manipulations and interventions. As noted earlier, on most occasions the changes in rhythm are short-lived and settle once the catheters are withdrawn. Nevertheless, anesthesia and airway control are recommended if the circulation is compromised, and a defibrillator and transvenous pacing must be immediately available.

Potential movement at the time of critical balloon dilation or stent placement must be prevented. Dilation of pulmonary arteries is painful and often causes patients to waken from sedation and move. In addition, dilation of the pulmonary arteries may induce coughing. The coughing usually is not a problem for isolated pulmonary artery dilation, but if the patient moves during stent placement, lobar or segmental branch pulmonary arteries may be obstructed inadvertently by the stent. Therefore the patient must be immobile, and additional sedation should be considered immediately prior to stent placement.

Occlusion Device Insertion

Although device closures of PDA and ASD are commonly performed interventions in the catheterization laboratory, they are relatively uncommon procedures in pediatric intensive care patients. A persistent left-to-right shunt at the atrial level contributing to right ventricular volume overload, increased pulmonary blood flow, and inability to wean from mechanical ventilation may be one indication for occlusion, although often the ASD must be of considerable size to cause these symptoms and may be too large for safe deployment of the device. Conversely, a large right-to-left shunt across an ASD may result in significant cyanosis and increase the risk for paradoxical embolism and cerebral vascular accident. A similar circumstance exists in patients who have undergone a fenestrated Fontan operation. Placement of a PDA or ASD device usually is associated with minimal hemodynamic disturbance. Although placement can be performed in most patients using sedation techniques,[49] endotracheal tube placement for airway protection may be necessary if transesophageal echocardiography is used to guide device placement.

Indications for VSD device placement include closure of a residual or recurrent septal defect, preoperative closure of defects that may be difficult to reach surgically while on CPB (Figure 24-7, *A*), and closure of acquired defects such as those due to myocardial infarction or trauma.[50] A residual VSD may cause considerable volume load to the ventricles and result in a low cardiac output state and congestive heart failure requiring prolonged mechanical ventilation and inotropic or vasoactive support. In contrast to our experience with closure of PDAs or ASDs, transcatheter VSD device closures are prolonged procedures that are often associated with profound hemodynamic instability and blood loss.[51] Although the clinical condition of patients undergoing VSD device placement may vary considerably, the preoperative clinical condition or ASA (American Society of Anesthesiologists physical classification) status is not a sole predictor of hemodynamic disturbance during device placement. Rather, it is the technique necessary for deploying the occlusion device that results in significant hemodynamic compromise; therefore all patients are susceptible. Factors contributing to hemodynamic instability include blood loss, arrhythmias from catheter manipulation

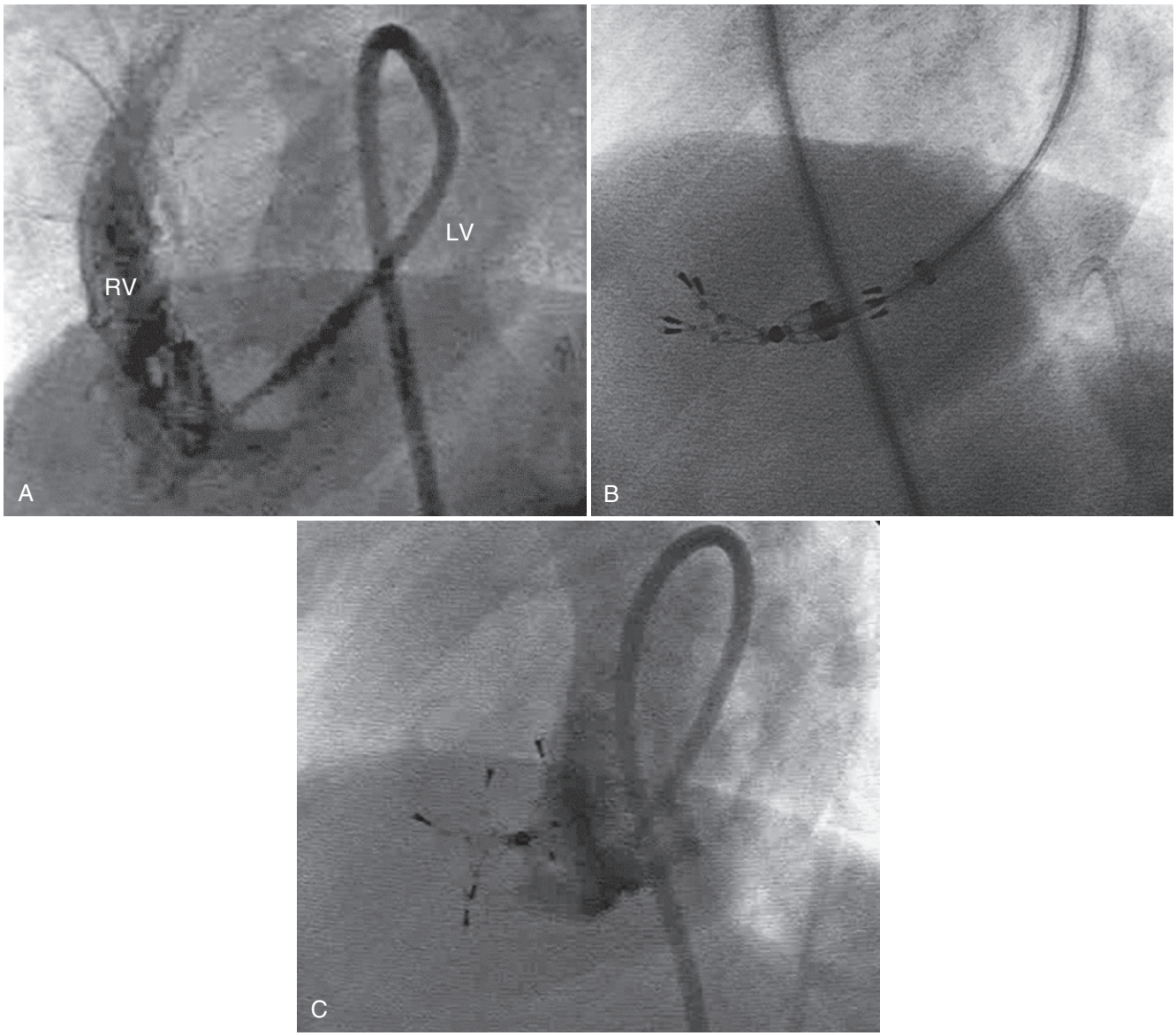

Figure 24–7. Ventricular septal defect closure using the CardioSEAL. **A,** Long axial oblique view of the interventricular septum reveals an apical muscular defect. The catheter course is from the inferior vena cava, the right atrium, across the atrial septum to the left atrium, and across the mitral valve to the left ventricle (***LV***). **B,** Same projection demonstrates dense delivery. The long sheath has been retracted over the arms positioned in the right ventricle (***RV***) and is still covering the left-sided arms. During this stage of the procedure, hemodynamic instability occurs with the large sheath and delivery system interfering with ventricular contraction and valve function. **C,** Left ventricular angiogram after device release.

in the ventricles and across the septum, atrioventricular or aortic valve regurgitation from stenting open of valve leaflets by stiff wire/catheters, and device-related factors such as malposition of the umbrella with arms impinging on valve leaflets or dislodgment from the ventricular septum.

Because of the large sheath required for positioning of the delivery pod and device (Figure 24-7, *B* and *C*) and the need for frequent catheter changes through the sheath, considerable blood loss may occur (often concealed by drapes) and the risk for air embolism is increased. In patients with intracardiac shunts, air embolization may be life-threatening and can be diagnosed by fluoroscopy. When unoccupied by the device carrier system and collapsed device, the large delivery sheath represents a potential space for air accumulation and subsequent delivery into the heart. In addition, when the entry port of the large delivery sheath is open during removal and reinsertion of various catheters and devices, extreme inspiratory efforts may introduce air into the heart. Air in the right atrium may be shunted across an ASD even in the presence of nominal left-to-right shunting. Left heart air embolization produces ST-segment elevation and, often, hemodynamic changes as it passes into the aorta. The resultant ST-segment changes, hypotension, arterial desaturation, and bradycardia generally respond to aspiration and then sealing of the entry port, along with administration of atropine and inotropic and pressor support to maintain coronary perfusion. Meticulous purging of air from the catheter system and sealing of open ports should help minimize the incidence of air embolism. Use of controlled positive-pressure ventilation through an endotracheal tube in an anesthetized, paralyzed patient also may decrease the potential for transcatheter air embolus.

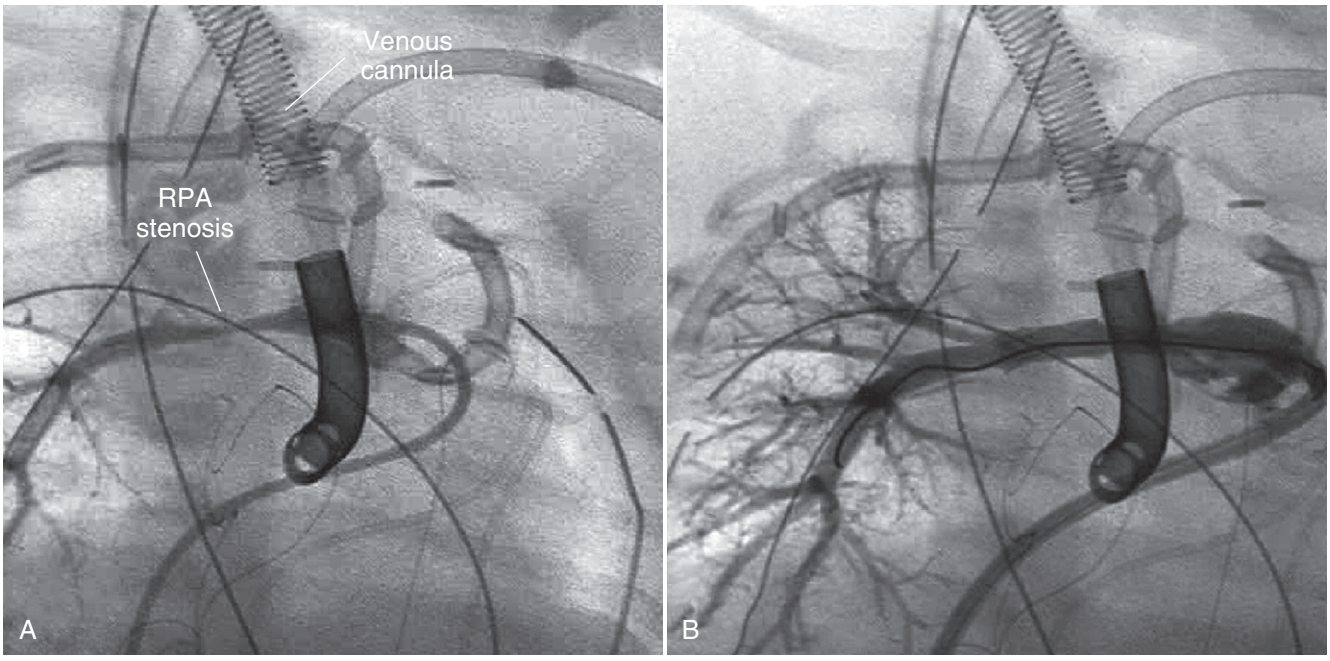

Figure 24–8. Catheterization procedure in a patient undergoing extracorporeal membrane oxygenation (ECMO). **A,** Note ECMO cannula and monitoring lines. A right pulmonary artery angiogram reveals significant proximal right pulmonary artery (*RPA*) stenosis. **B,** Much improved distal right pulmonary artery flow following stent placement across the stenotic area.

Cardiac Catheterization and Extracorporeal Membrane Oxygenation

Cardiac catheterization may be necessary in patients supported with ECMO for either diagnostic or therapeutic procedures, often to facilitate subsequent weaning and decannulation.[52] Reversible respiratory failure and pulmonary hypertension remain common indications for ECMO, but mechanical support of the failing circulation using ECMO has been increasingly used, given indications including refractory low cardiac output state, unexpected cardiac arrest, failure to wean from CPB, severe cyanosis, and refractory arrhythmias.[13,53] ECMO has also been used as a highly successful tool in the resuscitation of patients following hemodynamic deterioration due to catheter-induced complications, low output, or hypoxemia.[54]

A small number of published series have described the feasibility and utility of cardiac catheterization of patients supported by ECMO.[47,52,55,56] As the use of ECMO for supporting the circulation after cardiac surgery has increased,[57] so has the potential utility of cardiac catheterization during ECMO. Indications for catheterization have included assessment of surgical repair and interventions to treat residual defects, left heart decompression via a percutaneous transatrial vent in order to prevent overdistension of the left ventricle, hemodynamic assessment and myocardial biopsy in patients with fulminant myocarditis/cardiomyopathy, and catheter-based interventions such as arrhythmia ablation.[58] Despite the high risk, few complications during catheterization were reported in the series, and the complications did not contribute to morbidity or mortality.

It is important to have a high index of suspicion for residual lesions in postoperative cardiac surgery patients who cannot be weaned from ECMO within 72 hours of expected myocardial recovery.[53] Transthoracic echocardiography is often limited in this setting because of less satisfactory windows for standard views and altered hemodynamics during ECMO. Catheterization during the course of ECMO can make possible the diagnosis of residual lesions that could limit successful weaning from ECMO (Figure 24-8, *A* and *B*). Early catheterization and subsequent interventions may facilitate recovery of myocardial function, reduce ECMO duration, and lessen the potential for ECMO-related complications.

References are available online at http://www.expertconsult.com.

Pharmacology of the Cardiovascular System

Marc G. Sturgill, Michael Kelly, and Daniel A. Notterman

PEARLS

- Clinical acumen is needed to distinguish between the need for an inotropic agent, which is used to increase cardiac contractility, and the need for a vasopressor agent, which is used to increase vascular tone.
- The failing myocardium may need to be supported with an agent that increases contractility and reduces afterload, such as milrinone or dobutamine.
- Multiple polymorphisms have been discovered in receptors relevant to the intensivist. Although the clinical importance of these polymorphisms has yet to be determined, physicians need to stay abreast of changes in this rapidly expanding area.

In many pediatric critical care units, disorders of the cardiovascular and respiratory systems are the most frequent reasons for admission. Children with these disorders constitute a large group who may require pharmacologic support to maintain adequate end-organ perfusion and oxygenation. The catecholamines are the class of drug most often utilized for this support and remain a mainstay of therapy for the pediatric critical care physician, although the role of other agents has expanded. The bipyridines inamrinone and milrinone have been used in the support of patients with hemodynamic compromise of varying etiologies. In addition, the role of vasopressin and terlipressin in the management of patients with vasodilatory shock or after cardiopulmonary bypass, and of nesiritide in patients with decompensated congestive heart failure, continues to be investigated. This chapter examines the clinical pharmacology of the five clinically useful catecholamines as well as these newer agents and the venerable cardiac glycosides.

Mechanisms of Response

Pharmacologic manipulation of the cardiovascular system often entails increasing the inotropic state of the myocardium or altering the tone of the systemic vascular tree so as to improve perfusion. The final common mediator for both processes is the concentration of calcium in the cytosol. The pathway by which pharmacologic agents affect this parameter is a function of their specific cell surface receptors.

Adrenergic Receptors

Catecholamines modify cellular physiology by interacting with a specific adrenergic receptor. The classic paradigm of α and β classes of adrenergic receptors remains unchanged, although new subtypes and sub-subtypes continue to be investigated. Currently three subtypes of α_1 receptors and three subtypes of α_2 receptors have been described and three subtypes of β receptors are recognized.[1] Advances in the biology of the adrenergic receptor have led to a greater understanding of role of the α receptor in the heart, adrenergic receptor regulation of cardiac myocyte apoptosis, and the coupling of the β_2 receptor to more than one G protein. The discovery of various polymorphisms for the adrenergic receptors has served to add even more complexity, but the clinical relevance of many of these polymorphisms has yet to be elucidated. Despite this increase in our understanding of the adrenergic receptor, the clinical classification of the catecholamines into α and β agents remains functionally unchanged (Table 25-1).

Signal Transduction

Adrenergic receptors mediate their effects through G proteins and as such are classified as G protein coupled receptors. The adrenergic receptor itself contains seven membrane-spanning α-helical domains, an extracellular N-terminal segment, and a cytosolic C-terminal segment (Figure 25-1). G proteins are heterotrimeric proteins consisting of α, β, and γ subunits, each of which has multiple subfamilies.[2] There are at least 20 α subunits, five β subunits, and six γ subunits. The action resulting from a ligand binding to a particular adrenergic receptor is a function of the specific type of subunits compromising the G protein receptor complex. An evolving concept is spontaneous receptor activation, as described for the β_2 adrenergic receptor.[3,4] In this model, the receptor "toggles" between different conformational states, of which some are active and each of which may be bound to different G proteins. Binding of a ligand may stabilize or invoke a shift to a particular conformation and in doing so promote changes in the expression of second messengers, most commonly protein kinases. Hence the response of ligand binding may not only depend on the ligand involved but the state of the receptor at the time of binding.

Adrenergic receptors typically are coupled to one of three types of G proteins: G_s, G_i, or G_q. G_s proteins produce an increase in adenylate cyclase activity, while G_i proteins

Table 25–1 Adrenergic Receptors: Physiologic Responses, Agonist Potency, and Representative Antagonists

Receptor	G Protein	Physiologic Response	Agonist	Antagonist
α_1	G_q	Increase $InsP_3$, 1,2-DG, and intracellular Ca^{+2}; muscle contraction; vasoconstriction; inhibit insulin secretion	E > NE > D	Prazosin
α_2	G_i	Decrease cAMP; inhibit NE release; vasodilation; negative chronotropy	E > NE	Yohimbine
β_1	G_s	Increase cAMP; inotropy, chronotropy; enhance renin secretion	I > E ≥ D ≥ NE	Propranolol, metoprolol
β_2	G_s	Increase cAMP; smooth muscle relaxation; vasodilation; bronchodilation; enhance glucagon secretion; hypokalemia	I ≥ E > D > NE	Propranolol
D_1	G_s	Increase cAMP; smooth muscle relaxation	D	Haloperidol, metoclopramide
D_2	G_i	Decrease cAMP; inhibit prolactin and β-endorphin	D	Domperidone

cAMP, Cyclic adenosine monophosphate; *D,* dopamine; *1,2-DG,* 1,2 diacylglycerol; *E,* epinephrine; *I,* isoproterenol; *InsP3,* Inositol 1,4,5-triphosphate; *NE,* norepinephrine.
Modified from Notterman DA: Pharmacologic support of the failing circulation: an approach for infants and children, *Prob Anesth* 3:288.

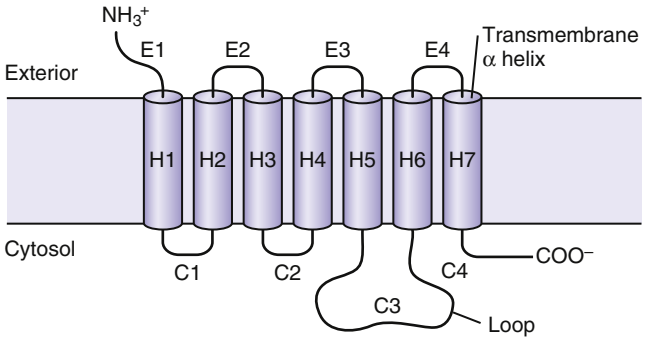

Figure 25–1. Schematic representation of typical G protein–coupled receptor with seven membrane spanning regions (H1–H7), cytoplasmic (C1–C4), and extracellular (E1–E4) loops. *(From Lodish H et al:* Molecular cell biology, *ed 4, New York, 1999, WH Freeman.)*

promote a decrease in adenylate cyclase activity. G_q protein receptors stimulate phospholipase C to generate diacylglycerol and inositol 1,4,5-triphosphate. The nature of the G protein is usually a function of the type of α subunit (α_s, α_I, α_q, and $\alpha_{12/13}$).[5] Events involving interaction of G proteins, the receptor protein, and adenylate cyclase are summarized in Figure 25-2. In the example of the G_s protein, ligand binding to the coupled receptor causes a conformational change in the G protein, resulting in guanosine diphosphate (GDP) disassociating from the Gsα subunit and guanosine triphosphate (GTP) binding to the α subunit. This GTP-G_α complex then disassociates from the $G_\beta\gamma$ subunit and binds to adenylate cyclase, leading to an increase in activity of this enzyme. Adenylate cyclase catalyses the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), thus increasing cellular levels of cAMP. G_i proteins have a different α subunit; when the $G_{i\alpha}$ GTP complex binds to adenylate cyclase, the enzyme is inactivated. By inhibiting this enzyme, G_i-coupled receptor agonists produce a decrease in the cellular concentration of cAMP. The specific cellular response that follows an alteration in the concentration of cAMP depends on the specialized function of the target cell.[6] Typically, an increase in concentration of cAMP leads to activation of a cAMP-dependent protein kinase. These kinases then phosphorylate and activate other structures and enzymes. Many compounds other than adrenergic agents also increase intracellular levels of cAMP. The question of how different agents produce specific responses through the expression of common second messengers continues to be investigated. One proposed mechanism involves anchoring proteins, such as A kinase anchoring proteins. These proteins localize protein kinase A (PKA) to particular cellular locales and also may offer binding sites for other regulatory proteins.[7] Similarly, anchoring proteins for both the active and inactive forms of protein kinase C have been described.[8] Different subtypes of anchoring proteins may serve to create another level of specificity in the effector response for a particular ligand by confining the response to a particular area.

β-Adrenergic Receptors

Myocardial β_1-adrenergic receptors are associated with G_s. When this receptor type is engaged by an agonist agent, the result is enhanced activity of adenylate cyclase and a rise in the concentration of cAMP. This process activates PKA. PKA in turn phosphorylates voltage-dependent calcium channels, increasing the fraction of channels that can be open and the probability that these channels are open, producing an increase in intracellular calcium concentration (Figure 25-3).[9] Calcium then binds to troponin C, allowing for actin-myosin cross bridge formation and sarcomere contraction. In addition, PKA phosphorylates phospholamban, relieving the disinhibitory effect of the unphosphorylated form on calcium channels in the sarcoplasmic reticulum. The accumulation of calcium by the sarcoplasmic reticulum is thus enhanced, increasing the rate of sarcomere relaxation (lusitropy) and subsequently increasing the amount of calcium available for the next contraction. This process leads to both enhanced contractility and active diastolic relaxation.

The question of a PKA-independent mechanism by which β-adrenergic receptors can activate calcium channels remains controversial.[10] Experimental evidence indicates that β_1 receptors are preferentially coupled to cardiac calcium channels in a cAMP-independent mechanism; however, a binding site on the calcium channel has not been delineated.[11,12] β_2-adrenergic receptors have been shown to physically complex, with the calcium channel v1.2 in neuronal tissue.[13] Of note,

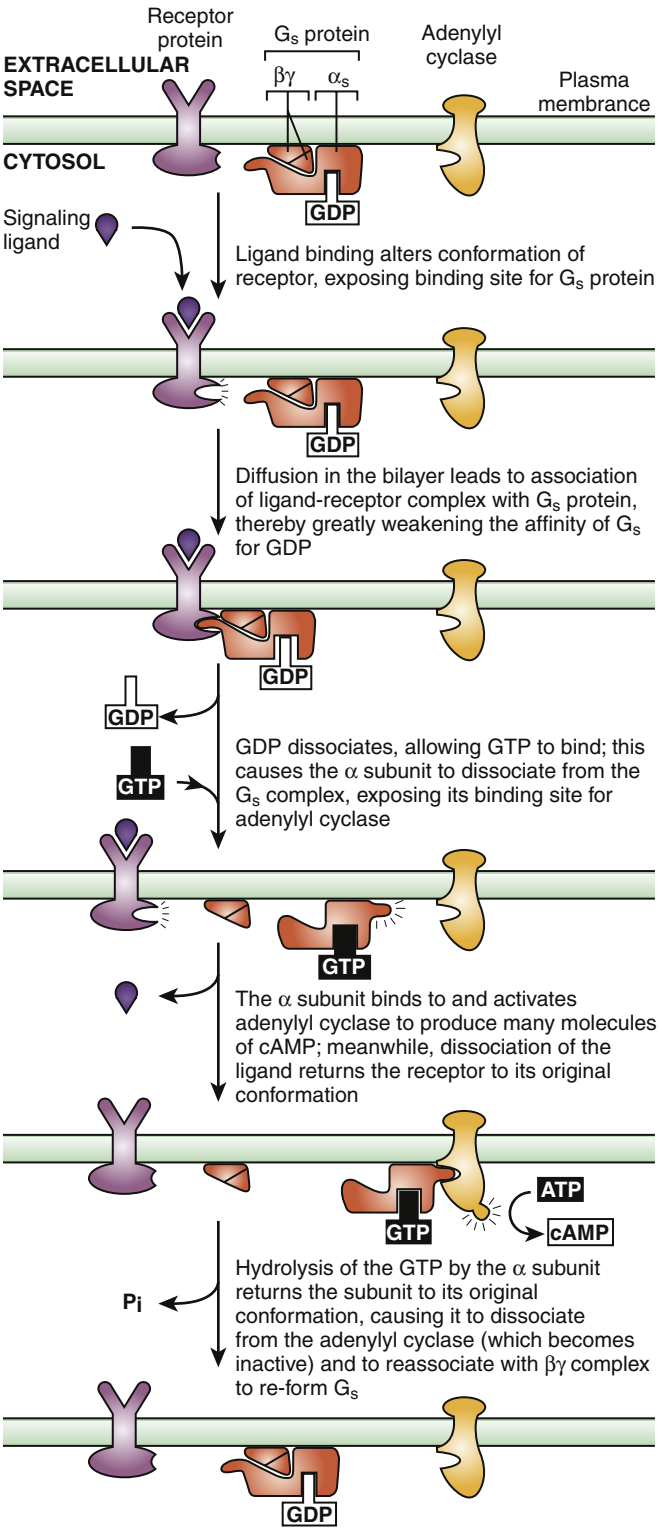

Figure 25–2. Adrenergic receptor complex. When the receptor is engaged by an appropriate ligand (e.g., isoproterenol for a β_1 receptor), the receptor associates with the α_s polypeptide of the G_s protein. This causes the α_s to extrude GDP and incorporate GTP; α_s then associates with and activates the adenylate cyclase. The process is terminated when GTP is hydrolyzed to GDP and α_s dissociates. *(©1994 From Molecular Biology of the Cell 3E by Alberts et al. Reproduced by permission of Garland Science/Taylor Francis LLC.)*

whereas it was once believed that the β_2 receptor had little presence and no role in the heart, recent evidence suggests just the opposite. β_2 receptors are present in the heart and in fact couple with both G_s and G_i.[14] The response to β_2 activation in the heart remains controversial. β_2 activation is actually more effective at increasing cAMP levels than β_1 activation, but the effect on PKA is localized rather than diffuse, as is the case following β_1 activation. This effect could be due to the localization of receptor signaling by the G_i component. Evidence for this hypothesis is that treatment with pertussis toxin (an inhibitor of G_i) transforms the β_2 signal from a local one to a diffuse one.[15] In summary, the role of β_2 receptors in the heart and the signaling processes involved are not fully resolved.[5,16] Their role in the failing heart and implications for disease also remain to be elucidated.[17,18] To add further complexity, functional β_3 receptors have been demonstrated in the heart and appear to have a negative inotropic effect.[19]

In vascular smooth muscle, both β_1 and β_2 receptors are present, although β_2 receptors predominate.[1] The β_2 receptor is coupled to G_s; therefore, activation of β_2 receptors promotes formation of cAMP. The resulting activation of cAMP-dependent protein kinase in vascular smooth muscle, however, stimulates pumps that remove calcium from the cytosol and also promotes calcium uptake by the sarcoplasmic reticulum. As cytosolic calcium concentration decreases, smooth muscle relaxes and the blood vessel dilates. Adrenergic receptors also have been demonstrated on the endothelium and are capable of producing relaxation of the vessel.[20] The exact mechanism involved, including the role of nitric oxide and the subtype of β receptors involved, remains under investigation.[1,21]

α Receptors

Vascular smooth muscle contraction is mediated via α_1 adrenergic receptors, of which there are three subtypes: 1A, 1B, and 1D. The individual contributions of each of these subtypes to the control of vascular tone remains an active area of investigation. Each subtype may be expressed in all of the vascular beds, but it is thought that one type will predominate for a particular bed.[22] A mouse knockout model of the α_{1D} receptor showed that α_1 binding in the aorta was lost but preserved in the heart. The knockout model also had lower blood pressures and a decreased response to norepinephrine.[23] α_{1A} and α_{1B} are thought to be involved in both the heart and vasculature.[24,25] A knockout model of α_{1A} demonstrated decreased blood pressure and response to phenylephrine.[22] An animal model of overexpression of the α_{1A} receptor was associated with marked increase in cardiac contractility without a change in blood pressure or heart rate.[26] In a knockout model of α_{1B} receptors in mice, chronic exposure to norepinephrine did not lead to cardiac hypertrophy or vascular remodeling.[27] Overexpression of a mutant α_{1B} receptor led to increased expression of mitogen-activated protein kinases and decreased responsiveness to isoproterenol in isolated cardiac preparations.[28] Thus while α receptors may have an inotropic effect less than that of β-adrenergic receptors, they do have significant effects in the myocardium. Interestingly, in patients with heart failure, downregulation of β receptors has been noted while α receptors are preserved.[29] The α_1 receptor is coupled to the family of $G_{q/11}$ proteins, which act independently of cAMP. Signal transduction across this receptor is initiated by the activation of phospholipase C, which hydrolyzes phosphatidylinositol 4,5-biphosphate to inositol 1,4,5-triphosphate ($InsP_3$) and 1,2

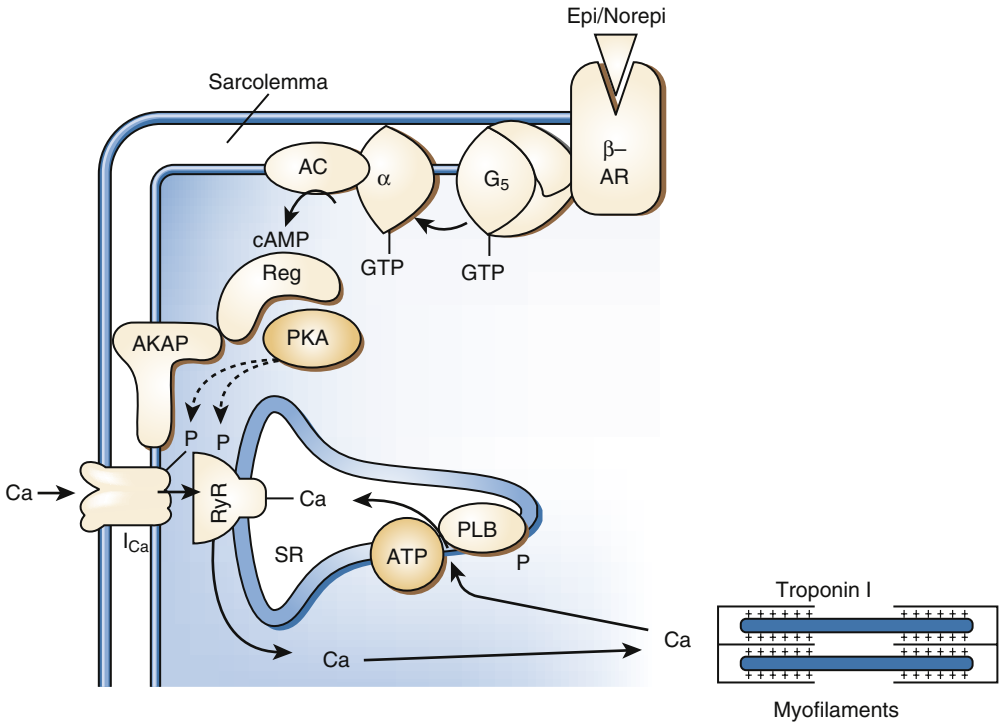

Figure 25–3. β_1-Adrenergic receptor signaling cascade. Agonist (epinephrine/norepinephrine [Epi/Norepi]) to β-adrenergic receptor (*β-AR*) results in the α subunit binding to GTP, which activates adenylate cyclase (*AC*). AC then converts adenosine triphosphate (*ATP*) to cyclic adenosine monophosphate (c*AMP*), which binds to regulatory unit (Reg) on protein kinase A (*PKA*). PKA then promotes an increase in the intracellular concentration of calcium (*Ca*) by acting on voltage-gated channels (I_{Ca}) and on the sarcoplasmic reticulum (*SR*). Calcium then promotes sarcomere contraction. *AKAP,* A kinase anchoring protein; *PLB,* phospholamban; *RyR,* ryanodine receptor. *(From Bers DM: Nature 415:198, 2003.)*

diacylglycerol (1,2DG). $InsP_3$ binds to specific receptors on the sarcoplasmic reticulum, causing a release of calcium into the cytosol, and promotes movement of extracellular calcium into the cell. 1,2DG with calcium activates protein kinase C (PKC), which regulates movement of calcium into the cytosol (Figure 25-4). In vascular smooth muscle, medium light chain kinase is activated as a result and phosphorylates myosin light chain 2, leading to smooth muscle contraction.[30] It also has been shown that a similar mechanism underlies the inotropic effect of the α_1 receptor in the myocardium.[31] The α_{1A} receptor appears to be the most efficiently coupled of the different subtypes.[32] The α_1 receptors also activate calcium influx through voltage-dependent and voltage-independent calcium channels.[33] The α receptors also promote the activation of the mitogen-activated kinase family, which are key regulators of cell growth.

Receptor Downregulation

The mechanisms described provide numerous sites at which the activity of the system can be modified, thereby affecting the sensitivity of target cells to both exogenous and endogenous catecholamines. Some of these receptor modifications are clinically important to the critical care physician. The best-documented type of modification involves agonist-mediated receptor desensitization. Exposure of receptors to agonists markedly reduces the sensitivity of the target cell to the agonist. Within seconds to minutes after agonist binding, the receptor may be uncoupled as a result of receptor phosphorylation. The receptor may be phosphorylated by PKA or PKC or by a member of the family of G receptor kinases (GRKS). These kinases, which include β-adrenergic receptor kinases 1 and 2, phosphorylate only receptors that have agonist bound. Compared with PKA and PKC, phosphorylation by GRKS enhances the ability of β arrestin, a cytosolic protein, or clathrin to bind to the receptor and disrupt further signaling. The role of GRKS has been established for β_1, β_2, and α_2 receptors.[17,34] Sequestration of receptors within the target cell and degradation of sequestered receptors is another mechanism by which receptors are downregulated. The desensitization of α_1 receptors has been extensively reviewed.[35] Homologous desensitization is mediated by GRKS, which are activated by soluble $G_{\beta\gamma}$ subunits and phosphatidylinositol biphosphate. As with the other adrenergic receptors, once phosphorylated, the receptors are internalized into vesicles. The α_1 receptors also demonstrate heterologous desensitization, in which a second messenger kinase, generated as a result of ligand binding, inactivates the receptor and prevents any further signaling from the receptor. In addition to agonist-mediated desensitization, other stimuli also have been implicated in downregulation, including endotoxin, tumor necrosis factor, and congestive heart failure (CHF).[36] Lymphocyte β-adrenergic receptor density in children with CHF was reduced in proportion to the degree of elevation in plasma norepinephrine concentration.[37] Several pharmacologic agents, such as corticosteroids and ketotifen, are thought to upregulate β-adrenergic receptors, and evidence exists that both immaturity and senescence are associated with β-adrenergic receptor desensitization.[38]

Polymorphisms

With the rapid advances in molecular biology, knowledge of polymorphisms within the genetic code has increased dramatically. Polymorphisms within the adrenergic receptors (see Table 25-2) is reviewed briefly here. The reader also is directed toward a recent comprehensive review.[39] Two polymorphisms have been described in the β_1 receptor. At position 49, glycine may

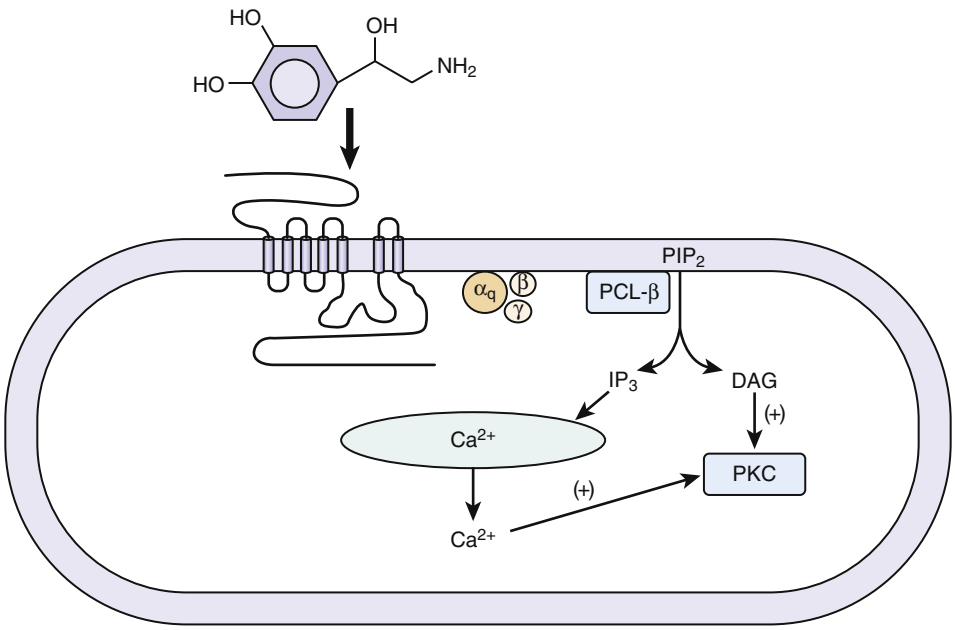

Figure 25–4. α_1-Adrenergic receptor signaling cascade. Binding of an agonist such as norepinephrine to a G protein–coupled receptor activates the $G_{q/11}$ protein, leading to disassociation of the α and βγ subunits. Phospholipase C (*PLC-β*) is activated in turn and cleaves phosphatidylinositol 4,5-biphospate (*PIP_2*) to inositol 1,4,5-triphosphate (*IP_3*) and diacylglycerol (*DAG*). IP_3 and DAG promote an increase in intracellular calcium through the sarcoplasmic reticulum and protein kinase C (PKC). *(From Zhong H, Minneman KP: Alpha-1 adrenoreceptor subtypes,* Eur J Pharm *375:26, 1999.)*

Table 25–2 Common Polymorphisms of Adrenergic Receptors

	Position		Alleles		
Receptor	**Nucleotide**	**Amino Acid**	**Major**	**Minor**	**Clinical Effect**
$A_{1A}AR$	1441	492	Cysteine*	Arginine	
$A_{2A}AR$	753	251	Asparagine	Lysine	
$A_{2B}AR$	901-909	301-303		Deletion Glutamic acid glutamic acid glutamic acid	
$A_{2C}AR$	964-975	322-325		Deletion	Minor allele associated with abnormal vasomotor regulation
				Glycine-alanine glycine-proline	
β_1AR	145	49	Serine	Glycine	Minor allele associated with increased affinity for agonists
	1165	389	Arginine	Glycine	Major allele associated with more efficient coupling
β_2AR	46	16	Glycine	Arginine	
	79	27	Glutamine	Glutamic acid	
	491	164	Threonine	Isoleucine	Minor allele associated with decreased affinity for agonists
β_3AR	190	64	Tryptophan	Arginine	

*In African Americans, arginine is a major allele.
Modified from Small KM, McGraw DW, Liggett SB: Pharmacology and physiology of human adrenergic receptor polymorphisms, *Ann Rev Pharmacol Toxicol* 43:381, 2003.

be substituted for serine. The frequency of the minor allele (gly) is about 15%. In cell culture studies, the minor allele is associated with enhanced agonist-promoted downregulation and increased affinity for agonists.[40] Another polymorphism occurs at position 389, where glycine may be substituted for arginine. This position is in the carboxy terminus, a site involved with binding with the G protein. In a fibroblast cell line, the arginine alleles (wild type) were observed to have higher levels of adenyl cyclase expression with agonist binding, representing more efficient coupling.[41] In a model utilizing isolated human myocardial tissue, the wild type allele (Arg 389) was associated with enhanced inotropic potency in response to norepinephrine,

although maximal force generated did not differ between the two alleles.[42] Another study demonstrated higher resting heart rates and diastolic blood pressure in patients with the Arg 389 allele.[43] Three polymorphisms have been demonstrated in the β_2 receptor. Of note, at position 164, isoleucine may be substituted for threonine. This polymorphism is associated with a threefold decrease in affinity for agonist binding.[44] In a transfected cell line, the Ile-164 type is associated with decreased basal adenyl cyclase activity and decreased activity after agonist stimulation.[45] Similar results were found in a study of patients heterozygous for the Ile-164 allele. These patients had blunting of the increase in both heart rate and duration of systole during terbutaline infusion, with a trend toward lower systolic blood pressure.[46] A single polymorphism has been delineated in the α_1 receptor; it does not appear to have any clinical significance. A restriction fragment length polymorphism was identified in the gene for the α_{2C} receptor.[47] This polymorphism was associated with abnormal vasomotor regulation, sodium excretion, and platelet function. The presence of both the Arg 389 β_1 receptor polymorphism and a deletion polymorphism in the α_{2C} receptor in black patients has been shown to increase the risk of heart failure.[48] This study is an example of the difficulty in linking genetic variations to the clinical scenario in that a single polymorphism may not have an effect except in the presence of another polymorphism. None of these particular polymorphisms has yet been shown to have a significant role in the pediatric intensive care unit (PICU), but they no doubt will continue to add to our understanding of the adrenergic pathways.

Vasopressin Receptors

Arginine vasopressin (AVP) is a nonpeptide hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. Three subtypes of vasopressin receptors exist, known as V_1, V_2, and V_3 (or V_{1b}). V_2 receptors are present in the renal collecting duct, while V_1 receptors are located in the vascular bed, kidney, bladder, spleen, and hepatocytes, among other tissues.[49] AVP is released in response to small increases in plasma osmolality or large decreases in blood pressure or blood volume.[50] The plasma osmolality threshold for release of AVP is 280 mOsm/kg; above this threshold there is a steep linear relation between serum osmolality and AVP levels.[50] Changes of at least 20% in blood volume are needed to effect a change in AVP levels, although levels may then increase by twentyfold to thirtyfold.[50] Hypovolemia also shifts the response curve for AVP to osmolalar changes to the left and increases the slope of the curve (Figure 25-5). Vasopressin can produce vasoconstriction through V_1 receptors in the vascular bed (discussed later), but it also activates V_1 receptors in the central nervous system (CNS), including receptors in the area postrema.[51] This region is responsible for the reflex bradycardia seen with AVP infusion. This reflex attenuates the increase in blood pressure that would result from the vasoconstrictor effects of AVP.[52,53] In fact, vasopressin causes a greater reduction in heart rate than other vasoconstrictors.[49] Thus if this feedback loop is abolished, AVP induces a greater vasopressor response than other agents.[51]

V_1 Receptors

Vasopressin receptors belong to the family of G protein–coupled receptors. V_1 receptors are coupled to G_q and V_2 receptors are coupled to G_s.[50] When vasopressin binds to the

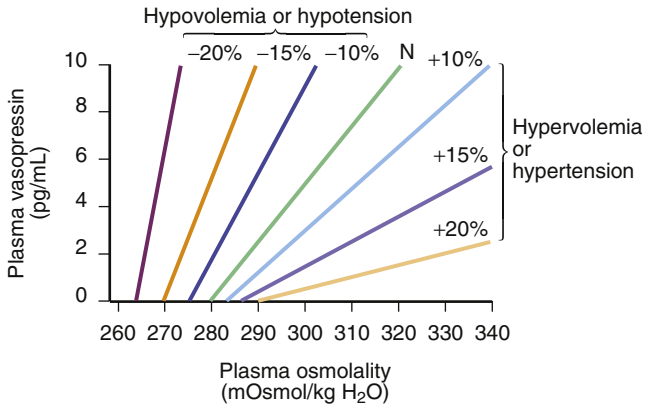

Figure 25–5. Relationship between plasma vasopressin levels and plasma osmolality. As hypovolemia worsens, vasopressin levels increase for any given plasma osmolality. *(Modified from Robertson GL, Athar S, Shelton RL: Osmotic control of vasopressin function. In Androli TE, Grantham JJ, Rector FC Jr, editors:* Disturbances in body fluid osmolality, *Bethesda, MD, 1977, American Physiological Society.)*

V_1 receptor, phospholipase C is activated with the eventual production of $InsP_3$ and 1,2 DG. These molecules serve to increase the release of calcium from the endoplasmic reticulum as well as increase the entry of calcium through gated channels (Figure 25-6).[54] The increase in intracellular calcium leads to an increase in the activity of myosin light chain kinase. This kinase acts upon myosin to increase the number of actin-myosin cross bridges, enhancing contraction of the myocyte. Of note, vasopressin has been shown to produce vasoconstriction in the skin, skeletal muscle, and fat while producing vasodilatation in the renal, pulmonary, and cerebral vasculature.[55] This effect may be mediated though nitric oxide or may be a function of the isoform of adenyl cyclase with which the receptor is coupled.[56] AVP also has been shown to increase the pressor effects of catecholamines, although in two different vascular smooth muscle cell lines, AVP had opposing effects on isoproterenol-induced activation of adenyl cyclase.[57-59] Other effects of vasopressin binding to V_1 receptors are also shown in Figure 25-6.

AVP also may increase vascular tone by interacting with so-called ATP-sensitive potassium channels termed K_{ATP}.[60] Activation of K_{ATP} channels hyperpolarizes the cell, closes calcium channels, and prevents contraction.[61,62] The result may be to protect the cell.[63] AVP can induce PKC, which in turn inhibits the K_{ATP} channel when the cellular concentration of ATP is low.[64] Inhibition of the K_{ATP} channels allows for cell depolarization and calcium entry, resulting in vasoconstriction (Figure 25-7).[65] V_1 receptors also have been demonstrated to have a weak positive inotropic effect in the heart, although the clinical significance of this effect has not been established.[66]

Receptor Downregulation

As with adrenergic receptors, vasopressin receptors undergo downregulation. AVP promotes the phosphorylation of it own receptor immediately after binding. The receptor is removed from the cell surface within 3 minutes after binding.[67] As with adrenergic receptors, G protein–coupled receptor kinases catalyze the phosphorylation of the receptor. PKC also mediates this reaction and may serve as the means by which other agents downregulate the vasopressin receptor in a heterologous manner.[67]

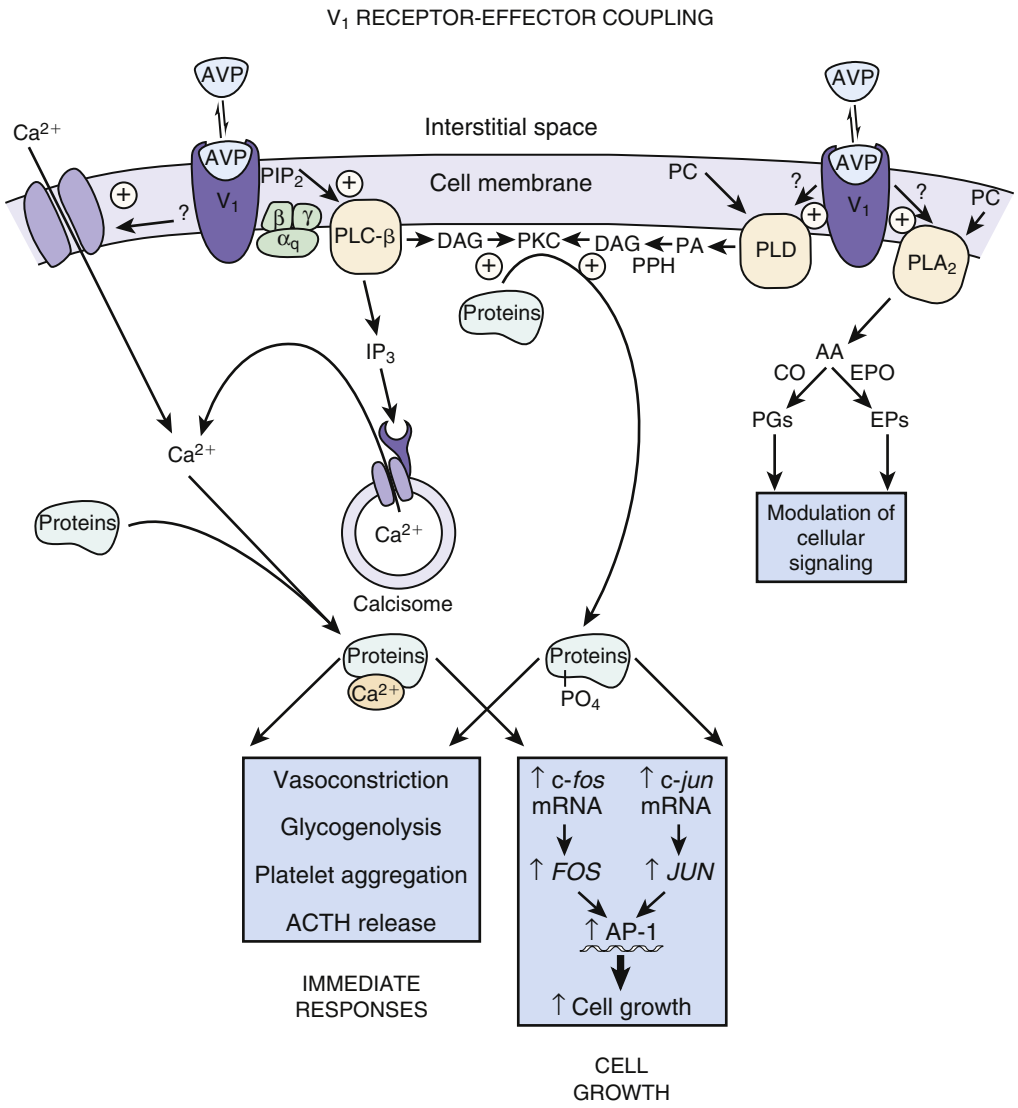

Figure 25–6. V_1 receptor signaling cascade. Binding of arginine vasopressin (AVP) to the V_1 vasopressin receptor (V_1) leads to activation of phospholipase C (*PLC-β*) via the Gq protein with the production of inositol 1,4,5-triphosphate (IP_3). IP_3 promotes an increase in intracellular calcium, resulting in figure. *AA,* Arachidonic acid; *ACTH,* adrenocorticotropic hormone; *AP-1,* transcription factor consisting of heterodimer of FOS and JUN; *CO,* cyclooxygenase; *DAG,* diacylglycerol; *EPO,* epoxygense; *EPs,* epoxyeicosatrienoic acids; *PA,* phosphatidic acid; *PC,* phosphatidylcholine; *PGs,* prostaglandins; PIP_2, phosphatidylinositol 4,5-biphosphate; *PKC,* protein kinase C; PLA_2, phospholipase A_2; *PLD,* phospholipase D; *PPH,* phosphatidate phosphohydrolase. "?" indicates the mechanism of coupling is unclear. *(From Jackson EK: Vasopressin and other agents affecting the renal conservation of water. In Hardman JG, Limbird LE, editors:* Goodman and Gilman's the pharmacologic basis of therapeutics, *ed 10, New York, 2001, McGraw Hill.)*

Polymorphisms

Although numerous mutations in the V_2 receptor exist and result in nephrogenic diabetes insipidus, much less is known about the V_1 receptor. One study established two polymorphisms in the V_1 receptor gene but failed to establish a linkage with hypertension.[68]

Phosphodiesterase Regulation of cAMP

Phosphodiesterases are a class of enzyme that catalyze the hydrolysis of cAMP and cGMP into AMP and GMP, respectively. Therefore, these enzymes can downregulate the signals transducted by cAMP, such as PKA activity (discussed previously). Several families of this enzyme exist, each with subtypes. Phosphodiesterase III (PDE3) is present in many cell types, including cardiac myocytes, vascular smooth muscle cells, adipocytes, platelets, and pancreatic islet cells. PDE3 has a much higher Vmax for cAMP than it does for cGMP and therefore is functionally a cAMP esterase.[69] Different isoforms of PDE3 are present in cardiac (PDE3A1) and vascular smooth muscle cells (PDE3A2) and are localized to different cellular compartments and as such are able to regulate the function of their target enzymes in response to particular cellular signals.[70] The C-terminus of the enzyme codes for the central catalytic core that is the active binding site and the N-terminus coding region may determine cellular targeting.[70] The bipyridines, such as milrinone, are competitive inhibitors of PDE3; that is, they bind to PDE3, preventing the enzyme from binding to cAMP.[71,72] They appear to bind near the binding site for cAMP, although different PDE3 inhibitors may have different binding sites.[73] Inhibition of PDE3 produces an increase in cAMP. This increase in

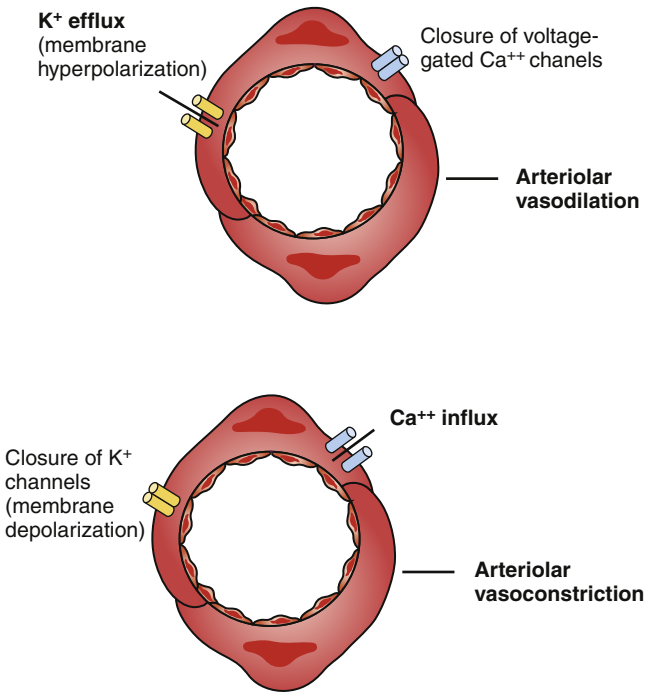

Figure 25–7. K^+ channels vascular tone. Diffusion of K^+ through open K_{ATP} channels in vascular smooth muscle cell results in membrane hyperpolarization, closure of voltage-gated Ca^{2+} channels, and decreased intracellular calcium, resulting in vasodilation. Closing of K_{ATP} channels has the opposite effects. *(From Jackson W: Ion channels and vascular tone,* Hypertension *35:173-178, 2000.)*

cAMP results in a positive inotropic effect in the myocardium and vasodilatation in the systemic and pulmonary vasculature.[74] In contrast, methylxanthines such as theophylline, which inhibit all phosphodiesterases, cause levels of both cGMP (thought to decrease contractility) and cAMP to increase. This dual increase attenuates their inotropic effects. Bipyridines also may enhance contractility by increasing the sensitivity of myofilaments to cytosolic calcium.[75] Milrinone has also been shown to enhance the sarcomere uptake of calcium and thereby augment left ventricular (LV) relaxation (lusitropy).[76] In the peripheral vasculature, PD3 inhibitors may produce vasodilatation via a cGMP mechanism.[77] The bipyridines offer the combination of positive inotropy, lusitropy, and afterload reduction. It has been speculated that long-term exposure to PDE inhibitors may result in adrenergic receptor desensitization via heterologous desensitization, although this has not been demonstrated clinically.[78]

ATPase Inhibition

Membrane-bound sodium-potassium adenosine triphosphatase (Na-K ATPase) is responsible for maintaining electrochemical gradients across the cellular membrane. It does so by extruding three molecules of sodium from the cell and incorporating two molecules of potassium into the cell, both against their respective concentration gradients. This process occurs at the cost of one molecule of ATP. The enzyme consists of an α and β subunit; there are four subtypes of α and three of β.[79] The β subunit may be involved in the trafficking of the enzyme.[80] The α subunit contains both the binding site and catalytic site.[79] The isoforms expressed are dependent on the type of tissue.[81] The putative mechanism of action of the cardiac glycosides is inhibition of the Na-K ATPase pump, which results in an increase in intracellular sodium. The elevated level of intracellular sodium then effects a decrease in the activity of the sodium/calcium exchange (NCX) pump. This pump exchanges three molecules of extracellular sodium for one molecule of intracellular calcium.[82,83] The net result is a rise in intracellular calcium and, in the cardiac myocyte, enhanced contractility. The particular α isoform expressed may affect the function of the enzyme. In a mouse knockout model, animals heterozygous for α_1 ($\alpha_1^{-/+}$) and α_2 ($\alpha_2^{-/+}$) were generated.[84] The cardiac myocytes from α_2 heterozygous animals demonstrated a hypercontractile state when compared with control subjects (similar to that seen with the administration of cardiac glycosides). In contrast, the α_1 heterozygous animals had a hypocontractile state. The authors note that this phenotype is similar to that seen with cardiac glycoside toxicity. Although the classical explanation has been described, the precise mechanism for the increase in intracellular calcium with Na-K ATPase inhibition remains controversial. Some studies have demonstrated a rise in intracellular calcium without the expected concomitant rise in intracellular sodium, suggesting that perhaps the NCX pump was not involved.[85,86] In contrast, a study in mice lacking the NCX pump demonstrated that ouabain (a Na-K ATPase inhibitor) did not increase intracellular calcium.[87,88] No evidence exists to suggest the development of tolerance to digoxin with long-term use.[89]

Developmental Issues

It is often stated that the immature myocardium is less sensitive to inotropic agents than the adult heart. The exact nature of the mechanism responsible for these differences represent an area of active investigation. The majority of studies involve animal models or isolated human tissue. Because there are inherent differences between intact healthy animal models and the ill child, as well as pharmacokinetic differences between the infant and adult patient, caution must be exercised when extrapolating laboratory data to the bedside.[90] Nonetheless, a brief review of developmental differences is appropriate.

Age-related differences exist in the response of the developing myocardium to inotropic agents, receptor regulation, and calcium handling.[82,91] In puppy heart models, the inotropic response to dopamine and isoproterenol increases with increasing age.[92,93] Maximal developed pressure and relaxation velocity in response to isoproterenol were higher in adult rabbit hearts compared with neonatal hearts.[94] However, in a model of rat ventricular myocytes, zinterol (a selective β_2 agonist) increased intracellular calcium gradients and cAMP accumulation and augmented cell shortening in neonatal myocytes at much lower concentrations than in adult myocytes.[95] Sun,[96] in a rabbit model, showed that isolated adult hearts had a greater increase in systolic function in response to isoproterenol than did neonatal hearts but that the response to continuous infusions was less attenuated in the neonatal hearts, suggesting less desensitization. In another study,[97] neonatal rat hearts did not show any evidence of homologous uncoupling in response to isoproterenol. In fact, the receptors demonstrated an enhanced response after prolonged exposure to agonist. This response occurred despite increased activity of β-adrenergic receptor kinase 1, which mediates receptor uncoupling and sequestration. The ability of the neonate to resist desensitization may be helpful given the higher levels of catecholamines present in the newborn period. The mechanism by which neonatal receptors accomplish this was examined in a rat model of the response

of cardiac and hepatic cells to isoproterenol and terbutaline.[98] Neonatal hearts did not show any evidence of desensitization with either single injections of or prolonged exposure to isoproterenol or terbutaline. Adult hearts had evidence of both homologous and heterologous desensitization to isoproterenol but not terbutaline. In marked contrast, neonatal hepatic cells demonstrated homologous desensitization to either single doses of or prolonged exposure to isoproterenol and terbutaline. In fact, there was increased sensitivity to agents that increase adenyl cyclase through nonadrenergic mechanisms. These results suggest that the resistance of neonatal myocytes to desensitization is the result of processes downstream from the adrenergic receptor and may involve developmental changes in the expression of adenyl cyclase isoforms or the compartmentalization of PKA activity.

Another area of difference is the handling of intracellular calcium. In the adult heart, the majority of released calcium is derived from the sarcoplasmic reticulum, but this is less so in the neonatal heart.[82] Calcium flux across the sarcolemma is the predominant source of calcium utilized in excitation-contraction coupling. Neonatal rabbit hearts express more NCX protein than do adult hearts. With maturation, expression of NCX decreases, accompanied by enhanced contractility. In addition, differences between neonatal and adult hearts could be demonstrated on the concentration-response curves for ouabain (dP/dt min) and calcium (dP/dt min), but not for isoproterenol.[94] An experimental agent that blocks the NCX did not increase contractility in the neonatal heart, although it did have an inotropic effect on adult myocardium.[94] The role of voltage-gated calcium channels as the source of intracellular calcium in the neonatal myocardium is unclear. Studies suggest that these channels are the major source of intracellular calcium, although their exact role is unclear.[82,99,100]

Developmental differences also may exist in the expression of phosphodiesterase (PDE) isoforms. In a model of rabbit ventricular myocytes, administration of IBMX (a nonselective PDE inhibitor) and rolipram (a PDE type IV inhibitor) increased intracellular calcium currents in neonatal cells both at baseline and in response to isoproterenol but not in adult cells. In contrast, milrinone (a PDE type III inhibitor) increased intracellular calcium currents at baseline and in response to isoproterenol only in the adult cells.[101] Thus it would appear that in the neonatal myocardium, PDE type IV may be the dominant isoenzyme that regulates intracellular calcium currents.

Developmental changes also may involve the peripheral vascular system. In developing swine, Gootman[102] found that the peripheral vascular response to several adrenergic agonists developed at different rates and that complete reflex integration was not present at birth. He predicted that overall responses to stress or to treatment with these agents would be age dependent. Gootman's physiological studies are complemented by receptor-binding studies that indicate that developmental changes exist in the adrenergic receptor content of a variety of organs, although more recent work indicates that lymphocyte β-adrenergic receptors are fully mature and functional at birth.[103,104] Structural and ultrastructural differences also exist between immature and mature hearts. These differences include reduced ventricular compliance, greater ventricular interdependence, and a reduction in the ratio of myocardial contractile to noncontractile protein in the immature heart. The net effect is that the immature myocardium neither responds to nor tolerates volume loading as well as the adult heart. In addition to this diminished "preload reserve," the baseline heart rate of infants and children is quite high, which limits the extent to which tachycardia can augment cardiac output before diastolic filling is compromised.

The combination of impaired preload reserve, limited chronotropic reserve, and reduced sensitivity of the heart and peripheral vasculature to adrenergic agents implies that the response of the immature organism to the infusion of inotropic and vasopressor agents may differ from the pattern noted in adults.[105,106]

Sympathomimetic Amines

Virtually all sympathomimetics currently used to treat hemodynamic problems are catecholamines. This class includes the endogenous compounds epinephrine, norepinephrine, and dopamine and the synthetic products isoproterenol and dobutamine. Catecholamines have a β-phenylethylamine core with hydroxyl (OH) substituents at the 3 and 4 aromatic ring positions (Figure 25-8). Minor differences in molecular substitution about the N-terminus or the α or β carbons produce marked differences in activity. Structure-activity relationships are complex for the catecholamines and have been reviewed; it is possible to generalize by noting that increasing size of the substituent on the amino group enhances β-adrenergic activity, whereas decreasing size is associated with α-adrenergic selectivity.[107] Tyrosine serves as the base compound for the synthesis of catecholamines. Tyrosine hydroxylase catalyzes the conversion of tyrosine to dopa, which undergoes decarboxylation, producing dopamine. Dopamine β-hydroxylase converts dopamine to norepinephrine. In the adrenal medulla, norepinephrine is converted to epinephrine by n-methyl transferase (Figure 25-9).

Catecholamines are subject to several different elimination processes.[107a] Infused dopamine provides an example in which elimination occurs through a variety of processes. A small proportion is excreted unchanged in the urine. It is likely that a proportion undergoes neuronal reuptake. The principal means of elimination appears to be O-methylation by catechol O-methyltransferase (COMT) to form metanephrines, followed by either sulfoconjugation (by phenolsulfotransferase) or by deamination (by monoamine oxidase [MAO]) to homovanillic acid.[108] Substitution at the α carbon determines the rate of deamination by MAO.[109] The contribution of these pathways to total body clearance of catecholamines varies with age and the particular circulatory bed. In newborn lambs, the lungs accounted for 35% of the total body clearance of norepinephrine and 15% of the clearance of epinephrine. Inhibition of MAO by desipramine decreased pulmonary clearance to near zero and decreased total body clearance of norepinephrine and epinephrine clearance by 51% and 30%, respectively.[110] In adult rabbits, inhibition of COMT and MAO simultaneously decreased pulmonary clearance of norepinephrine, epinephrine, and dopamine but had only minor effects on total body clearance.[111] Inhibition of COMT did not change extracellular levels of catecholamines in the CNS.[112] Furthermore, individual differences in COMT activity are not well correlated with dopamine clearance.[113] The liver and gut have been shown to clear between 30% to 52% of the circulating norepinephrine and epinephrine.[114,115] It is likely that processes or drugs that disturb these routes of elimination will decrease the overall metabolic clearance of catecholamines. Organ dysfunction associated with critical illness is known to increase the blood concentration of dopamine during a given

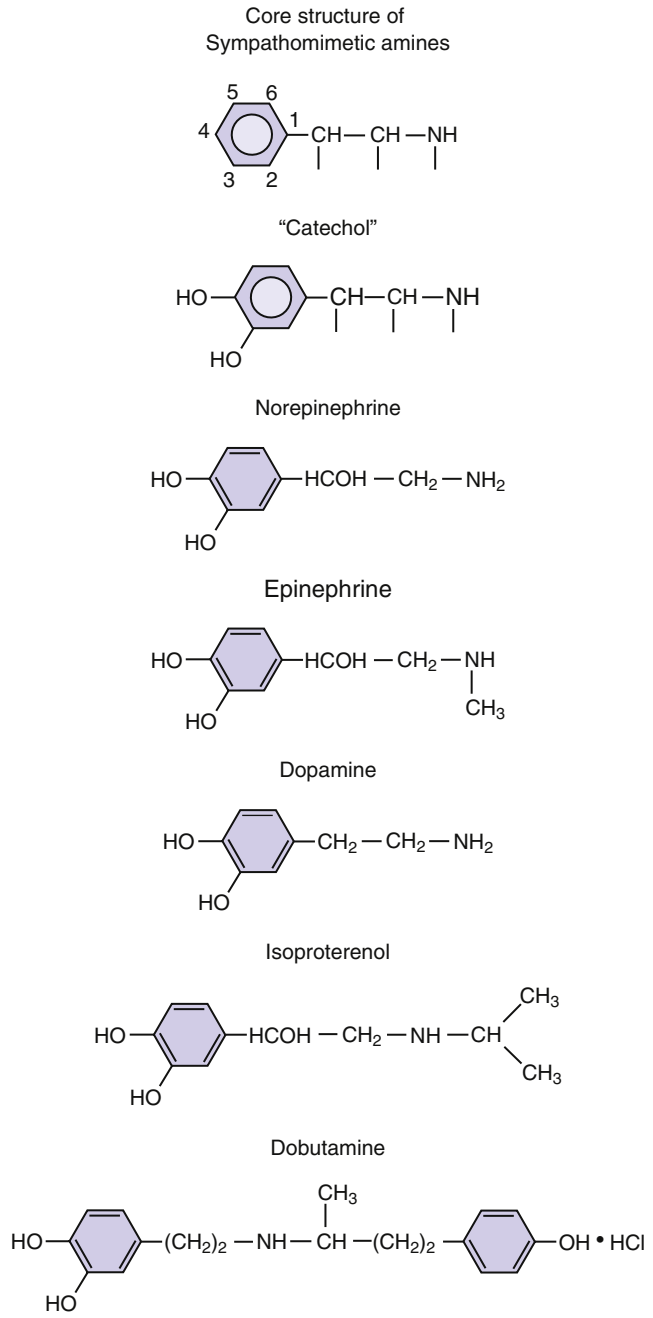

Figure 25–8. Chemical structure of the catecholamines. *(Modified from Chernow B, Rainey T, Lake R: Endogenous and exgoenous catecholamines in critical care medicine,* Crit Care Med *10:409, 1982.)*

infusion rate of the compound. For example, with liver dysfunction the clearance of dopamine is reduced.[116]

It is practical to divide the properties of catecholamines into their inotropic and vasopressor effects. An inotropic agent increases stroke work at a given preload and afterload. Typically, these agents engage receptors of the β_1-adrenergic class. Agents that stimulate β_1-adrenergic receptors also tend to increase heart rate modestly, unless other properties of the drug prevent this increase. Some inotropic agents also activate β_2 receptors, promoting peripheral vasodilatation and reflex tachycardia. In addition, the improvement in cardiac output these agents provide may permit a reflex relaxation of vascular tone and systemic vascular resistance.

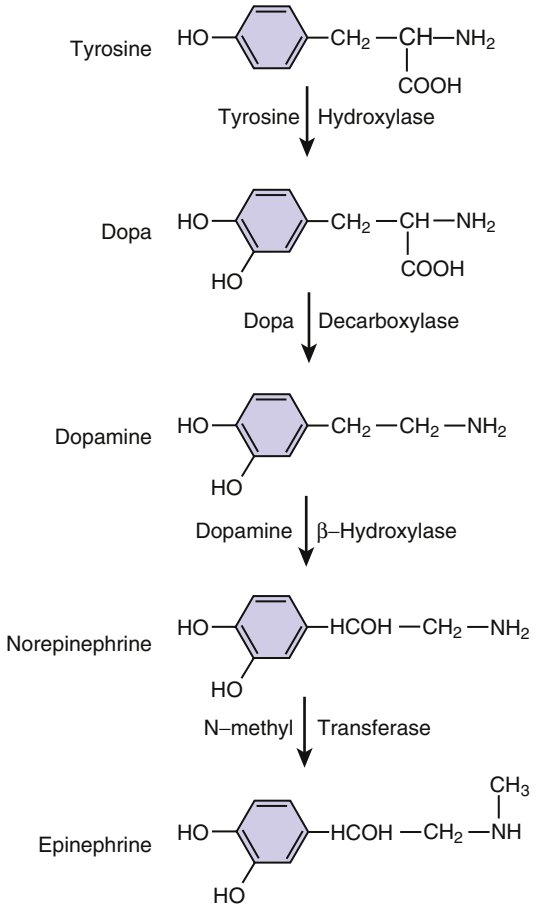

Figure 25–9. Biosynthetic pathways of the endogenous catecholamines. *(Modified from Chernow B, Rainey T, Lake R: Endogenous and exgoenous catecholamines in critical care medicine,* Crit Care Med *10:409, 1982.)*

A vasopressor agent increases peripheral vascular tone, elevating systemic vascular resistance and blood pressure. Typically, vasopressors engage α_1-adrenergic receptors, causing contraction of vascular smooth muscle. In principle, the physician will use a vasopressor agent to treat peripheral vascular failure and an inotropic agent when the major problem is impaired cardiac contractility. In practice, most available agents display a blend of inotropic, chronotropic, and vasopressor activity. Norepinephrine has both inotropic and vasopressor effects, although it is most commonly used as a vasopressor agent. Phenylephrine (a noncatecholamine) has considerable specificity for the α-adrenergic receptor; so it is almost a pure pressor. Isoproterenol and dobutamine have little α-adrenergic agonist activity but considerable activity at the β receptor; they are mostly used as inotropes. Epinephrine and dopamine have both inotropic and vasopressor activity. At relatively low infusion rates, they enhance myocardial function and increase heart rate (β_1 and β_2). At higher rates, pressor activity (α_1) becomes manifest.

Dopamine

Basic Pharmacology

In the enzymatic pathway leading from tyrosine to epinephrine (Figure 25-9), decarboxylation transforms L-dopa to dopamine. Dopamine is a central neurotransmitter and is also found in sympathetic nerve terminals and in the adrenal

Table 25–3 Major Hemodynamic Effects of Adrenergic Receptor Activation by Catecholamines

	Receptor			
Agent	α_1	β_1	β_2	D_1
Dopamine*	Vasoconstriction; F SVR, PVR	Inotropy; chronotropy	Vasodilation	Vasodilation (renal)
Norepinephrine	Vasoconstriction; F SVR, PVR	Inotropy (minor)	—	—
Epinephrine†	Vasoconstriction; F SVR, PVR	Inotropy; chronotropy	Vasodilation	—
Isoproterenol	—	Inotropy	Vasodilation	—
Dobutamine	See text	Inotropy	—	—
Amrinone/milrinone		Nonreceptor-mediated inotropy and vasodilation		

D1, Dopamine receptor; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance.
*Dose related. At low infusion rates, D1 receptor effects predominate; at intermediate rates, β_1 and β_2 receptor effects predominate; and at high rates, α receptor effects predominate.
†Dose related. At low infusion rates, β receptor effects predominate; at high rates, α receptor effects predominate.
Modified from Notterman DA: Pharmacologic support of the failing circulation: an approach for infants and children, *Prob Anesth* 3:288.

medulla, where it is the immediate precursor of norepinephrine. In healthy persons, plasma levels of dopamine are in the range of 50 to 100 pg/mL.

Clinical Pharmacology

Dopamine simulates dopamine (D_1 and D_2) receptors located in the brain and in vascular beds in the kidney, mesentery, and coronary arteries (Table 25-3).[117] It also stimulates α and β receptors, although the compound's affinity for these receptors is lower. D_1 receptors are coupled to G_s and thus enhance adenylate cyclase and produce a rise in cAMP, which evokes vasodilatation. This increases blood flow to these organs and may enhance renal solute and water excretion by the kidney. Dopamine also modulates release of aldosterone and prolactin (D_2 receptors), which also may affect renal solute clearance.[118] The physiological role of dopamine has been extensively reviewed.[119,120]

In healthy adult volunteers, infusion rates between 1 and 10 μg/kg/min increase stroke volume and cardiac output without major effect on heart rate or blood pressure.[121-123] These infusion rates are associated with plasma concentrations of 50 to 100 ng/mL. Low infusion rates augment renal sodium excretion; intermediate rates (10 μg/kg/min) produce chronotropic and inotropic effects, and still higher infusion rates increase vascular resistance.[124] Renal blood flow, glomerular filtration rate, and sodium excretion are maintained or even increase during dopamine infusion in patients with poor cardiac output. Work by Gundert-Remy and colleagues[125] in healthy adults indicated that even at a relatively low infusion rate of 400 μg/min (5 to 6 μg/kg/min) there is significant augmentation of heart rate and blood pressure that likely plays a role in improved renal function.

Evidence for the view that infants display reduced sensitivity to dopamine is not conclusive. In support of reduced sensitivity, Perez and associates[126] found that in critically ill neonates, infusion rates of 50 μg/kg/min did not cause clinically evident impairment of cutaneous or renal perfusion. Some experimental evidence for diminished sensitivity to dopamine in infants also exists; however, this evidence is limited to studies in immature animals. A contrary observation was made by Padbury and co-workers,[127] who measured cardiac output in a group of infants and found that mean blood pressure increased at doses of 0.5 to 1 μg/kg/min, whereas heart rate increased beyond 2 to 3 μg/kg/min. Cardiac output and stroke volume increased before heart rate, and systemic vascular resistance (SVR) did not change within the range of dopamine infusion rates (0.5 to 8 μg/kg/min). The threshold values obtained were 14 ± 3.5 ng/mL for increase in mean blood pressure, 18 ± 4.5 ng/mL for increase in systolic blood pressure, and 35 ± 5 ng/mL for increase in heart rate. The steady-state concentration at infusion rates between 1 and 2 μg/kg/min was 16.5 ± 3.4 ng/mL. Thus newborns may exhibit clinical response at doses as low as 0.5 to 1 μg/kg/min. Seri and colleagues[128] demonstrated an increase in blood pressure without a change in heart rate in premature infants. Doses ranged from 2.5 to 7.5 μg/kg/min.[128] Interestingly, in this study, a greater increase in blood pressure was associated with a lower gestational age. The authors attributed this finding to the enhanced α adrenergic sensitivity of the immature myocardium.

Infused dopamine crosses the blood-brain barrier in preterm neonates but was shown not to increase blood flow velocity in the middle cerebral artery; dopamine inhibits the release of prolactin, thyrotropin, growth hormone, and the gonadotropins, but the clinical significance of these effects is unclear.[128-130] A study in 35 very low birth weight neonates with hypotension randomly assigned to receive dopamine or dobutamine confirmed an inhibitory dopamine effect on prolactin, thyroid-stimulating hormone, and thyroxine secretion. However, hormone levels rapidly normalized following the discontinuation of the dopamine infusion, and the authors speculated that there would be no long-term consequences.[131] This study also confirmed that dopamine is significantly more effective for blood pressure support in this population than dobutamine. The effectiveness of dopamine for blood pressure support also was shown in a separate study in 17 premature neonates with hemodynamically significant patent ductus arteriosus. A mean dopamine infusion rate of 8 μg/kg/min significantly increased systemic arterial pressure (30 ± 3 to 41 ± 5 mm Hg; $P < .05$), pulmonary artery pressure (25 ± 5 to 32 ± 8 mm Hg; $P < .05$), and superior vena caval blood

flow (130 ± 40 to 170 ± 44 mL/kg/min; $P < .05$), leading to a decrease in left-to-right ductal shunting of blood flow.[132]

Low infusion rates of dopamine are frequently employed to augment renal function during critical illness.[133] Although evidence exists that this treatment may increase the fractional excretion of sodium and the creatinine clearance, a large randomized, double-blind placebo control study of low-dose dopamine (2 μg/kg/min) administered to critically ill patients at risk of renal failure did not show any benefits.[134,135] The study group and the control group did not differ in peak creatinine concentration, need for renal replacement therapy, length of ICU or hospital stay, or mortality. Seri and colleagues[128] demonstrated an increase in urine output among premature infants associated with an increase in blood pressure and decrease in renal vascular resistance with dopamine, although they did not take into account the role of postnatal physiologic changes in urine volume. Use of low-dose dopamine in pediatric and neonatal ICUs to augment renal function is not uncommon despite the lack of evidence to suggest a beneficial effect.[136]

Pharmacokinetics

Plasma dopamine clearance ranges from 60 to 80 mL/kg/min in normal adults and is lower in patients with renal or hepatic disease.[116,137] In subjects with normal renal function, the elimination half-life of infused dopamine is approximately 2 minutes.[138] Among critically ill children, the elimination half-life is 26 ± 14 minutes, and in neonates the elimination half-life is 5 to 11 minutes.[139,140] Age has a striking effect on clearance of dopamine, and clearance in children younger than 2 years of age is approximately twice as rapid as it is in older children (82 vs. 46 mL/kg/min).[116] Wide interindividual variations in the rate of dopamine clearance have been reported in critically ill children as well as in healthy adults.[141,142] Dopamine clearance may also decrease after 24 hours of continuous infusion.[7] Allen and colleagues[113] confirmed that during the first 20 months of life, clearance of infused dopamine decreased by almost 50%, with an additional 50% decrease from ages 1 to 12 years. Another study did not show a correlation between age and dopamine clearance, although the patients in this study had a mean age of 37 months.[141] Age-related differences in COMT activity cannot account for the higher dopamine clearance values exhibited in neonates.[113] Banner and colleagues[143] studied the pharmacokinetics of infused dopamine in 15 patients ranging in age from 3 days to 8 years and noted nonlinear behavior, possibly resulting from saturable plasma protein binding in neonates. Although dopamine clearance correlated significantly with body weight, the authors questioned the utility of evaluating total body clearance in this age group. Differences in the rate of sulfoconjugation as a route of elimination also may contribute to the wide variations in the clearance of dopamine in critically ill children.[113,116,141] The possible role of concomitantly administered dobutamine on the clearance of dopamine has been suggested by some authors, but an in vitro study showed that although dopamine and dobutamine are competitors for both COMT and MAO, the concentrations achieved under clinical situations are unlikely to produce clinically significant levels of inhibition.[140,144] A pharmacokinetic difference between children and infants, rather than a difference in receptors or myocardial sensitivity, may account for the observation that infants require and tolerate higher infusion rates. Dopamine crosses the human placenta, but the effect on the fetus is not known. The pharmacokinetics of dopamine and other cardiovascular drugs has been reviewed.[145]

Clinical Role

Clinicians use dopamine to enhance renal function and to exploit its inotropic and vasopressor properties. Dopamine has been shown to be an effective inotropic and vasopressor agent in neonates and infants with a variety of conditions associated with circulatory failure, including hyaline membrane disease, asphyxia, sepsis syndrome, and cyanotic congenital heart disease.[146,147] Very few trials of pharmacological therapy for hypotension in the neonate have been conducted. Osborn and colleagues[148] found that although dopamine increases blood pressure, dobutamine produced a greater increase in blood flow, as judged by superior vena cava flow. Four other trials showed that dopamine was more effective than dobutamine in treating hypotension, but there was no difference in mortality.[149] Fewer data evaluating the efficacy of dopamine in older children are available. However, it remains a mainstay of pharmacologic support for the child with inadequate perfusion. Dopamine is recommended as the first-line agent for children with fluid refractory septic shock and has been recommended for adults as well, but this topic is debated.[150-152] Dopamine also may be appropriate for children with mild impairment of myocardial function and hypotension after resuscitation from cardiac arrest.[153,154] Severe impairment of vascular tone or of cardiac contractility suggest the need for other agents. Children with primary myocardial disease not complicated by frank hypotension will benefit from a more selective inotropic agent such as dobutamine or milrinone. Infusion rates of dopamine needed to improve signs of severe myocardial dysfunction may be associated with troublesome tachycardia or dysrhythmia and may increase myocardial oxygen consumption disproportionately to myocardial perfusion.

Although dopamine is used extensively following cardiac surgery, reports indicate that dopamine is less effective following cardiac surgery in infants than it is in older children or adults.[155] Lang and colleagues[156] treated five children with dopamine following cardiac surgery. For the group as a whole, hemodynamic improvement did not occur at infusion rates less than 15 μg/kg/min. When cardiac output did increase, it was attributed to an increase in heart rate rather than to improved stroke volume. Another study indicated that following cardiac surgery, dopamine and dobutamine have similar inotropic efficacy, but that dopamine was associated with pulmonary vasoconstriction at dosages greater than 7 μg/kg/min in the absence of α-adrenergic blockade.[157] Dopamine at 10 μg/kg/min improved right ventricle (RV) function after RV injury in a young swine model.[158] Increased RV ejection fraction with a decrease in end-systolic RV volume was noted in premature hypotensive infants treated with dopamine.[159] To treat shock associated with hypotension, therapy is initiated with an infusion rate of 5 to 10 μg/kg/min. The rate of infusion is increased in steps of 2 to 5 μg/kg/min, guided by evidence of improved blood flow (skin temperature, capillary refill, sensorium, and urine output) and by restoration of a blood pressure that is appropriate for age. Infusion rates greater than 25 to 30 μg/kg/min of dopamine are not customary, even if they maintain a "normal" blood pressure. At infusion rates of this magnitude, the effect on blood pressure is likely to represent

an increase in SVR (α-adrenergic activation) rather than cardiac output. A requirement for a dopamine infusion of this magnitude suggests that the physician reexamine the physiological diagnosis or select a different agent, such as epinephrine or norepinephrine.

Adverse Effects

Dopamine toxicity is mainly cardiovascular, resulting in tachycardia, hypertension, and dysrhythmia. Dopamine is less likely to produce severe tachycardia or dysrhythmias than either epinephrine or isoproterenol.[160] With the possible exception of the bipyridines, all inotropes increase myocardial oxygen consumption because they increase myocardial work. If the resulting increase in oxygen consumption is balanced by improved coronary blood flow, the net effect on oxygen balance is beneficial. When shock is caused or complicated by myocardial disease, improved myocardial contractility may reduce preload and afterload, improve coronary perfusion pressure (increase oxygen supply), and prolong diastolic coronary perfusion by reducing heart rate. If the same drug is administered to a patient with normal myocardial contractility, the result may be an increase in cardiac oxygen consumption without an increase in oxygen delivery to the myocardium. Tachycardia, by both increasing oxygen consumption and shortening diastole, is a particular burden. Thus the effect of dopamine on myocardial oxygen balance is better than that of isoproterenol, but not as good as dobutamine, amrinone, and milrinone.[161] Dopamine depresses the ventilatory response to hypoxemia and hypercarbia by as much as 60%.[162] Dopamine (and other β-agonists) decrease PaO_2 by interfering with hypoxic vasoconstriction.[163] In one study dopamine increased intrapulmonary shunting in patients with acute respiratory distress syndrome (ARDS) from 27% to 40%.[164] The effect of dopamine on perfusion to the splanchnic bed is widely debated. Evidence suggests that dopamine may increase splanchnic blood flow during sepsis and after cardiac surgery, increase gastric pH, and lead to less lactate production than epinephrine.[165-168] However, dopamine may increase blood flow or oxygen delivery but reduce oxygen consumption in patients with sepsis.[169,170] In infants and children who have undergone cardiac surgery, dopamine may have several endocrinologic effects. Prolactin levels are decreased, the pulsatility of growth hormone is decreased in infants, and thyrotropin levels are decreased.[118] Dopamine can cause or worsen limb ischemia, gangrene of distal parts and entire extremities, and extensive loss of skin.[171] Infusion rates as low as 1.5 μg/kg/min have been associated with limb loss. Because dopamine promotes release of norepinephrine from synaptic terminals (and is also converted to norepinephrine in vivo), it is more often associated with limb ischemia than other adrenergic compounds. Extravasations of dopamine should be treated immediately by local infiltration with a solution of phentolamine (Regitine, 5 to 10 mg in 10 mL of normal saline solution) administered with a fine hypodermic needle.[172]

Preparation and Administration

Dopamine hydrochloride is available in 5-mL vials at concentrations of 40 mg/mL, 80 mg/mL, and 160 mg/mL, and as 250 mL or 500 mL premixed solutions for infusion at concentrations of 0.8 mg/mL, 1.6 mg/mL, and 3.2 mg/mL in 5% dextrose.[139] Dopamine is administered by central vein to avoid the risk of skin injury resulting from extravasation. In an emergency, dopamine may be administered through an intraosseous needle.[173] Table 25-4 and Table 25-5 provide information regarding preparation of infusions and compatibility.[174,175] Table 25-4 presents a dilution method sometimes referred to as the "rule of 6." Evidence suggests that preparation of medicated infusions on patient care units, rather than in a hospital pharmacy, is associated with an increased incidence of medication errors. Therefore several groups and agencies now discourage use of the rule of 6 or any other system that involves nonstandard medication concentrations. Practitioners should consult the policies of their institution before prescribing any of the drugs listed in Table 25-4. Dopamine is not compatible with some of the 3-in-1 solutions utilized for parenteral nutrition or with sodium bicarbonate.[176] Dopamine is stable in solutions of 5% dextrose or normal saline solution for 24 hours to 84 hours.[176a,177]

Interactions

Dopamine is metabolized by MAO, and concurrent use of a MAO inhibitor (e.g., pargyline) potentiates its effect.[107] In this rare circumstance the initial dosage of dopamine should be reduced to one tenth the usual dosage.[178] Both α-adrenergic blockers and β-adrenergic blockers antagonize the effects of dopamine; dopamine antagonists such as metoclopramide or haloperidol also may attenuate response to dopamine. An increase in dopamine infusion rate will overcome the receptor blockade if necessary.

Table 25–4 A Method for Preparing Vasoactive Infusions in Pediatric Patients*

Drug	Preparation	Infusion Rate	Maximum Concentration	Drug
Isoproterenol	**0.6** mg × body weight (kg), added to diluent to make 100 mL	1 mL/h delivers 0.1 μg/kg/min	6.4 mg/100 mL	Isoproterenol
Epinephrine			24 mg/100 mL	Epinephrine
Norepinephrine			12.8 mg/100 mL	Norepinephrine
Milrinone			40 mg/100 mL	Milrinone
Dopamine	**6** mg × body weight (kg), added to diluent to make 100 mL	1 mL/h delivers 1 μg/kg/min	1280 mg/100 mL	Dopamine
Dobutamine			800 mg/100 mL	Dobutamine
Inamrinone†				Inamrinone

*Several groups and agencies now discourage use of the rule of 6 or any other system that involves nonstandard medication concentrations. Practitioners should consult the policies of their institution before prescribing any of the drugs listed in this table.
†Not compatible with dextrose.

Table 25–5 Compatibility of Vasoactive Drugs with Commonly Used Continuous Infusions

	Aminophylline	Cisatracurium	Dobutamine	Dopamine	Epinephrine	Fentanyl	Furosemide	Heparin	Inamrinone	Isoproterenol	Lidocaine	Lorazepam	Midazolam	Milrinone	Nesiritide	Norepinephrine	Vasopressin	Vecuronium
Aminophylline		**C/I**	**I**	C	**I**		C	C			C					**I**		C
Cisatracurium	**C/I**		C	C	C	C	**C/I**	**C/I**			C	C	C			C		
Dobutamine	**I**	C		C	C	C	**C/I**	**C/I**	C		C	C	**C/I**	C		C	C	C
Dopamine	C	C	C		C	C	**C/I**	**C/NS**	C		C	C	C	C		C	C	C
Epinephrine	**I**	C	C	C		C	C	C	C			C	C	C		C		C
Fentanyl		C	C	C	C		C	C				C	C	C		C		C
Furosemide	C	**C/I**	**C/I**	**C/I**	C	C		C			C	C	**I**	**I**		C		**I**
Heparin	C	**C/I**	**C/I**	**C/NS**	C	C	C				C	C	C	C		C		C
Inamrinone	C	C	C	C	C					C	C					C		
Isoproterenol	**I**	C	C				**I**	C	C					C				C
Lidocaine	C	C	C	C	C		C	C						C				
Lorazepam		C	C	C	C	C	C	C					C	C		C		C
Midazolam		C	C	C	C	C	**I**	C				C		C		C		C
Milrinone			C	C	C	C	**I**	C		C	C	C	C		C	C	C	C
Nesiritide			**C/I**[1]	**C/I**[1]	**C/I**[1]	C[2]	**I**	**I**			**C/I**[1]			C[2]		**C/I**[1]		
Norepinephrine	**I**	C	C	C	C	C	C	C	C			C	C	C			C	C
Vasopressin			C	C	C		**I**	C			C			C		C		
Vecuronium	C		C	C	C	C	**I**	C				C	C	C		C		

C, Compatible; *C/I*[1]*,* may be unstable at higher concentrations of additives; *C/NS,* this combination more stable in normal saline solution (NS) than in D5W because of an exothermic reaction; *I,* incompatible.
*Norepinephrine = More stable in D5W at higher concentrations because of its high level of acidity (pH 3).
1, Incompatible with products containing bisulfite antioxidants.
2, Stable for 4 hours.
From Trissel LA: *Handbook on injectable drugs,* ed 15, Bethesda, MD, 2009, American Society of Health-System Pharmacists.

Summary

Dopamine is used to treat mild to moderate cardiogenic or distributive (septic; hypoxic-ischemic) shock associated with moderate degrees of hypotension. In the absence of hypotension, acute severe cardiac failure is treated with dobutamine or amrinone. When septic or cardiogenic shock is complicated by severe hypotension, epinephrine, or norepinephrine is preferred, depending on hemodynamic measurements (Table 25-6).

Norepinephrine

Basic Pharmacology

Dopamine is hydroxylated at the β-carbon to produce norepinephrine, the principal neurotransmitter of the sympathetic nervous system (Figure 25-8 and Figure 25-9). Because there is no substituent on the N (amino)-terminus, norepinephrine has little β_2 activity and is considerably less potent at that receptor than epinephrine.[107] It is a moderately potent α and β_1 agonist.

Clinical Pharmacology

Infusion in normal subjects elevates SVR because α-adrenergic stimulation is not opposed by β_2 stimulation.[107] Reflex vagal activity reduces the rate of sinus node discharge, thereby blunting the expected β_1 chronotropic effect. In normal subjects renal, splanchnic, and hepatic blood flows decrease. The increase in afterload may augment coronary blood flow. This effect may be enhanced by α-adrenergic receptors located in the coronary arteries, although in coronary arteries from explanted human hearts, the vasodilatation in response to norepinephrine was mediated via β_2 receptors.[179] Norepinephrine does have inotropic effects on the heart, mediated via α_1 and β_1 receptors. The proportion of inotropic response related to α_1 stimulation may be affected by the pressure load on the right ventricle.[180] In the failing heart, the relative contribution from each type of adrenergic receptor appears to be equal.[181] In the isolated rat heart, the inotropic effects of norepinephrine are diminished in the presence of a nitric oxide synthetase inhibitor but restored when a nitric oxide donor is present.[182] Interestingly, the contractile effects of norepinephrine in the rat are lost when it is pretreated with peroxynitrite.[183] In healthy volunteers norepinephrine produces a decrease in creatinine clearance because of the effect on renal blood flow; however, in patients with hypotension, the improvement in global perfusion may actually produce an increase in urine output.[184]

The acute hemodynamic effects of norepinephrine are compared with those of epinephrine and isoproterenol in Figure 25-10. Experience in critically ill children indicates that the hemodynamic responses are not different from those observed in adults. Use of norepinephrine in 18 neonates with persistent pulmonary hypertension–associated heart dysfunction revealed significant increases in systemic blood pressure (33 ± 4 to 49 ± 4 mm Hg; $P < .05$) and left ventricular output (172 ± 79 to 209 ± 90 mL/kg/min; $P < .05$), along with improvement in postductal transcutaneous oxygen saturation (89% ± 1% to 95% ± 4%; $P < .05$), pulmonary-to-systemic blood pressure ratio (0.98 ± 0.1 to 0.87 ± 0.1; $P < .05$), and a 20% increase in the velocity of pulmonary artery blood flow ($P < .05$).[185] In a separate study in 22 neonates with septic shock refractory to fluid support, dopamine, and/or dobutamine, norepinephrine (mean infusion rate 0.5 ± 0.4 μg/kg/min) significantly increased mean arterial blood pressure (36 ± 5 to 51 ± 7 mm Hg; $P < .001$) and urine output (1 ± 0.5 to 1.7 ± 0.4 mL/kg/hr; $P < .05$), while decreasing blood lactic acid concentrations (4.8 ± 2.3 to 3.3 ± 1.8 mmol/L; $P < .01$).[186]

Pharmacokinetics

Basal plasma levels of norepinephrine are much higher than basal plasma levels of epinephrine (250 to 500 vs. 20 to 60 pg/mL). The minimum concentration at which norepinephrine produces detectable hemodynamic activity is at least 1500 to 2000 pg/mL, suggesting that endogenous plasma norepinephrine simply represents "spillover" from sympathetic activity and that norepinephrine is not a true hormone.[187] The

Table 25–6 Selecting Inotropic and Vasopressor Agents for Specific Hemodynamic Disturbances in Children

	Blood Pressure or SVR		
Hemodynamic Pattern	**Normal**	**Decreased**	**Elevated**
SEPTIC SHOCK			
Stroke index ↑ or ↔		Norepinephrine	
Stroke index ↓	Dobutamine or dopamine	Dopamine or epinephrine (or dobutamine and norepinephrine)	Dobutamine plus vasodilator and/or PDIII inhibitor
Cardiogenic shock	Dobutamine or dopamine or PDIII inhibitor, **nesiritide**	Dopamine or epinephrine	Dobutamine plus vasodilator and/or PDIII inhibitor, **nesiritide**
Myocardial dysfunction* (complicating critical illness)	Dobutamine or dopamine or PDIII inhibitor, **nesiritide**	Dopamine or epinephrine	Dobutamine plus vasodilator and/or PDIII inhibitor, **nesiritide**
Congestive heart failure	Dobutamine or dopamine or PDIII inhibitor, **nesiritide**		Dobutamine plus vasodilator and/or PDIII inhibitor, **nesiritide**
Bradycardia		Isoproterenol	

*For example, acute respiratory distress syndrome or anthracycline therapy.
PDIII inhibitor, Amrinone or milrinone; SVR, systemic vascular resistance.
Modified from Notterman DA: Pharmacologic support of the failing circulation: an approach for infants and children, *Prob Anesth* 3:288.

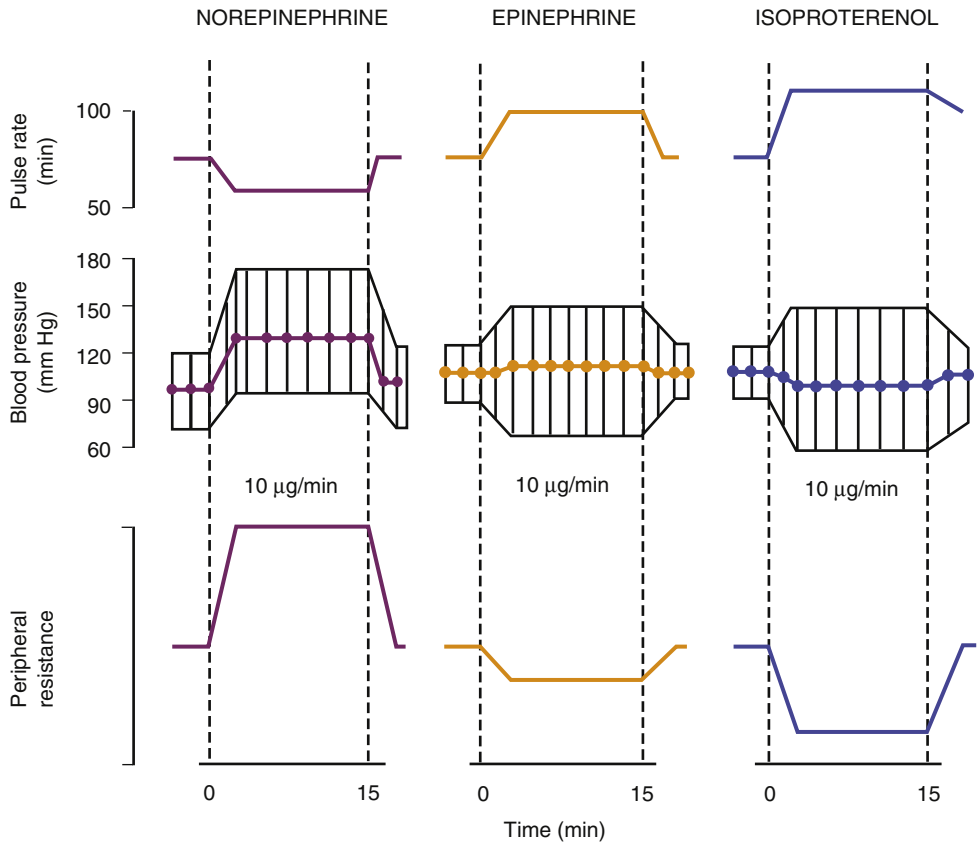

Figure 25–10. Effects of intravenous infusion of norepinephrine, epinephrine, and isoproterenol in adult humans. *(Modified from Allwood MJ, Cobbold AF, Ginsberg J: Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine,* Br Med Bull *19:132, 1963.)*

clearance of norepinephrine in healthy adults is 24 to 40 mL/kg/min, with the half-life averaging 2 to 2.5 minutes.[188] The clinical effect of norepinephrine ceases within 2 minutes of the infusion being stopped.[188] Little pharmacokinetic information in children is available. Norepinephrine is inactivated by reuptake into nerve terminals, with some elimination occurring by enzymatic degradation in the liver, adrenal glands, and kidney, either by methylation to normetanephrine (by COMT) or by oxidative deamination.[189] Most of the metabolites formed by either MAO or COMT are then reduced or oxidized further. 3-Methoxy-4-hydroxymandelic acid is the major metabolite in the urine.[107]

Clinical Role

Norepinephrine improves perfusion in children with low blood pressure and a normal or elevated cardiac index. Septic shock is the usual context in which norepinephrine is beneficial. Norepinephrine is administered only after intravascular volume repletion and is best guided by estimates of cardiac output and SVR. Very little experience on the use of norepinephrine to treat distributive shock in children has been published; however, publications concerning adult patients provide a rationale for using this agent in patients with hypotension that is unresponsive to volume repletion and infusion of dopamine.[190-193a] In children, norepinephrine is the recommended agent for warm shock refractory to fluid loading and dopamine.[150] A prospective, unblinded randomized study (in adults) indicates that norepinephrine is superior to dopamine for treating hypotension and other hemodynamic abnormalities associated with hyperdynamic septic shock. In this study, the average infusion rate for norepinephrine was 2.7 μg/kg/min compared with the average dopamine dose of 22 μg/kg/min.[194] Others have reported that somewhat lower average dosages (0.4 μg/kg/min) were effective in adults with sepsis.[195] Coronary and renal blood flow increased in lambs at a dose of 0.4 μg/kg/min while mesenteric blood flow decreased.[196] Thus titration is important and may entail fairly rapid escalation of dosage. Norepinephrine produces increases in SVR, arterial blood pressure, and urine flow. It is most valuable in the context of tachycardia because infusion of the drug does not produce significant elevation of heart rate and may even lower heart rate through reflex mechanisms. In a study of adults with abdominal sepsis, norepinephrine infusion was associated with increases in systemic blood pressure and SVR. Stroke volume increased as heart rate declined. Cardiac index did not change, although creatinine clearance increased substantially.[195] Norepinephrine has been shown to improve right ventricular performance in adults with hyperdynamic septic shock.[194]

The usual starting dosage is an infusion of 0.1 μg/kg/min (Table 25-7), with a goal of elevating perfusion pressure so that the flow to vital organs is above the threshold needed to meet metabolic requirements.[197] Arbitrary values of SVR or blood pressure are not appropriate end points for therapy, and the lowest infusion rate that improves perfusion as judged by skin color and temperature, mental status, urine flow, and reduction in plasma lactate level should be used.[198]

Other causes of distributive shock (e.g., vasodilator ingestion and intoxication with CNS depressants) also should respond to norepinephrine infusion when the predominant hemodynamic problem is low SVR and blood pressure.

Table 25–7 Suggested Infusion Rates for Inotropic and Vasopressor Agents (μg/kg/min)

Agent	Clinical Indication	
	Inotropic	Pressor
Dopamine	2-15	>12
Epinephrine	0.05-0.5	0.10-1
Norepinephrine		0.05-1
Vasopressin		0.0002-0.002*
Dobutamine	2.5-20	
Inamrinone†	5-10	
Milrinone†	0.25-0.75	
Nesiritide†	**0.01**	
Isoproterenol	0.05-1	

*mU/kg/min; the optimal dosage and infusion rate have not been established in children.
†Loading dose required.

Adverse Effects

The increase in afterload that norepinephrine produces should increase myocardial oxygen consumption, but norepinephrine may reflexively decrease heart rate, which should reduce oxygen consumption and improve diastolic coronary perfusion.[107] Injudicious use of norepinephrine will lead to compromised organ blood flow. Norepinephrine infusion may elevate blood pressure yet not improve clinical indices of perfusion. This type of poor clinical response is usually associated with a low cardiac index, stroke volume, LV stroke work index, and an elevated pulmonary capillary wedge pressure.[190,191] Employing excessive dosages or using norepinephrine to elevate blood pressure without improving perfusion may produce multiple organ system failure.

Preparation and Administration

See Tables 25-4 and 25-5 for information regarding preparation and compatibility. Norepinephrine bitartrate is available in 4 mL ampules at a concentration of 1 mg/mL.[188] Norepinephrine should be diluted in 5% dextrose or 5% dextrose in 0.9% sodium chloride for preparation of infusions. Norepinephrine is administered only by central venous catheter, except in extreme emergency. Extravasation of norepinephrine should be treated immediately by local infiltration with a solution of phentolamine (Regitine, 5 to 10 mg in 10 mL of normal saline solution) administered with a fine hypodermic needle.[188,172] As with dopamine, norepinephrine should be administered by a syringe type of infusion device.

Interactions

Tricyclic antidepressants potentiate the action of norepinephrine by reducing neuronal uptake of the compound.[188] MAO inhibitors do not appear to enhance the activity of infused norepinephrine. α-Adrenergic blocking agents reduce efficacy of norepinephrine.

Summary

Norepinephrine is the agent of choice when the principal hemodynamic disturbance involves hypotension with an abnormally low SVR and a normal or high cardiac output after fluid resuscitation (Table 25-6). Septic shock is the usual indication, but it is frequently useful in other diseases associated with distributive shock.

Epinephrine

Basic Pharmacology

Epinephrine is synthesized in the adrenal medulla where it is formed from norepinephrine by addition of a methyl group to the N-terminus.[160] The reaction is catalyzed by N-methyltransferase (Figure 23-9). Epinephrine is a hormone, and endogenous levels of epinephrine change with the physiological state of the organism via afferent input to the adrenal medulla. Resting levels are less than 50 pg/mL; heavy exercise produces concentrations of 400 pg/mL or greater.[187] In a group of critically ill children not receiving catecholamines, epinephrine levels between 0 and 1378 pg/mL at admission (mean, 508 pg/mL) have been reported.[198a] Epinephrine activates α, β_1, and β_2 receptors. It is a principal hormone of stress and produces widespread metabolic and hemodynamic effects, which have been extensively reviewed.[160]

Clinical Pharmacology

β_1 receptors are affected by very low concentrations of epinephrine; consequently, one of the early effects of epinephrine infusion is activation of β_1 receptors in the myocardium and conducting systems, which accelerates phase 4 of the action potential. The rate of sinoatrial node discharge and heart rate increase, and systolic time intervals are shortened. The inotropic state of the myocardium is also enhanced, producing an increase in force of contraction and rate of rise of pressure. Evidence indicates that myocardial oxygen consumption is out of proportion to the increase in force of contraction, decreasing myocardial efficiency.[160] High concentrations of epinephrine or exposure to the compound when the myocardium is sensitive because of infarction, operation, or myocarditis may produce serious atrial and ventricular dysrhythmias.[160]

Stimulation of peripheral β_2 receptors promotes relaxation of resistance arterioles; SVR decreases and diastolic blood pressure falls (Figure 25-10). The decrease in SVR enhances the direct chronotropic effect of epinephrine. Higher plasma concentrations are associated with activation of vascular α receptors, and SVR increases. Higher doses also are associated with an increase in pulmonary vascular resistance, from direct effect and as a result of increased venous return to the right side of the heart.[160] The effect of epinephrine on the pulmonary vasculature may vary as a result of the dose used.[158] During infusion of epinephrine, hepatic and splanchnic blood flow increase, while renal blood flow may be reduced.[160]

The thresholds for producing these effects in healthy adults have been examined.[187] Normal basal levels are around 40 pg/mL. Heart rate accelerates between 50 and 100 pg/mL; changes in blood pressure (systolic blood pressure increases, diastolic blood pressure decreases) occur between 75 and 100 pg/mL. Various metabolic effects (hyperglycemia, hyperglycemia, cytogenesis, and glycolysis) occur between 150 and 200 pg/mL. Concentrations of this magnitude are achieved during therapeutic infusion of the drug. Other metabolic effects include hypophosphatemia and hypokalemia. Desensitization to elevated levels of epinephrine occurs rapidly and may be present prior to administration of exogenous catecholamines in the ICU.

Pharmacokinetics

In healthy male volunteers the plasma clearance of epinephrine is 35 to 89 mL/kg/min.[199,200] The elimination half-life is approximately 1 minute.[138] Epinephrine is methylated by COMT to metanephrine in the liver and kidneys or deaminated via the action of MAO.[140] It also may be metabolized by extraneuronal uptake.[189] The resulting catabolites then may be conjugated to sulfate or glucuronide and excreted in the urine. A wide interindividual variation in clearance is observed in healthy adults. In critically ill children receiving epinephrine at doses from 0.03 to 0.2 μg/kg/min, plasma concentrations at steady state ranged from 0.67 to 9.4 ng/mL and were linearly related to dose.[201] In this study, clearance ranged from 15 mL/kg/min to 79 mL/kg/min, demonstrating wide interindividual variation as with dopamine. It also should be noted that variability between the ordered dose of catecholamines and the measured dose have been noted.[202] Combined with the interindividual variation in clearance, there may be significant differences in serum levels between patients receiving the "same" dose of epinephrine or dopamine.

Clinical Role

Epinephrine is employed to treat shock associated with myocardial dysfunction. Thus it may be appropriate for treatment of cardiogenic shock that is unresponsive to dopamine or following cardiac surgery.[180] In a model of RV injury, epinephrine increased pulmonary artery blood flow and RV power with greater efficiency than did dopamine or dobutamine.[158] It also may be used to increase pulmonary flow across left to right shunts.[118] The patient with sepsis who does not improve adequately after intravascular volume repletion and treatment with dopamine or dobutamine may benefit from an infusion of epinephrine. Epinephrine is most likely to be useful when hypotension exists in the context of a low cardiac index and stroke index ("cold shock").[150] At modest infusion rates (0.05 to 0.1 μg/kg/min), SVR decreases slightly; heart rate, cardiac output, and systolic blood pressure increase. At intermediate infusion rates, α_1-adrenergic activation becomes important but is balanced by the improved cardiac output and activation of vascular β_2 receptors. Even though epinephrine constricts renal and cutaneous arterioles, renal function and skin perfusion may improve. Very high infusion rates (more than 1 to 2 μg/kg/min) are associated with significant α_1-adrenergic-mediated vasoconstriction; blood flow to individual organs will be compromised, and the associated increase in afterload may further impair myocardial function. The effects of epinephrine on splanchnic blood flow continue to be investigated. Studies have shown decreased splanchnic blood flow, decreased oxygen uptake, and increased lactate with epinephrine compared with norepinephrine despite similar increases in global oxygen delivery.[203] Dopamine led to a decrease in lactate and an increase in arterial pH, whereas epinephrine was associated with increases in lactate and metabolic acidosis despite similar increases in cardiac index and oxygen delivery.[165] At a dose of 3.2 μg/kg/min in newborn piglets, epinephrine increased SVR and PVR, with a decrease in hepatic blood flow and oxygen delivery and an increase in lactate.[204] However, these effects may be a result of the dosages used as well as concomitant catecholamines that are employed. Seguin and colleagues[205] demonstrated increased gastric blood flow with epinephrine compared with norepinephrine with dobutamine. They note that the doses of norepinephrine they used were higher than in previous studies. Other studies have shown that the degree of shock also may influence splanchnic blood flow.[206] In a study involving adult patients with septic shock, stepwise infusion of epinephrine was associated with linear increases in cardiac rate, mean arterial pressure (MAP), cardiac index, LV stroke work index, oxygen consumption, and oxygen delivery. In that study, neither pulmonary nor systemic vascular resistance was affected by epinephrine infusion.[108]

Epinephrine also has been evaluated in the treatment of hypotension in very low birth weight infants.[207] Epinephrine increased blood pressure and the heart rate without decreasing urine output in infants with hypotension who were not responding to a dopamine infusion up to 15 μg/kg per minute. Urine output tended to increase among infants who had been oliguric.

Bolus injections of epinephrine are used to treat asystole and other nonperfusing rhythms. The recommended initial dosage is 0.01 mg/kg (10 μg/kg or 0.1 ml/kg of the 1:10,000 solution).[208] The recommendation that subsequent doses be tenfold greater (so-called "high-dose epinephrine") has been deemphasized. Although initial studies utilizing high-dose epinephrine were encouraging, recent publications indicate no improvement in return of spontaneous circulation or survival after high-dose epinephrine following out-of-hospital cardiac arrest in children or adults.[209,210] Epinephrine may be given by endotracheal tube; the dosage is 100 μg/kg. Intraosseous administration is appropriate for both bolus and continuous administration of epinephrine. The dosage is the same as for intravenous injection. Epinephrine by infusion is also the agent of choice for hypotension or shock following successful treatment of cardiac arrest. Shock following an episode of hypoxemia or ischemia is usually cardiogenic and may respond to epinephrine infusion.

Preparation and Administration

Epinephrine for injection is available in 1-mL ampules at a concentration of 1 mg/mL, vials at concentrations of 0.1 mg/mL (1:10,000) and 1 mg/mL (1:1,000), and auto-injector syringes at concentrations of 0.15 mg/0.3 mL and 0.3 mg/0.3 mL.[208] The 1:10,000 injection may be administered undiluted. The 1:1000 injection must be diluted with 0.9% sodium chloride for injection prior to administration; that is, 1 mg (1 mL) epinephrine 1:1000 diluted with 9 mL 0.9% sodium chloride to a final concentration of 0.1 mg/mL (1:10,000). To prepare a continuous infusion of epinephrine, 1 mg (1 mL) of 1:1000 should be diluted with 250 mL of 0.9% sodium chloride or 5% dextrose in water (D5W) to a final concentration of 4 μg/mL. Epinephrine should be infused by a syringe type of pump into a central vein. Consult Tables 25-4 and 25-5 for further dilution and compatibility information.

Adverse Effects

Epinephrine produces CNS excitation manifested as anxiety, dread, nausea, and dyspnea.[161] Enhanced automaticity and increased oxygen consumption are the main serious cardiac toxicities.[160] Extreme tachycardia carries a substantial oxygen penalty, as does hypertension. A severe imbalance of myocardial oxygen delivery and oxygen consumption produces characteristic electrocardiogram changes of ischemia. A subischemic but persistently unfavorable ratio of oxygen delivery to consumption also may be harmful to the myocardium.

This subject has not been adequately examined in the setting of critical illness in children. Epinephrine produces tachycardia. Increases in infusion rate lead to successively more serious events, including atrial and ventricular extrasystoles, atrial and ventricular tachycardia, and, ultimately, ventricular fibrillation. Ventricular dysrhythmias in the pediatric age group are not common but may occur in the presence of myocarditis, hypokalemia, or hypoxemia. Hypokalemia is produced by epinephrine infusion because of stimulation of β_2-adrenergic receptors, which are linked to sodium-potassium-ATPase located in skeletal muscle.[211] Infusion of 0.1 μg/kg/min lowered serum potassium by 0.8 mEq/L. Hyperglycemia results from β-adrenergic-mediated suppression of insulin release. Epinephrine is an α_1-adrenergic agonist, and infiltration into local tissues or intraarterial injection can produce severe vasospasm and tissue injury.[160] Concurrent activation of β_2 receptors by epinephrine limits vasospasm, and local injury to tissue is less frequent than with either norepinephrine or dopamine.

Epinephrine overdosage is serious. Several neonates died when inadvertently subjected to oral administration of huge amounts of epinephrine.[212] The syndrome mimicked an epidemic of neonatal sepsis with shock and metabolic acidosis. Intraaortic injection in infants (per umbilical artery) produces tachycardia, hypertension, and renal failure. Intravenous overdosage of epinephrine is immediately life-threatening. Manifestations include myocardial infarction, ventricular tachycardia, extreme hypertension (up to 400/300 mm Hg), cerebral hemorrhage, seizures, renal failure, and pulmonary edema. Bradycardia also has been observed. Manifestations of acute overdosage are treated symptomatically. β-receptor antagonists such as propranolol are contraindicated. Hypertension is treated with short-acting antihypertensives (e.g., nitroprusside).

Interactions

Tricyclic antidepressants and antihistamines such as diphenhydramine may potentiate the effects of epinephrine; use of fluorinated anesthetic agents such as halothane may increase the frequency of ventricular dysrhythmia.[160,213-215] Administration of epinephrine with a β-adrenergic antagonist such as propranolol may be dangerous because of residual unopposed α_1 activity; the result can be severe hypertension and bradycardia terminating in asystole. The concomitant use of α- or β-adrenergic antagonists also may antagonize the therapeutic effects of epinephrine.

Summary

Epinephrine is useful in treating shock associated with myocardial dysfunction and hypotension. In pediatric critical care, the most frequent indications for epinephrine infusion are cardiogenic shock, septic shock associated with reduced stroke volume, and shock following severe hypoxemia-ischemia (see Table 25-6).

Isoproterenol

Basic Pharmacology

Isoproterenol is the synthetic N-isopropyl derivative of norepinephrine (see Figure 25-8). The bulky N-terminal substituent confers β (β_1 and β_2) receptor specificity; the compound does not affect the α-adrenergic receptor. Thus the principal cardiovascular activities of isoproterenol relate to its inotropic, chronotropic, and peripheral vasodilator effects.[160]

Clinical Pharmacology

Isoproterenol enhances cardiac contractility and cardiac rate.[160] Peripheral vasodilatation produces a fall in SVR, augmenting the direct chronotropic action of the drug. Significant tachycardia ensues. Systolic blood pressure increases while mean and diastolic pressures fall (see Figure 25-10). If they were normal prior to infusion of isoproterenol, mesenteric and renal perfusions fall; however, if the subject was in shock, then the increase in cardiac output associated with isoproterenol administration may result in an increase in blood flow to these tissues.[160] Isoproterenol increases myocardial demand for oxygen and decreases supply by reducing diastolic coronary filling. If intravascularly the patient is fluid depleted, hypotension may complicate initiation of isoproterenol infusion.

Pulmonary bronchial and vascular bed β_2-adrenergic receptors produce bronchodilation and pulmonary vasodilatation, respectively.[216] For this reason isoproterenol by continuous intravenous infusion was employed as adjunctive therapy in children with refractory or rapidly worsening status asthmaticus.[69] At present, continuously nebulized albuterol and intravenous infusion of albuterol or terbutaline have largely supplanted isoproterenol for this indication.

Isoproterenol has few important metabolic effects. Hyperglycemia is not usually observed, although the drug does promote release of free fatty acids. Isoproterenol infusion causes sympathetic neurons to release norepinephrine, producing an increase in plasma levels of norepinephrine; however, this effect relative to the hemodynamic response to isoproterenol has not been studied.[189]

Pharmacokinetics

Isoproterenol is metabolized by COMT.[160] The plasma elimination half-life of isoproterenol is 1.5 to 4.2 minutes.[217,218] Information about therapeutic isoproterenol concentrations is not available in critically ill patients. In healthy volunteers, tachycardia and increases in stroke volume were observed at 50 pg/mL.[189]

Clinical Role

In the past isoproterenol was used for a variety of indications, including septic shock and cardiogenic shock associated with myocardial infarction; however, newer agents such as dopamine and dobutamine, together with a more subtle understanding of the pathophysiology of shock, have limited the use of this compound to very few specific indications.

Isoproterenol may be used to treat hemodynamically significant bradycardia.[219] However, epinephrine infusion is probably preferable.[197] When bradycardia results from heart block, placement of a pacemaker is definitive treatment. Bradycardia due to anoxia is treated by administering oxygen and improving gas exchange.

Preparation and Administration

Isoproterenol is available in 1 mL and 5 mL ampules at a concentration of 0.2 mg/mL (1:5000).[220] Prior to administration, dilute 1 mL (0.2 mg) to a final volume of 10 mL with 0.9% sodium chloride for injection or D5W to a final concentration of 20 μg/mL (1:50,000). To prepare an intravenous infusion of

isoproterenol, 1 to 10 mL of 1:5000 injection should be diluted with 500 mL of D5W to a final concentration of 0.4 to 4 μg/mL. The reader is directed to Table 25-4 for further dilution information.

Adverse Effects

Adverse effects associated with isoproterenol include fear, anxiety, restlessness, insomnia, and blurred vision.[220] Other effects may include headache, dizziness, tinnitus, sweating, flushing, pallor, tremor, nausea, vomiting, and asthenia. Cardiovascular effects may include ventricular tachycardia and other ventricular dysrhythmias that may be life-threatening. Isoproterenol may cause hypertension and also can cause severe hypotension.

Interactions

The concomitant administration of a halogenated general anesthetic such as halothane or an intravenous methylxanthine such as aminophylline may potentiate the adverse cardiovascular effects of isoproterenol.[220] Propranolol given before an operation to repair tetralogy of Fallot attenuates the response to isoproterenol postoperatively.[221] Isoproterenol decreases serum theophylline concentrations during concomitant therapy of status asthmaticus, and it may be necessary to increase theophylline dosage when isoproterenol therapy is initiated and reduce theophylline dosage when isoproterenol is discontinued.[222]

Summary

Isoproterenol is rarely used to treat children or adults. In the acute setting, it may play a role in the treatment of symptomatic bradycardia. Although it is effective adjunctive therapy for respiratory failure associated with status asthmaticus, more selective β_2 agonists are safer to use and are preferred.

Dobutamine

Basic Pharmacology

The structure of dobutamine, a synthetic catecholamine, resembles dopamine in that the β carbon is not hydroxylated. Unlike other catecholamines, there is a large aromatic substituent on the N-terminus. Like isoproterenol, dobutamine is administered as a racemate; (+) dobutamine is a strong β agonist and an α antagonist, and (–) dobutamine is an α agonist and a weak βagonist.[223] That dobutamine delivers significant inotropic and usually trivial chronotropic and vasopressor activity has been ascribed to this blend of receptor activities.

Clinical Pharmacology

In adults with CHF, dobutamine increased cardiac index from 2.4 to 2.9 L/min/m, decreased LV end-diastolic volume and increased the LV dP/dt.[224] Although renal function and urine output may improve as the increase in cardiac output fosters relaxation of sympathetic tone and improved perfusion, dobutamine did not improve indices of renal function compared with dopamine in critically ill patients.[135] Dobutamine improved RV systolic function and decreased pulmonary vascular resistance in piglets with RV injury.[158] In healthy children, dobutamine increased LV systolic function and relaxation.[225] In the newborn piglet, dobutamine increased superior mesenteric and renal artery blood flow after 60 minutes, increased cardiac index, and decreased SVR.[226] A threshold model with a log-linear dose-response relationship above the threshold has been demonstrated in critically ill term and preterm neonates and in children between 2 months and 14 years of age.[141,227] In one small study, dobutamine infusion (10 μg/kg/min) was associated with increases in cardiac output (30%), blood pressure (17%), and heart rate (7%). The thresholds for these increases were 13, 23, and 65 ng/mL, respectively, demonstrating that dobutamine is a relatively selective inotrope with little effect on heart rate at customary infusion rates.[228] Somewhat greater thresholds for improved cardiac output were observed in a second group of children and in infants, but in all studies, dobutamine improved cardiac contractility without substantially altering heart rate unless high infusion rates were employed.[227,229] Dobutamine has been shown to increase cerebral blood flow velocity but not cerebral oxygen consumption in patients with septic shock.[230]

Pharmacokinetics

The plasma elimination half-life of dobutamine in adults is approximately 2 minutes.[138] CHF increases the volume of distribution. In adults with CHF the terminal elimination half-life ($t_{½\beta}$) of dobutamine has been reported to be 2.37 minutes, with an apparent volume of distribution of 0.2 L/kg and total body clearance of 2.33 L/min/m^2.[231] Reported clearance values in children have ranged from 32 to 625 mL/kg/min in one study and from 40 to 130 mL/min/kg in another.[143,228] Infusions in the range used clinically yield plasma dobutamine concentrations from approximately 50 to 190 ng/mL in children and adults.[228] The principal route of elimination is methylation by COMT, followed by hepatic glucuronidation and excretion into urine and bile.[160] 3-O-methyldobutamine also represents a major route of elimination for dobutamine, with up to 33% of the infused drug being eliminated as the sulfoconjugated compound.[232] Dobutamine also is cleared from the plasma by nonneuronal uptake. Some investigators have reported nonlinear elimination kinetics, but other data suggest that dobutamine's kinetics can be adequately described by a simple first-order (linear) model.[141,143,145,228]

Clinical Role

In adults dobutamine produces improvement in a variety of conditions associated with poor myocardial performance, such as cardiomyopathy, atherosclerotic heart disease, and acute myocardial infarction. Dobutamine has been used following surgery for myocardial revascularization, cardiac transplantation, and other procedures associated with postoperative myocardial dysfunction, although undesirable chronotropic effects have been recorded when it has been used after cardiac surgery.[233] It is not clear that septic shock is an appropriate context in which to prescribe dobutamine, unless the primary disturbance is complicated by myocardial dysfunction. Although impaired myocardial performance can be demonstrated early in patients with septic shock, the main problem relates to regulation of vascular tone, and preferred agents are those that increase systemic vascular resistance. When ventricular dysfunction becomes an important complicating factor, however, dobutamine may be a useful adjunct. In this context, dobutamine alone or in combination with dopamine has produced an increase in cardiac output, LV stroke work, and blood pressure.[89] As indicated in Table 25-6, dobutamine also can be combined with norepinephrine

in treating the patient with myocardial dysfunction that is associated with hyperdynamic shock (e.g., a child who has received a cardiotoxic agent to treat cancer and in whom septic shock subsequently has developed).

Several studies in infants and children demonstrate that dobutamine improves myocardial function in a variety of settings.[141,227,228] Stroke volume and cardiac index improve without a substantial increase in cardiac rate. SVR and pulmonary vascular resistance (PVR) may decrease toward normal.[234] Dobutamine has been evaluated in children following cardiac surgery with cardiopulmonary bypass. In a study by Bohn and colleagues,[90] dobutamine enhanced cardiac output by increasing heart rate; indeed, tachycardia prompted discontinuation of the infusion in several patients. The expected fall in SVR was not observed in children who received the drug after cardiopulmonary bypass. The authors found no benefit compared with isoproterenol or dopamine. These differences between adults and children may be due to the fact that myocardial dysfunction and CHF are not characteristic of the circulatory status of many children undergoing repair of congenital heart disease. Unlike in adults, the indication for the operation involves abnormalities in ventricular architecture or abnormal circulatory anatomy. Berner and associates[235] found that children undergoing operations for mitral valve disease responded to dobutamine with an increase in stroke volume, whereas children with tetralogy of Fallot repair did not, and their cardiac output increased only through a higher heart rate. A more recent report by the same group indicated that following repair of tetralogy of Fallot, dobutamine did enhance cardiac output when it was combined with atrial pacing to increase heart rate. Isoproterenol without pacing provided a higher cardiac output than either dobutamine alone or dobutamine in combination with pacing.[236] Booker and colleagues[157] found that dobutamine and dopamine had equivalent inotropic effects in children following cardiac surgery. Specific indications for prescribing dobutamine in the pediatric age group are those associated with low output CHF and a normal to moderately decreased blood pressure (see Table 25-6). Typical examples include viral myocarditis; cardiomyopathy associated with use of anthracyclines, cyclophosphamide, or hemochromatosis (related to hypertransfusion therapy); or myocardial infarction (Kawasaki disease).

Dobutamine is *not* a first-line agent to treat low output states that are caused by intracardiac shunt or abnormal cardiac chamber structure. Dobutamine is used following corrective or palliative cardiovascular surgery in the child; however, in this context, its use also should be limited to occasions in which demonstrated or suspected myocardial dysfunction exists. Dobutamine may be of adjunctive value in treating myocardial dysfunction that complicates a primary condition such as ARDS or septic shock. Rarely, however, will it be appropriate to use dobutamine as the sole agent to treat hemodynamic compromise associated with sepsis, ARDS, or shock following an episode of severe hypoxia-ischemia.

Adverse Effects

Dobutamine usually increases myocardial oxygen demand. In subjects with myocardial dysfunction, coronary blood flow and oxygen supply improve with the increase in demand. However, if dobutamine is used when myocardial contractility is normal, oxygen balance will be adversely affected.[237] Tachycardia greatly increases oxygen use by the heart and should prompt a reduction in the dosage of dobutamine (or use of an alternate agent).

Although dobutamine is less likely than other catecholamines to induce serious atrial and ventricular dysrhythmias, these may occur in patients receiving dobutamine, particularly in the context of myocarditis, electrolyte imbalance, or high infusion rates.[234] Dobutamine and other inotropes should be administered cautiously to patients with dynamic LV outflow obstruction (hypertrophic aortic stenosis). Prolonged infusion of dobutamine inhibits the second wave of adenosine diphosphate induced platelet aggregation; in a few adult patients petechial bleeding attributed to dobutamine has developed.[238]

Preparation and Administration

Dobutamine is available at a concentration of 12.5 mg/mL in 20-mL, 40-mL, and 100-mL vials.[239] Prior to administration, dobutamine must be diluted to a final concentration of no greater than 5 mg/mL. Dobutamine also is available in premixed infusion bags at concentrations of 0.5 mg/mL, 1 mg/mL, 2 mg/mL, and 4 mg/mL in D5W. For further information regarding dilution and compatibility, refer to Table 25-4 and Table 25-5. Therapy is initiated at a rate of 2.5 to 5 μg/kg/min (see Table 25-7). One should consider a change to epinephrine if no substantial improvement occurs with infusion rates of 20 μg/kg/min.

Adverse Effects

Adverse cardiovascular effects may include hypertension, tachycardia, and ectopic heart beats.[239] Dobutamine also may cause headache, nausea, vomiting, paresthesia, and dyspnea. Dobutamine also may decrease serum potassium concentrations.

Interactions

The concomitant use of a β-adrenergic antagonist such as propranolol may antagonize the cardiovascular actions of dobutamine.[239] Halogenated anesthetic agents such as halothane may potentiate the adverse cardiovascular effects of dobutamine. Dobutamine may increase the insulin requirement of diabetic patients, and dobutamine may interfere with measurement of chloramphenicol by high-performance liquid chromatography.[240,241]

Summary

Dobutamine is a positive inotropic agent that should be reserved to treat poor myocardial contractility. Following cardiac surgery, dobutamine may be used when contractility is abnormal. For septic shock and other acute hemodynamic disturbances, dobutamine is an adjunct when the primary problem is complicated by poor myocardial function (see Table 25-6). In this context, concomitant use of a vasopressor such as norepinephrine may be appropriate.

Vasopressin

Basic Pharmacology

Vasopressin is a highly conserved hormone, and vasopressin-like peptides are present in numerous species. Its main function is to preserve fluid balance in the organism. In humans, it is released in response to two main stimuli: increases in plasma osmolality and decreases in effective circulating volume or

blood pressure. Although vasopressin has long been used for the treatment of diabetes insipidus, its name derives from its vasopressor effect. Vasopressin has a number of effects beyond volume regulation. It acts as a neurotransmitter in the CNS, has a role regulating adrenocorticotropin hormone release, and is involved in thermoregulation, platelet aggregation, and smooth muscle contraction in the uterus and gastrointestinal tract.[49,50]

Clinical Pharmacology

As noted previously, the response patterns are different for the two stimuli for vasopressin release. An increase in plasma osmolality above 280 mOsm/kg leads to a dramatic increase in the release of vasopressin from the posterior pituitary, and the hormone exerts its effect by increasing water reabsorption in the renal collecting duct. The dose/response curve is so steep that when osmolality is 290 mOsm/kg, vasopressin levels exceed those that produce maximal urinary concentration. In contrast, the threshold for release in response to hypovolemia or hypotension is much higher, with decreases of greater than 20% required. However, once the threshold is reached, plasma levels rise twentyfold to thirtyfold (far exceeding levels seen with hyperosmolality).[50] Vasopressin exerts its hemodynamic effects via the V_{1a} receptor, which is coupled to G_q. In the peripheral vasculature, intracellular calcium is increased, enhancing contraction and restoring systemic vascular tone. Vasopressin also inhibits potassium channels, further increasing intracellular calcium.[62,242] Baroreceptors in the left atrium, LV, and pulmonary veins sense changes in volume while baroreceptors in the carotid sinus and aorta sense changes in arterial pressure.[50] Decreased pressure leads to a reduced rate of firing and release of the tonic inhibition of vasopressin release.[49]

Vasopressin is a potent vasopressor when present in the plasma at high concentrations. At the lower concentrations associated with the vasopressin response to hyperosmolarity rather than hypotension, it does not elevate blood pressure because the resulting decrease in heart rate offsets the increase in SVR. For this reason, vasopressin was not considered to be a clinically useful agent to treat hypotension.[243] Landry and colleagues[244] measured plasma vasopressin levels in 19 patients with septic shock and 12 patients with cardiogenic shock (all receiving catecholamine support). Surprisingly, plasma levels of vasopressin were not elevated in patients with septic shock (mean 3.1 pg/mL; normal <5 pg/mL). Patients with cardiogenic shock had an expected mean level of 22.7 pg/mL. Vasopressin infusion (0.04 units/min intravenously) in 10 patients with septic shock who were receiving catecholamines produced an increase in SVR and MAP, which was associated with a decrease in cardiac index (CI). The resulting plasma level of vasopressin was 30 pg/mL, an appropriate concentration considering the level of hypotension. Therefore vasopressin plasma levels are inappropriately low in patients with vasodilatory septic shock, possibly because of impaired baroreflex-mediated secretion. The authors hypothesized that this phenomenon contributes to the hypotension of vasodilatory septic shock.

It appears that in the early stages of septic shock, vasopressin levels are higher than normal but decrease to either low levels or levels that represent a relative deficiency (normal level in the setting of hypotension) as shock continues.[245] This pattern has also been shown in a model of hemorrhagic shock.[246] In this study, neurohypophysis stores of vasopressin were depleted. In three patients with septic shock and low levels of vasopressin, the high intensity signal from the posterior pituitary on T1 weighted magnetic resonance imaging was lost, suggesting depletion of vasopressin.[245] Hence vasopressin deficiency may occur early in vasodilatory shock and contribute to its pathogenesis.

Pharmacokinetics

Vasopressin circulates as a free peptide and does not exhibit any protein binding.[55] It is degraded rapidly in the kidneys and liver, with 5% to 15% of an intravenous dose eliminated unchanged in the urine.[178] Renal failure or hepatic insufficiency can prolong the elimination half-life.[247,248] The normal elimination half-life is 10 to 20 minutes.[178]

Clinical Role

The original report by Landry and colleagues[244] has generated intense investigation into the clinical applications of vasopressin in the setting of vasodilatory shock. The same group prospectively evaluated vasopressin in patients with vasodilatory shock after placement of an LV assist device.[249] At a dose of 0.1 units/min, vasopressin increased MAP and SVR but not CI. Among patients with a high level of endogenous vasopressin, the increase in blood pressure tended to be less. A rapid response to vasopressin was noted in all patients, allowing for the dose to be decreased to as low as 0.01 units/min. This group also published experience with vasopressin in patients with septic shock and children after cardiac surgery.[250,251] In five patients with septic shock, vasopressin was given at doses ranging from 0.03 to 0.05 units/min. Again, blood pressure and SVR increased, allowing for discontinuation of catecholamine support in four patients. In 11 children, vasopressin was used to treat hypotension following cardiac surgery. At doses ranging from 0.0003 to 0.002 units/kg/min, vasopressin increased blood pressure within 1 hour, and the epinephrine infusion could be decreased in five of eight patients. Two patients who had echocardiographic evidence of poor function died. The remaining nine patients with vasodilatory shock survived and were discharged from the ICU. The authors cautioned against the use of vasopressin in patients with cardiogenic shock, in view of the potential effect on CI. Vasopressin levels were measured in three patients; two had an absolute deficiency and one had a relative deficiency of vasopressin. In adults, vasopressin deficiency (relative or absolute) was associated with shock following cardiopulmonary bypass. Hemodynamic function improved with vasopressin, and the need for other vasopressors decreased.[252] In a small double-blind randomized study, prophylactic vasopressin (0.03 units/minute) decreased the need for norepinephrine and ICU length of stay in patients receiving angiotensin-converting enzyme inhibitors who underwent cardiopulmonary bypass.[253] In another small study (N = 10), patients admitted to a trauma unit with the diagnosis of septic shock were randomly assigned to placebo or vasopressin at 0.04 units/min if they remained in shock with catecholamine support.[254] In the treatment group (n = 5), systolic blood pressure and SVR increased. Other vasopressors were discontinued within 24 hours in patients receiving vasopressin; in only one patient in the placebo group was other vasopressor support discontinued. In a larger, prospective, randomized study, the combination of vasopressin and norepinephrine was evaluated versus

norepinephrine alone in patients with catecholamine resistant vasodilatory shock.[255] Vasopressin was given at a dose of 0.06 units/min. The patients in the vasopressin-norepinephrine arm had a lower heart rate and higher blood pressure, SVR, and CI. They also had reduced requirements for norepinephrine; additionally, the norepinephrine group had a higher rate of new-onset dysrhythmias. Gastric perfusion also was better preserved in the vasopressin group.

In summary, in several studies of patients with vasodilatory shock, vasopressin has been shown to improve blood pressure, increase SVR, lessen the need for catecholamines, improve markers of myocardial ischemia and improve urine output.[139,256-258] Published experience in pediatric patients with septic shock is limited. Bojko and colleagues[259] published an abstract based on one case. At a dose of 0.02 units/min, blood pressure and SVR index increased and urine output improved with subsequent discontinuation of catecholamine therapy. Liedel and colleagues[260] published their experience with five patients, ranging in age from 2 weeks (23 week premature infant) to 14 years. Doses utilized were between 0.0006 units/kg/min and 0.008 units/kg/min (one patient was given 0.06 units/min). In all five patients, blood pressure increased (in one patient, blood pressure increased briefly prior to rapid deterioration and death) and catecholamine support could be decreased. In three patients, urine output improved. No formal randomized trial of vasopressin in pediatric patients with septic shock or following cardiac surgery has been published to date. Vasopressin also has been used as a vasopressor in children undergoing evaluation for brain death.[261] At a dose of 0.04 units/kg/h, blood pressure increased and α agonist support was decreased. No deleterious effect on organ function was noted.

Vasopressin also has become part of the Advanced Cardiac Life Support protocol for ventricular fibrillation in adults.[153] For children, however, the guidelines state that insufficient evidence exists, based on inconsistent results in adult patients, to make a recommendation either for or against the use of vasopressin in children who experience cardiac arrest.[262] Mann and colleagues[263] published their experience with vasopressin during cardiopulmonary resuscitation in pediatric patients. In six events involving four patients, vasopressin was given at a dose of 0.4 units/kg after conventional therapy had failed to achieve restoration of spontaneous circulation (ROSC). In all six events, pulseless electrical activity was the initial rhythm; at the time vasopressin was given, four patients were in asystole, one had pulseless ventricular tachycardia, and one had ventricular fibrillation. In four events (three patients), ROSC was achieved for more than 60 minutes. Of the two patients who survived for longer than 24 hours, one was discharged home in a condition close to her neurologic baseline; in the other patient, care was electively withdrawn. A recent review of the American Heart Association National Registry of Cardiopulmonary Resuscitation in children suggested a lower rate of return of spontaneous circulation (ROSC) in patients to whom vasopressin was administered during in-hospital resuscitation.[264] The authors emphasize that this result should be interpreted with caution, however, because vasopressin was only administered in 5% of the 1293 cases reviewed, in cases involving resuscitation efforts and vasopressin use after epinephrine had failed.

Preparation and Administration

Vasopressin is available at a concentration of 20 pressor units per mL in 0.5-mL, 1-mL, and 10-mL vials.[178]

Adverse Effects

Few adverse events have been reported with the use of vasopressin in the setting of vasodilatory shock. Elevation of liver enzymes and total bilirubin with a decrease in platelet count has been noted, and one series noted six cardiac arrests among 50 patients receiving vasopressin for hemodynamic support.[257,265] All six patients had "severe refractory shock," and five were receiving a vasopressin dose greater than 0.05 units/min. In 30% of patients receiving vasopressin, ischemic skin lesions of the distal limbs, trunk, or tongue were noted to develop. Preexisting peripheral arterial occlusive disease and the presence of septic shock were identified as risk factors.[265] Extravasation of vasopressin from a peripheral intravenous catheter was associated with skin necrosis.[266]

Interactions

The antidiuretic effect of vasopressin may be antagonized with the concomitant administration of epinephrine, heparin, lithium, or demeclocycline.[178] Tricyclic agents, chlorpropamide, carbamazepine, clofibrate, phenformin, and fludrocortisone may exert additive antidiuretic effects when used in combination with vasopressin. The concomitant use of vasopressin with a ganglionic blocking agent can enhance the pressor effect of vasopressin.

Summary

Vasopressin is a recent addition to the PICU practitioner's armamentarium for the treatment of decreased systemic vascular resistance. Its use may elevate blood pressure and urine output in patients with catecholamine refractory vasodilatory shock. The optimal dose has yet to be determined and the pharmacokinetics of the drug in conditions such as septic shock or after cardiopulmonary bypass need to be investigated. It may have a role in the future in pediatric advanced life support. Vasopressin should not be used in settings where impaired myocardial function is the principal problem. Controlled trials in the pediatric age group are urgently needed and should be accompanied by appropriate pharmacokinetic measurements.

Terlipressin

Basic Pharmacology

Telipressin (N_{α}-triglycyl-8-lysine vasopressin) is a synthetic analogue of lysine vasopressin, the endogenous vasopressin peptide found in mammals such as marsupials and pigs (arginine vasopressin is endogenous to humans).[267] Following intravenous administration, the three glycyl groups on terlipressin are enzymatically cleaved by endopeptidases, resulting in prolonged release of the active lysine vasopressin moiety. As a result, terlipressin has a longer duration of vasoconstrictive action (4 to 6 hours) than does arginine vasopressin (6 to 20 minutes).[267,268] Interestingly, the vasoactive effects of terlipressin are due in part to direct terlipressin effects and not solely to the liberated lysine vasopressin moiety.[269,270]

Clinical Pharmacology and Adverse Effects

Clinical trials in adults with refractory septic shock have demonstrated the ability of terlipressin administered as 1- to 2-mg intravenous boluses to significantly increase systemic vascular

resistance and MAP, PVS, and urine output, along with a reduction in blood lactate levels and the use of vasoactive catecholamines.[268,271-273] However, terlipressin also exhibits a number of troublesome adverse effects on the myocardium, including significant reductions in cardiac index, heart rate, oxygen delivery index, and oxygen consumption index. Trials are currently in progress to identify the optimal dosing strategy, including low-dose bolus or continuous intravenous infusion regimens.

A limited number of trials in children with refractory septic shock suggest a similar pharmacodynamic profile as that observed in adult patients.[274-277] A study in 14 children (mean age 5.6 years) with septic shock refractory to fluid resuscitation and vasopressors evaluated the addition of terlipressin intravenous boluses at an initial dose of 7 μg/kg twice daily, titrated based on blood pressure response to 20 μg/kg every 6 hours.[275] Terlipressin was associated with significant increases in mean arterial pressure (54 ± 3 to 72 ± 5 mm Hg; $P = .001$) at 10 minutes, and urine output (1.6 ± 0.5 to 4.3 ± 1.2 mL/kg/h; $P = .011$) at 1 hour after administration. The investigators also noted a significant reduction in heart rate (153 ± 6.5 to 138 ± 7.5 beats per minute; $P = .003$) at 12 hours, and a trend toward an increase in Pa_{O2} (95.1 ± 12.3 to 110.1 ± 20.5 mm Hg) and decrease in oxygenation index (10.2 ± 2.2 to 9.2 ± 1.7). Terlipressin has also been administered in the setting of prolonged pediatric cardiopulmonary resuscitation.[278] Terlipressin was administered as a 15 to 20 μg/kg intravenous bolus to 7 infants and children (age range, 2 months to 6 years) with asystole, representing eight episodes of cardiac arrest, who were undergoing cardiopulmonary resuscitation and had failed to respond to conventional therapy. Return of spontaneous circulation was achieved in six of the eight cardiac arrest episodes, with four patients surviving to discharge from the hospital. These results should be interpreted with caution until information from additional studies is available.

Bipyridines

Inamrinone, milrinone, enoximone, and piroximone are nonsympathomimetic inotropic agents. The structure (not a catecholamine) of inamrinone and milrinone are is shown in Figure 25-11. Inamrinone and milrinone are currently available for intravenous use only. As described previously, the pharmacologic effects of the bipyridines result from selective inhibition of phosphodiesterase III and not from interaction with adrenergic receptors or inhibition of sodium-potassium ATPase.[72] These agents produce positive inotropic and lusitropic effects on isolated ventricular tissue as well as relaxation of vascular smooth muscle. They often are used to improve myocardial contractility and to decrease ventricular afterload.

Inamrinone

Clinical Pharmacology

Administration of phosphodiesterase inhibitors to subjects with CHF results in an increase in cardiac output and a reduction of SVR, central venous pressure, and pulmonary capillary wedge pressure.[279] Heart rate is not affected. In a newborn lamb model it was demonstrated that amrinone is a direct pulmonary vasodilator, and this effect occurred at lower dosages than those effecting increase in cardiac output.[280] When amrinone is administered to patients whose volume is depleted

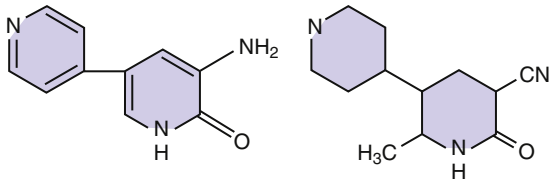

Figure 25–11. Structure of amrinone plus milrinone.

intravascularly or in whom the expected improvement in cardiac output does not occur, hypotension may result.[281] It is likely that improvement in cardiac function is due to a combination of a positive inotropic effect and a direct reduction of preload and afterload.[72,282] In patients with CHF, the amelioration in global hemodynamic function is associated with an improvement in the ratio of myocardial oxygen delivery to consumption.[283] Inamrinone may improve contractility in patients who have failed to respond to catecholamines and may further increase the CI even in patients who have responded to dobutamine. Therapeutically effective concentrations are in the range of 2.0 to 7.0 μg/mL, and there is a strong correlation between concentration and improvement in hemodynamic function.[284] Inamrinone reduces PVR in children with intracardiac left-to-right shunts. In one study, children with elevated PVR exhibited a 47% reduction in PVR upon infusion of amrinone.[130] The PVR/SVR ratio decreased by 45%. In these children, both pulmonary blood flow and left-to-right shunt increased. In children with normal pulmonary pressure, amrinone infusion was associated with a decrease in SVR but not PVR. Inamrinone may be undesirable in children with an elevated pulmonary artery pressure associated with a high-flow left-to-right shunt but normal PVR. Conversely, the phosphodiesterase type III inhibitors may be an effective adjunctive therapy in the child with elevated PVR and reduced pulmonary blood flow. Inamrinone increases CI and decreases SVR after the Fontan procedure.[285] It has been questioned whether the inotropic effects of amrinone derive more from its ability to decrease systemic vascular resistance than from a positive inotropic effect.[286] Bailey and colleagues[287] compared the effects of nitroprusside and inamrinone. Although both agents decreased SVR to a similar extent, inamrinone increased the cardiac index and produced a greater increase in the ratio of change in cardiac index to change in mean arterial blood pressure. In infants following cardiac surgery, inamrinone increased LV fractional shortening and the mean velocity of circumferential fiber shortening and decreased LV end diastolic wall stress.[288]

In a cell culture line, inamrinone was shown to decrease the expression of nF-kappa β and inducible nitric oxide synthetase in cardiac myocytes exposed to lipopolysaccharide and tumor necrosis factor-α. IL-1_{β} production in response to tumor necrosis factor-α was also decreased, as was intercellular adhesion molecule expression.[289] The authors of the study note that the results imply that inamrinone is acting downstream at a central point for proinflammatory signaling. The clinical implications of these findings have yet to be explored.

Pharmacokinetics

Inamrinone is metabolized by N-acetyltransferase; in addition, up to 40% is eliminated unchanged in the urine.[290] In healthy adults, the half-life of inamrinone in "slow acetylators" is 4.4

hours and in "fast acetylators" is 2.0 hours.[291] It is unclear if this difference is clinically important.[292] Protein binding is not extensive. One study of children younger than 1 year following cardiopulmonary bypass found that the half-life was prolonged in those younger than 4 weeks and that volume of distribution (1.7 to 1.8 L/kg) was threefold greater than others have reported in adults.[284] A second study among children older than 1 month found wide interpatient variability in pharmacokinetic measurements. No relation was found between age and any measured pharmacokinetic parameter. Average clearance was approximately 1.2 mL/kg/min, with a range of 0.4 to 2.2 mL/kg/min. The mean half-life was 5.5 hours.[202] No correlation was noted between inamrinone pharmacokinetics and hepatic or renal function. In infants younger than 1 month, half-life is increased and clearance is decreased.[292] Neonates were noted to have a smaller volume of distribution at steady state.[292]

Clinical Role

In adults with CHF, phosphodiesterase type III inhibitors are safe and effective when given intravenously, and their clinical place in short-term management of patients with refractory heart failure is clearly established. Bipyridines are most useful in management of children and adolescents with isolated cardiac dysfunction, particularly when it is due to myocardial failure, or in the setting of decreased cardiac output following cardiopulmonary bypass. They provide both inotropic and afterload reduction and may be an alternative to coadministration of dobutamine and an afterload-reducing agent (see Table 25-7). Although inamrinone has been shown to be useful in increasing cardiac index and decreasing SVR in children following cardiac surgery, its role has been largely supplanted by milrinone because of concern over thrombocytopenia induced by inamrinone (seethe section that follows on adverse effects).

Preparation and Administration

Inamrinone lactate is available in 5 mg/mL vials for injection.[293] Loading doses may be administered undiluted over 2 to 3 minutes. In adults the manufacturer recommends an inamrinone loading dose of 0.75 mg/kg, which may be repeated once. This dose is followed by a continuous infusion of 5 to 10 μg/kg/min. Maintenance infusions should be prepared in 0.45% or 0.9% Sodium Chloride Injection United States Pharmacopeia (USP) at a final concentration of 1 to 3 mg/mL. Inamrinone is not compatible with 5% Dextrose USP or furosemide. The dosage in children has not been conclusively established, although the publication previously cited contains a suggestion for a much higher loading dose (children younger than 1 year of age: initial intravenous inamrinone bolus of 3.0 to 4.5 mg/kg in four divided doses followed by a continuous infusion of 10 μg/kg/min; neonates: a similar bolus followed by a continuous infusion of 3 to 5 μg/kg/min).[284] These recommendations are supported by a second study, in which this regimen was associated with a generally satisfactory plasma concentration of ianmrinone.[290] As with the catecholamines, significant differences between the ordered concentration and the measured concentration of inamrinone have been shown.[290]

Adverse Effects

Inamrinone produces reversible dose-dependent thrombocytopenia (incidence 2.4%), which is more common during prolonged therapy. This finding was not seen in the largest published pediatric study, but case reports suggest that it occurs in children as well.[284] In one series, thrombocytopenia developed in eight of 18 patients.[294] The plasma concentration of inamrinone did not correlate with thrombocytopenia, although the levels of *n*-acetylamrinone were increased in the patients with thrombocytopenia. Supraventricular and ventricular dysrhythmias have occurred during infusion of inamrinone but may have been related to the underlying condition of the patient. Fatal progressive hypotension not responsive to peritoneal dialysis has been reported for inamrinone overdose.[295] When inamrinone or milrinone is infused too rapidly during the loading dose, hypotension is produced. This problem is exacerbated in patients whose volume is depleted.

Interactions

The concomitant use of inamrinone and digoxin results in additive inotropic effects.[293] The combined use of inamrinone and disopyramide was associated with profound hypotension in a single patient during clinical testing; as a result concomitant use is not recommended.

Milrinone

Clinical Pharmacology

A derivative of inamrinone, milrinone shares the same mechanism of action and pharmacodynamic profile. The major advantage is that, unlike inamrinone, milrinone does not appear to evoke thrombocytopenia. In adults, milrinone acts both as an inotrope and vasodilator. In adults with CHF, milrinone causes a much greater decrease in left and right filling pressures and SVR than does dobutamine, even at equivalent contractility dosing.[296] Compared with dobutamine, milrinone produces a greater reduction in SVR for a given degree of improvement in inotropic state.[297] Blood pressure is well maintained, even in the face of reduced SVR, because of the associated improvement in contractility and stroke volume. Increasing doses of milrinone have been shown to correlate with increasing mixed venous oxygen saturation (Svo_2).[298] It has been extensively used following cardiac surgery and in adults with CHF, where it increases cardiac index and reduces SVR, filling pressures, and, often, systemic blood pressure.[74,299,300] When given perioperatively, milrinone attenuated decreases in gastric mucosal pH in patients undergoing coronary artery bypass grafting.[301] Splanchnic oxygenation improved and systemic levels of endotoxin and IL-6 were decreased. Although a cell culture study failed to show a decrease (with a possible increase) in proinflammatory markers in response to milrinone, milrinone decreased serum levels of IL-1β and IL-6 following cardiopulmonary bypass.[216,289] The decrease in IL-6 correlated inversely with levels of cAMP.

Several studies have evaluated milrinone in children following surgery for congenital heart disease. In one study, a loading dose of 50 μg/kg followed by a continuous infusion of 0.5 μg/kg/min was associated with mild tachycardia and a slight decrease in systemic blood pressure.[302] Cardiac index increased from 2.1 to approximately 3.1 L/min/m^2, while SVR index and PVR index decreased from approximately 2100 to 1300 and 488 to 360 dyne-sec/cm^5/m^2, respectively. In a recently completed double-blind, placebo-controlled trial, high-dose milrinone (75 μg/kg bolus followed by continuous infusion at 0.75 μg/

kg/min) was associated with a decreased incidence of low cardiac output syndrome.[119] Length of hospital stay was similar among the treatment groups, but prolonged stay (greater than 15 days) was more common in the placebo arm. Milrinone also has been evaluated in children with nonhyperdynamic septic shock (i.e., normal to low CI and normal to elevated SVR). In a double-blind crossover study, milrinone increased CI, stroke volume index, and oxygen delivery while decreasing SVR.[302a] No differences in blood pressure or PVR were seen. Milrinone was given at a dose of 0.5 μg/kg/min as a continuous infusion after a bolus dose of 50 μg/kg.

Pharmacokinetics

In contrast to inamrinone, milrinone is approximately 70% bound to plasma proteins, with approximately 85% renal elimination.[303] Hepatic glucuronidation accounts for a minor elimination pathway. In healthy adults, milrinone has an apparent volume of distribution of 0.32 ± 0.08 L/kg, clearance of 6.1 ± 1.3 mL/kg/min, and an elimination half-life of 0.8 ± 0.22 hours.[303] Both renal dysfunction and congestive heart failure affect the elimination profile of milrinone, extending the elimination half-life to approximately 2 hours.[304] In infants and young children undergoing cardiac surgery, the weight-adjusted clearance of milrinone was shown to increase with age, ranging from 2.6 mL/kg/min at age 3 months to 5.6 mL/kg/min at age 22 months.[305] In a separate study of milrinone in infants and children (ages 1 to 13 years) following open heart surgery, milrinone clearance was significantly lower in infants than in children (3.8 ± 1 versus 5.9 ± 2 mL/kg/min, respectively).[306] Importantly, the milrinone clearance values for both infants and children were significantly higher than the clearance of milrinone reported in adults following cardiac surgery (2 ± 0.7 mL/kg/min).[307] In the pediatric study just described, the plasma concentration versus time data fit a two-compartment model.[306] The apparent volume of distribution by area (Vβ), which reflects the volume of distribution during the terminal elimination phase, was not significantly different between infants and children (0.9 ± 0.4 versus 0.7 ± 0.2 L/kg). However, the value reported for infants differed significantly from the value reported in adults following cardiac surgery (0.3 ± 0.1 L/kg). [307] In children with septic shock, the median half-life of milrinone was 1.5 hours.[308] Plasma levels did not correlate with changes in CI or SVR. One patient with acute renal failure had an eightfold increase in the serum level of milrinone even though the same dosing regimen was used as in the patients without renal failure.

Clinical Role

Based on its shorter elimination half-life and possibly a lower incidence of thrombocytopenia, milrinone is generally preferred to amrinone for pediatric patients.[305] Milrinone may be used to increase cardiac contractility following cardiac surgery and may have a role in improving perfusion in patients with "cold shock." Its properties as a vasodilator also would suggest that milrinone may be useful in the setting of pulmonary hypertension.[309]

Preparation and Administration

Milrinone lactate is available in 10-mL, 20-mL, and 50-mL single-dose vials, each at a concentration of 1 mg/mL, and in 100-mL and 200-mL flexible containers at a concentration of 200 μg/mL in 5% dextrose.[310,311] Loading doses may be drawn from a single-dose vial and administered undiluted over 15 minutes. A loading dose of 50 μg/kg is generally used in children.[302,305] For preparation of maintenance infusions, milrinone should be diluted with 0.45% or 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP to a final concentration of ≤200 μg/mL. Maintenance infusion rates are generally initiated at 0.5 μg/kg/min, titrated to clinical response. Based on the higher clearance and volume of distribution values previously discussed, Ramamoorthy and colleagues[306] suggested a loading dose and initial maintenance infusion rate of 104 μg/kg and 0.49 μg/kg/min, respectively, in infants, and 67 μg/kg and 0.61 μg/kg/min, respectively, in children. In patients not given a loading dose of milrinone, changes in CI and plasma levels of milrinone after 3 hours were similar to those seen in patients given a loading dose.[312] Milrinone is not compatible with furosemide but is compatible with a large number of drugs used in the PICU, including dopamine, epinephrine, fentanyl, and vecuronium.[313,314]

Adverse Effects

In the largest pediatric study, serial measurements showed no difference in platelet count over time (baseline, 36 hours, 72 hours, and discharge) by treatment arm, and there was no difference in the incidence of thrombocytopenia (platelet count less than 50,000) during the study infusion (7.4% placebo, 8.8% low dose, and 2.6% high dose).[119]

Summary

The bipyridines offer an attractive combination of positive inotropy with decreased SVR. The bipyridines are likely to be effective in short-term management of the infant and child with myocardial disease. Milrinone has an established role in the management of impaired cardiac contractility following cardiopulmonary bypass; its role in other settings has not been conclusively established by randomized trials.

Nesiritide

Basic Pharmacology

Nesiritide is a recombinant human B (brain)-type natriuretic peptide (rhBNP) that exerts a direct vasodilatory effect on arterial and venous blood vessels, along with potent natriuretic and diuretic effects on the kidney.[193,315] These effects result from the binding of rhBNP to natriuretic peptide receptors A and B on vascular smooth muscle cells, endothelial cells, kidney, and adrenal gland; inhibition of peripheral vascular sympathetic neurotransmission; and inhibition of the renin-angiotensin-aldosterone pathway (Figure 25-12).[164,193,315,316] Binding to natriuretic peptide receptors A and B activates guanylyl cyclase, resulting in an intracellular rise in cGMP.[164,317] cGMP regulates vascular smooth muscle relaxation via a decrease in intracellular calcium.[317]

Endogenous BNP is secreted primarily by the left ventricle, with increased wall tension thought to be the main stimulus for secretion.[318] BNP seems to exert a protective effect on the heart, maintaining homeostasis (preventing excess accumulation of salt and water) in the setting of early heart failure.[164] Indeed, plasma BNP concentrations are higher in patients with CHF, with the increase strongly correlated with the degree of LV dysfunction.[164] BNP levels also have been used to differentiate cardiac from noncardiac causes of respiratory

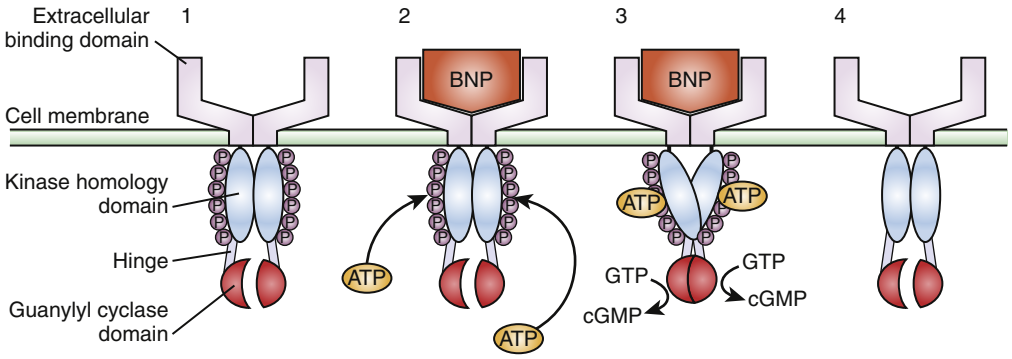

Figure 25–12. Interaction of brain natriuretic peptide (*BNP*) with type A natriuretic peptide receptor (*NPR-A*). NPR-A is a member of the family of transmembrane guanylyl cyclase (*GC*) receptors and is comprised of an extracellular natriuretic peptide binding site, a juxtamembraneous kinase homology domain (*KHD*), and two active guanylyl cyclase catalytic sites. (1) In the basal state, phosphorylation of the KHD enhances binding affinity for BNP and inhibits guanylyl cyclase activity. (2) Binding of BNP to the peptide binding site triggers the binding of adenosine triphosphate (ATP) to the KHD. (3) ATP binding induces a conformational change in the KHD and hinge region, resulting in activation of guanylyl cyclase and the conversion of GTP to the intracellular second messenger cyclic guanosine monophosphate (*cGMP*). cGMP subsequently produces the physiologic effects of BNP by regulating the activity of various third messengers, including phosphodiesterase (*PDE2* and *PDE3*) and protein kinase enzymes (*PKG I* and *PKG II*), and by reducing the intracellular concentration of calcium. cGMP reduces intracellular calcium by inhibiting calcium influx via L-type calcium channels and by enhancing calcium efflux via calcium-magnesium ATPase and the sodium-calcium exchanger. (4) The conformational change in the KHD also triggers the activity of phosphatase enzymes, resulting in transient dephosphorylation of the KHD and nonresponsiveness to subsequent BNP binding. *(Modified from Potter LR, Hunter T: Guanylyl cyclase-linked natriuretic peptide receptors: structure and regulation,* J Biol Chem *276:6057-6060, 2001; Kuhn M: Molecular physiology of natriuretic peptide signaling,* Basic Res Cardiol *99:76-82, 2004 and Lucas KA, Pitari GM, Kazerounian S et al: Guanylyl cyclases and signaling by cyclic GMP,* Pharmacol Rev *52:375-413, 2000.)*

distress in infants and children and have been shown to correlate with the presence of hemodynamically significant patent ductus arteriosus in neonates.[319-321a]

Clinical Pharmacology

The hemodynamic effects of nesiritide in adult patients with decompensated CHF include a reduction in both preload (decreased pulmonary capillary wedge pressure) and afterload (decreased systemic vascular resistance), resulting in an increase in CI even though BNP appears to exert no direct inotropic effects.[297,322-326] The diuretic and natriuretic effects of nesiritide resulted in fewer patients requiring concomitant diuretic therapy in comparison with nitroglycerin or dobutamine.[297,327] In contrast to dobutamine, nesiritide appears not to be arrythmogenic.[328] The most common adverse effect of nesiritide is hypotension; however, this effect is not associated with reflex tachycardia.[323,328]

The beneficial effects of nesiritide have been confirmed in a limited number of studies involving infants and children with heart failure.[276,315,329-331] These studies consistently revealed significant improvement in urine output with nesiritide administration. Significant hemodynamic changes were not consistently observed, although pulmonary artery catheters were placed in only one reported trial. A placebo-controlled trial in children with dilated cardiomyopathy undergoing right heart catheterization revealed significant reductions in pulmonary capillary wedge pressure, mean pulmonary arterial pressure, and systolic blood pressure with nesiritide administration.[329] Nesiritide was generally well tolerated, although a retrospective review of nesiritide administration to neonates (mean postnatal age 16 ± 8 days) at one institution reported an 18% incidence of hypotension requiring intervention.[331]

Pharmacokinetics

Nesiritide is administered by intravenous infusion and in adults follows a two-compartment pharmacokinetic model, with a brief distribution half-life of approximately 2 minutes, followed by a terminal elimination half-life of only 18 minutes.[193,323] The apparent volume of distribution is 0.19 L/kg, essentially reflecting distribution into extracellular fluid. Nesiritide is eliminated via binding to natriuretic peptide receptor C on target cell surfaces (internalization and enzymatic degradation), hydrolysis by neutral endopeptidase-24.11 on the surface of vascular endothelial cells, and by the kidney via glomerular filtration. Dosage adjustment is not indicated in patients with renal dysfunction. Pharmacokinetic information is not available in infants or children.

Preparation and Administration

Nesiritide can be reconstituted using any of the following preservative-free diluents (250 mL bag): 5% Dextrose in Water Injection, USP; 0.9% Sodium Chloride Injection, USP; or 5% Dextrose and 0.2% Sodium Chloride Injection, USP.[193,332] Each 1.5-mg vial of nesiritide is reconstituted with 5 mL of diluent and the resulting solution withdrawn and added to the 250-mL bag, yielding a final nesiritide concentration of 6 μg/mL. The reconstituted solution must be administered within 24 hours of preparation.

Nesiritide is administered as a 2 μg/kg intravenous bolus (drawn from the 250-mL infusion bag) pushed over 60 seconds, followed by an initial continuous infusion rate of 0.01 μg/kg/min.[193] To avoid or minimize hypotension, titration should be limited to increments of 0.005 μg/kg/min no more often than every 3 hours, to a maximum of 0.03 μg/kg/min.

Adverse Effects

Symptomatic hypotension has been reported in approximately 4% of adult patients receiving nesiritide.[193] Careful blood pressure monitoring is therefore advised, and nesiritide is not recommended in adults with baseline systolic blood pressure less than 100 mm Hg. Nesiritide may decrease renal function in patients with severe CHF whose kidney function is dependent on renin-angiotensin-aldosterone function.

Drug Interactions

Symptomatic hypotension with nesiritide may be more common in patients concurrently receiving angiotensin-converting enzyme inhibitors.[193]

Clinical Role

Nesiritide appears to offer a number of potential advantages in patients with decompensated heart failure, including rapid improvement in hemodynamic measurements and symptoms.[323] Nesiritide is also devoid of the arrhythmogenic properties associated with dobutamine and milrinone. Nesiritide is not approved by the Food and Drug Administration for pediatric use, and pediatric information is limited.

Digitalis Glycosides

The role of digoxin in the acute care of critically ill children has always been limited by a narrow therapeutic range, slow onset of action, and the potential for life-threatening adverse effects. With the advent of new therapies for both the acute and chronic management of CHF and myocardial dysfunction, its role has been further decreased. A review is offered here as the practitioner in the PICU may still encounter patients taking the drug, particularly for control of dysrhythmias. Digoxin, as do the catecholamines and other drugs discussed in this chapter, exerts its inotropic effects by increasing intracellular calcium.

Basic Pharmacology

The cardiac glycosides consist of a steroid moiety with one to four sugar molecules attached.[333] The number and composition of the associated sugar molecules affect the pharmacokinetics of the specific glycoside; all digitalis glycosides have similar pharmacodynamic properties. Glycosides bind to and inhibit sodium-potassium ATPase. Binding of digoxin to ATPase is affected by serum potassium. Hyperkalemia depresses digoxin binding, whereas hypokalemia has the opposite effect, accounting in part for potentiation of digoxin-induced dysrhythmias during hypokalemia.[334] As described earlier in this chapter, inhibition of ATPase produces an increase in intracellular calcium and enhances the inotropic state of the myocardium.

Clinical Pharmacology

In patients with CHF, the positive inotropic action of digoxin leads to increased cardiac output and reductions in filling pressures, edema, and sinus node rate. In a study of 10 adult patients with acute myocardial failure, a single dose of 10 μg/kg of digoxin produced a 69% increase in LV stroke work index, a 25% reduction in wedge pressure, a 16% to 28% increase in cardiac index, and a 25% increase in stroke index within 2 hours of infusion.[131] Many of these changes were present within 60 minutes. In infants, digoxin is known to produce changes in echocardiographic measurements that are associated with an improved inotropic state, although detailed invasive hemodynamic measurements have not been made in infants or children.[25,229,335,336] When CHF is due to obstructive lesions or left-to-right shunts, it is more difficult to demonstrate benefit than when CHF is due to myocardial failure.

In patients with CHF who have a sinus rhythm, administration of digoxin produces a decrease in heart rate, likely because of improvement of the inotropic state and withdrawal of compensatory sympathetic activity. In addition, digoxin enhances vagal tone by increasing baroceptor sensitivity and by directly stimulating central vagal centers,[334] which causes direct slowing of heart rate in addition to that permitted by improved function. Another effect of digoxin-mediated enhanced vagal tone is slowed conduction of atrial impulses through the atrioventricular node to the ventricle. This property is exploited in use of digoxin to control or treat supraventricular rhythm disturbances such as supraventricular tachycardia and atrial flutter or fibrillation. This aspect of digitalis pharmacology is reviewed in Chapter 28.

Use of digoxin in the PICU is further complicated by the large number of pharmacokinetic and pharmacodynamic interactions between digoxin and other pharmacologic agents used in critical care.[337] For example, carvedilol (a β-blocker) has been shown to decrease the elimination of digoxin in children, necessitating a reduction in digoxin dosage.[338] Toxicity is a major limiting factor in administering digitalis glycosides to critically ill patients. The most frequent side effects are gastrointestinal; the most serious are disturbances in cardiac rhythm.[25,316,333] Digitalis toxicity is reviewed in several of the references.[339,340] In adults and older children the dominant manifestations of digoxin toxicity are tachydysrhythmias such as ventricular premature contractions, ventricular tachycardia, and ventricular fibrillation. Atrial tachycardia and junctional tachycardia also may be noted. Bradycardia and A-V conduction block are noted with acute, profound intoxication. In infants enhanced vagal tone and diminished sympathetic activity alter this pattern; the dominant findings are A-V conduction block and sinus bradycardia.

Digitalis toxicity is made more likely by factors that increase myocardial irritability, such as myocarditis, ischemia, hypoxemia, or catecholamine support. Hypokalemia and alkalosis also potentiate digoxin-induced dysrhythmias. Treatment of digoxin toxicity involves supportive treatment and correction of electrolyte disturbances.[341] Specific pharmacologic support (e.g., with atropine, lidocaine, phenytoin, or magnesium sulfate) may be necessary (although frequently unsuccessful), and in life-threatening circumstances, treatment with digoxin-specific Fab antibody fragments is indicated.[342]

Pharmacokinetics

The dosage of digoxin prescribed for young children and infants is much higher than that applied to older children and adults. In the past, this disparity was ascribed to the incorrect belief that developmental immaturity was associated with decreased myocardial sensitivity to digitalis. It is now understood that neonates are not less sensitive to digoxin but eliminate digoxin more rapidly.[25] Clearance is dependent on age, although there is wide interindividual variation during the first year of life.[278] Thus infants may require higher loading ("digitalizing") and maintenance dosages to achieve a therapeutically effective plasma concentration of 1 to 2 ng/mL. Distribution of digoxin is relatively

slow; therefore plasma levels will be misleadingly elevated if determined sooner than 6 hours following administration of a dose. At distribution equilibrium, the concentration of digoxin in the heart is 15 to 30 times greater than that in the plasma. In the nonacutely ill child, the half-life of digoxin is 36 hours with a clearance of 8.6 L/h.[58] Digoxin is eliminated by the kidney through glomerular filtration and renal tubular secretion, through renal tubular mechanism, including the efflux pump, P-glycoprotein (P-gp). A polymorphism that decreases the activity of this enzyme was associated with increased serum digoxin levels.[343] Elimination is also strongly affected by renal dysfunction, complicating use of the agent in the critically ill child.

Clinical Role

The role of digoxin in the care of the pediatric patient continues to be refined and narrowed. Its role as an inotropic agent has been supplanted by other drugs (milrinone, for example) with a more favorable pharmacodynamic profile in the acute setting. The use of digoxin to improve cardiac function in children with systemic to pulmonary shunts also has decreased greatly, and its use primarily now is in control of certain dysrhythmias and the improvement of systolic function in children without structural lesions.[340] Because digoxin does not produce β-adrenergic receptor desensitization and has beneficial effects by virtue of decreased sympathetic activity, it continues to have a clinical role.

Preparation and Administration

Digoxin for injection is available in concentrations of 250 μg/mL and a pediatric formulation of 100 μg/mL.[337] Digoxin may be administered undiluted, or it may be diluted with sterile water for injection, D5W, or 0.9% sodium chloride for injection. A dilution of at least fourfold (1 mL digoxin/4 mL diluents) must be used to avoid precipitation.

Adverse Effects

Cardiovascular adverse effects may include sinus bradycardia, atrioventricular block, ventricular tachycardia, and other dysrrhythmias.[337] Gastrointestinal adverse effects of digoxin include nausea, vomiting, anorexia, diarrhea, constipation, abdominal pain, and abdominal distension. Other effects may include visual disturbances, photophobia, headache, muscle weakness, fatigue, drowsiness, dizziness, vertigo, seizures, and neuropsychiatric abnormalities.

Interactions

The adverse cardiovascular effects of digoxin may be potentiated by agents that lower serum potassium or magnesium concentrations, such as thiazide diuretics, loop diuretics, ethacrynic acid, amphotericin B, corticosteroids, polystyrene sodium sulfonate, and glucagon.[337] The concomitant administration of digoxin with intravenous calcium results in additive or synergistic inotropic and adverse cardiovascular effects. β-adrenergic antagonists can cause complete heart block when administered with digoxin. The concomitant use of digoxin with succinylcholine or sympathomimetics increases the risk of dysrhythmias. Digoxin has a narrow therapeutic index; serum digoxin concentrations are increased with concomitant administration of amiodarone, flecainide, quinidine, propafenone, verapamil, captopril, itraconazole, and indomethacin.

Summary

Digitalis glycosides are effective inotropic agents that have the desirable property of slowing rather than accelerating heart rate. As a result of its narrow therapeutic window, long half-life, and the emergence of newer medications, the role of digoxin in the acute setting has diminished.

Conclusion

There continues to be a growing understanding of the mechanisms underlying adrenergic receptor signaling, the control of vascular tone, and the influence of genetic polymorphisms on the pathways involved in these processes. Despite this growing understanding, the therapeutic options for supporting the patient with evidence of impaired end-organ perfusion has not significantly changed. The catecholamines remain the mainstay of therapy, with dopamine often the initial drug of choice for either inotropic or vasopressor support. Epinephrine or norepinephrine is used when poor cardiac performance or decreased systemic vascular tone, respectively, is the hemodynamic derangement and perfusion is not improving with dopamine. Milrinone (or amrinone) or dobutamine can be used to increase myocardial contractility if there is no frank hypotension. Milrinone is particularly useful for hemodynamic support after surgery for congenital heart disease. Vasopressin has emerged as an option for vasodilatory shock that is resistant to catecholamine therapy. Often the clinical picture is mixed and the patient may require both inotropic and vasopressor support. Careful attention to the clinical signs of end-organ perfusion and an understanding of cardiovascular pharmacology are necessary for the care of these patients.

References are available online at http://www.expertconsult.com.

II

Chapter 26

Cardiopulmonary Interactions

Bradley P. Fuhrman

PEARLS

- Mechanical ventilation can alter right ventricular preload and ejection, pulmonary vascular resistance, left ventricular preload, and left ventricular afterload.
- In patients who are hypovolemic, effects of positive airway pressure on right ventricular preload generally predominate, whereas in patients who have myocardial dysfunction, effects on left ventricular afterload may predominate.
- Changes in arterial pulse pressure over the respiratory cycle help to predict which patients will increase cardiac output with fluid resuscitation.
- Changes in arterial pulse pressure over the respiratory cycle on pulmonary end-expiratory pressure (PEEP) compared to changes in pulse pressure over the respiratory cycle at zero PEEP may identify those patients whose cardiac output has been adversely effected by PEEP.
- Respiratory effort imposes critical loads on the heart, and respiratory muscle failure from inadequate circulation is a final common pathway to death in shock and circulatory impairment.

Both spontaneous and mechanical ventilation affect the circulation in predictable ways. The cardiovascular system also has important effects on respiration, ventilation, and gas exchange.

Effects of Ventilation on Circulation

For clarity of discussion, wherever the term *positive pressure ventilation* is used in this chapter, the patient is presumed to respond passively, as though subjected to neuromuscular blockade.

As shown by Cournand[1] in his sentinel paper, mechanical ventilation can have important effects on circulation. The magnitude of these effects may be accentuated by factors that compromise cardiovascular adaptability, such as hypovolemia, cardiac dysfunction, or disordered vascular tone.

Mechanical ventilation can alter right ventricular preload and ejection, pulmonary circulation, left ventricular preload, and left ventricular afterload. These interactions may occur simultaneously and yet not act in the same direction on cardiac output. The net effect on cardiac output depends on which interaction predominates over the course of the respiratory cycle. For this reason, it is often easier to rationalize an interaction than to predict it.

Right Ventricular Filling and Stroke Volume

The effects of mechanical ventilation on filling of the right heart are the best understood of the various heart-lung interactions and are generally the preponderant effects on cardiac output. They are mediated by changes in intrathoracic pressure and venous return over the respiratory cycle. Spontaneous breathing and positive pressure mechanical ventilation have opposite effects on intrathoracic pressure, which largely explains their different effects on cardiac output.

Venous Return

The mean systemic pressure of the circulation (P_{ms}) is thought to be the inflow pressure driving blood toward the right ventricle.[2] This driving pressure is not measurable in the intact patient, but it can be thought of as the static mean pressure that might exist throughout the circulation if there were no blood flow.[3] P_{ms} approximates the weighted average of pressures in venous reservoirs throughout the body during the circulation of blood.[4] The backpressure that opposes flow toward the right heart is the right atrial pressure (P_{ra}). The impact of these pressures on return of venous blood to the heart is described by the venous return curve (Figure 26-1, *A*). Picture the systemic circulation as compliant arteries and veins separated by high-resistance arterioles and a pump that receives venous return and propels it into the arteries (Figure 26-1, *B*). The faster the pump circulates the blood, the more blood piles up before the arterioles and the higher the arterial pressure will be. In contrast, the faster the pump moves blood from vein to artery, the less blood resides on the venous side of the circuit and the lower the venous pressure will be. As the pump is slowed down, venous pressure rises until flow reaches zero and pressure equilibrates throughout the circulation at P_{ms}. Resistance to venous return (R_{vr}) is the reciprocal of the slope of the linear part of the venous return curve. Simply stated:

$$\text{Venous return} = (P_{ms} - P_{ra}) / R_{vr} \quad (1)$$

P_{ms} is sensitive to the volume of blood in the circulation and to the capacitance of the venous reservoir. It can be altered by transfusion, volume infusion, hemorrhage, and diuresis. It also is sensitive to changes in venous tone. P_{ms} is an extrathoracic

measurement and is less sensitive than P_{ra} to changes in intrathoracic pressure.[5] P_{ra}, in contrast, is quite sensitive to changes in intrathoracic pressure.

At functional residual capacity (FRC), the thorax exerts recoil force, tending to spring outward, whereas the lung exerts recoil force (mostly as a result of alveolar surface tension), tending to collapse inward. These forces result in subambient pleural pressure. The cardiac fossa, or juxtacardiac space, which surrounds the pericardium and heart, shares in this balance of forces and has slightly negative pressure at apneic FRC. At any right atrial volume, P_{ra} is influenced by juxtacardiac pressure because these two forces act together to oppose the right atrium's balloonlike tendency to recoil inward. Therefore it is not surprising that all of these pressures (pleural, juxtacardiac, and right atrial) are influenced by the respiratory cycle.[6-8]

During spontaneous breathing, lung volume rises from FRC to end-inspiratory volume by expansion of the rib cage and descent of the diaphragm. This reshaping of the thorax stretches the lung, increasing its recoil tension, so pleural pressure and juxtacardiac pressure both become more negative (subambient). At any right atrial volume, this process reduces P_{ra}. Therefore spontaneous inspiration reduces pleural, juxtacardiac, and right atrial pressures. By the mathematical relationship in Equation 1, this augments venous return.[9] Over the course of passive spontaneous expiration, all three pressures return toward their values at FRC. It follows that intrathoracic pressure, during relaxed spontaneous breathing, is always least negative at end-inspiration and falls continuously throughout the rest of the respiratory cycle.

Right Ventricular Preload and Stroke Volume

Transmural pressure is the pressure difference across (inside to outside) a hollow structure. This pressure difference and the wall tension of the structure determine its radius. P_{ra} approximates the pressure within the right ventricle during cardiac filling. Juxtacardiac pressure approximates the pressure surrounding the ventricle. During spontaneous inspiration, systemic venous return to the right atrium and ventricle are augmented (Equation 1), and end-diastolic ventricular volume rises. P_{ra} falls, but not as much as juxtacardiac pressure falls. Transmural pressure is, therefore, increased by spontaneous inspiration. Despite the falling P_{ra}, right ventricular stroke volume normally rises during spontaneous inspiration; hence, there is a paradoxical inverse relationship between P_{ra} and right ventricular stroke volume over the spontaneous respiratory cycle (Figure 26-2).[10] If *transmural* P_{ra} is plotted against right ventricular stroke volume during various respiratory maneuvers, the expected positive slope is revealed (Figure 26-3).[11]

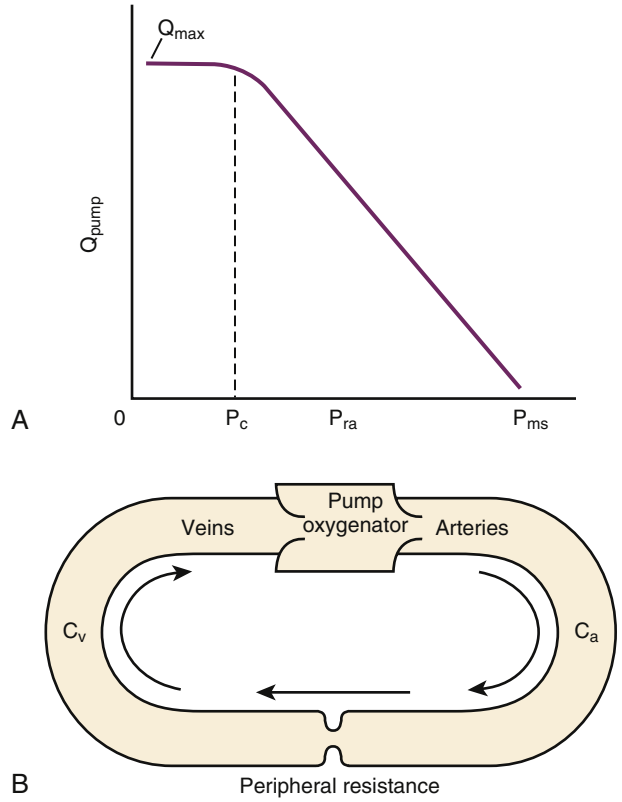

Figure 26–1. A, Systemic venous return curve. Flow (Q_{pump}) is plotted on the ordinate, but is treated as the independent variable. Right atrial pressure (P_{ra}), the dependent variable, is plotted on the abscissa. **B,** Circulation is treated as though a pump transferred blood from veins to arteries, generating arterial pressure sufficient to overcome peripheral arterial resistance. Arterial compliance (C_a) and venous compliance (C_v) determine the volume of blood distending arteries and veins at any Q_{pump}. When there is no flow, pressure equilibrates throughout the circulation at the mean systemic pressure of the circulation P_{ms}. As pump flow is progressively increased, venous pressure falls and arterial pressure rises because of the net transfer of blood from veins to arteries by the pump and because of the accumulation of blood before the peripheral resistance. When venous pressure falls to P_c, the critical closing pressure of the venous system, no further increase in pump flow is possible. *(Modified from Guyton AC: Determination of cardiac output by equating venous return curves with cardiac response curves, Physiol Rev 35:123, 1955.)*

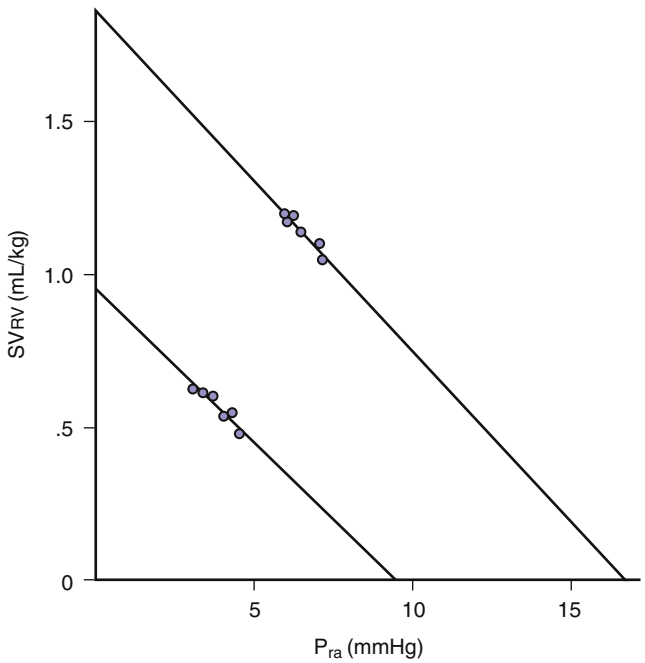

Figure 26–2. During spontaneous inspiration, right atrial pressure (P_{ra}) falls, but this decline is associated with an increase in right ventricular stroke volume (SV_{RV}). Shown at two different mean P_{ra}. *(From Pinsky MR: Instantaneous venous return curves in an intact canine preparation,* J Appl Physiol *56:765, 1984.)*

Positive Pressure Mechanical Ventilation and Right Ventricular Preload

The effects of positive pressure ventilation on pleural, juxtacardiac, and right atrial pressure are opposite those of spontaneous breathing. A common goal in the application of positive end-expiratory pressure (PEEP) is restoration of normal end-expiratory lung volume (normal FRC). All other things being equal, pleural pressure, which opposes thoracic recoil, should be the same at end-expiration whether breathing is spontaneous or mechanical. Pleural pressure is, after all, determined by thoracic volume.

During spontaneous inspiration, active reshaping of the thorax by the respiratory muscles and diaphragm inflates the lungs by reducing pleural pressure. In contrast, throughout positive pressure mechanical inspiration, pleural pressure rises because the passive thorax is pushed outward (from FRC to end-inspiratory volume) by the expanding lungs. Passive expiration restores pleural pressure to that of FRC. Averaged over the entire respiratory cycle, pleural pressure is higher during positive pressure breathing than it would be during spontaneous breathing (Figure 26-4). (This elevation of pleural pressure during positive pressure mechanical ventilation is generally called transmission of airway pressure to the pleural space.) Positive pressure ventilation, therefore, reverses the effects of spontaneous breathing on venous return[12] and right ventricular transmural pressure.

Positive pressure inspiration impedes venous return by raising P_{ra}. Right ventricular stroke volume declines over positive pressure inspiration because right ventricular transmural pressure is reduced. Averaged over the entire respiratory cycle, P_{ra} is raised and right ventricular stroke volume and cardiac index are reduced by positive airway pressure relative to their expected values during spontaneous breathing (Figure 26-5).

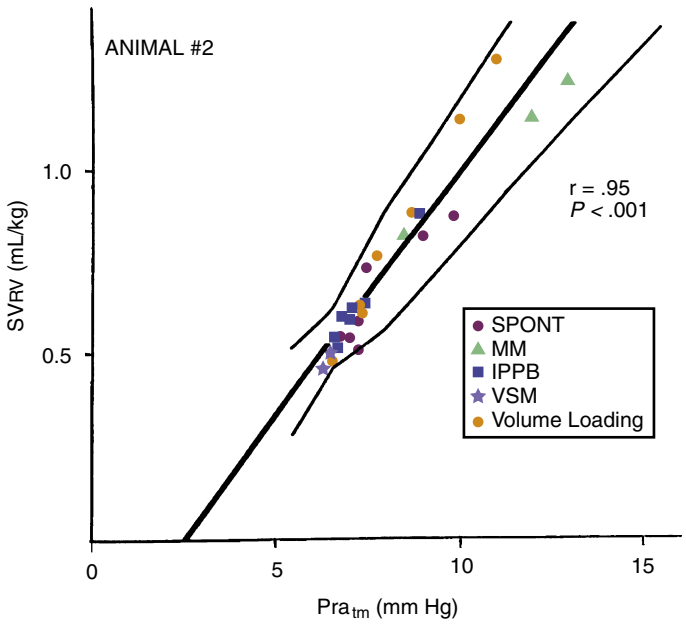

Figure 26–3. Over a wide range of respiratory maneuvers, right ventricular stroke volume (*SVRV*) varies directly with transmural right atrial pressure (Pra_{tm}). *IPPB,* Intermittent positive pressure breathing; *MM,* Müller maneuver; *SPONT,* spontaneous breathing; *VSM,* Valsalva maneuver. *(From Pinsky MR: Determinants of pulmonary arterial flow variation during respiration,* J Appl Physiol *56:1237, 1984.)*

It is easy to argue from these observations that positive pressure ventilation will invariably decrease venous return to the right heart, but this is not always the case. PEEP tends to elevate intrathoracic pressure over the entire respiratory cycle and opposes venous return. However, it may also displace blood from the pulmonary circulation and from the abdominal viscera (by descent of the diaphragm), thereby raising P_{ms}. Positive airway pressure may also have favorable effects on left heart function (see the section on left ventricular afterload). In patients whose left heart function improves, both left and right ventricular inflow pressures fall, enhancing venous return.

Critical Illness and Effects of Positive Pressure Breathing on the Right Heart

Among the effects of critical illness are capillary leak, chest wall edema, pulmonary edema, surfactant dysfunction, abnormal blood volume, and abdominal distension. Each modifies the effects of positive pressure breathing on the right heart. Capillary leak alters the compliance of the atrial and ventricular chambers, modifying the responsiveness of the heart to changes in preload. Sepsis and inflammation decrease cardiac

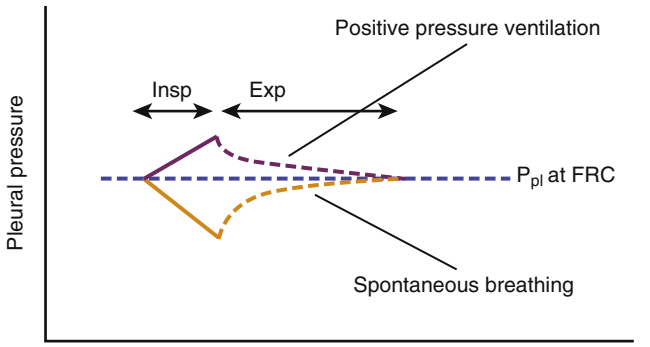

Figure 26–4. Over the course of the respiratory cycle, if spontaneous and positive pressure breaths both begin and end at the same functional residual capacity (*FRC*), spontaneous breathing takes place at lower pleural pressure than does positive pressure ventilation.

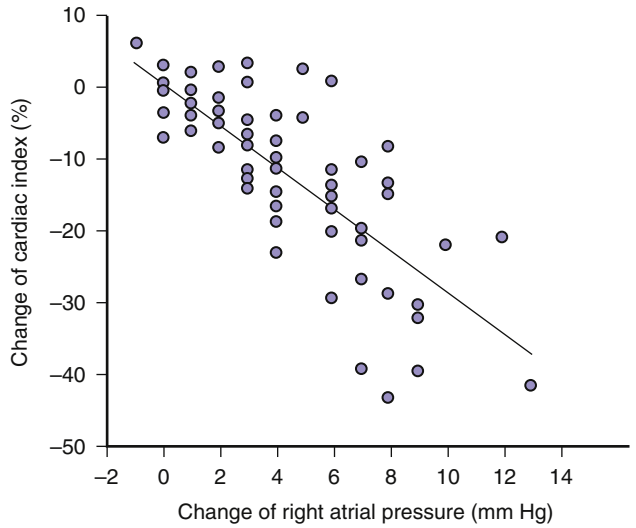

Figure 26–5. Relationship between the percentage change in cardiac index and the percentage change in right atrial pressure that was produced by the application of graded levels of positive airway pressure in adults. *(From Jellinek H, Krafft P, Fitzgerald RD, et al: Right atrial pressure predicts hemodynamic response to apneic positive airway pressure,* Crit Care Med *28:672, 2000.)*

contractility, directly altering the way the heart responds to changes in preload. Chest wall edema, pulmonary edema, surfactant dysfunction, and abdominal distension alter thoracic and pulmonary compliances, which in turn alter pleural and juxtacardiac pressures.

Reduced respiratory system compliance diminishes the transmission of alveolar pressure to the juxtacardiac space.[13] The change in intrathoracic pressure that occurs with a change in static airway pressure is essentially the same as the change observed in pulmonary artery wedge pressure,[14] which is readily measured. Recognizing this relationship in adults has made it possible to estimate percent transmission of airway pressure to the juxtacardiac space by measurement of respiratory system compliance (Figure 26-6).

Both abnormal blood volume and abnormal vascular compliance can change P_{ms} and thereby alter venous return. Vascular hypovolemia can exaggerate the adverse effects of positive pressure ventilation on preload.

Pulmonary Circulation

By modifying pulmonary vascular resistance (PVR), the effects of breathing on pulmonary circulation modify right ventricular afterload. The effects of breathing also can change the distribution of pulmonary blood flow within the lung. Both effects are significant.

Lung Volume

The alveolar septae are highly vascular (Figure 26-7). More than 90% of the alveolar surface makes contact with alveolar capillaries. These vessels can be separated into two categories according to their location or their response to lung inflation. Most alveolar vessels are capillaries and lie in septa, which separate adjacent alveoli. Other alveolar vessels are termed *corner vessels* because they are located at the intersection of alveolar septa. These corner vessels are generally larger and most likely will divide later in their course to become alveolar capillaries located in septa between adjacent alveoli. When the lung is stretched, either by spontaneous inspiration or by positive pressure distension, corner vessels are pulled open by radial traction and their resistance to blood flow is reduced. When alveolar septa are stretched, alveolar capillaries thin and restrict flow. The net effect of these factors is a U-shaped relation of PVR to lung volume (Figure 26-8)[15-18]; PVR is least at FRC and rises with either atelectasis or overdistension.

Alveolar Pressure

When alveolar pressure is greater than ambient, as it is during positive pressure ventilation, the vessels that course through alveolar septae between adjacent alveoli can be compressed.[19,20] This behavior is akin to that of a Starling resistor, a collapsible tube traversing a rigid housing (Figure 26-9). Flow (Q) is propelled through the tube by inflow pressure (P_i) and is opposed by outflow pressure (P_o). The tubing has some intrinsic resistance (R). If the housing is pressurized to a surrounding pressure (P_s), flow through the tube is determined as follows:

$$\text{For } P_s < P_o < P_i,\ Q = (P_i - P_o)/R \quad (2)$$

$$\text{For } P_o < P_s < P_i,\ Q = (P_i - P_s)/R \quad (3)$$

$$\text{For } P_o < P_i < P_s,\ Q = 0 \quad (4)$$

Except when $P_s < P_o$, alveolar pressure appears to modulate local pulmonary blood flow as though it surrounds the pulmonary capillary (Figure 26-10).

From this discussion, the degree to which P_s affects pulmonary blood flow is influenced by the magnitude of inflow pressure,

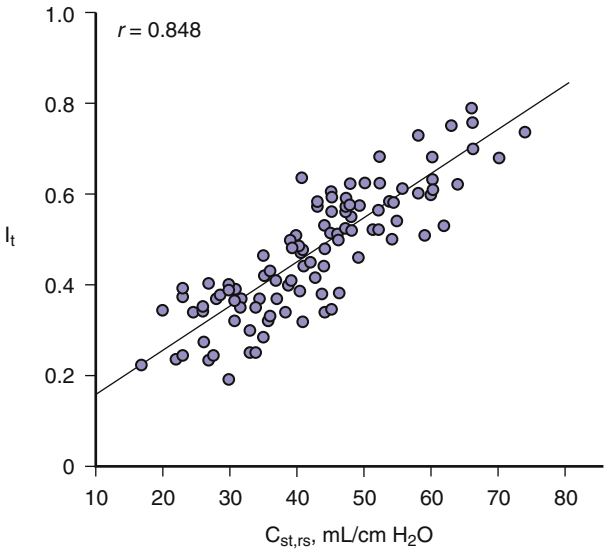

Figure 26–6. Relationship between the static compliance of the respiratory system ($C_{st,rs}$) and the index of transmission (I_t, decimal fraction) of a change in static airway pressure to the pulmonary circulation in adults. I_t values for pleural and juxtacardiac spaces are presumed to be comparable. *(From Teboul JL, Pinsky MR, Mercat A, et al: Estimating cardiac filling pressure in mechanically vented patients with hyperinflation,* Crit Care Med *28:3631, 2000.)*

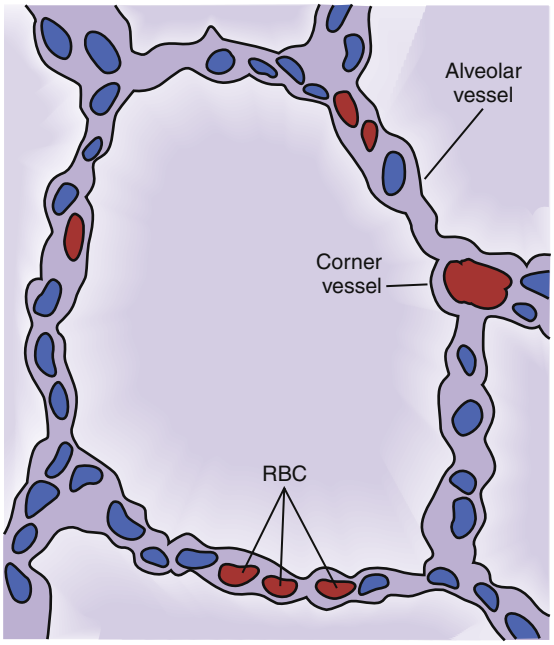

Figure 26–7. Alveolus is encased in a network of capillaries. Alveolar vessels are those that lie between adjacent alveoli. Corner vessels are those that lie at the intersection of alveolar septa. *RBC,* Red blood cell.

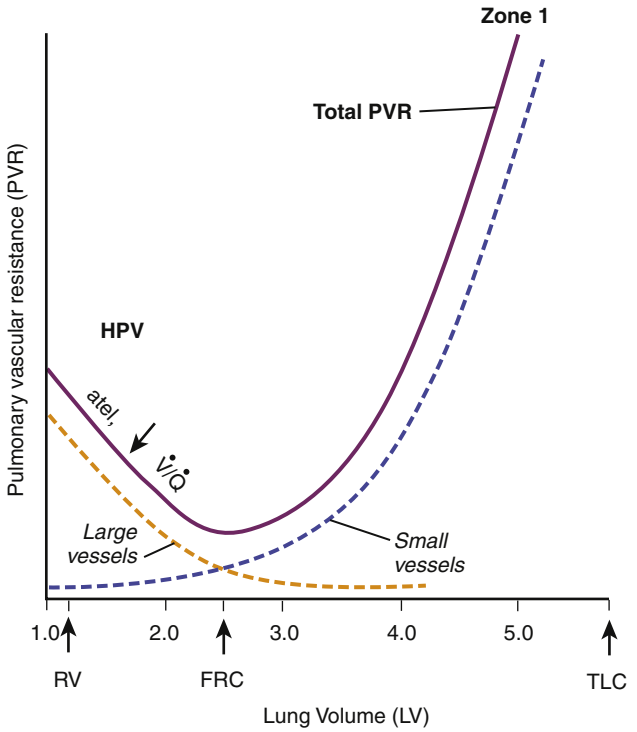

Figure 26–8. Effects of lung volume on pulmonary vascular resistance (*PVR*). As whole lung is distended from functional residual capacity (*FRC*) toward total lung capacity (*TLC*), PVR rises, predominantly by increasing resistance to flow through the small alveolar vessels that course between adjacent alveoli (alveolar vessels). As whole lung is collapsed from FRC toward residual volume, PVR rises, predominantly by effects on corner vessel that traverse the intersection of alveolar septa. *(Modified from Cassidy SS, Schwiep F: Cardiovascular effects of positive end-expiratory pressure. In Scharf SM, Cassidy SS, editors:* Heart lung interactions in health and disease, vol 42, Lung biology in health and disease, *New York, 1989, Dekker.)*

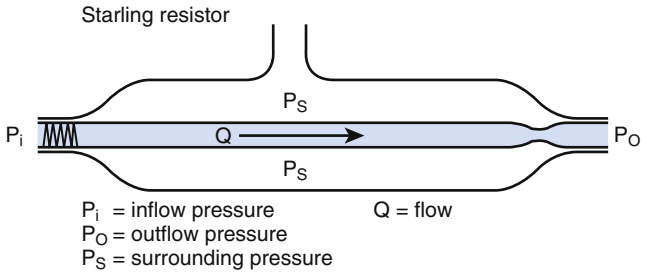

Figure 26–9. Starling resistor is a compressible conduit traversing a rigid housing, which is pressurized to a surrounding pressure (P_s). Flow (Q) traverses the conduit, propelled by inflow pressure (P_i) and opposed by outflow pressure (P_o) such that driving pressure is ($P_i - P_o$) for $P_s < P_o$. As P_s is increased, it begins to influence flow, but only after it exceeds P_o. At $P_s > P_o$, the driving force for flow becomes ($P_i - P_s$). *(Modified from Knowlton FP, Starling EH: The influence of variations in temperature and blood pressure on performance of the isolated mammalian heart,* J Physiol *44(3):206-219, 1912.)*

which, for the pulmonary capillary, must be adjusted for vertical height. Alveolar pressure causes greater reduction in flow at low pulmonary artery pressure than it does at high pressure. Pulmonary hypertension (high P_i) dampens this cardiopulmonary interaction, whereas hypovolemia (low P_i) accentuates it.

Hydrostatic pressure in the lung is a function of vertical height (see Chapter 20).[21] To estimate the hydrostatic inflow pressure of a pulmonary capillary, a pressure equivalent to

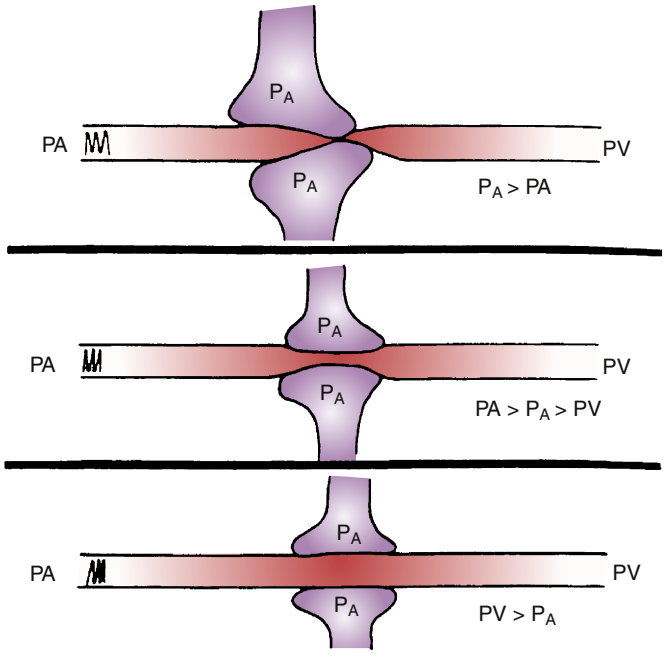

Figure 26–10. Pulmonary capillaries are, in essence, surrounded by gas-filled alveoli. The influence of alveolar pressure (P_A) on regional lung blood flow is similar to the influence of surrounding pressure on flow through a Starling resistor. At ambient values of P_A, pulmonary vein pressure (*PV*) opposes inflow. As P_A rises, it begins to oppose inflow only after $P_A > PV$. It modulates inflow until P_A reaches hydrostatic inflow pressure (*PA*), at which point flow ceases.

that exerted by a water column extending from the left atrium to the capillary must be subtracted from the pressure within the main pulmonary artery. The greater the vertical height of the pulmonary capillary, the lower its inflow pressure and the greater the attenuation of flow by alveolar pressure. This can produce areas of no flow, especially at peak inspiration, high in the supine lung. These high ventilation/perfusion ratio (Va/Q) alveolar capillary units waste ventilation and can cause hypercarbia (see Chapter 40). Vertical height (h) of the capillary also alters the backpressure to flow. At a left atrial pressure of 10 cm H_2O (7 mm Hg), for example, there is (10 − h) cm H_2O opposing flow up to a vertical height 10 cm above the heart. Above that, there is no back pressure, and P_i and P_s determine flow through the capillary. Compression of pulmonary capillaries is a local phenomenon. It can divert pulmonary blood flow away from normal lung segments toward consolidated or atelectatic lung segments whose airways do not effectively transmit airway pressure to the alveolus.[22] By this mechanism, the application of high PEEP in the presence of lobar pneumonia may increase blood flow through unventilated lung and worsen hypoxemia (Figure 26-11). From a more positive perspective, PEEP may relieve atelectasis and improve ventilation, thereby relieving alveolar hypoxic vasoconstriction. Whether PEEP benefits or impairs pulmonary blood flow may depend on the balance of its effect on atelectasis and its effect on alveolar capillaries.

Regulation of Pulmonary Vascular Resistance

The resistance to flow through a vessel is described by the following:

$$R = 8\,\eta l / \pi r^4 \qquad (5)$$

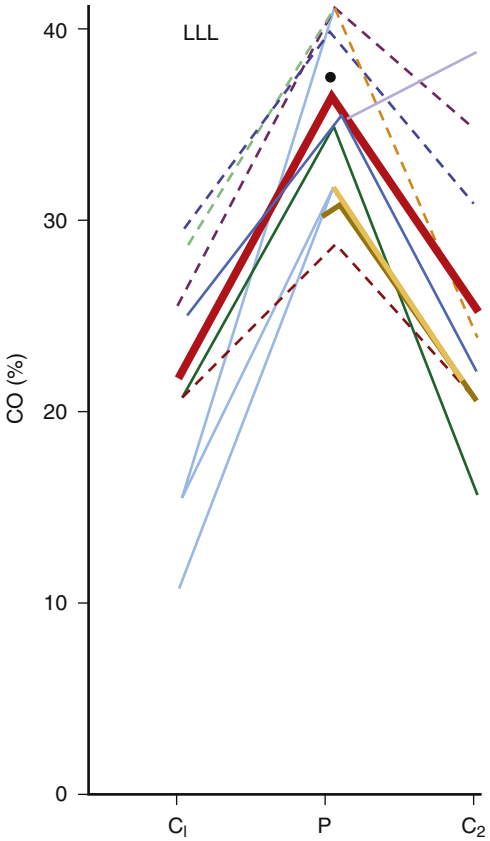

Figure 26–11. Blood flow to the left lower lobes (*LLL*) of dogs with LLL pneumonia, measured at zero positive end-expiratory pressure (*PEEP*) (C_1), 6–12 cmH_2O PEEP (*P*), and on cessation of applied PEEP (C_2). PEEP diverted blood flow away from more normal lung toward the consolidated LLL. *(From Mink SN, Light RB, Cooligan T, et al: Effect of PEEP on gas exchange and pulmonary perfusion in canine lobar pneumonia,* J Appl Physiol *50:517, 1981.)*

where η is viscosity, *l* is length, and *r* is radius. It follows that PVR can be effectively controlled by active changes in vessel radius. Mechanical ventilation may alter blood pH and alveolar oxygen tension (po_2), both of which influence vessel tone and radius (Figure 26-12).[23,24]

Hypoxic pulmonary vasoconstriction is a powerful mechanism for sustaining systemic oxygenation in the face of lung disease.[25-28] Relief of atelectasis and restoration of segmental ventilation not only increases the fraction of the lung that is ventilated but also restores blood flow to those segments by several mechanisms. Segmental alveolar hypoxia is relieved. Segmental volume is restored, which returns segmental vascular resistance toward its volume-dependent nadir. Gas exchange is also improved, favorably altering pH, pco_2, and po_2, and thereby reducing global PVR.

Direct Effects of Airway Pressure on Pulmonary Vascular Tone

Pulmonary vessels are stretched by lung inflation. The lung of infant lambs responds to abrupt changes in airway pressure with changes in vascular tone. Abrupt distension of one lung of the intact infant lamb increases the PVR of that lung alone.[29] The resistance change is sensitive to the waveform of the lung distension[30] and persists for some time after relief of distending pressure and return of lung volume to baseline.[31] This effect is calcium channel dependent[32] and resembles a myogenic reflex whereby direct vessel stretch causes constriction.

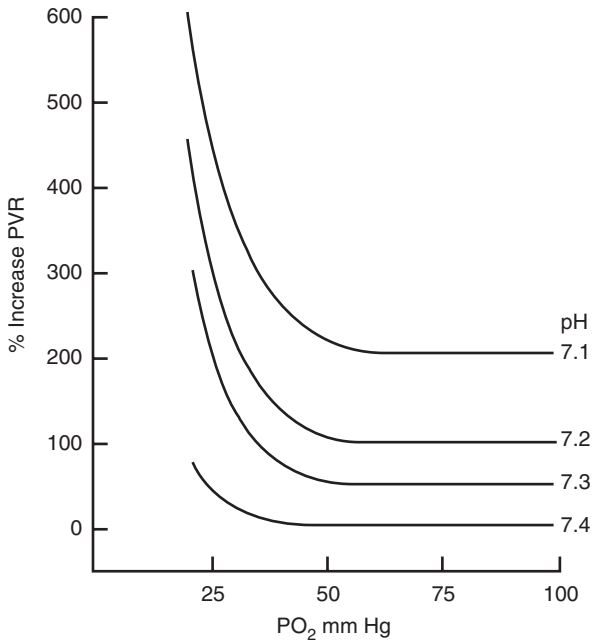

Figure 26–12. Pulmonary vascular resistance (*PVR*) is a function of both pH and arterial po_2. *(From Rudolph AM, Yuan S: Response of the pulmonary vasculature to hypoxia and H^+ ion concentration changes,* J Clin Invest *45:399, 1966.)*

Left Ventricular Preload

Positive airway pressure can impede left ventricular filling via several mechanisms. The first is impaired systemic venous return. Other mechanisms involve functional reduction in left ventricular compliance.

Decreased Venous Return

The reduction in venous return to the right heart seen at high airway pressure should directly reduce filling of the left heart. But there is a trap in this line of reasoning. Venous return, when averaged over several respiratory cycles, equals cardiac output. If other cardiopulmonary interactions and compensatory mechanisms restore cardiac output to normal, then right and left heart venous return will not be diminished.

Ventricular Interdependence

The right and left ventricles share a common muscle mass and pericardial space. It follows that compliance of either ventricle will be influenced by volume of the other chamber (Figure 26-13). Increased venous return to the right heart, as occurs during spontaneous inspiration and especially during execution of a Müller maneuver, tends to shift the interventricular septum to the left, reducing compliance of the left ventricle.[33] Similarly, excessive compression of the pulmonary circulation by positive airway pressure may impede right ventricular ejection, causing the right ventricle to dilate and encroach on the left. Reduced left ventricular compliance tends to diminish stroke volume by diminishing left ventricular muscle stretch and ejection force (by the Frank-Starling mechanism).

Ventricular interdependence may play a major role in cyclic changes in left ventricular stroke volume across single respiratory cycles. During spontaneous breathing, inspiration dilates the right ventricle by augmented filling. This pushes the interventricular septum to the left and makes the left ventricle less

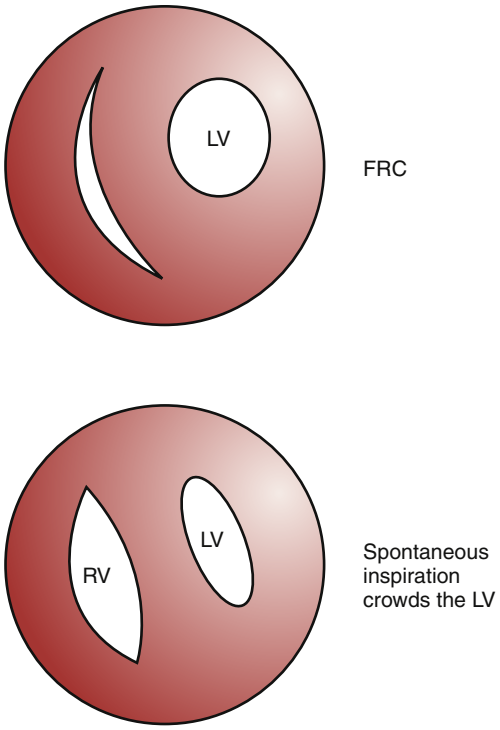

Figure 26–13. Increasing the diastolic volume of the right ventricle (*RV*) reduces compliance of the left ventricle (*LV*). *FRC,* Functional residual capacity.

compliant, reducing stroke volume, pulse pressure, and both systolic and diastolic pressures.[34]

During positive pressure inspiration, right ventricular filling may be reduced. The septum is displaced to the right, making the left ventricle more compliant. Stroke volume is augmented by increased left ventricular filling. Stroke volume, pulse pressure, and both systolic and diastolic pressures increase.

Cardiac Crowding

Overinflation of the lungs may crowd the cardiac fossa in which the heart resides. To the extent that this creates a mechanical barrier to cardiac filling, it may reduce left ventricular compliance, end-diastolic volume, and force of contraction.

Left Ventricular Afterload

The left ventricle ejects blood from within the thorax to the extrathoracic arteries and arterioles. Most of the resistance to this forward flow resides in the arterioles. From a practical point of view, the pressure in the extrathoracic arteries can be described by the following equations:

$$(P_{artery} - P_{ms}) = Q \times R_{arteriole} \quad (6)$$

or

$$P_{artery} = Q \times R_{arteriole} + P_{ms} \quad (7)$$

where Q is cardiac output, P_{artery} is inflow pressure before the arteriole, and P_{ms} is outflow pressure after the arteriole as defined for the venous return curve.

It follows that, at any given blood volume, arterial pressure is determined by forward flow and arteriolar resistance. These two parameters set the afterload opposing left ventricular ejection.

When the left ventricle contracts, it creates internal pressure against the closed aortic valve by generating tension in the myocardium that encircles the ventricular chamber. This "wall tension" causes ventricular pressure to rise until it reaches aortic diastolic pressure, opening the aortic valve and ejecting the stroke volume. Creation of wall tension and subsequent shortening of myocardial fibers perform the external mechanical work of the heart (see Chapter 19).

When the heart squeezes, it creates a pressure difference between the ventricle and the juxtacardiac space. In effect, the myocardium creates a transmural pressure to produce a ventricular pressure sufficient to open the aortic valve. Aortic diastolic pressure and external (juxtacardiac) pressure determine the myocardial wall tension needed to open the aortic valve. Both pressures represent afterloads to left ventricular ejection.[35,36]

An infusion of phenylephrine, by raising $R_{arteriole}$, increases the afterload of the left ventricle (Figure 26-14). It raises the pressure required to open the aortic valve. This increases the wall tension the heart must generate to eject blood.

The Müller maneuver, forced inspiration against a closed glottis, does the same thing. It reduces juxtacardiac pressure, thereby raising the transmural pressure required to open the aortic valve. Thus the Müller maneuver also increases the afterload of the left ventricle.

Positive pressure inspiration or application of PEEP may raise juxtacardiac pressure to such an extent that the wall tension required to open the aortic valve is diminished. Mechanical ventilation may, therefore, reduce the afterload of the left ventricle.

The net effect of positive pressure inspiration often is augmentation of left ventricular ejection. Stroke volume may consequently rise, cardiac output increase, and arterial pressure rise. Arterial pressure is commonly observed to rise during positive pressure inspiration, whereas it falls during spontaneous inspiration. These are effects of afterload on stroke volume.

Cardiac Contractility

Studies of the effects of positive airway pressure on left ventricular contractility have yielded conflicting results. Certainly changes in preload and afterload have secondary effects on stroke volume, but independent effects of positive airway pressure on left ventricular contractility have not been consistently demonstrated. Negative inotropic effects modulated by reflexes, mediators, or alterations in coronary blood flow have been described,[37-42] but most animal and human studies fail to show that positive airway pressure has any primary effect on myocardial contractility.[43-46]

It has been suggested that high levels of PEEP may compress coronary vessels, cause myocardial ischemia, and thereby impair ventricular function.[47-49] The left ventricular myocardium is perfused predominantly in diastole. To the extent that juxtacardiac pressure exceeds left ventricular diastolic pressure, such an effect is plausible. This assertion appears more compelling for patients in shock and for those with intrinsic coronary blood flow limitations than for otherwise normal individuals.

Right ventricular myocardial perfusion normally occurs in both systole and diastole. In systole, right ventricular coronary

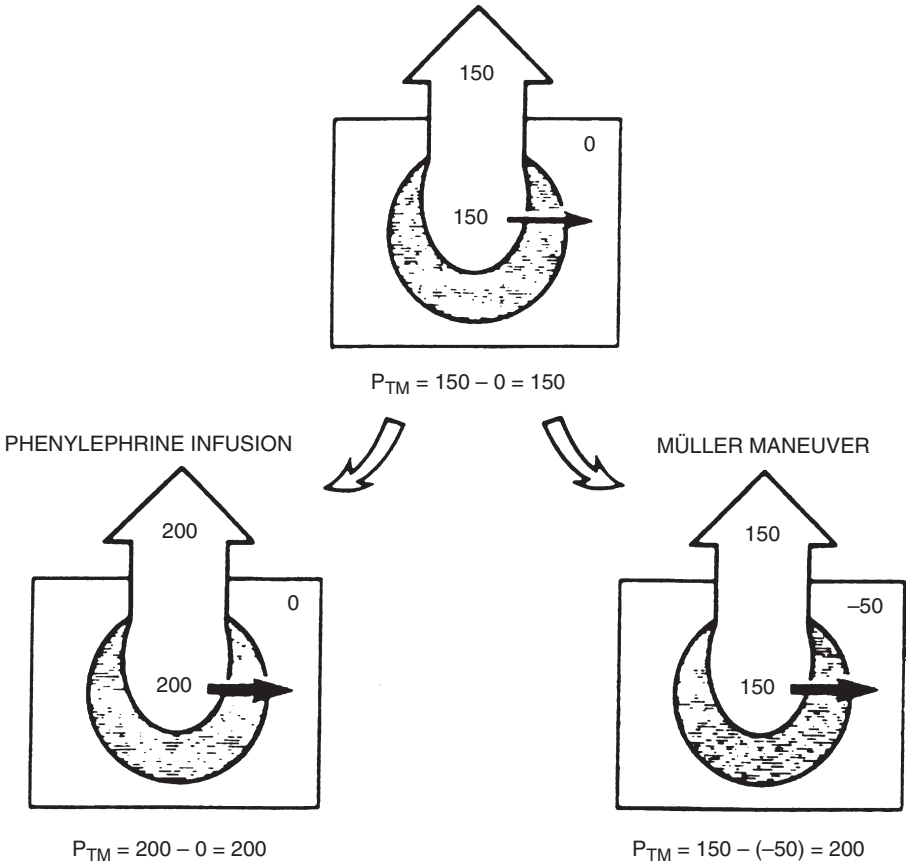

Figure 26–14. Negative pressure in the juxtacardiac space (Müller maneuver) increases the wall tension required to eject blood into the aorta. This respiratory maneuver acts like a phenylephrine infusion to increase left ventricular afterload. *(From Buda AJ, Pinsky MR, Ingels NB Jr, et al: Effect of intrathoracic pressure on left venticular performance,* N Engl J Med *301:453, 1979.)*

inflow pressure is aortic systolic pressure, and right ventricular coronary outflow (or surrounding) pressure is right ventricular or pulmonary artery systolic pressure. To the extent that positive pressure ventilation impedes pulmonary blood flow and increases pulmonary artery pressure, it may impede right ventricular systolic myocardial perfusion. Right ventricular diastolic myocardial perfusion may be subject to modulation by positive airway pressure as described for the left ventricle. Overall, it does not appear likely that judicious levels of positive airway pressure have much effect on myocardial contractility.

Preload Dependence Versus Afterload Dependence

The expected effects of an abrupt rise in airway pressure are as follows:

1. Decreased filling of the right ventricle acts to decrease right ventricular stroke volume.
2. Impaired pulmonary blood flow or increased right ventricular afterload acts to decrease right ventricular stroke volume.
3. Both diastolic displacement of the interventricular septum toward the left ventricle (with resultant crowding of the left ventricle) and crowding of the juxtacardiac space by the expanding lung reduce left ventricular compliance. Both of these factors act to decrease left ventricular stroke volume.
4. Reduced left ventricular afterload acts to increase left ventricular stroke volume.

Although these effects are not incompatible, they do make the aggregate effect of positive airway pressure on cardiac output less predictable.

In general, positive airway pressure has its most pronounced effect on right ventricular filling; therefore, positive airway pressure reduces cardiac output in most patients. Such patients may be thought of as "preload dependent" because the effect of positive airway pressure on cardiac output is dominated by its effect on right heart filling. This effect is greatest in patients who are hypovolemic because the driving pressure for systemic venous return ($P_{ms} - P_{ra}$) is more sensitive to change in P_{ra} when P_{ms} is low. In adults, the P_{ra} threshold (at zero PEEP) below which increasing airway pressure reduces cardiac output is approximately 12 mm Hg.[50] Furthermore, the rise in P_{ra} with positive airway pressure is mechanical and does not appear to be a function of blood volume, so the percent reduction in driving pressure is exaggerated in the hypovolemic patient.

Another definition of preload dependence is responsiveness to vascular volume infusion. By this definition, when the dominant effect of positive airway pressure is to impede right heart filling, vascular volume infusion raises cardiac output. Four measurable parameters (Figure 26-15) predict responsiveness to vascular volume infusion: variation over the respiratory cycle (Maximum − Minimum) in pulse pressure, arterial systolic pressure, P_{ra}, and pulmonary artery wedge pressure.[51] Of these parameters, the inspiratory increase in arterial pulse pressure is the most sensitive and specific predictor of

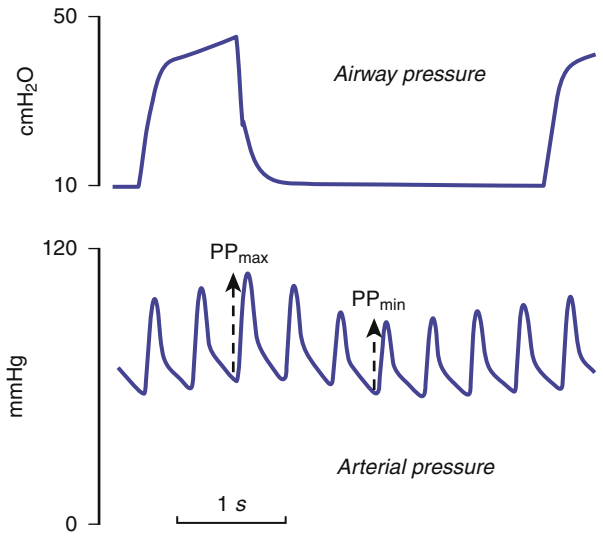

Figure 26–15. Positive pressure inspiration generally raises aortic pulse pressure (*PP*), systolic pressure (*SP*), and diastolic pressure (*DP*) as well as right atrial pressure, and pulmonary artery wedge pressure. *(From Michard F, Chemla D, Richard C, et al: Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP,* Am J Respir Crit Care Med *159:935, 1999.)*

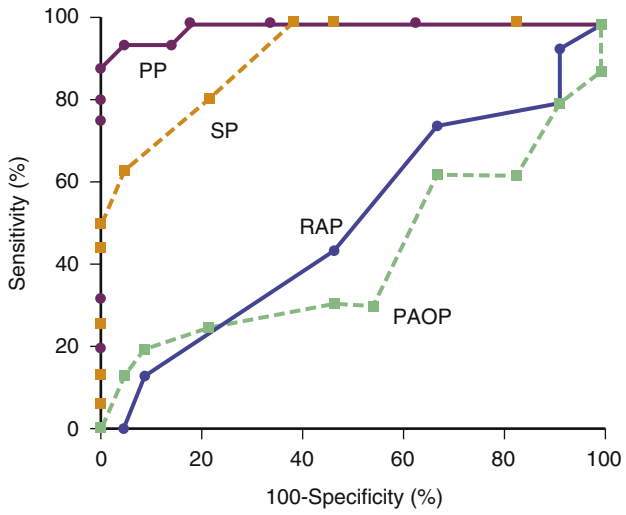

Figure 26–16. Septic patients on positive end-expiratory pressure were challenged by volume infusion. In response to volume loading, some patients had a greater than 15% increase in cardiac index. These responsive patients were deemed preload dependent. The sensitivity and specificity of variation in pulse pressure (*PP*) across the respiratory cycle as a predictor of responsiveness to volume loading yielded a near-perfect receiver operating characteristic curve. Greater than 15% inspiratory rise in PP appears to identify adults with preload dependence during positive pressure ventilation. *PAOP,* Pulmonary artery occlusion pressure; *RAP,* right atrial pressure: *SP,* systolic pressure. *(From Michard F, Boussat S, Chemla D, et al: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure,* Am J Respir Crit Care Med *162:134, 2000.)*

"preload dependence" (by receptor operating characteristic curve) (Figure 26-16). Greater than 15% inspiratory rise in pulse pressure appears to identify adults with preload dependence during positive pressure ventilation.[52]

One might expect the converse also to apply. Reduced magnitude of the effects of positive pressure ventilation on right ventricular filling or augmented effects on left ventricular ejection may make the patient "afterload dependent." Patients who have high blood volume, such as those in congestive cardiac failure or those with chronic anemia, should have high P_{ms} and decreased sensitivity to changes in P_{ra}.[53] Moreover, the patient with poor left ventricular contractility may greatly benefit from the afterload reduction of positive pressure ventilation.[54] If positive airway pressure enhances the ejection of blood into the systemic circulation, this may directly reduce left atrial pressure. From these considerations, better cardiac output may also reduce P_{ra} by transferring blood from veins to arteries and reducing venous capacitance vessel blood volume (see Figure 26-1, *B*). When favorable effects on left ventricular ejection act to reduce right and left atrial pressures, cardiac output improves. Such a patient might be thought of as "afterload dependent."

Fluid Responsiveness During Positive Pressure Ventilation

In the intensive care unit, whether volume infusion will augment cardiac output or merely contribute to vascular volume overload is often a vital issue. In adults, about half of all hemodynamically unstable critical care patients are not volume responsive.[55] The traditional guides to volume resuscitation have focused on measurement of cardiac filling pressures and responses to fluid challenges. In critically ill patients and in normal subjects, the stroke volume response to vascular volume infusion is poorly predicted by measurement of either right arterial or pulmonary artery occlusion pressure.[56] Much recent interest has focused on minimally invasive estimation of likelihood of responding to fluid infusion.

The cardiopulmonary interactions described previously can be used to predict response to fluid challenge. The change in stroke volume over the course of the positive pressure respiratory cycle strongly predicts fluid responsiveness, the greater the percentage change in stroke volume the greater the response to volume infusion.[57] Similar relations have been shown between fluid responsiveness and respiratory variation in aortic blood flow velocity[58] and arterial pulse pressure.[50] Inspiratory collapsibility of the inferior[59] and superior[60] vena cavae have also been shown to predict volume responsiveness. The strong linear relationship of increase in cardiac index after fluid resuscitation to preinfusion pulse pressure variability over the respiratory cycle (ΔPP) is shown in Figure 26-17, which depicts data from 14 adults with acute lung injury.

This same parameter, change in arterial pulse pressure over the respiratory cycle, can be used to estimate the effect of PEEP on cardiac index. The strong linear relationship of ΔPP to PEEP-induced change in cardiac index is shown in Figure 26-18.

Changes in cardiac index induced by either fluid resuscitation or by application of PEEP appear to be predicted by measurement of ΔPP.[51] In general, in these patients, the greater the ΔPP, the more preload dependent the patient to PEEP and the more preload responsive to fluid resuscitation.

Elevated Work of Breathing and the Circulation

During quiet respiration, the heart has no difficulty satisfying the demand of the respiratory muscles for perfusion and muscle oxygen delivery. In respiratory failure, however, respiratory muscle perfusion may not be adequate. The diaphragm and the accessory muscles of respiration all are taxed to the limit by respiratory distress. Unlike cardiac muscle, respiratory

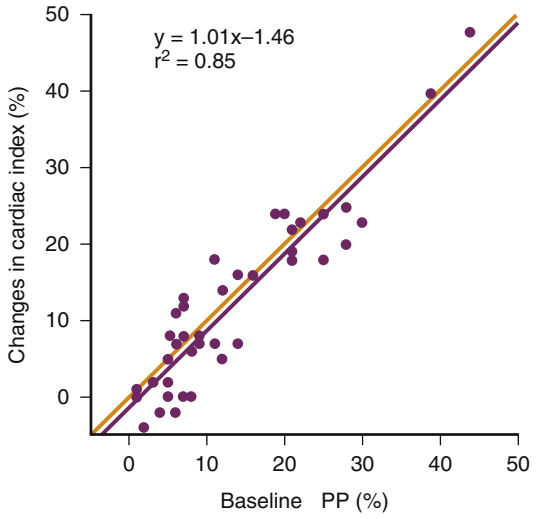

Figure 26–17. Relationship between ΔPP before volume expansion (baseline) and % change in cardiac index in 40 adult patients with septic shock during mechanical ventilation. Volume expansion comprised 500 mL 6% hydroxyethyl starch. ΔPP = 2 × (Peak arterial pulse pressure – Lowest arterial pulse pressure)/(Peak PP + Lowest PP). *(From Michard F, Boussat S, Chemla D, et al: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure,* Am J Respir Crit Care Med *162:134, 2000)*

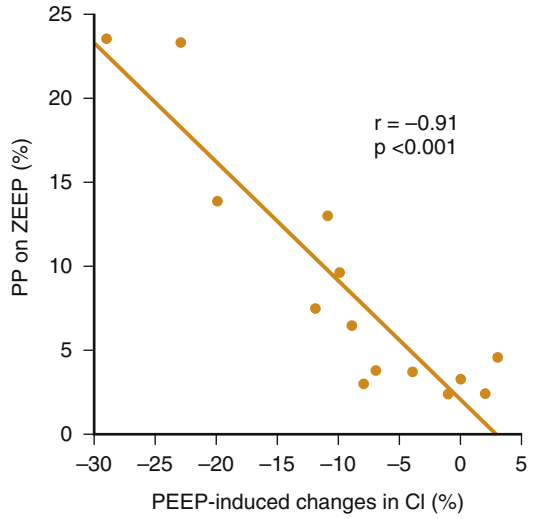

Figure 26–18. Relationship between ΔPP on zero PEEP and % decrease in cardiac index on application of 10 cm H_2O PEEP. ΔPP = 2 × (Peak arterial pulse pressure – Lowest arterial pulse pressure)/(Peak PP + Lowest PP). *(From Michard F, Chemla D, Richard C, et al: Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP,* Am J Respir Crit Care Med *159:935, 1999.)*

muscles can accumulate a limited oxygen debt, but persistent hypoperfusion may interfere with their ability to perform the requisite work of breathing. In many clinical scenarios, including shock, congestive heart failure, and respiratory disease, the inability of the circulation to maintain adequate respiratory muscle blood flow causes weakness, respiratory muscle fatigue, and ultimate respiratory arrest.[61] Loaded breathing,[62] respiratory muscle failure, and impending respiratory arrest all pose a strain on the circulation, demanding greater cardiac output.

Mechanical ventilation is, therefore, a highly effective if not essential intervention in the patient with cardiac decompensation and respiratory distress.

Pulsus Paradoxicus in Respiratory Distress

Arterial pressure normally falls during spontaneous inspiration, which is best explained as a result of increasing left ventricular afterload at a time in the respiratory cycle when ventricular interdependence restricts left ventricular filling. It is well known that pericardial tamponade causes accentuation of the normal inspiratory decrease in systemic blood pressure, a phenomenon known as pulsus paradoxus. This finding has been attributed to accentuation of ventricular interdependence, which favors right over left ventricular filling, at the same time in the respiratory cycle when inspiration is raising left ventricular afterload.

During loaded spontaneous inspiration, as in the Müller maneuver or in the presence of inspiratory airway obstruction (e.g., croup), the inspiratory fall in juxtacardiac pressure is exaggerated, and left ventricular afterload is accentuated. Again, the result is pulsus paradoxicus, an accentuated drop in blood pressure during inspiration.

Blood pressure commonly rises during positive pressure inspiration, which is termed *reverse pulsus paradoxus*. This finding has been attributed to left ventricular afterload reduction by the rise in juxtacardiac pressure that occurs during positive pressure inspiration.[63] Reverse pulsus paradoxicus is a normal finding during positive pressure ventilation but may be accentuated in afterload-dependent states (e.g., left ventricular dysfunction) as discussed in the Preload Dependence versus Afterload Dependence section).

Effects of Breathing on Measurement of Hemodynamic Parameters

Because hemodynamic measurements vary with respiration, mechanical ventilation may complicate assessment of cardiac function. Yet it may not be advisable to discontinue PEEP or mechanical ventilation to assess hemodynamics. Measuring vascular pressures at a consistent time in the respiratory cycle usually is sufficient. End-expiratory measurements are generally used because airway pressures are least at that time and hemodynamic measurements most closely approximate those at FRC.

It should be understood that the effects of mechanical ventilation on the circulation are not merely artifactual. They are real. There is no greater accuracy of measurements made off the ventilator. Measurements performed after ventilator disconnect are subject to the effects of respiratory dysfunction and instability.

A special circumstance can occur when a balloon flotation catheter with its tip in zone I lung is used to measure pulmonary artery pressure and when such a catheter with its tip in zone I or II lung is used to measure pulmonary artery wedge pressure.[64] Under such circumstances, airway pressures that exceed vascular pressures may be erroneously reported as vascular pressures.

Effects of Cardiovascular Function on Respiration

Shock States and Respiratory Function

Shock of any cause diminishes perfusion of respiratory muscles and can lead to respiratory failure and respiratory arrest. It also causes metabolic acidosis, which constricts

pulmonary vessels and opposes lung blood flow.[65,66] Acidosis is a potent stimulus of respiratory effort and contributes to tachypnea and respiratory distress, which in turn worsen the demand on the heart. Shock is injurious to both heart and lung, and one final common pathway to recovery is the initiation of mechanical ventilation, which benefits both organ systems.

Hypovolemic shock can create extreme preload dependency.[67] In hypovolemic shock, diastolic blood pressure may fall during positive pressure inspiration, impairing coronary perfusion. This may cause myocardial ischemia and worsen cardiac function.

Cardiogenic shock, by reducing oxygen delivery to tissues, elevates tissue oxygen extraction from the blood. The resultant decline in venous oxygen tension has a paradoxical effect. It increases the efficiency of pulmonary blood flow by allowing greater oxygen uptake per unit of pulmonary blood flow. That is, the more desaturated the blood that enters the pulmonary circulation, the more new oxygen it can upload. This process requires that alveolar po_2 not limit the amount of oxygen available for uptake and is one reason to administer oxygen to patients suffering cardiorespiratory failure.

Congestive Heart Failure

All that has been said about shock is equally true of congestive heart failure (CHF). In fact, there is a continuum from CHF to cardiogenic shock. CHF elicits physiologic responses that restore cardiac output toward normal. As these homeostatic responses are exhausted, cardiac output declines and the patient develops obvious manifestations of cardiogenic shock and respiratory failure.

In addition to the impact of shock on respiratory function and reserve, CHF generally causes fluid retention and pulmonary edema. Treatment of cardiogenic shock by vascular volume expansion may, by augmenting cardiac filling pressures, improve cardiac output at the expense of pulmonary edema. The edematous lung is stiff, may have elevated airway resistance, and can have alveolar flooding, atelectasis, intrapulmonary shunt, and severe ventilation/perfusion mismatch.

When a premature infant has a large patent ductus arteriosus, the primary manifestation of cardiac volume overload may be respiratory embarrassment.

Again, mechanical ventilation addresses most of these issues. Furthermore, PEEP improves lung function and supplemental oxygen supports gas exchange. Treatment of CHF can itself dramatically improve lung function. In contrast to hypovolemic shock, cardiogenic shock generally causes elevated atrial pressures. When this is the case, venous return may be insensitive to airway pressures during positive pressure ventilation. The patient is then usually afterload dependent and responds favorably to the afterload reducing effects of positive pressure ventilation.

When treating the patient with CHF on positive pressure ventilation, there is a risk of worsening pulmonary edema during fluid resuscitation. It is wise to assess pulse pressure and systolic pressure and diastolic pressure because they vary across the respiratory cycle to predict volume responsiveness before fluid challenge.[68] These parameters may also prove useful in assessing the impact of changes in PEEP on cardiac index.[51]

Cardiac Disease as a Cause of Blood Gas Abnormalities

Cardiac disease can cause arterial hypoxemia or hypercarbia by several mechanisms. The most obvious cardiac cause of arterial hypoxemia is right-to-left intracardiac shunting of blood as seen in tetralogy of Fallot. This situation allows venous blood to directly reenter the arterial circulation, causing arterial desaturation. In admixture lesions, such as transposition of the great arteries, tricuspid atresia, or total anomalous pulmonary venous connection, there is obligatory mixing of the systemic and pulmonary circulations, which allows desaturated blood to reach the systemic circulation, causing hypoxemia.

Arterial oxygen tension in right-to-left shunt lesions is sensitive to the volumes of systemic and pulmonary venous return that enter the aorta. The greater the ratio of pink to blue blood, the greater the arterial saturation. When oxygen-enriched air is administered after an excessively large aortopulmonary shunt, arterial blood may become fully saturated as a result of oxygen dissolved at high po_2 in the torrential pulmonary venous return.

In transposition of the great arteries, arterial oxygenation may be inherently limited by the degree of mixing that can occur. Pulmonary blood flow may be enormous, yet little of the pink pulmonary venous return escapes to the systemic circulation. Only the pulmonary venous return that reaches the systemic circulation delivers oxygen to the tissues.

In hypoplastic left heart syndrome, which is an admixture lesion, supplemental oxygen may, by reducing PVR, dramatically divert blood flow to the pulmonary circulation at the expense of systemic blood flow. This can both dramatically drop blood pressure and raise arterial po_2. In this situation, the rise in po_2 can be attributed to the fall in cardiac output and to the increase in pulmonary blood flow. These two changes alter the ratio of pink to blue blood that admixes in the atria.

Cardiac disease can cause hypercarbia by several mechanisms.[69] CHF can cause pulmonary edema, which interferes with lung function. As discussed in the Shock States and Respiratory Function section of this chapter, it can weaken the muscles of respiration and thereby reduce minute ventilation during spontaneous breathing.

Certain cardiac defects (or their treatments) can create large-scale ventilation/perfusion (V/Q) abnormalities, which may include underperfusion of large volumes of lung. An example is branch pulmonary artery stenosis, which may accompany tetralogy of Fallot or follow its surgical repair. Another example is maldistribution of pulmonary blood flow caused by a surgical shunt, which predominantly perfuses only one lung. The resultant high ventilation/perfusion defect functionally wastes ventilation. The airflow to high V/Q (underperfused) segments does not contribute to carbon dioxide (CO_2) clearance (as the scanty perfusion carries little, if any, CO_2 to that region of the lung). This waste of ventilation functionally reduces effective minute alveolar ventilation, causing CO_2 retention. In contrast, the gas exhaled by high V/Q segments mixes with gas from perfused alveoli during expiration, lowering the end-tidal pco_2. The result is elevated arterial pco_2 and markedly lower end-tidal pco_2, an apparent high arterial-alveolar pco_2 gradient. This is also called elevated alveolar dead space.

One additional mechanism of hypercarbia in cardiac disease is extremely low pulmonary blood flow in the presence

of admixture or right-to-left shunting. In this situation, so little blood reaches the lung that the circulation cannot deliver to the alveoli as much CO_2 per minute as the body produces until venous pco_2 becomes quite elevated. This can occur in ductus-dependent cyanotic cardiac defects on ductus closure and presents the paradoxical findings of clear (underperfused) lung fields and hypercarbia despite adequate ventilation. When there is no right-to-left shunt, elevation of venous (and occasionally arterial) pco_2 can occur without cyanosis. This commonly occurs during cardiopulmonary resuscitation (or in severe shock) when circulation is inadequate.

Hypercyanotic Spells

One special scenario that warrants discussion is the hypercyanotic spell, often called a tetrad spell. In these episodes, pulmonary blood flow is inadequate to take up sufficient oxygen from the lung to meet the mitochondrial demand for oxygen. Mixed venous po2 progressively falls. In the presence of admixture or right-to-left shunting, this directly reduces arterial oxygen tension. Sometimes the cause of the spell is abrupt reduction in pulmonary blood flow, as occurs with worsening obstruction of the infundibulum of the right ventricular outflow tract in tetralogy of Fallot or increased right-to-left shunting because of systemic vasodilation. However, pulmonary blood flow need not fall for a hypercyanotic spell to occur. Oxygen demand may rise (e.g., because of crying, fever, or exertion), outstripping the capacity of pulmonary blood flow to take up oxygen from alveolar air. Blood loss or acute anemia can cause worsening hypoxia and acidosis in the presence of underlying cyanotic disease. Hypercyanotic spells can occur in any cyanotic heart defect or in the child with lung disease and cyanosis.

The cycle put in place by this abrupt inadequacy of pulmonary oxygen uptake includes acidosis, physical distress, exaggerated skeletal muscle work, respiratory distress, exaggerated respiratory muscle work, and a further increase in muscle oxygen utilization. The cycle can progress to death unless it is interrupted.

Although respiratory distress and tachypnea may suggest a pulmonary cause, the treatment is directed at restoration of pulmonary blood flow (volume expansion, squatting, propranolol, transfusion if there has been blood loss), assurance of adequate alveolar oxygen for uptake (supplemental oxygen), reduction of oxygen demand (calming, sedation, paralysis, intubation, and mechanical ventilation, propranolol), or ductus manipulation (prostaglandin E_1).

Glenn and Fontan Procedures

Hearts that cannot support two separate circulations after repair (univentricular hearts and hearts having one hypoplastic ventricle) often are palliated and then repaired by routing systemic venous return to directly perfuse the lung without a pump (Glenn and Fontan procedures). This procedure frees the one functional ventricle to support the systemic circulation.

After such a procedure, the pressure of venous return drives pulmonary blood flow. At low pulmonary artery driving pressures, gravitational and airway pressure-mediated changes in V/Q matching may be exaggerated. The pressure of alveolar gas impinging on alveolar capillaries mediates this effect during mechanical ventilation. High airway pressure (from high PEEP or high tidal volume) tends to create alveolar dead space and waste ventilation as described in the Alveolar Pressure section of this chapter. Use of high PEEP and large tidal volumes in Glenn and Fontan patients requires caution and attention to gas exchange, although low levels of PEEP are generally well tolerated.

One additional effect of elevated airway pressure in these patients is impaired venous return. The heart does not compensate for increases in right ventricular afterload following a Fontan procedure. It is predictable that venous filling pressure will rise in proportion to the rise in alveolar pressure, so a 5 cm H_2O rise in PEEP is expected to raise venous pressure by 4 mm Hg. This might reduce cardiac output in proportion to the reduction in venous return as described for the normal circulation.

The advisability of PEEP after a Fontan or Glenn procedure must take into account the heart's inability to compensate for any elevation of PVR that may accompany atelectasis or lung disease. After either one of these procedures, the disadvantages of PEEP must be weighed against the risks of low FRC lung dysfunction.

Pulmonary Hypertension

Pulmonary hypertension makes the pulmonary circulation less susceptible to gravitational and airway pressure (Starling resistor)-mediated changes in V/Q matching. In contrast, it raises the tension in pulmonary vessels and invariably leads to smooth muscle hypertrophy and increased vasomotor reactivity. Even the infant with pulmonary hypertension because of a large interventricular communication and large left-to-right shunt (low PVR) may be capable of intense pulmonary vasoconstriction after repair. The lung with pulmonary hypertension must be ventilated with special attention to blood pH, arterial pco_2, alveolar po_2, and probably degree of lung stretch, all of which alter PVR.

Pulmonary hypertensive crises can be transparent unless pulmonary artery pressure is monitored. They are only obvious in the presence of a right-to-left shunt. In the absence of such a shunt, an abrupt rise in PVR presents as a fall in cardiac output, sometimes associated with right ventricular ischemia, which may be evident on the electrocardiogram. Cardiovascular deterioration in a patient with underlying pulmonary hypertension should always direct attention to the patient's respiratory status.

There are numerous potential treatments of pulmonary hypertensive crises. Central to these is assurance of normal gas exchange and adequate (but not excessive) lung expansion. Oxygen, inhaled nitric oxide, selective phosphodiesterase inhibitors, calcium channel blockers, and other vasodilators have been used. Treatments that address oxygen demand also are essential.

Vascular Impingement on the Lungs

There are several recognizable cardiovascular syndromes of vascular impingement on airways.[70,71] The respiratory effects of these lesions are predictable from their location. Complete vascular rings may compress the trachea, causing airway narrowing, obstruction, and localized tracheomalacia. A pulmonary artery sling is origin of the left pulmonary artery from the right. The left pulmonary artery then wraps around the right

mainstem bronchus to pass between the trachea and esophagus on its course to the left lung. It may impinge on the right mainstem bronchus, often causing right lung air trapping and overdistension. In congenital cardiac defects, pulmonary hypertension and left atrial hypertension often occur together. In this situation, the left atrium may elevate the left mainstem bronchus and trap it against the hypertensive left pulmonary artery.[72] This situation often leads to left lung atelectasis. In tetralogy of Fallot with absent pulmonary valve, massive dilation of the main pulmonary artery may occur with impingement on the bifurcation of the trachea. Tracheobronchial malacia may cause critical respiratory problems in this lesion, even after successful repair of the cardiac defect.

Effect of Initiating Mechanical Ventilation

At the time of initiation of mechanical ventilation, the interactions between breathing and circulation are abruptly altered. Moreover, these changes are superimposed on simultaneous sedation, paralysis, other pharmacologic regimens, and instrumentation of the pharynx and airway. Whereas narcotics, paralytics, atropine, and other drugs have well-defined effects, the effects of initiation of mechanical ventilation on circulation are not as consistent.

In many cases, effects on right ventricular preload predominate. This is generally the case in patients who are hypovolemic, such as asthmatics who have not been taking enough oral fluids at home, patients who are dehydrated, and septic children who may be hypovolemic because of capillary leak syndrome. Air trapping, as occurs in asthma, may be worsened by positive pressure ventilation, high ventilator rates, or use of long inspiratory times,[73] with consequent amplification of effects on venous return. Vascular volume expansion should accompany intubation in these patients.[74] It is noteworthy that the decrease in stroke volume that is often caused by positive pressure ventilation is not generally accompanied by a compensatory rise in heart rate,[75,76] so hemodynamic embarrassment that occurs upon institution of mechanical ventilation is not generally signaled by tachycardia.

Patients with segmental lung disease may undergo redistribution of blood flow on initiation of positive pressure ventilation. Patients with lobar pneumonia or large segments of atelectasis may become more hypoxemic on institution of positive pressure breathing because of diversion of pulmonary blood flow away from normal lung toward low V/Q lung segments. In contrast, application of PEEP may quickly reexpand collapsed areas of lung, improving V/Q matching and enhancing oxygenation.

Patients with pulmonary vascular disease may benefit from restoration of normal blood gases and alveolar gas composition, because alveolar hypoxia, arterial hypercarbia, and acidosis all increase pulmonary vascular tone. Inadvertent overdistension of lung may, in contrast, cause a calcium channel mediated rise in PVR.[77]

Patients in congestive cardiac failure, especially those with elevated filling pressures, may benefit almost immediately from afterload reduction as described in the Left Ventricular Afterload section of this chapter. Relief of respiratory distress and diminished work of breathing can quickly benefit the circulation. Septic patients with myocardial depression also may show prompt improvement.

References are available online at http://www.expertconsult.com.

Myocardial Dysfunction, Ventricular Assist Devices, and Extracorporeal Life Support

Cherissa Hanson, Keith C. Kocis, and Ana Lía Graciano

PEARLS

- Advances in medical management, surgical techniques, and mechanical circulatory support for pediatric patients with congestive heart failure continue to improve patient outcomes.
- Indications for use of mechanical circulatory support continue to evolve.
- Patient size, expected duration of support, and goals of support (i.e., bridge to recovery versus bridge to transplant) must be considered in the choice of mechanical circulatory support device.
- Mechanical circulatory support is a life-saving therapeutic option for patients with advanced heart failure. Device options in children remain limited because of their size constraints.
- Selection of the appropriate mechanical circulatory device is critical to a successful outcome.

Myocardial dysfunction resulting in heart failure and low cardiac output syndrome (LCOS) is a common occurrence in the pediatric intensive care unit. The primary goal in the management of these patients is to ensure adequate tissue oxygen delivery, because an imbalance between oxygen delivery and consumption will result in further organ failure. Initial therapies to treat decompensated heart failure should target decreasing metabolic demands (i.e., work of breathing), heart rate and rhythm control, augmentation of preload, decreasing afterload, and augmenting cardiac contractility. Despite advances in medical therapy (e.g., milrinone and amiodarone),[1,2] a group of patients will continue to deteriorate or require excessive vasoactive and inotropic support. This group should be evaluated for mechanical circulatory support.

Mechanical circulatory support has become an essential component of pediatric cardiac intensive care units (ICUs). Results of mechanical cardiopulmonary support in infants, children, and young adults have steadily improved in the past decade. Novel and innovative forms of mechanical circulatory support are being developed while extended indications are currently being explored. Extracorporeal life support (ECLS) remains the most commonly deployed form of mechanical support.[3,4]

In this chapter we review the basics of myocardial dysfunction in children with an emphasis on LCOS and its treatment with regard to mechanical circulatory support. We outline the principles of appropriate use of ECLS along with its current indications and important technical aspects, including the use of ventricular assist devices (VADs). Finally, we outline indications, patient management, present research, and future directions of these technologies for use in pediatric patients.

Myocardial Dysfunction

Patients admitted to the pediatric intensive care unit for heart failure often demonstrate inadequate cardiac output to meet the metabolic needs of the body (i.e., shock). The etiology of heart failure in pediatric patients encompasses a broad spectrum of pathology that has environmental, structural, metabolic, and other origins.

Low Cardiac Output Syndrome

LCOS describes a clinical and biochemical state where there is inadequate systemic oxygen delivery (Do_2) to meet the metabolic demands of the patient. This condition has been described since the 1960s, and multiple studies have documented the predicted change in physiologic parameters. LCOS is frequently seen in patients with severe sepsis, myocarditis, and cardiomyopathies and after pediatric cardiac surgery.[5] Postoperative physiologic changes resulting from cardiopulmonary bypass, residual lesions, cardioplegia, ventriculotomy, changes in the loading conditions of the myocardium, or myocardial ischemia during aortic cross-clamping all may contribute to the development of LCOS. A variety of proinflammatory triggers are activated during cardiopulmonary bypass as a result of blood contact with foreign surfaces, ischemia, reperfusion, tissue trauma, and temperature changes. This complex inflammatory response includes complement activation, cytokine release, leukocyte and platelet activation, and the expression of adhesion molecules.[6] LCOS has been

reported to affect up to 25% of infants and children, typically occurs between 6 and 18 hours after cardiac surgery, and results in longer intensive care stay and increased mortality.[7] It is associated with elevated systemic and pulmonary vascular resistances, impaired myocardial function, and arrhythmias. When unrecognized or inadequately treated, LCOS can result in irreversible end organ failure, cardiac arrest, and even death. Prevention, early recognition, and optimal treatment are essential components for reversing its course.

Although detailed assessment of oxygen delivery in critically ill children is extremely challenging, numerous hemodynamic and biochemical parameters can help guide the bedside clinician. Arterial lactate and mixed or central venous saturation are important biochemical markers in patients with LCOS. An elevated lactate level on admission and one that rises at 0.9 μm per hour postoperatively is associated with major adverse events including death in infants after cardiac surgery.[8] Furthermore, lower mixed venous saturation may increase the predictive power of elevated arterial lactate levels for mortality after pediatric cardiac surgery.[9-13] The predicted changes in cardiac output have been systematically demonstrated in newborns following the arterial switch operation for transposition of the great vessels.[14] The median maximal decrease in cardiac index (32%) occurred approximately 6 to 12 hours after separation from cardiopulmonary bypass, and nearly a quarter of these newborns reached a nadir of cardiac index that was less than 2 L/min/m^2. The drop in cardiac index was coupled with a rise in the calculated systemic and pulmonary vascular resistance. Perfusion strategy with either low-flow bypass or circulatory arrest was not associated with postoperative hemodynamic or other nonneurologic postoperative events.[14]

Therapeutic Considerations

The treatment of LCOS aims at providing adequate oxygen delivery to meet the demands of end organs. Achieving a balance between O_2 supply and demand is essential and can be achieved by decreasing oxygen consumption (Vo_2) and/or increasing Do_2. Normally the ratio between Do_2 and Vo_2 is 5:1, and when Vo_2 increases according to increased metabolic demands, Do_2 readjusts by also increasing. When the rate of oxygen consumption exceeds Do_2, anaerobic metabolism begins. Mixed venous saturation is a reflection of the Do_2/Vo_2 ratio and can be an important indicator of O_2 delivery in critically ill patients. Management of patients with this malady should aim to decrease Vo_2 and increase Do_2.

Decreasing Oxygen Consumption

LCOS has been an active area of research, and multiple reviews of current therapies are available to guide the intensivist.[15-17] Vo_2 is determined by tissue metabolism and is increased during periods of increased muscular activity, infection, hyperthermia, or with increased levels of catecholamines. Supportive care for decompensated heart failure begins with strategies aimed at decreasing the child's metabolic demands. These strategies often include basic critical care therapies such as intubation and mechanical support for respiratory insufficiency, analgesia and sedation, and treatment of anemia (Figure 27-1). Likewise, temperature control is a routine but important part of intensive care, and even a modest increase in body temperature can result in major increases in systemic Vo_2 during the early postoperative period.[18]

Increasing Oxygen Delivery

Systemic oxygen delivery (Do_2) is defined as the amount of O_2 delivered to peripheral tissues each minute and is determined by cardiac output and the oxygen content of arterial blood as shown by the Fick equation (listed below), where Do_2 refers to oxygen delivery and CO to cardiac output. Arterial oxygen content (Cao_2) is determined by hemoglobin (Hb) concentration, the arterial oxygen saturation (Sao_2), and the partial pressure of oxygen in the arterial blood (Pao_2). CO is defined as the product of heart rate (HR) × stroke volume (SV).

$$Vo_2 = CO\,(Cao_2 - Cvo_2)$$

$$Do_2 = CO \times Cao_2$$

$$Cao_2 = (Hb \times 1.36 \times Sao_2) + (Pao_2 \times 0.003)$$

$$CO = HR \times SV$$

Oxygen delivery can be improved by oxygen therapy, red blood cell transfusions, intravenous fluids, and inotropic support. Mechanical respiratory support not only decreases metabolic needs by decreasing the work of breathing but also can improve the arterial oxygen saturation (by the administration of oxygen and positive end-expiratory pressure [PEEP]), thus increasing Cao_2. However, endotracheal intubation can be risky in these patients and requires a clear understanding of the patient's current pathophysiology. Cao_2 also can be increased by transfusing packed red blood cells to increase the hemoglobin concentration. Packed red blood cells can help ameliorate tachycardia caused by anemia, but risks of transfusion exist. A continuous assessment of the patient's volume status (preload) is needed to avoid hypovolemia or fluid overload with worsening pulmonary edema. Optimizing preload will allow for greater diastolic filling, perfusion of the coronary arteries, and increased stroke volume. LCOS has been traditionally managed using catecholamines or their analogues (i.e., epinephrine, dopamine, and dobutamine); however, these agents can be deleterious on global and myocardial Vo_2, and when used in high doses they can lead to increased mortality.

Pharmacologic Treatment of Pediatric Heart Failure

In contrast to adult patients, tremendous heterogeneity exists between the etiology and pathophysiology of congestive heart failure in pediatric patients. Despite these differences, treatment strategies for pediatric patients have traditionally followed the recommendations extrapolated from large, randomized, multicenter trials in adult patients because of a lack of pediatric clinical trials. Symptom management with digitalis and diuretics formed the basis of early therapy (~1970s) of pediatric patients with congestive heart failure. Angiotensin-converting enzyme inhibitors (ACEI) exert favorable effects on cardiac remodeling and survival in adults with congestive heart failure. Their role in children is less clear. A randomized, placebo-controlled trial in children evaluated the effect of ACEI in patients with a single ventricle by

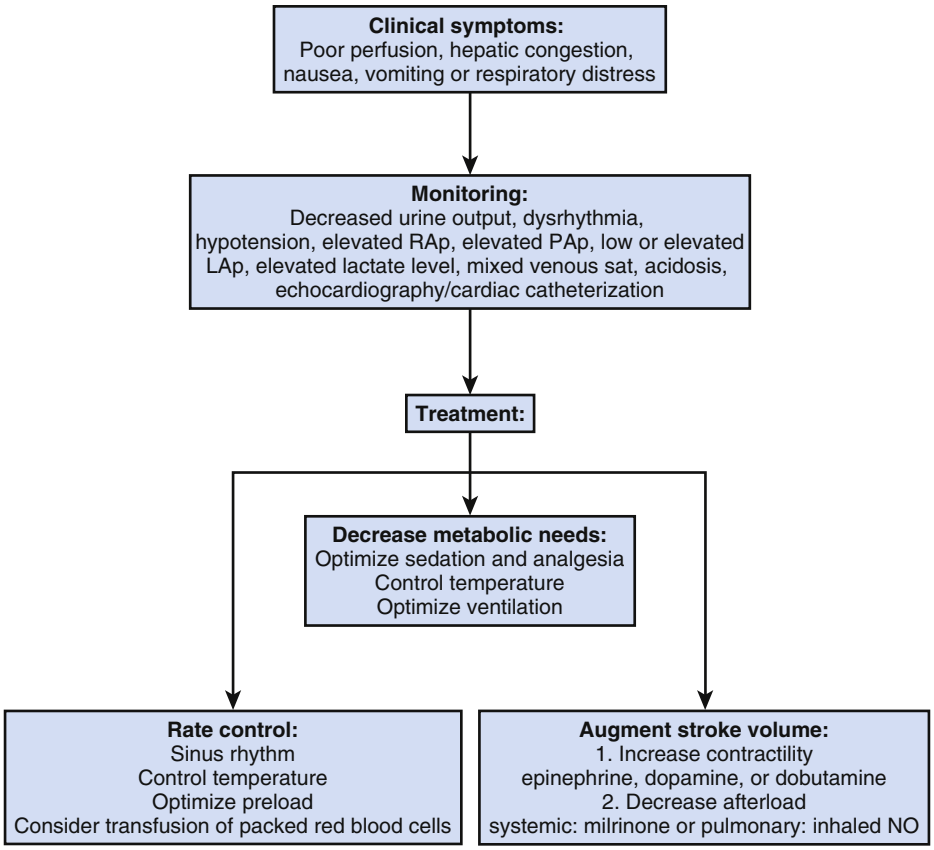

Figure 27–1. Algorithm for treatment of ventricular dysfunction. *NO,* Nitric oxide.

measuring exercise capacity, but this study failed to demonstrate a beneficial effect.[19]

β-Blockade utilization in pediatrics primarily has been extrapolated from the positive effects seen in adult trials that demonstrated a reduction in mortality and risk of hospitalization with the use of carvedilol.[20-21] A few reports have been made of the efficacy of propranolol in children with severe congestive failure as a result of left-to-right shunts[22] and of metoprolol in children with dilated cardiomyopathy.[23] Single-center trials have demonstrated both improved ejection fraction with the use of carvedilol in children awaiting heart transplantation with dilated cardiomyopathy[24,25] and a delayed time to transplantation or death.[25] However, the most recent and largest multicenter, randomized, double-blind, placebo-controlled trial of carvedilol for children and teenagers with symptomatic systolic heart failure failed to demonstrate an improved survival benefit.[26]

Milrinone, a phospodiesterase-3 inhibitor, has emerged as an important "inodilating" agent that is widely used in children after open heart surgery.[1-2,27-29] A landmark study showed that the prophylactic use of milrinone was associated with a decreased likelihood of LCOS in children after certain types of open-heart surgery.[28] This benefit is thought to result from both improved myocardial contractility as well as pulmonary and systemic vasodilatory effects.[2,28] Milrinone reduces right ventricular (RV) and left ventricular (LV) afterload through systemic and pulmonary vasodilatation and improves diastolic relaxation (lusitropy) of the myocardium through its enhanced cyclic adenosine monophosphate (cAMP)–dependent reuptake of calcium after systole.[30,31] A loading dose of 25 to 50 μg/kg generally is administered followed by a continuous infusion at doses between 0.25 to 0.75 μg/kg/min.

Calcium sensitizing agents (Levosimendan) have been shown to improve cardiac function and survival in adults with decompensated heart failure.[32] but pediatric data is scarce.[33-37] Nitric oxide is another therapy that may improve right heart failure.[38-39] Adult patients who undergo open heart surgery and receive triiodothyronine supplementation have demonstrated a dose-dependent increase in cardiac output that has been associated with an improved clinical outcome. However, a recent systematic review concluded that there is lack of evidence that triiodothyronine supplementation is beneficial in the prevention of morbidity and mortality in children undergoing cardiac surgery.[40]

Fenoldopam, a selective dopamine-1 receptor agonist, causes systemic vasodilatation and increased renal blood flow, with improved renal function.[41-43] Its use in critically ill adult patients with renal dysfunction has become routine. Two recent meta-analyses have concluded that the use of fenoldopam in critically ill adult patients at risk of acute kidney injury appears to decrease the development of acute tubular necrosis, the requirement for renal replacement therapy, overall patient mortality, and length of ICU stay.[44-45] One study also demonstrated a reduction in the time on mechanical ventilation.[44] However, few data exist regarding the use of fenoldopam in neonatal or pediatric patients. One retrospective study evaluated the use of fenoldopam in neonates after cardiopulmonary bypass with poor urine output despite conventional diuretic therapy and demonstrated a significant improvement in diuresis.[46] However, a subsequent prospective trial failed to demonstrate a beneficial effect.[47]

Terlipressin is a synthetic long-acting analogue of vasopressin with a higher affinity for vascular V1 receptors than vasopressin. Terlipressin has been used in adult patients to treat extremely low cardiac output,[5] but its application in children is limited. Terlipressin demonstrated an improvement in respiratory, hemodynamic, and renal indices in postoperative pediatric cardiac patients with refractory LCOS.[48-49] While these results are encouraging, further investigation with prospective randomized trials are needed to provide data regarding the efficacy and safety of terlipressin in infants and children.

Mechanical Circulatory Support

LCOS is a critical condition that requires prompt and aggressive treatment When medical treatment is ineffective, patients should be considered for mechanical circulatory support. Successful institution of this therapy can allow for recovery or be a bridge to heart transplantation. Mechanical circulatory support for cardiopulmonary failure refers to the use of mechanical devices to temporarily support (generally less than 30 days) heart or lung function (partially or totally) when maximal conventional medical treatment fails. Mechanical circulatory support can be provided by ECLS (via a roller or centrifugal pump) or via a VAD. The patient's underlying physiopathology, size, and expected length of support dictates which technique is best. In children, the majority of mechanical circulatory support continues to be achieved with ECLS.

Historical Perspective

Since 1953, when John Gibbon first utilized extracorporeal perfusion in the operating room, the indications and utilization of this therapy have continued to expand. Technological advances in ECLS have afforded support for thousands of patients per year with a variety of respiratory and/or cardiac indications. As of July 2009, a total of 37,092 pediatric and neonatal patients were registered patients within the Extracorporeal Life Support Registry.[50]

Early trials of ECLS were marked by mixed results. In 1985, Bartlett[51] reported the first successful use of ECLS in a newborn. Since then, neonates with diagnoses of meconium aspiration syndrome, persistent pulmonary hypertension, and congenital diaphragmatic hernia have been treated for severe respiratory failure that is unresponsive to conventional therapies.[52,53] ECLS was first used for cardiac support in the 1970s by Baffes, but it was not until the 1990s that ECLS became a common therapeutic technique for this patient population.[54-55]

In 1971, DeBakey reported the first successful use of a VAD in adults.[56] During the past 20 years, the favorable results seen in the adult population has prompted the adaptation of adult technology for pediatric patients. Two pulsatile paracorporeal devices were introduced for use in children, the Medos-HIA and the Berlin Heart. Worldwide experience with these devices to support the neonatal and infant population as a bridge to either recovery or transplantation is increasing.

Mechanical Support Devices

Mechanical support devices can be categorized according to the expected duration of support. Short-term devices are used to support the myocardium in the intensive care setting for hours to days but rarely beyond 30 days; long-term devices are suitable for extended periods of support. The basic classification of mechanical support devices according to the expected length of treatment provided is as follows: Short-term (less than 30 days) mechanical support devices include (1) ECLS, (2) centrifugal VADs, and (3) intraaortic balloon pumps (IABPs). Long-term (>30 days) mechanical support devices include (1) pulsatile and (2) rotary axial devices.

Short-Term Mechanical Support Devices

Extracorporeal Life Support

ECLS is primarily utilized for short-term support of patients with decompensated heart failure who are unresponsive to medical therapy. Adaptations to the traditional cardiopulmonary bypass circuit have resulted in the standard ECLS circuit (Figure 27-2). The ECLS cannulation is initiated by placement of vascular cannulas within the patient's circulatory system.

Venoarterial (V-A) ECLS provides both biventricular and typically pulmonary support. It is important to note that complete cardiac support cannot be provided by V-A ECLS because of incomplete drainage of the right heart. Routine cannulation for V-A ECLS occurs via one of three arterial and venous access points: (1) The transcervical approach places the venous cannula in the right atrium via the right internal jugular vein and the arterial cannula in the ascending aorta via the right carotid artery; (2) the transthoracic approach with direct cannulation of the right atrium and aorta through a median sternotomy is utilized for postoperative cardiac patients who either cannot be weaned from cardiopulmonary bypass or require mechanical circulatory assistance in the immediate post-operative period; and (3) femoral artery and vein cannulation is an option for older/larger children via the femoral artery and vein. The transcervical and transthoracic approaches are the preferred methods for small children. Figure 27-3 demonstrates a chest radiograph evaluation of cannula placement in a patient supported by V-A ECLS.

Venovenous (V-V) ECLS provides pulmonary support without cardiac support. In V-V ECLS a single cannula is placed in the right atrium through a transcervical approach. This cannula provides both inflow and outflow for the circuit. V-V ECLS can improve RV dysfunction as a result of oxygenated, pH-balanced blood flowing to the lungs, thus decreasing pulmonary vascular resistance and right heart afterload. In addition, improved filling of the LV can occur through decreasing RV overdistension. Likewise, the absence of an aortic cannula prevents the increase in LV afterload seen with venoarterial ECLS. However, at times the indirect cardiac effects of V-V ECLS do not adequately improve ventricular dysfunction and conversion from V-V ECLS to V-A ECLS is required. See Table 27-1 for a comparison of V-A versus V-V ECLS.

The no membrane oxygenator VAD is an adaptive technique to traditional ECLS that several centers have utilized. This form of ECLS eliminates the oxygenator from the standard circuit configuration. This technique allows for mechanical circulatory support while limiting both the harmful inflammatory effects of the oxygenator and reducing the initial need for anticoagulation.[57] It allows the ECLS device to be utilized as either an RV assist device, LV assist device, or a biventricular assist device.

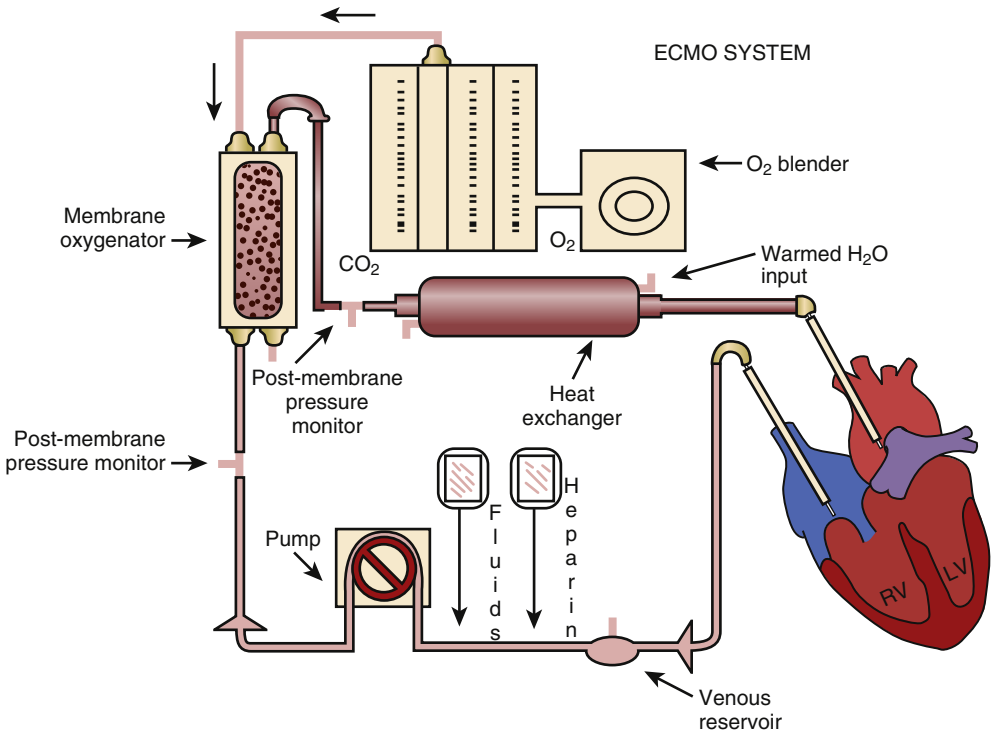

Figure 27–2. Extracorporeal membrane oxygenation circuit.

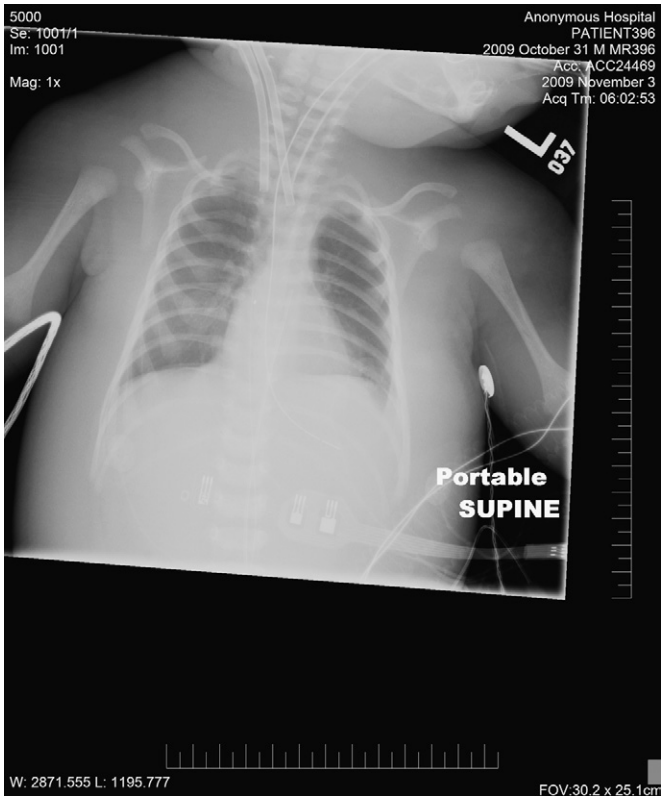

Figure 27–3. Chest radiograph showing extracorporeal membrane oxygenation cannulas.

Extracorporeal Life Support Circuit

Through either extrathoracic or transthoracic placement, the most common configuration involves placement of a venous drainage cannula in the right atrium where blood is passively drained from the patient to the venous reservoir. Blood then passes through a servoregulated roller-head or centrifugal pump that pumps blood through the remainder of the system. Gas exchange (O_2 addition and CO_2 removal) is provided through an artificial lung (oxygenator) where a sweep gas passes in counter current to the blood, allowing diffusion to occur. Blood temperature is controlled by a countercurrent heat exchanger. Finally, blood is pumped to the body into the aorta at systemic pressure. Additional components include ports for infusion of medications, a hemofilter for fluid control or dialysis, and monitoring systems that regulate gas exchange, flow, and pressure.

Extracorporeal Life Support Physiology

Patient circulatory physiology is altered by the initiation of mechanical circulatory support, and it is important to understand how ECLS affects these patients. Mechanical circulatory support affords recovery of myocardial function through a variety of mechanisms. Alteration of both RV and LV preload and afterload occurs to varying degrees based on which device is utilized and how it is utilized. Some of these alterations can be deleterious. Adequate decompression of the left heart decreases left atrial hypertension and reduces cardiac wall stress, cardiac work, and myocardial oxygen consumption, allowing for improved coronary perfusion. Mechanical circulatory support of the LV allows for reverse molecular remodeling with normalization of heart failure and apoptosis markers, normalized expression of genes involved in calcium homeostasis, cell growth, and differentiation, and up-regulation of structural proteins.[58] With adequate venous drainage, both right atrial and left atrial pressures are lowered. This effect is important to prevent complications such as pulmonary edema or hemorrhage, pleural effusions, ascites, superior vena cava syndrome, or stroke. Likewise, a low to normal central venous pressure is important for patients who have experienced

Table 27–1 Venoarterial vs. Venovenous ECMO

	Venovenous ECMO	Venoarterial ECMO
Organ support	Pulmonary	Pulmonary and cardiac
Cannulation site	Transcervical or femoral	Transcervical, transthoracic, or femoral
Pump	Roller or centrifugal	Roller or centrifugal
Length of support	Days to weeks	Days to weeks

ECMO, Extracorporeal membrane oxygenation.

Table 27–2 ELSO Registry Outcomes as of July 2009

Category	Total	% Survival
Neonate		
Respiratory	23,191	75
Cardiac	3749	39
ECPR	492	37
Pediatric		
Respiratory	4188	56
Cardiac	4564	46
ECPR	908	38

ECPR, Extracorporeal cardiopulmonary resuscitation; *ELSO,* Extracorporeal Life Support Organization.
From Extracorporeal Life Support Organization, Ann Arbor, Mich.

cardiac arrest and are at risk for ongoing cerebral ischemia as a result of cerebral edema and increased intracranial pressure.

Extracorporeal Life Support Indications and Contraindications

It is widely accepted that all patients considered for mechanical circulatory support should have either a reversible physiologic process or be a candidate for a bridge to transplant or a bridge to destination therapy. The time frame in which recovery is expected and the severity of cardiac and/or other organ failure is used to guide medical personnel regarding optimal selection of a mechanical circulatory support device. Appropriate patient selection and stabilization is vital to maximize survival and outcome with any mechanical circulatory support system. The ELSO Registry Outcomes as of July 2009 are listed in Table 27-2.

Myocarditis

The clinical course of patients with myocarditis is variable. Some patients present with subclinical disease, others have an indolent course that progresses to dilated cardiomyopathy, and a subset of patients demonstrate fulminant disease. Those with fulminant acute myocarditis often experience a rapidly progressive course leading to death. Without mechanical circulatory support, patients with a fulminant course had expected survival rates of only 25% to 50%.[59-61] With the aggressive utilization of ECLS as a bridge to transplantation or recovery (or VAD if a longer recovery time is anticipated), survival rates for patients with any form of myocarditis are now reported to be as high as 90% to 93%.[62-64] It has been suggested that the institution of ECLS may aid in the normalization of ventricular geometry, a phenomenon that is referred to as reversible remodeling. This process is thought to improve ventricular dysfunction because of favorable influences on the neurohormonal cardiovascular milieu and unloading of the LV.[65] For patients with the most severe disease, that is, end-stage dilated cardiomyopathy resulting from fulminant myocarditis, the use of mechanical circulatory support without transplantation has resulted in survival rates as high as 67% to 80%.[66-68]

Postcardiopulmonary Bypass

Failure to wean from cardiopulmonary bypass occurs in approximately 1% to 3.2% of pediatric congenital cardiac surgery cases.[69-71] Individual institutions have reported survival rates to hospital discharge between 32% and 54% for pediatric patients who require ECLS after cardiac surgery.[70-77] One small series has reported a survival rate as high as 80%.[69] However, the July 2009 ELSO registry report for postoperative cardiac surgery patients younger than 16 years reported an overall survival rate of only 40%.[50] All of these patients demonstrate LCOS refractory to medical management as detailed in prior sections. It has been demonstrated that in patients with decompensated heart failure, a rising blood lactate level >0.75 mmol/L/hour on serial measurements despite escalating inotropic support may accurately predict a poor outcome.[10] For this patient population, it is anticipated that cardiac arrest or end-organ dysfunction will occur. The use of mechanical circulatory support is a widely accepted tool to support the vital organs while allowing for myocardial recovery.[78-80] It is imperative that this group of postoperative cardiac patients be evaluated for residual cardiac defects before considering mechanical circulatory support. Diagnostic or interventional cardiac catheterization may guide treatment pathways or be therapeutic. On occasion a patient's condition may warrant immediate mechanical support in order to safely proceed with cardiac catheterization. In these instances it is feasible to obtain hemodynamic and angiographic data or to perform therapeutic interventions in the cardiac catheterization laboratory. Balloon valvuloplasty or angioplasty of aortic arch obstructions, device closure of residual atrial or ventricular septal defects, coiling of aortopulmonary collateral vessels, and/or balloon or blade atrial septostomy all may be crucial interventions to improve cardiac output and allow for separation from mechanical circulatory support. If these defects cannot be managed in the catheterization laboratory, prompt return to the operating suite will be required. Residual cardiac defects, if left untreated, have been shown to be nearly universally fatal for patients requiring mechanical circulatory support.[80]

The use of ECLS for postcardiotomy support in neonates and infants with single-ventricle physiology remains controversial and continues to be considered a relative contraindication in some centers. The 2009 ELSO report lists a 34% survival rate for ECLS use in patients following the stage I Norwood procedure,[50] which is lower than for other postcardiotomy patients.[50,81]

Extracorporeal Cardiopulmonary Resuscitation

In-hospital cardiac arrest in children continues to be associated with dismal outcomes despite advances in cardiopulmonary resuscitation (CPR). A prospective multicenter

Table 27–3 Summary of Literature for Extracorporeal Cardiopulmonary Resuscitation

Article	Date	Patients	Survival D/C (%)	CPR (min)
Prodhan et al, 2009	2001-2006 all	N = 33	73	NR
Meert et al, 2009	2003-2005 all	N = 353	48.7	NR
Barrett et al, 2009	1992-2005 all	N = 682	39 36 good neurologic outcome	NR
Chan et al, 2008	1992-2005 cardiac	N = 492	42	NR
Huang et al, 2008	1999-2006 all	N = 27	41 (1999-2002) 58 (2002-2006)	50 (30-60) IQR
Tajik et al, 2008	1990-2007 all	N = 288	39.6	NR
Alsoufi et al, 2007	2000-2005 all	N = 80	34	Favorable outcome = 46 (14-95) Unfavorable outcome = 41 (19-110)
Ghez et al, 2007	2003-2006 cardiac	N = 15	57	44 (10-110)
Allan et al, 2006	1996-2004 cardiac cath	N = 19	79	29 (20-57)
Kelly et al, 2005	Case report all	N = 2	100	176/97 min
Morris et al, 2004	1995-2002 all	N = 66 Cardiac = 45 Other = 21	All Cardiac = 44 Other = 9.5	Survivors = 50 (5-105) Nonsurvivors = 46 (15-90)
Aharon et al, 2001	1997-2000 cardiac	N = 50 Cardiac arrest = 10	80	42 (5-110)
Parra et al, 2000	1995-1997 cardiac	N = 4	100	16 (12-20)
Del Nido et al, 1992	1981-1991 cardiac	N = 11	64	65 ± 9 min
Von Allmen et al, 1991	1885-1988 all	N = 10	60	NR

IQR, Interquartile range; *NR,* not recorded.

observational study from the National Registry of Cardiopulmonary Resuscitation reported a good neurologic outcome for 73% of survivors of an in-hospital cardiac arrest, yet the rate of survival to hospital discharge was only 27%.[82] Another multicenter observational study from the Pediatric Emergency Care Applied Research Network reviewed in-hospital cardiac arrests that occurred during an 18-month period between 2003 and 2004. It also reported a good neurologic outcome for 76% for survivors and an improved (49%) rate of survival to hospital discharge with the utilization of extracorporeal CPR. Both reviews excluded out-of-hospital, do-not-resuscitate, or neonatal ICU patients.[83] However, while neurocognitive outcome has improved for survivors of cardiac arrest, the duration of CPR has been inversely proportional to survival. One center demonstrated that a witnessed in-hospital cardiac arrest of >30-minute duration was universally fatal without the utilization of ECLS.[84] This knowledge has led to an emerging interest in the use of ECLS for patients who have failed to reestablish a perfusing rhythm and adequate circulation with conventional CPR rescue techniques. The American Heart Association guidelines for in-hospital pediatric cardiac arrest now recommend consideration of ECLS during CPR if the conditions leading to the arrest are likely to be reversible or amenable to heart transplantation.[85] However, wide variability in patient selection and the ability to institute ECLS in a timely fashion (5 to 176 minutes) has led to variable success reports ranging from 0% to 100%.[86-95] Table 27-3 presents a summary of the current literature on ECPR. Thus large centers have increasingly dedicated resources for the rapid deployment of ECLS, utilizing a team that is immediately available to cannulate with a pre-primed circuit. The 2009 ELSO Registry for neonatal and pediatric patients supported with ECLS following cardiac arrest reported a survival to hospital discharge rate of 38%.[50]

Myocardial Failure: Bridge to Transplantation

While heart transplantation is the treatment of choice for patients with end-stage myocardial failure, many children die every year waiting for a suitable organ to become available.

As a result, mechanical circulatory support is now increasingly utilized as a bridge to heart transplantation. The most common indications for ECLS as a bridge to transplant include end-stage congenital heart disease, cardiomyopathy, and graft rejection after heart transplantation. To date, no randomized controlled trials have been performed in the pediatric age group to determine if mechanical circulatory support as a bridge to cardiac transplantation confers improved survival for patients with myocarditis. Children with myocardial failure resulting from myocarditis demonstrate increased short-term survival when treated with ECLS and transplantation,[67] however; long-term survival reports suggest that bridge to transplantation may only be indicated for patients with giant cell or the acute form of myocarditis but not those with the fulminant form.[62-63,96]

Factors that dictate which mechanical circulatory support device is used include patient size, the need for pulmonary support, and duration of wait time. Complications associated with ECLS generally limit the duration of support with this device to approximately 2 weeks, although support that lasts >4 weeks has been rarely reported. As long as complications precluding transplant have not developed, there should be no arbitrary cutoff for duration of support. A recent review of the United Network for Organ Sharing Database from 1995 to 2005 evaluated both clinical status at transplantation and risk factors for short- and long-term mortality of patients supported with various mechanical circulatory support devices. This study revealed that 30-day survival was significantly decreased for patients who received a bridge to transplant with ECLS versus VAD; long-term (10-year) survival was not affected. Not surprisingly, preoperative severity of illness also predicted early survival following cardiac transplantation. The overall 10-year survival rate was 56.8%.[97]

ECLS has been the mainstay of therapy for small children and neonates in the United States for short-term support (~2 weeks) because of a paucity of devices for this age group. The use of paracorporeal pulsatile assist devices (Berlin Heart and Medos HIA) for neonates in European countries has demonstrated early promising results.[98-100] The utilization of this technology is in its nascent stage in the United States. However, a retrospective review that compared survival outcomes of children supported with ECLS versus Berlin Heart to heart transplantation or recovery at Arkansas Children's Hospital favored the use of the Berlin Heart (57% vs. 86%).[101]

Malignant Dysrhythmias

Mechanical circulatory support is an essential therapy for patients with malignant dysrhythmia that is unresponsive to pharmacotherapy. A subset of patients with acute fulminant myocarditis presents with refractory LCOS and dysrhythmia that further compromises end-organ perfusion. If these patients do not rapidly respond to antiarrhythmic agents, many progress to cardiac arrest and death. In this scenario, mechanical circulatory support may be beneficial as a bridge to recovery or transplantation.[63] Several potentially lethal tachyarrhythmias, such as supraventricular tachycardia, junctional ectopic tachycardia, or ventricular tachycardia, can occur congenitally or are acquired in the postoperative period as a result of the ingestion of toxic substances or medications.[102-104] Again, ECLS can allow time for resolution of dysrhythmia, for medical treatment to take effect, and/or for recovery of cardiac function.

Refractory Respiratory Failure

Severe neonatal respiratory failure refractory to maximal medical therapy that requires ECLS is the most common indication for ECLS. Diagnoses include meconium aspiration syndrome, congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn, sepsis, respiratory distress syndrome, or other congenital lung abnormalities. Three randomized controlled trials involving neonates have been conducted and all reported that ECLS improved the survival rate.[53,105-107] It has been reported that of infants treated with ECLS, the proportion of infants with congenital diaphragmatic hernia has been increasing, whereas the proportion with respiratory distress syndrome, meconium aspiration syndrome, and sepsis has been decreasing.[108] However, the overall patient survival for this group remains at 75%.[1] A recent report, the first to perform a systematic comparison of neonatal ECLS practice patterns and respiratory failure deaths between countries, demonstrated distinct differences between the United States and the United Kingdom. It concluded that U.S. clinicians seem more willing to utilize ECLS for persistent pulmonary hypertension of the newborn and congenital diaphragmatic hernia. This difference in practice pattern was correlated with a decrease in the U.S. neonatal death rate from congenital diaphragmatic hernia in comparison with the United Kingdom.[109]

During the past 2 decades, successful treatment of pediatric patients with ECLS is increasingly being described in patient groups that would have been excluded in the past. ECLS is now considered for patients with trauma, immunosuppression, underlying bleeding disorders, sickle cell disease, status asthmaticus, pulmonary embolism, established multiple organ system failure, and more. However, reported survival rates are variable. For example, whereas a survival rate of 94% is reported in patients treated with ECLS for refractory status asthmaticus,[110] that of immunocompromised patient populations is only 31% to 36%.[111-112] Even of greater concern is that although case reports of survival with good neurologic outcome exist for the hematopoietic stem cell transplant population, review of the ELSO database demonstrates an almost universal fatal outcome for these patients.[113-114] The duration of ECLS required until successful decannulation is often longer for respiratory indications of use. This finding is likely due to the fact that parenchymal lung disease often requires a longer period of recovery than does myocardial dysfunction. The most common diagnosis in the pediatric respiratory ECLS group of patients is acute respiratory distress syndrome. Overall survival for this group of patients remains at 56%.[50] Although no randomized controlled trials for pediatric patients with refractory respiratory failure have been performed, a prospective, observational study with matched control subjects demonstrated improved survival of ECLS patients when compared with conventional support.[115]

Contraindications

If a patient has been selected as an appropriate candidate for consideration of mechanical circulatory support, then few absolute contraindications exist. While each institution may have slight variations of this list of contraindications, it is generally accepted that weight <2 kg, irreversible cardiac failure without the option for transplantation, severe neurologic dysfunction, severe intracranial or intraabdominal bleeding,

Table 27–4 Complications of ECMO, ELSO Registry, July 2009

% Reported	Respiratory Runs: Neonatal N = 23,495 (%)	Respiratory Runs: Pediatric N = 4263 (%)	Cardiac Runs: 0-30 Days N = 3980 (%)	Cardiac Runs: 31 Days to 1 Year N = 2527 (%)	Cardiac Runs: 1-16 Years N = 2131 (%)
Raceway rupture	**0.3**	0.7	0.3	0.7	0.8
Oxygenator failure	**5.9**	13.3	7.5	8.4	9.2
Pump malfunction	**1.7**	2.8	1.6	2.1	2.3
Seizures	**9.9**	6.2	7.8	9.6	5.2
CNS infarct	**7.8**	3.8	3.6	3.9	4.1
CNS hemorrhage	**6.7**	5.7	11.3	5.2	3.2
Brain death	**1.0**	5.7	1.2	3.9	7.9
Hypertension	**12.6**	15.3	8.2	11.5	10.8
CPR	**2.3**	5.8	3.4	3.1	4.3
Cardiac stun	**5.1**	1.6	6.9	5.0	5.5
Tamponade	**0.6**	2.2	6.4	5.7	5.6
Cannulation site bleeding	**6.9**	14.4	9.8	10.6	16.1
Surgical site bleeding	**6.2**	14.7	32.0	34.5	30.0
GI hemorrhage	**1.7**	4.2	1.0	2.0	2.9
Culture + infection	**6.1**	18.9	7.8	12.6	11.4
Hemofiltration	**14.3**	20.1	25.6	21.1	18.8
CAVHD	**1.4**	6.2	5.6	4.5	6.1
Dialysis	**3.3**	14.5	11.0	12.5	13.3

CAVHD, Continuous arteriovenous hemodialysis, *CNS,* central nervous system, *CPR,* cardiopulmonary resuscitation, *ECMO,* Extracorporeal membrane oxygenation, *ELSO,* Extracorporeal Life Support Organization, *GI,* gastrointestinal.
From Extracorporeal Life Support Organization, Ann Arbor, Mich.

and lethal congenital abnormalities are all absolute contraindications. Technical limitations would include an inability to obtain vascular access as a result of thrombosis, abnormal anatomy, or prior surgery. As previously discussed, when considering a postoperative cardiac patient for mechanical circulatory support, it is prudent to rule out the possibility of a residual cardiac defect. Furthermore, cardiac arrest is not an absolute contraindication if rapid resuscitation is available and the underlying etiology is deemed to be reversible.

Critical Care Management During Extracorporeal Life Support

Patients who require mechanical circulatory support are critically ill, often with loss of multiple end-organ function. It is not surprising that complications occur with a greater frequency for this group of patients than for other critically ill pediatric patients. The basic management principles are discussed in this section. Table 27-4 will be referred to frequently throughout this section because it summarizes the most common reported complications for pediatric patients supported by ECLS as of July 2009.

Cardiac Output

When assessing the hemodynamic state of a patient, one must consider to what degree the patient is contributing to cardiac and or pulmonary circulation versus the ECLS device. The amount of flow provided by the ECLS device is easily obtained from circuit monitors, although least accurately from revolutions per minute (rpm)/circuit diameter calculations. For most cardiac ECLS patients, flow is initiated at 120 to 150 mL/kg/min. However, it is important to note that flow should be adjusted to fit the physiologic needs of each patient. Patients with single-ventricle physiology or sepsis may require higher flows approaching 200 mL/kg/min to support their metabolic needs. Assessment of the patient's intrinsic cardiac output is often unobtainable. However, indirect evaluation of the patient's cardiac output is possible through assessment of arterial systolic blood pressure, pulse pressure, heart rate, organ perfusion, mixed venous oxygen saturation, and lactic acid levels on a given flow rate. Comparisons of these variables over time allow the clinician to make decisions regarding the adequacy of circulatory support or the readiness to wean from support. An echocardiogram also can provide valuable information and help guide therapy. Mixed venous saturation is measured in the venous return portion of the circuit, with a goal of 65% to 80% in acyanotic patients. However, if a "left-to-right" shunt exists, such as a left atrial vent, the mixed venous saturation will be falsely elevated. In cyanotic patients an arterial venous oxygen saturation difference ($Sa\text{-}Vo_2$) of 20% to 25% is typically targeted. Serial lactate measurements often are a helpful aid in the assessment of total end-organ perfusion. A delay in clearance may occur in patients with

ongoing hepatic dysfunction, sepsis, low CO, and end-organ hypoperfusion. An approximation of the relative contributions of the patient and circuit pulmonary parameters is possible. This assessment is permitted through analysis of serial patient and circuit blood gas assays such as pH, Pco_2, and Pao_2, with consideration of the mechanical ventilation settings (includes fraction of inspired oxygen [Fio_2] and PEEP), circuit flow rate, CO_2 sweep rate, and circuit oxygen concentration.

Finally, "shunts" within the patient or the circuit must be taken into consideration. An example of a "right-to-left" patient shunt includes a patient with a patent ductus arteriosus and pulmonary artery hypertension, or an atrial septal defect or ventricular septal defect with pulmonary artery hypertension or RV outflow tract obstruction. Circuit "left-to-right" shunts are generally limited to a left atrial vent, the hemodialysis filter, and continuous arterial blood gas devices. Patient shunts that have the potential to be bidirectional, such as a patent ductus arteriosus or an intracardiac shunt, typically confound analysis. For these reasons an optimal cardiac repair with closure of residual "defects" should be performed prior to institution of mechanical circulatory support or early within the course of treatment. Therefore total blood flow for the patient on mechanical circulatory support requires the addition of ECLS circuit flow with the patient's native cardiac output minus any "shunt" within the system as a whole.

Troubleshooting

Hemodynamic compromise can continue despite mechanical circulatory support, and often low-dose inotropes and/or inodilators can aid cardiac contractility to augment native cardiac output and reduce afterload to both the RV and LV. The most commonly utilized agents are dopamine (3 to 5 μg/kg/min), epinephrine (0.03 to 0.05 μg/kg/min), dobutamine (5 μg/kg/min) and/or milrinone (0.25 to 0.75 μg/kg/min). High-dose catecholamine use is detrimental to cardiac recovery, and circuit flow should be increased to provide adequate circulation and allow for the lowest dosing possible. Tachyarrhythmias and pulseless electrical activity requiring cardiopulmonary resuscitation occurs in 3% of neonatal and pediatric extracorporeal membrane oxygenation (ECMO) runs (see Table 27-4).[50] Chemical/electrical cardioversion of any dysrhythmia to sinus rhythm should be attempted to promote recovery of cardiac function. Pacing often is utilized to maximize cardiac output as well.

Hypovolemia is a common occurrence during mechanical circulatory support for a variety of reasons. Inadequate venous drainage secondary to cannula malposition, cardiac tamponade, tension pneumothorax, or hemothorax may occur and generally result in hypotension that requires immediate correction (see Table 27-4).[50] Ongoing evaporative losses from the circuit and bleeding as a result of coagulopathy can contribute to hypovolemia. Initiation of ECLS activates a host of inflammatory mediators, resulting in capillary leak and hypovolemia.[6] Hypertension resulting from high renin levels is one of the most common and unavoidable cardiovascular complications of ECLS (see Table 27-4).[50] While hypertension has not been demonstrated to negatively affect survival, its potential deleterious effects such as bleeding and cardiac function recovery are a cause for concern.[116]

Cardiac Stun

The phenomenon of reversible global dyskinesia of the ventricle was coined "cardiac stun" by Braunwauld and Kloner in 1982.[117] Reversible cardiac dysfunction that results in a lack of LV ejection and thus no arterial pulsation and which resembles electromechanical dissociation also has been observed in patients following the initiation of ECLS.[116,118-119] Excluding conditions of physiologic tamponade from thoracic tissues, blood, or air, an infant on ECLS should have sufficient cardiac function to generate a minimal pulse pressure of 10 mm Hg. More recent evaluations of patients who experience cardiac stun upon initiation of ECLS defined this condition as the absence of aortic valve opening, equalizing of the patient and membrane Pao2 in the absence of a patent ductus arteriosus, and narrowing of the aortic pulse pressure to <5 mm Hg.[116] The etiology of cardiac stun is multifactorial and hypothesized to be the sequelae of acute ischemia followed by reperfusion.[117-118,120] The incidence of stun on ECLS is 5% to 12% in neonates and results in a significant increase in mortality for these patients[119-120] (see Table 27-4). Stun typically occurs during the first few hours of initiation of bypass and resolves within days. The patients in whom cardiac stun developed were reported to be more hypoxic, hypercarbic, and acidotic and were more likely to have had a cardiac arrest prior to initiation of ECLS.[119-120]

Diagnostic and Therapeutic Uses of Cardiac Catheterization

Initial diagnostic and hemodynamic assessment should be made by transthoracic echocardiography and Doppler. However, sometimes diagnostic transthoracic echocardiography is either suboptimal or suggestive of a significant lesion. Transesophageal echocardiography may improve the diagnostic accuracy but may not be possible because of bleeding risks. Cardiac catheterization is a useful tool for select sets of patients who fail to wean from ECLS. Diagnostic catheterization can provide a hemodynamic assessment that clinicians may use in their decision to utilize mechanical support.[96,121] Therapeutic interventions that might be performed in the catheterization laboratory include balloon or blade atrial septostomy to alleviate left atrial hypertension; balloon valvuloplasty or angioplasty of vascular obstructions; and device closure of residual atrial, ventricular, or aortopulmonary shunts. Correction of these defects in the catheterization laboratory or operating room often is required to allow for separation from mechanical circulatory support. In a recent review of 216 courses of ECLS for pediatric patients, 50 of 60 catheterizations performed led to an intervention either during or after the catheterization procedure.[122] Complications included left myocardial perforation in 2 infants each weighing less than 3.5 kg. Both were treated for the complication and survived the procedure. However, the risk of bleeding and death are not insignificant.

For patients with significant LV failure, it may be necessary to decompress an over- distended left atrium to prevent complications such as pulmonary edema or hemorrhage or mitral regurgitation and to improve coronary perfusion.[79,122-126] In this scenario, "venting" of the LV occurs through placement of a LV inflow cannula in the left atrial appendage in the operating room or creation of an intraatrial connection via balloon or blade septostomy. Improvement in LV function has been demonstrated after LV venting.

Patients with a Single Ventricle

The lower survival rates in patients with a single ventricle have in part been attributed to the added demands of balancing the systemic and pulmonary circulations while supporting

an increased volume burden on a postoperative patient with innately compromised single-ventricle physiology. When an imbalance between the two circulations exits, it places these patients at risk for impaired coronary perfusion resulting from diastolic run-off into the pulmonary bed. Despite the challenges presented, large centers continue to report improved outcomes with the accumulation of experience and the application of innovative new strategies. For example, initial efforts to balance the systemic and pulmonary circulations on ECLS included either completely or partially occluding the aortopulmonary shunt. However, this method has fallen out of favor because the lack of antegrade pulmonary blood flow that results from shunt occlusion has been demonstrated to increase mortality.[127-128] Also, smaller size shunts are now being placed during the initial surgery. Of note, higher mechanical support flows of ≥200 mL/kg/min may be required to provide adequate systemic and pulmonary support when the shunt is left open. Several centers have utilized an adaptive strategy to traditional ECLS that eliminates the oxygenator from the standard circuit configuration, instituting a VAD-like configuration that has been termed *NOMO-VAD* for "no membrane oxygenator-ventricular assist device." In patients who have hypoplastic left heart syndrome after undergoing a Norwood procedure, the shunt is left open and routine mechanical ventilation strategies are utilized as oxygenation is provided by the infant's own lungs.

Anticoagulation Strategies

Hemorrhagic and thrombotic complications are major concerns for patients during ECLS. Bleeding can manifest at surgical sites (arterial/venous cannulation sites) or covertly at areas such as the thorax, intracranial vault, or the gastrointestinal tract (see Table 27-4). Prevention strategies that target reduction of hematologic complications focus on maintenance of the hemostatic regulatory mechanisms as nearly normal as possible.[129] All forms of ECLS require some degree of anticoagulation to prevent thrombotic complications. The patient's age in conjunction with the ECLS device flow and mechanical properties will dictate which anticoagulation agents and strategies are used. Most commonly, a heparin infusion is utilized for patients receiving ECLS.

ECLS requires the most aggressive management of hemostasis and will be the focus of discussion. Apart from single-center experience, no well-defined consensus and/or protocol is available for pediatric and neonatal ECLS.[130-131] Platelets are consumed by surgical bleeding sites and sequestered by the membrane oxygenator, and routine transfusions are required to maintain counts greater than 100,000/mm^3. Administration of fresh frozen plasma to restore overall factor activity is the most routine procoagulation method utilized. Most centers measure platelet, hematocrit, prothrombin time/partial thromboplastin time, fibrinogen, specific factor levels, and activated clotting times (with a goal of an activated clotting time of 180-220 on full flows and of 160 if significant bleeding is present) to guide heparin infusion rates; however, considerable variability exists in management.[130] Treatment with Coumadin, aspirin and clopidogrel, and low molecular weight heparin can be selectively used with certain mechanical support devices. Newer treatment strategies include use of additional agents such as antithrombin III (AT III) in either bolus or infusion form to supplement anticoagulation.[131] AT III is an α_2-glycoprotein, a serine protease inhibitor, that inactivates a number of enzymes from the coagulation system, including the activated forms of factor II, VII, IX, X, XI, and XII. Replacement of AT III is required when its level is low (less than 30%) and heparin infusion rates are increased without an resultant increase in activated clotting time. Medical monitoring of both low molecular weight heparin administration through anti-Xa levels and of heparin administration through both quantitative heparin levels are utilized. Heparin-induced thrombocytopenia (HIT) is a rare but serious complication of heparin administration caused by antibodies binding to a complex of heparin and platelet factor 4 that leads to increased mortality.[132] A drop in platelet count by more than 50% of the highest previous value should raise suspicion of HIT and trigger investigation. In an evaluation of 9 patients supported by ECLS for severe acute respiratory distress syndrome with a greater than 50% drop in platelet count, HIT antibodies were found in three of the nine patients.[132] Treatment includes discontinuing heparin administration and initiating Argatroban if continued anticoagulation is needed.

Ventilation Strategies

Ventilator management during ECLS remains controversial. While data exist to guide clinicians regarding prevention of barotrauma, volutrauma, and oxygen toxicity for mechanically ventilated patients with acute respiratory distress syndrome in general, it is lacking for patients receiving ECLS support.[133] Lung collapse strategies used for respiratory support on ECLS are not utilized by most cardiac ECLS centers. Goals continue to target the prevention of atelectasis with utilization of appropriate PEEP in order to maximize oxygenation of nonbypassed blood returning to the left atrium, which then is ejected by the LV to perfuse the coronary arteries. This coronary blood flow also should be pH/P_{CO_2} corrected. In addition, providing modest ventilation can be achieved with either a pressure or volume limited mode of ventilation, setting the tidal volume at 8 to 10 mL/kg. Respiratory rates between 10 and 25 are set depending on the age and "rest" strategy being used and the degree to which the patient's lungs are required for gas exchange. Optimizing P_{aO_2} to the patient and circuit by blending F_{IO_2} to keep the F_{IO_2} less than 0.6 prevents free radical formation and ocular oxygen toxicity, thus providing adequate oxygenation to decrease pulmonary hypertension and optimize coronary O_2 delivery. Chest radiographs are routinely performed to assess and guide strategies to optimize lung volume so that volutrauma and barotrauma are avoided.

Fluid, Nutrition, and Renal Strategies

Fluid overload and electrolyte disturbances such as high or low serum levels of potassium, calcium, magnesium, and phosphorous (K, Ca, Mg, and PO_4) are common and need immediate correction. Most cardiac patients on ECLS receive total parenteral nutrition because of increased risk of gastrointestinal complications in patients with cardiac defects, umbilical artery catheters, poor perfusion, or other bowel abnormalities. A select subset of this population may tolerate trophic/full enteral feedings. Diuretics, commonly furosemide, often are used to provide optimal fluid balance in patients with significant capillary leak and fluid retention (see Table 27-4). Optimization of fluid status is essential to weaning and eventual separation from ECLS support. For anuric or oliguric patients, early placement of an in-line hemofilter into the ECLS circuit with or without countercurrent dialysate

is recommended. However, the management decisions that balance the use and timing of diuretics versus hemofiltration are controversial. The indications for initiation of dialysis are the same as for other critically ill patients with renal failure. Multiple retrospective reviews of patients supported by ECLS have found renal replacement therapy to be a risk factor for increased mortality.[70,72,81,92-93] No causal relationship has been identified, and further investigation in this area is warranted.

Analgesia and Sedation

Initially, adequate analgesia and sedation are essential for both safety, comfort, and to minimize metabolic demands in patients with circulatory compromise in the early postoperative recovery period. Typically an opiate in addition to a benzodiazepine class drug is utilized. Infusions may be used with cautious monitoring because toxicity from propylene glycol and other solvents have been reported with benzodiazepine use.[134-135] Neuromuscular blockade should be largely avoided to limit critical care myopathy, promote regular evaluation of the central nervous system, and limit soft tissue fluid accumulation. Central nervous system infarcts, hemorrhage, or seizures are all known complications of ECLS (see Table 27-4). For infants with an open fontanel, a daily head ultrasound should be performed early in the course of treatment and with any change in clinical neurologic status. For older patients, a significant change in their neurologic status has a high likelihood of heralding major intracranial pathology, which needs to be promptly diagnosed by computed tomography in order to guide treatment and proceed in determining patient viability.[136] For patients with VADs that are either fully implantable or paracorporeal, it often is possible to lighten analgesia and sedation following perioperative stabilization to permit extubation and mobilization. Some devices are truly portable with battery packs.

Infection

It is not surprising that patients receiving ECLS are at a high risk of the development of nosocomial bloodstream infections (BSI). Identified risk factors that increase the incidence of infection include duration of ECLS,[137-142] open versus closed chest cannulation,[138,142] presence of central venous lines,[139] and undergoing a major procedure just before or while on ECMO.[138,141-142] In July 2009, the ELSO reported an incidence of reported an incidence of 6.1% to 18.9% culture-proven BSIs. It appears that older patients receiving ECLS for respiratory failure may be at higher risk of health care–associated infection than are neonates or cardiac patients (see Table 27-4).[50] Bloodstream infections during ECLS support for both pediatric cardiac patients after cardiopulmonary bypass and neonates with cardiac or respiratory failure have been associated with a poor outcome.[140,143]

The diagnosis of sepsis is difficult for patients supported with ECLS. While variable degrees of leukopenia have been documented for neonates supported with ECLS, an increase in phagocytosis and intracellular killing by neutrophils also occurs.[144-145] Temperature is completely controlled by the circuit's heat exchanger, so infection generally is not manifested by fever in these patients. Hypotension or thrombocytopenia may occur for a variety of reasons. In view of this, the standard of care in many ECLS centers has been to perform both routine surveillance cultures and provide prophylactic antibiotics. However, management strategies to limit infectious risks continue to evolve. Because of a lack of proven benefit and concerns regarding the long-term impact of broad-spectrum antibiotics on local bacterial resistance profiles, an increasing number of centers now perform daily blood cultures without the routine use of prophylactic antibiotics.[137-138] Additional retrospective data may suggest that routine surveillance cultures may not be warranted.[139-140] Further investigation is warranted to determine the impact of prophylactic antibiotic use on incidence of BSI, local antimicrobial flora, length of stay, survival, and cost.

Intrahospital Transport

Crucial situations exist for patients supported with ECLS that require intrahospital transport. This can include mobilization from the intensive care unit to a variety of locations such as the catheterization laboratory, radiology, or the operating suite. Reluctance to perform essential diagnostic or therapeutic interventions often includes a fear of potential disastrous complications during intrahospital transport. These fears are not unfounded.[146-148] Guidelines designed to promote the establishment of an organized, efficient transport process supported by appropriate equipment and personnel have been recognized and are increasingly utilized in hospitals.[149] Intrahospital transport for patients who receive ECLS is a labor-intensive process that should be approached in a coordinated effort with specific focus on the preparatory phase, the transfer phase, and posttransport stabilization. However, with careful attention to these aspects, centers have demonstrated that intrahospital transport for patients who receive ECLS support can be carried out safely and without major complications.[136]

Ventricular Assist Devices

VADs are classified as extracorporeal (when the assist device is situated outside of the body), intracorporeal (when the assist device is fully implantable), or paracorporeal (when the assist device is situated adjacent to the body). Percutaneous VADs, which are devices placed by an interventional cardiologist in the catheterization laboratory, also have been developed.[150] Most VADS share similar basic principles. Cannulation depends on the type of support required. The right atrium (venous drainage) and pulmonary artery (arterial return) are cannulated for right ventricular assist device (RVAD), and the left atrium (venous drainage) and aorta (arterial return) are cannulated for left ventricular assist device (LVAD). A combination of both right and left ventricular assist devices is termed biventricular assist device (BiVAD). The pump is connected to a controller and power supply. Pumps have differences in modes of operation, size, and placement. A comparison of ECLS and VAD support is listed in Table 27-5.

Centrifugal Ventricular Assist Devices

Centrifugal ventricular assist devices pumps have been available since the late 1970s to support neonates and older children with postoperative cardiac failure and preserved lung function.[151] They have been an effective support for infants and children with myocardial failure from a variety of etiologies (i.e., acute myocarditis, dilated cardiomyopathy, acute transplant rejection, anomalous left coronary artery from the pulmonary artery, and others).[65,67] The most commonly used centrifugal pump VAD (Figure 27-4) is the BioMedicus centrifugal pump (Medtronic, Eden Prairie, Minnesota). The BioMedicus centrifugal pump can be utilized for cardiopulmonary

Table 27–5 Extracorporeal Life Support vs. Ventricular Assist Device

	ECLS	Centrifugal VAD	Pulsatile VAD
Oxygenator	Yes	No, but can be added	No
Anticoagulation	ACT 180-200	ACT 160-180	Aspirin/warfarin/LMWH
Support	Cardiac ± respiratory	Cardiac ± respiratory	Cardiac
Type of ventricular support	Biventricular	Univentricular or biventricular	Univentricular or biventricular
Ventricular decompression	May need LA "venting"	Via direct drainage cannula in LA or LV apex	Via direct drainage cannula in LV apex
Risk of air embolus	Low	Yes (especially with LVAD)	Yes (especially with LVAD)
Length of support	Short term	Short term	Long term
Cannulation site	Transthoracic or transcervical	Transthoracic	Transthoracic

ACT, Activated clotting time; *ECLS,* extracorporeal life support; *LA*, left atrial; *LV,* left ventricular; *LVAD,* left ventricular assist device; *LMWH,* low molecular weight heparin; *VAD,* ventricular assist device.

bypass, ECLS, or ventricular assistance. The pump consists of a polycarbonate cone built around several rotator cones. It is magnetically coupled to a driver that controls the RPM. The pump spins at an adjustable rate, generating a vortex continuous flow. This creates a negative pressure that allows blood to drain into the pump and redirects it out the top of the vortex ("tornado effect"). The BP-80 and BP-50 models have cone volumes of 80 and 50 mL, respectively, with maximal flows of 10 L/minute. The centrifugal pump output (flow) is proportional to the rotational speed of the pump (RPM), pump preload (patient's intravascular volume), and pump afterload (impedance to the outflow). Actual flow is measured with a flow probe on the arterial limb as RPM may not correlate accurately with flow. Heparin-bonded tubing can be used to minimize the need for aggressive anticoagulation. Mean arterial pressure is maintained by varying intravascular volume and adjusting rpm on the VAD console. Large negative pressures can be generated. If excessive negative pressure is generated, cavitation and hemolysis can occur. A VAD system can be used for temporary assistance of stunned myocardium of the LV. Although the system is designed for univentricular support (LVAD or RVAD), with two pumps connected in series it can provide biventricular support (BiVAD).

Advantages of this VAD over ECLS include its simplicity in design, ease of cannulation, small priming volumes, decreased hemolysis, reduction in the degree of systemic inflammatory response syndrome seen following initiation, and less anticoagulation (if an oxygenator or a heat exchanger are not used). Klotz and colleagues[152] compared the outcome of primary VAD implantation versus primary ECLS in 183 patients with LCOS after heart surgery. Primary VAD was performed in 20 patients, and 163 patients underwent ECLS. In the ECLS group, 13 patients were converted from ECLS to a VAD (ECLS-VAD). Thirty-day mortality rates were 50% (VAD), 75% (ECLS), and 46% (ECLS-VAD). Survival was best with VAD implantation within 1.2 days following onset of LCOS. The authors concluded that early VAD support promotes survival in patients with LCOS after heart surgery.[152]

The BioMedicus Pump is the most common centrifugal VAD system used in children in the United States. The centrifugal VAD requires a functional RV since the RV supplies preload to the LV supported by the pump. Complications of the centrifugal VAD system include occasional thrombus formation in the circuit, hemolysis, nonpulsatile blood flow, bleeding and infection. Duncan and colleagues[153] reported the outcomes of 29 pediatric patients supported with BioMedicus VADs; there was a survival rate of 71% among patients with anomalous origin of the left coronary artery arising from the pulmonary artery or with cardiomyopathy. In those who underwent heart transplantation after support, survival was 50%, and fewer instances of neurologic complications and hemolysis were seen than in the ECLS group reported in the same study.[153] Successful use of the centrifugal VAD as a bridge to implantable VAD and then to heart transplantation in a patient with single-ventricle physiology has been reported.[154]

The CentriMag VAD (Levitronix, Zürich, Switzerland) is approved as an investigational device in the United States. It belongs to a new class of magnetically levitated devices operating in a bearingless rotor that floats with a rotating magnetic field. Because of its contact-free environment and absence of seals or valves, this device minimizes blood trauma, virtually eliminating thrombus formation and hemolysis. It is capable of operating over a range of speeds up to 5500 RPM, generating flows up to 9.99 L/minute under normal physiologic conditions. The PediVas VAD (Levitronix) is capable of operating over a range of speeds up to 5500 RPM, generating flows up to 1.7 L/min under normal physiologic conditions. Other available centrifugal pumps VADs include the RotaFlow (Jostra, Hirrlingen, Germany) and Capiox (Terumo, Ann Arbor, Mich.).

Intraaortic Balloon Pump

Since their invention and introduction into clinical practice in the 1960s, IABPs have become a therapeutic tool for the management of refractory low cardiac output states in adults.[155-156] In 1980, Pollock[157] first described the use of an intraaortic balloon pump in pediatric patients with the advent of modified equipment and pediatric-sized balloon catheters. The IABP is a polyethylene balloon mounted on a catheter that is usually inserted into the aorta via the femoral artery. The balloon is guided into the descending aorta approximately 2 cm from the subclavian artery. The balloon pump works by inflating in the aorta during diastole (after aortic valve closure) for improved retrograde coronary flow augmentation; the balloon then deflates before systole to decrease LV afterload. Cardiac output may be augmented by as much as 40%, decreasing LV stroke work and myocardial oxygen requirements. The pump

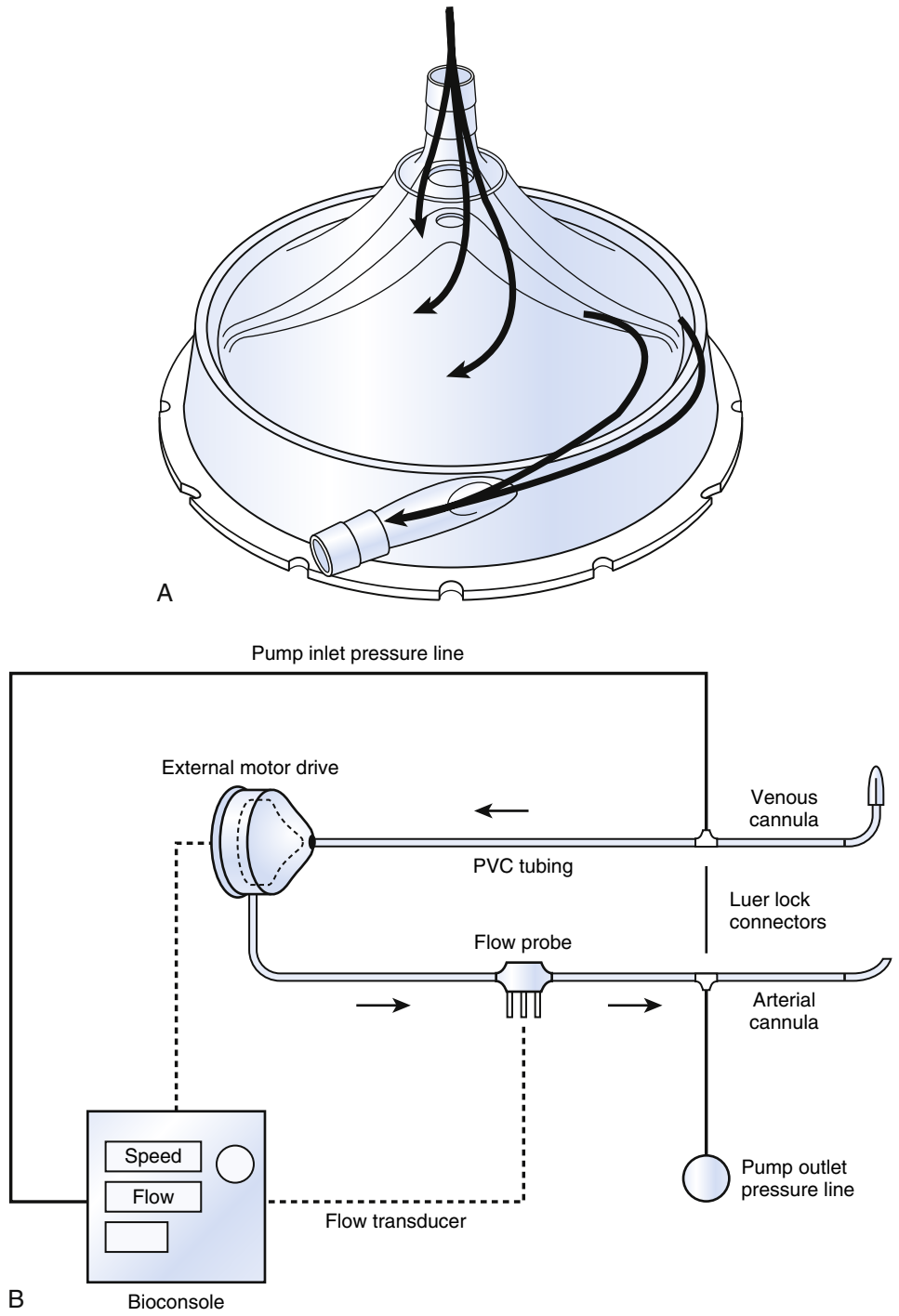

Figure 27–4. **A,** Schematic diagram of the BioMedicus centrifugal pump (Medtronic). Blood enters the cones via the apex of the cone, and the kinetic energy of the spinning cones is transferred to the blood leaving the side port. **B,** Centrifugal pump setup. (From Karl TR, Horton SB: *Centrifugal pump ventricular assist device in pediatric cardiac surgery. In Duncan BW, editor: Mechanical support for cardiac and respiratory failure in pediatric patients, New York, 2001, Marcel Dekker.*)

is available in a wide range of sizes (2.5 to 50 mL), and it is driven by an external console. A review of the use of IABPs to support 24 postoperative cardiac patients with LCOS despite optimal repair and maximal medical support was performed. The mean age was 5 years (7 days to 17.5 years), with a mean weight of 19 kg (3.5 to 59 kg). Eighteen of 24 patients (75%) were weaned off the IABP, with 15 long-term survivors (62%). Major complications associated with increased mortality included two patients with limb ischemia and one patient with both limb and mesenteric ischemia, which resulted in a fatal outcome. Additional complications included bleeding that necessitated reexploration of the chest and sepsis.[158] A similar review of 29 patients supported with IABP for medical, postoperative surgical, and bridge to transplant indications demonstrated survival to hospital discharge of 18 of 29 patients (62%).[158-159]

Advantages of IABP include its relative ease of use and its placement without surgical dissection. Disadvantages include infrequency of use, which is limited as an isolated LV support modality; contraindication with patients of a certain anatomy/physiology (e.g., patent ductus arteriosus or aortic insufficiency); and serious complications that include mesenteric ischemia and arterial injury. In children, failure to augment CO can occur because of a highly distensible aorta. The pediatric IABP catheters differ from adult catheters in a variety of ways. The catheter shafts are smaller (4 or 5 Fr) with balloon sizes of 0.75 to 10 mL. Early failed reports of the use of IABP in children were primarily due to the use of inappropriate sized balloons and failure to gate to the electrocardiogram at fast heart rates.[157,160] Adequate timing of the balloon inflation and deflation is essential; radial artery tracings were used in the past to aid timing of balloon inflation, but rapid heart rates led to significant timing errors.[161] The use of M-mode echocardiography to aid in timing of the balloon inflation and deflation with aortic valve opening and closing has significantly improved the efficiency of IABP therapy.[161] As a result of these difficulties, the use of IABP therapy in the pediatric population has remained limited to a small number of patients in a few institutions.

The Hemopump (Johnson & Johnson Interventional Systems, Rancho Cordova, Calif.) was the first device that showed the clinical feasibility of using high-speed, implantable rotary pumps for cardiac support. The Hemopump was initially studied at the Texas Heart Institute in 1988 as a short-term device for treatment of cardiogenic shock. The Hemopump included a tiny axial flow pump that provided up to 3.5 L/minute of circulatory support. Today the Hemopump is no longer used, but its design has served as the base for the development of other circulatory assist devices.

The Impella 2.5 (Impella Cardiotechnik AG, Aachen, Germany) is a minimally invasive, catheter-based cardiac assist device designed directly to unload the LV decreasing myocardial workload and oxygen consumption and increase CO and coronary and end-organ perfusion. The Impella 2.5 can be inserted into the LV in the catheterization laboratory via a standard guidewire through the femoral artery, into the ascending aorta, across the aortic valve, and into the LV. The tip of the catheter contains a "pigtail" that crosses the patient's aortic valve, rendering it open. This pump generates up to 2.5 L/min. A randomized trial is currently being conducted to compare the effectiveness of the Impella 2.5 versus IABP in patients with cardiogenic shock due to acute myocardial infarction.[162] The Impella 2.5 and a larger version, the Impella 5.0, are investigational devices.

Long-Term Mechanical Support Devices

The emergence of this newer type of device has provided a better range of equipment for mechanical support for children in the intensive care setting, but longer term mechanical support devices, especially for neonates and children, are still lacking. Much progress has been made since the early VAD initially described by Michael DeBakey.[56] Clinical experience with these devices in adults is extensive and includes patients with postcardiotomy failure, acute myocardial infarction, cardiogenic shock, ischemic cardiomyopathy, and even myocarditis.

The pediatric experience with long-term devices is limited. However, two important trials have shown the effectiveness of these devices in adults. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial in adult patients with severe heart failure who were ineligible for heart transplantation reported a significant improvement in quality of life and short-term survival in patients with severe heart failure with use of VADs as destination therapy (compared with optimal medical management).[163] The Harefield Recovery Protocol Study trial evaluated whether patients with advanced heart failure requiring VAD support can recover sufficient myocardial function to allow device removal (explantation). The Harefield Recovery Protocol Study combined the HeartMate XVE with conventional oral heart failure medications, followed by the novel β_2 agonist clenbuterol. The study reported that 73% (11 of 15) of patients who underwent the combination therapy regimen demonstrated sufficient recovery to allow explantation and avoid heart transplantation. Freedom from recurrent heart failure in surviving patients was 100% and 89% at 1 and 4 years after explantation, respectively.[164]

Various devices are indicated for single or biventricular assist depending on the patient's needs. Long-term devices (support longer than 30 days) have been placed in pediatric patients as a bridge to transplantation, a bridge to recovery, or destination therapy when permanent circulatory support is needed for patients who are not candidates for heart transplantation.[158,165-167]

Pulsatile-Type Devices

Pulsatile VADs function on the principle of "positive displacement" by trapping a fixed amount of blood and then forcing (displacing) that trapped volume into an exit cannula. Pneumatic pulsatile VADs have been available in pediatric sizes since 1992. Since the early report of pneumatic paracorporeal VADs in children, the pediatric experience with long-term pulsatile devices has been growing.[98] Advantages of these devices include the ability to provide long-term biventricular support (i.e., weeks to months) without an oxygenator, patient mobility out of the intensive care setting, the need for low-level anticoagulation heparin or warfarin with antiplatelet therapy, and, of course, their pulsatile flow nature. Disadvantages include a propensity for thromboembolic complications, high cost when compared with centrifugal VADs, the need for exteriorization of the cannulas, and size limitations usually suitable for patients with body surface area (BSA) 0.8 m^2 or greater, especially when biventricular support is needed. Infection is also a serious complication, although immobilization of the cannulas close to the exit site can decrease the incidence. Hypertension while on support is commonly seen and can be treated with different pharmacologic agents such as milrinone, calcium channel blockers, ACE inhibitors, β-blockers, α-antagonists, nitroprusside, or nitroglycerin. Thus far only the Berlin Heart EXCOR (Berlin Heart AG, Berlin, Germany)and the Medos HIA (Medizenintechnik, Berlin, Germany) pulsatile systems have proved successful in children of all ages and in children weighing as little as 2 kg. Both systems are paracorporeal. They have a special silicone system that connects the blood pump to the body; these cannulas are anastomosed to the right atrium and pulmonary artery for the RV (RVAD) and to the apex of the LV or more rarely to the left atrium and the ascending aorta for LV support (LVAD).[98,99]

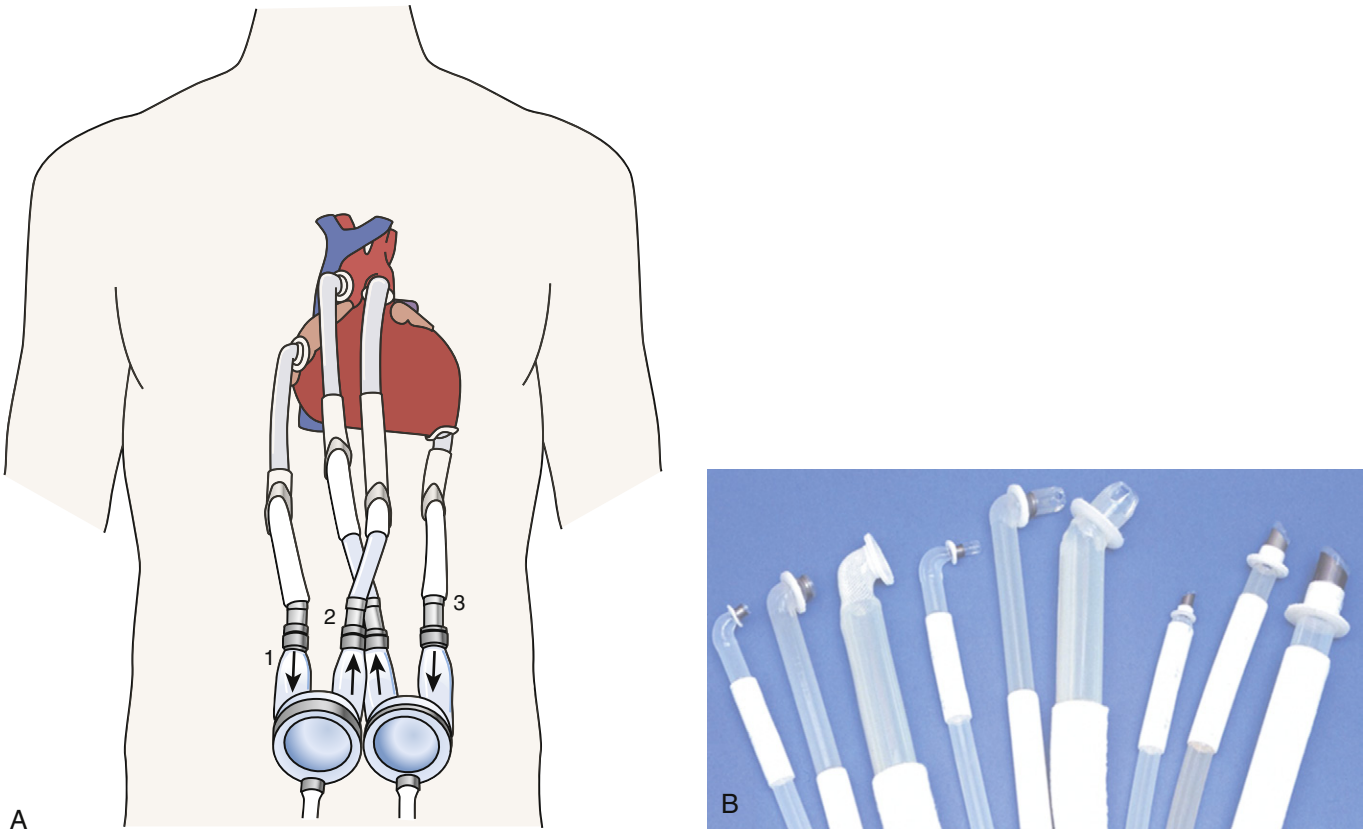

Figure 27–5. A, Schematic diagram of the Berlin Heart biventricular assist device showing apical cannulation, which allows better left ventricular unloading and decreased afterload to the right ventricle. *1,* Deoxygenated blood flows from the body into the right atrium. Since the right ventricle is unable to pump blood into the lungs, the blood goes into the device. *2,* The blood is pumped out from the device into the pulmonary artery. *3,* Once the blood is oxygenated in the lungs, it flows into the left atrium. Since the left ventricle is unable to pump, the blood goes into the device. *4,* The Berlin heart pumps blood into the aorta and systemic circulation. **B,** Set of cannulas available for the Berlin Heart assist device. The cannulas are available in different diameters, lengths, and tip configurations. *(Courtesy Berlin Heart AG, Berlin, Germany.)*

Berlin Heart Ventricular Assist Device or EXCOR

The Berlin Heart VAD or EXCOR is a paracorporeal pulsatile device that has been in use since 1988 and has been used in pediatric patients since 1992 (Figure 27-5 device and cannulas). The EXCOR pediatric VAD was specially designed and developed for pediatric patients. The pumps and cannulas are available in different sizes, making the system suitable for children a few days old to adolescents. The pump sizes vary between 10 mL to 80 mL. The 10-mL pumps are suitable for neonates and infants with body weight of up to 9 kg (BSA of 0.2 m^2); the 25-mL and 30-mL pumps can be used in children up to the age of 7 years (weight 30 kg and BSA of about 0.95 m^2); and adult-size pumps (50 and 60 mL) can be implanted in older children. All Berlin Heart EXCOR cannulas exit the body through the upper abdominal wall. The system is internally heparin coated. The Berlin Heart VAD can provide univentricular or biventricular support.

Hetzer and colleagues[99,100] reported a 15-year experience with the use of the Berlin Heart EXCOR pulsatile assist device in children aged 3 days to 15.5 years who had severe myocardial failure resulting from cardiomyopathy, fulminant myocarditis, end-stage congenital heart disease, or acute heart failure following surgery for congenital heart repair with a survival rate of 62%. Mean support was 17 days (range, 12 hours to 98 days).[99-100] Survival rates of up to 70% recently have been reported in small infants.[98] A recent North American single-center experience with the Berlin Heart EXCOR in a group of 17 children (13 LVAD and 4 BiVAD), in which six patients were supported by ECMO and one by a centrifugal pump prior to EXCOR placement, reported a survival to hospital discharge of 75%. Three children died on support while awaiting a transplant, 11 children were bridged to transplantation, 2 were explanted, and 1 was still on support at the time the study was published. The main complications were stroke in seven patients, two of whom eventually died, and bleeding or hematoma formation that required surgical intervention.[168]

The Medos Ventricular Assist Device

Since 1994, the Medos VAD pump chambers have been successfully implanted as a mechanical heart support system. The variety of available pump chamber sizes can accommodate adult, infant, and pediatric applications, providing a complete range of patient support. The Medos VAD system is a pneumatically driven paracorporeal VAD with three LV sizes (10, 25, and 60 mL maximum SV) and three RV sizes (9, 22.5, and 54 mL SV).

Survival with the Berlin EXCOR and the Medos VADs has been reported at 36% in children from 2 weeks up to age 16 years, including an infant with BSA less than 0.3 m^2. Diagnosis included fulminant myocarditis, dilated cardiomyopathy,

endocardial fibroelastosis, Ebstein anomaly, and status post redo aortic valve replacement.[169,170]

Thoratec Ventricular Assist System

The Thoratec Ventricular Assist System (Thoratec Corp, Berkeley, Calif.) is a pneumatically driven, polyurethane sac enclosed in a plastic housing designed for intermediate and long-term use (weeks to years). The Thoratec VAD has a stroke volume of 65 mL and can be operated at rates up to 100 beats/min, providing blood flow rates of almost 7 L/min. Patients require systemic anticoagulation for the duration of the VAD support. There are two Thoratec VAD systems, one paracorporeal (PVAD) and one implantable (IVAD). The Thoratec pneumatic PVAD is indicated as a bridge to transplantation or bridge to recovery. It can provide acute or intermediate univentricular or biventricular support. The external position of the pump allows device exchange in cases of malfunction, thrombus, or infection. Furthermore, it can be used in smaller patients who are poor candidates for implantable devices, with the smallest reported patient weighing 17 kg (BSA, 0.73 m^2). The Thoratec IVAD is a small, simple, and versatile intracorporeal device with the same features as the Thoratec PVAD except that it is used when longer support is anticipated. The device has been approved by the Food and Drug Administration (FDA) since 2004 for circulatory assistance as bridge to transplant or bridge to recovery. In a recent multicenter study (in the United States and Germany), the Thoratec PVAD was used in 19 children with a mean BSA of 1.09 m^2 (range, 0.73 to 1.29), a mean age of 10 years (range, 7 to 14), and a mean weight of 31 kg (range, 17 to 41). Indications for support were end-stage cardiomyopathy in eight patients, myocarditis in three patients, end-stage congenital heart disease in seven patients, and transplant graft failure in one patient. Mean duration of support was 43 days (range, 0 to 120). Survival through hospital discharge occurred in eight (72%) of 11 patients with cardiomyopathy or myocarditis; however, only one of seven patients with congenital heart disease survived. Neurologic complications were significant and predominant in the congenital heart disease group.[171] Neurologic complications in these pediatric patients seem to be higher when cannulation is performed in the left atrium versus the LV.[172]

The Abiomed BVS 5000 VAD

The Abiomed BVS 5000 VAD (Abiomed, Inc, Danvers, Mass.) was the first assist device approved by the FDA to be used in postcardiotomy patients. It is a pneumatically drive, pulsatile, extracorporeal pump that it is used in adults for short-term univentricular or biventricular support. The BVS 5000 can produce a stroke volume of 80 mL and flows up to 6 L/min. It has been used in patients with a BSA 1.2 m^2 or greater. It is usually used as a bridge to recovery in patients who have exhausted all other medical options.

Rotary/Axial-Type Devices

The rotary/axial-type devices are small, almost entirely implantable, continuous flow, rotary pumps with axial flow. The apex of the LV is used as the inflow cannulation site (to maximize flow conditions), and the ascending aorta has been used for the outflow graft. Thrombus formation has occurred when the graft was placed in the descending aorta. Advantages of the axial system include its relatively small size, relatively easy implant/explant procedures, noiseless system, lower infection risk, and continuous flow that not only provides unloading throughout the cardiac cycle but also minimizes stasis and thrombus formation. Disadvantages include a size limitation for pediatric patients with less than 1.5 m^2 BSA. The DeBakey LVAD (MicroMed Technology, Inc, Houston, Tex.), the Jarvik 2000 (Jarvik Heart, Inc., New York), and the HeartMate II (Thoratec) are described in the following section.

MicroMed DeBakey and HeartAssist 5

In the early 1990s, collaboration between the National Aeronautics and Space Administration (NASA), Dr. Michael DeBakey, and Dr. George Noon produced the MicroMed DeBakey VAD. In 1998, this effort culminated in the first clinical implant of an axial flow pump into a patient with heart failure. Since that time, more than 440 implants of this VAD technology have been performed in patients around the world. Recent design changes have been made to create the HeartAssist 5 (MicroMed) (Figure 27-6, *A* and *B*), which supports pediatric patients who weigh as little as 18 kg. It provides a wide degree of cardiac support, with blood flows from 1 to 10 L/min. The HeartAssist 5 Pediatric VAD provides precise blood flow as low as 1 L/min, and the entire implanted device weighs only 235 g. This is an implantable LVAD, intended for more than 3 months' support, focusing on bridge to transplantation. It represents the first miniaturized device, approximately one tenth the size of other currently marketed pulsatile VADs. The advantages of this device include small size; relative ease of implant and explant; decreased infection risk; and continuous flow, which unloads the ventricle throughout the cardiac cycle while minimizing stasis and the associated risk of thrombus formation. It can operate up to 8 hours on batteries. The long battery life allows for better patient mobility. Disadvantages include the rapid impeller speed, which leads to hemolysis. This device has been granted FDA "humanitarian device exemption" and is indicated for use as temporary left-sided mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients (5 to 16 years old, with BSA greater than 0.7 m^2 and less than 1.5 m^2 who are in NYHA class IV end-stage heart failure refractory to medical therapy and who are [listed] candidates for cardiac transplantation). An adult version of the HeartAssist 5 is also available. The HeartAssist 5 Pediatric VAD is contraindicated in patients who have RV failure that is unresponsive to medical therapy; patients with a primary coagulopathy or platelet disorders; and patients with an allergy or sensitivity to heparin.[173-175]

Jarvik 2000

The Jarvik 2000 is an intraventricular assist device with a relatively small surface area measuring 1.8 cm in diameter by 5 cm in length. The device usually is implanted into the left ventricular apex via a left thoracotomy, and the outflow graft is placed into the descending aorta. Blood flow ranges from 2 to 7 L/min and is determined by impeller speed and systemic vascular resistance, with the usual setting at 9000 rpm (range, 8000 to 12,000 rpm). It offers several advantages over pulsatile flow pumps, including a smaller size that reduces the risk of infections, simpler implantation, fewer moving parts, absence of valves to direct blood flow, smaller blood-contacting surfaces, and reduced energy requirements that enhance simplicity and durability. The recent addition of sintered titanium microspheres on its intraventricular blood-contacting surface

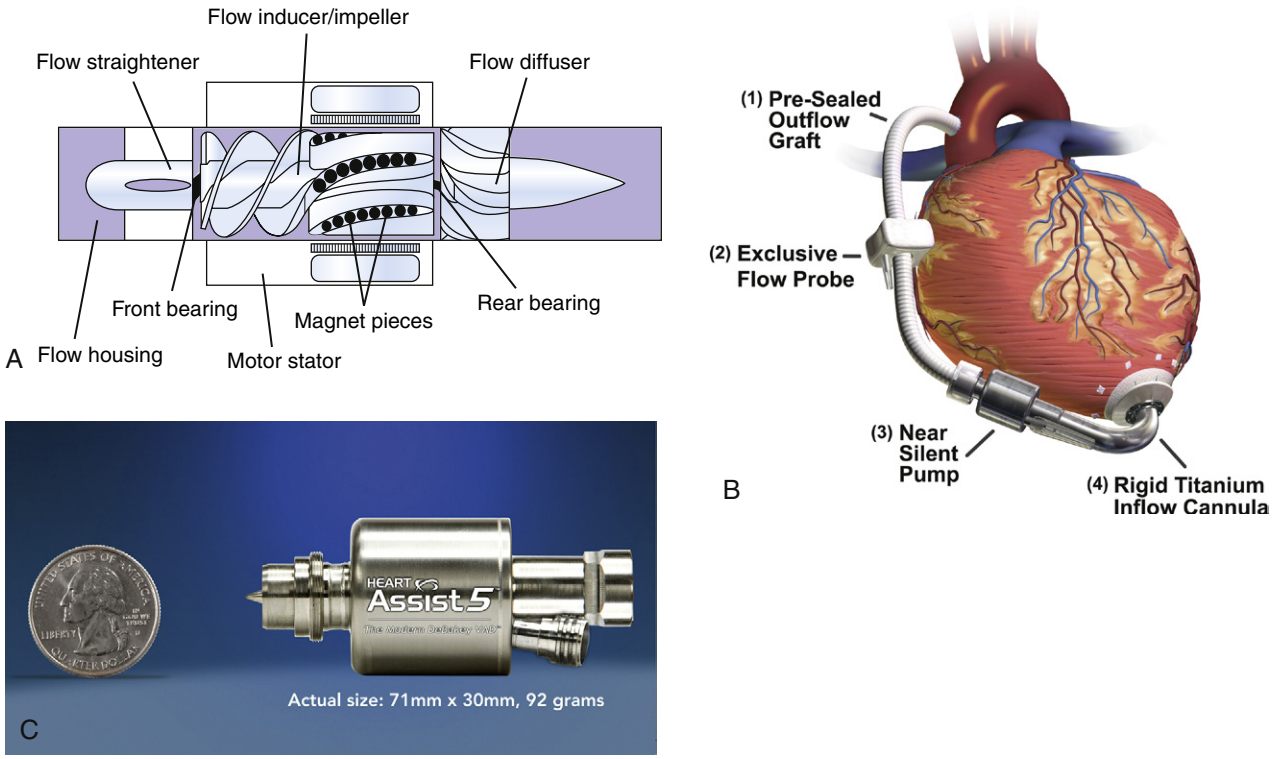

Figure 27–6. HeartAssist 5 pediatric ventricular assist device (modern DeBakey ventricular assist device). **A,** DeBakey ventricular assist device in a cutaway view. **B,** HeartAssist 5 with its position in the heart. **C,** HeartAssist 5 shown with a U.S. quarter for size comparison. *(Courtesy MicroMed Technology, Houston, Tex.).*

has decreased the incidence of thrombus formation. This device has an external speed control that can easily be adjusted according to the patient's physiologic needs. The Jarvik 2000 is FDA approved as an investigational device to be used for a bridge to transplantation. In Europe, the Jarvik 2000 is certified to be used as a bridge for both, transplantation and destination therapy. A pediatric Jarvik 2000 is under development.

HeartMate II

The HeartMate II is an axial flow rotary pump that utilizes blood-immersed mechanical bearings with textured blood-contacting surfaces. The transcutaneous version is totally implantable. The HeartMate II is a rotary pump that is smaller than the first-generation devices, principally because of the elimination of the sac or reservoir necessary in pulsatile pumps. This device has two cannulas (inflow and outflow) without valves. It has smooth surfaces in the outlet and inlet stators, but anticoagulation is still required. Clinical experience shows that the HeartMate II LVAD provides excellent support, with significant improvement in functional capacity. In a multicenter, prospective study, 42% of 133 adult heart transplant candidates supported with HeartMate II underwent transplantation within 6 months of support, with an overall 6-month survival of 75% and 1-year survival of 68%. More recently, an improved 6-month survival of 86.9% and 3% incidence of device malfunction with a mean duration of support of 6 months has been reported. The FDA has already approved its use as a bridge to transplant and for destination therapy. The HeartMate II has demonstrated great device reliability and significantly reduced device noise. It has low thrombogenicity and low thromboembolic risk, making it a good device option for destination therapy.

Total Artificial Heart

Total artificial heart (TAH) devices completely replace the patient's native ventricles and all four cardiac valves and are used as bridge to destination therapy. Because of their large size, these devices have very limited use in children.

CardioWest (SynCardia Systems, Inc, Tucson, Ariz.) is the modern version of the Jarvik 7, which was first implanted in 1982. The CardioWest temporary TAH is the only artificial heart in the world. The CardioWest TAH is used as a bridge for heart transplant for eligible patients dying from end-stage biventricular failure. The 70 mL CardioWest TAH is suitable for patients with a BSA 1.7 m^2 or greater; a 50-mL version of the device is under research investigation.

The AbioCor Replacement Heart is a new mechanical device that replaces the pumping function of the diseased heart. It is used as destination therapy in patients who are ineligible for heart transplant and have no other suitable treatment options. The AbioCor Replacement Heart has been granted FDA approval for Humanitarian Device Exemption.

Next Generation Levitated Devices

New generations of devices include centrifugal continuous-flow pumps with an impeller or rotor suspended in the blood flow path using a noncontact bearing design that uses either magnetic or hydrodynamic levitation. The levitation systems suspend the moving impeller within the blood field without any mechanical contact, thus eliminating frictional wear and reducing heat generation. This feature hopes to promise longer durability and higher reliability with low incidence of device failure and need for replacement. Usually, magnetic

levitation devices are larger because of the need for complex position sensing and control system. Examples of third-generation devices are the VentrAssist (Ventracor Ltd, Sydney, Australia), Levitronix CentriMag (Thoratec Corp.), DuraHeart (Terumo), the HVAD (HeartWare Corp, Framingham, Mass.), and the EVAHEART LVAS (Sun Medical Technology Research Corp., Nagano, Japan).

Ethics

Although advances in medical management, surgical techniques, and mechanical circulatory support for pediatric patients with cardiomyopathy or congenital heart defects continue to improve outcomes, the morbidity and mortality related to pediatric heart failure continue to exist.[15] The overall quality of life can be adversely affected in some patients because of therapy-related complications. In addition, the caregivers of these patients may experience significant burdens due to posttraumatic stress disorder, anxiety, depression, or poor physical health.

While the randomized controlled trial remains the most powerful tool for unambiguous comparison of various therapies, it is a well-recognized problem that such trials to compare either pharmacologic agents or mechanical circulatory support devices used to treat pediatric heart failure are lacking. Obstacles exist that limit the ability to perform research on pediatric patients with congestive heart failure. For example, invasive procedures are more difficult, noninvasive procedures in small children often require anesthesia to ensure adequate data collection, and consent to participate in research must be obtained by proxy requiring a greater level of preexisting evidence that the therapy being studied is safe and efficacious. Lastly, given the current level of observational data that exists to perform a randomized controlled trial, investigators must reconcile the ethical difficulty of allowing a patient to receive what is believed to be a less effective treatment in the interest of "objectively" evaluating therapeutic efficacy.[176] For example, a randomized controlled trial was never performed for ECLS in pediatric cardiac patients. All of these barriers impart a greater risk for performing research in children.

Future Directions

Several new mechanical support devices are under investigation. Options for circulatory support of pediatric patients younger than 5 years are still limited to short-term extracorporeal devices. The need for devices suitable for small patients has been recently addressed by the National Heart, Lung, and Blood Institute (NHLBI), which has funded research for the development of mechanical support devices in children from 2 to 25 kg with congenital heart or acquired cardiovascular disease. Five contracts were awarded to develop a family of devices that include (1) an implantable mixed-flow VAD designed specifically for patients up to 2 years of age, (2) another mixed-flow VAD that can be implanted intravascularly or extravascularly depending on patient size, (3) compact integrated pediatric cardiopulmonary assist systems, (4) apically implanted axial-flow VADs, and (5) pulsatile-flow VADs. These investigational devices include (1) the PediaFlow (World Heart Corporation, Oakland, Calif.),[177] (2) the PediPump (Foster-Miller Technologies, Albany, NY),[178] (3) the Pediatric Cardiopulmonary Assist System (pCAS) (Ension, Pittsburgh, Pa.),[179] and (4) the Penn State Pediatric Ventricular Assist Device (University Park, Pa.)[180] and (5) the Pediatric Jarvik 2000.[181] The NHLBI established the Pediatric Circulatory Support Program in 2004 by funding the development of these five novel circulatory support devices for infants and young children with congenital or acquired cardiovascular disease. In early 2010, the NHLBI awarded four contracts to begin preclinical testing of these devices. This 4-year program, called Pumps for Kids, Infants and Neonates (PumpKIN), is the next phase of NHLBI support for the clinical realization of these devices. The devices are supposed to support patients from 1 to 6 months of age, be sufficiently small and reasonable portable, and be routinely positioned and functioning in less than 1 hour. PumpKIN contractors are the University of Pittsburgh, Ension, Inc., the University of Maryland, and Jarvick Heart, Inc.

Conclusion

Principles of mechanical circulatory support require an individualized approach. Indications should include not only postpericardiotomy syndrome but pediatric patients with a variety of disease processes leading to LCOS such as myocarditis and septic shock. Short-term experience with mechanical devices had been limited to ECMO, but pediatric experience with VADs is growing, especially with centrifugal VADs. The pediatric experience with long-term devices is limited but evolving. With better clinical management and advances in technology, survival of pediatric patients with severe heart failure should continue to improve.

References are available online at http://www.expertconsult.com.

II

Chapter 28

Disorders of Cardiac Rhythm

Frank A. Fish, Prince J. Kannankeril, and James A. Johns

PEARLS

- Arrhythmias may result from ongoing therapies; ask, "What's the DEAL?"
  - — *D*rugs and drips
  - — *E*lectrolytes
  - — *A*irway and acid base
  - — *L*ines
- Appropriate diagnosis is key. Always attempt to document arrhythmia in multiple leads before instituting therapy.
- For ventricular fibrillation or pulseless ventricular tachycardia, begin cardiopulmonary resuscitation and defibrillate immediately.
- Involve a cardiologist before initiating (chronic) antiarrhythmic drug therapy.
- Whenever possible, use available means to document atrial rate to discern correct ventricular-atrial relationship.
- "Supraventricular tachycardia" is a nonspecific electrocardiographic pattern. Multiple types of supraventricular tachycardia exist, and appropriate therapy depends on appropriate diagnosis.
- Whenever possible, opt for therapies that maintain atrioventricular synchrony.

Cardiac rhythm disturbances (arrhythmias) are common in intensive care settings, where they may represent the primary disease process or occur as a complication of management (Table 28-1).[1,2] It is important to note that arrhythmias that might otherwise be well tolerated hemodynamically may be immediately life-threatening to the critically ill child. In addition, certain treatment strategies may be available in the critical care unit that normally might not be considered, particularly for serious but transient arrhythmias. Therefore response to arrhythmias in this setting should emphasize prompt restoration of hemodynamic stability concurrent with identification of the arrhythmia mechanism and predisposing factors. This chapter emphasizes the most common clinical scenarios and treatment approaches encountered in the intensive care setting while providing a broader overview of the array of arrhythmia mechanisms and their associated presentations in pediatric patients.

Classification of Arrhythmias

Arrhythmias are commonly classified according to rate, electrocardiographic (ECG) findings, and, when possible, the underlying electrophysiologic mechanisms. Electrocardiographically, arrhythmias can be characterized as bradycardias, tachycardias, or extrasystoles. Bradycardias are further subdivided into the level of dysfunction: sinus node or atrioventricular (AV) conduction. Extrasystoles and tachycardias are categorized as supraventricular or ventricular in origin. Tachycardias can be further characterized by the level of origin (supraventricular vs. ventricular) and functional mechanism: reentry, automaticity, or triggered activity. Whereas most treatment algorithms assume a reentrant mechanism, abnormal triggering and automaticity may be particularly important in the critically ill patient and may respond quite differently to given therapies, such as pacing or direct current cardioversion. Although differentiating between these mechanisms is sometimes difficult, it may be essential in guiding appropriate therapy, especially if initial therapies prove ineffective.

Bradycardias

Appropriate Versus Normal Heart Rate

Normal heart rate ranges vary tremendously during childhood as a function of age and autonomic tone. Thus in a given clinical situation, "appropriate" heart rate is a more useful concept than "normal" heart rate. Critically ill patients typically manifest some degree of sinus tachycardia in response to pain, sepsis, shock, fever, or adrenergic agonist infusions, and the degree of tachycardia also serves as a gauge of pain or hemodynamic instability. Thus inappropriately fast or slow rates for a given circumstance warrant evaluation for underlying factors affecting the sinus rate or the possibility of a nonsinus mechanism.

Sinus Bradycardia and Sinus Pauses

Sinus bradycardia may result from high vagal tone, hypothermia, acidosis, increased intracranial pressure, drug toxicities, or direct surgical trauma to the sinoatrial (SA) node. In otherwise well patients, intermittent sinus bradycardia or prolonged sinus pauses may be caused by intense vagal episodes, such as those occurring during neurocardiogenic syncope. Whereas vagal stimulation may produce profound bradycardia, pauses, or even asystole lasting for several seconds, transient bradycardia

Table 28–1 Classification of Arrhythmias by Type and Basis

Arrhythmia	Primary	Secondary
Ventricular premature beats and supraventricular premature beats	+++	+++
Sinus bradycardia, sick sinus syndrome	++	++
Incomplete AV block		
Mobitz I	++	+++
Mobitz II		++
Congenital third-degree AV block	+++	++
Acquired third-degree AV Block		++
Paroxysmal SVT (AV reentrant tachycardia, AV nodal reentrant tachycardia)	+++	
Ectopic atrial tachycardia	++	
Atrial flutter and intraatrial reentry	++	+++
Atrial fibrillation	+	+++
Chaotic atrial tachycardia		++
Junctional ectopic tachycardia	+	+++
Monomorphic ventricular tachycardia	++	++
Torsades des pointes	+	+
Ventricular fibrillation	+	++
Bidirectional ventricular tachycardia	++	+

AV, Atrioventricular; *SVT*, supraventricular tachycardia; +++, typical; ++, occasional; +, rare.

should not be construed as an absolute indication for pacing. However, in the hemodynamically tenuous patient, persistent or recurring bradycardias, whether attributed to sinus node exit block (periodic loss of sinus impulse) or sinus arrest, often warrant intervention with vagolytic, sympathomimetic, or pacing therapies. It is important to recognize that blocked premature atrial depolarizations (where premature P waves may be obscured in the preceding T wave) may also mimic sinus pauses or even sinus bradycardia when occurring in a bigeminal pattern. In cardiac patients, sinus node dysfunction may be the result of surgical injury or heterotaxy syndromes. Primary sinus node dysfunction in childhood is rare but has been described.[3]

Conduction Abnormalities

First-degree, second-degree, and third-degree AV blocks are characterized by conduction delay, intermittent interruption, or complete interruption in AV conduction. As with sinus bradycardia, AV conduction delay may be the result of intense vagal tone, metabolic derangements, drug toxicity, or direct injury to the AV node. Second-degree block can be further characterized: Mobitz type I, also called Wenckebach conduction, displays progressively prolonged AV conduction prior to a single nonconducted atrial impulse, whereas Mobitz type II occurs abruptly without such delay. Wenckebach conduction is best recognized by comparing the PR interval prior to block to the conducted PR immediately after the blocked beat. Mobitz I usually represents block in the AV node and is less likely to progress suddenly to high-grade block. In some settings, such as in well-conditioned athletes, a Mobitz I block may be benign. Mobitz type II, characterized by abrupt failure to conduct without prior lengthening of the PR interval, usually is attributed to block within the His conduction system and may indicate greater potential for sudden progression to complete AV block. As such, type II block may be more ominous and may require more aggressive intervention (i.e., pacing).

Higher grades of second-degree AV block can occur as a progression from either Mobitz I or Mobitz II block and are best characterized by the ratio of atrial to ventricular depolarizations (2:1, 3:1, 4:1, etc.). The level of block cannot be inferred and may even occur physiologically in the setting of atrial tachyarrhythmias, including atrial flutter, which often result in second-degree AV block in the presence of normal AV nodal function. Likewise, vagally mediated AV block may result in transient high-grade block (although the sinus rate usually slows concurrently).

Complete or third-degree AV block represents complete loss of AV conduction, usually with a junctional or idioventricular escape rhythm that is regular but may be quite slow. Periodic shortening of the RR interval may be the only clue to distinguish complete AV block from high-grade second-degree block with intermittent conduction (Figure 28-1) or from a junctional rhythm with slower atrial rate and intermittent AV conduction.

Bundle branch block patterns occur when impaired conduction in the specialized intraventricular conduction system results in delayed right or left ventricular depolarization, resulting in an aberrant widened QRS complex. Bundle branch block and AV block sometimes represent normal physiologic responses to abrupt shortening of the cycle length (as with premature atrial systoles or tachycardia initiation) or may result from drug effects, surgical injury, or primary disease within the specialized conduction tissue.

Escape Rhythms

In the presence of sinus bradycardia or AV block, escape rhythms typically emerge from AV nodal or Purkinje cells. These rhythms are slower than the appropriate sinus rate but may become accelerated with enhanced adrenergic tone and compete with the underlying sinus rhythm. It is important to distinguish these accelerated subsidiary rhythms from both pathologic tachycardias and escape rhythms resulting from AV block. Only rarely does an accelerated junctional or ventricular rhythm result in significant symptoms in a healthy child.[4] However, in the critically ill patient, the resultant loss of AV synchrony may warrant atrial pacing at a slightly faster rate if cardiac output is compromised.

Tachycardias

Classification by Mechanism

As discussed earlier, some degree of sinus tachycardia is expected in most critical care patients as an appropriate response to the primary illness. The degree of sinus tachycardia for age may provide important insights into the level of sedation, pain, or hemodynamic stress of a given patient. However, exaggerated or persistent sinus tachycardia must be distinguished from other tachycardia mechanisms that may appear similar electrocardiographically.

Most abnormal tachycardias encountered clinically are caused by abnormal impulse propagation in the form of reentry. This may represent reentry using an accessory AV

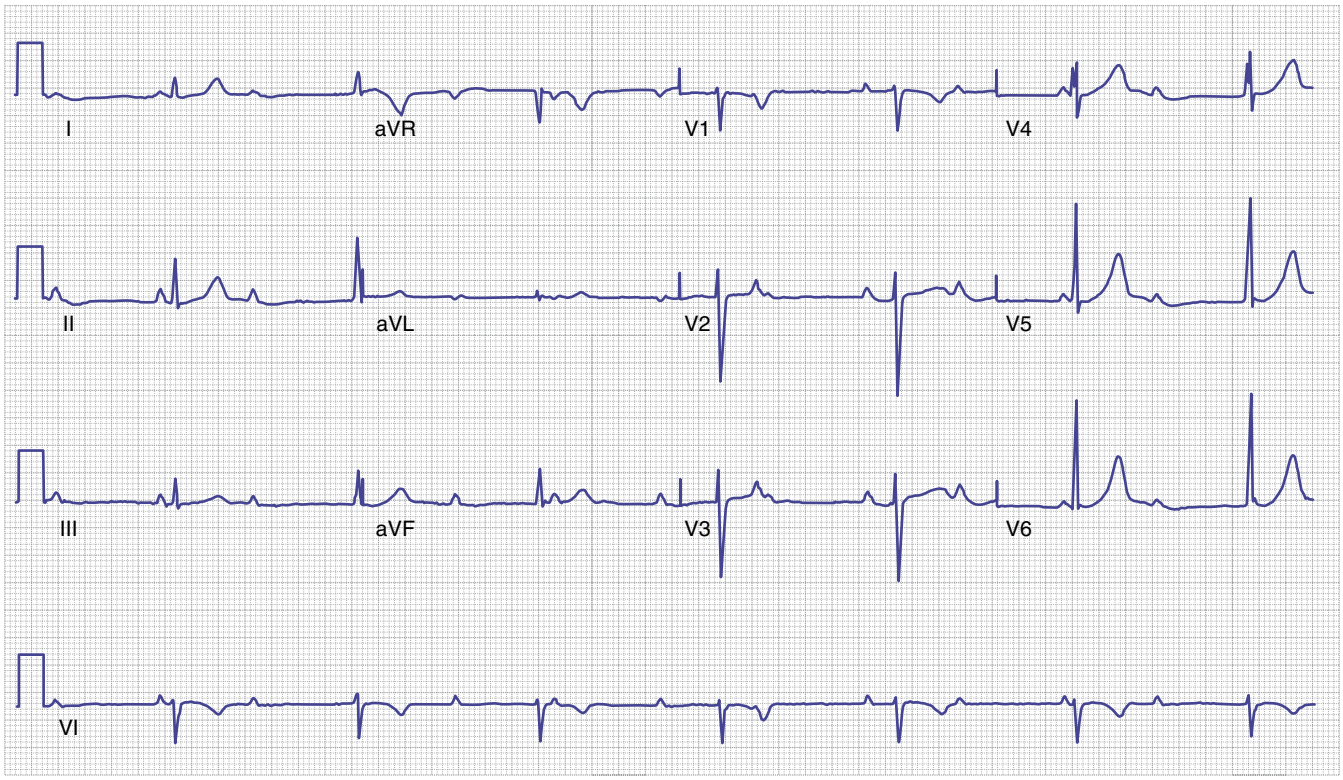

Figure 28–1. Complete AV block, presumably congenital, in an asymptomatic 9-year-old with slow resting heart rate. Note the regular RR interval, which confirms complete rather than incomplete (second-degree) AV block.

connection (AV reentry), the AV node and its adjacent tissues (AV nodal reentry), atrial myocardium (intraatrial reentry including atrial flutter and fibrillation), or ventricular myocardium (most ventricular tachycardias). Automatic tachycardias represent abnormal impulse formation arising from either ectopic foci or usual subsidiary pacemaker tissues (atrial, junctional, or ventricular) but at a significantly accelerated rate. These tachycardias may be due to an abnormally accelerated rate of depolarization of normally automatic tissues or to diseased atrial or ventricular myocardium with a propensity to abnormal spontaneous depolarization. Triggered tachycardias are thought to arise from abnormal secondary depolarizations (afterdepolarizations) following normal myocardial depolarizations, which may propagate to adjacent tissues. These tachycardias probably are important in several specific situations such as cardiac glycoside toxicity (delayed afterdepolarizations) and drug-induced long QT syndromes (early afterdepolarizations), and they also are important in many hereditary arrhythmias syndromes. Triggered activity is often dependent on the underlying heart rate, a feature that may sometimes be exploited therapeutically.

Classification by Site

Tachycardias usually are subdivided first according to the site of origin as supraventricular or ventricular. This anatomic distinction is the basis for most treatment algorithms. However, both supraventricular and ventricular tachycardias include a diverse group of arrhythmias with varying substrates, mechanisms, and electrocardiographic features that become increasingly important when simple treatment algorithms fail or when arrhythmias become recurrent and require repeated or ongoing therapies.

Supraventricular Tachycardias

"Supraventricular tachycardia" (SVT), "paroxysmal atrial tachycardia," and "paroxysmal supraventricular tachycardia" (PSVT) are descriptive but nonspecific terms commonly used interchangeably to describe tachycardias with a regular rate (usually in excess of 200 to 220 beats/min), normal QRS morphology, and P waves that either are not discernible or follow the QRS complex. This phenotype represents the most common form of SVT seen in otherwise healthy neonates and children and usually can be attributed to AV nodal reentry or AV reentry using an accessory connection (see next section). However, these typical ECG features can be produced by a more diverse array of tachycardia mechanisms.[5] Furthermore, intermittent AV block or QRS prolongation may be observed in certain types of "SVT," such that the ECG distinction of "SVT" from other atrial arrhythmias becomes obscured. Likewise, some tachycardias of supraventricular origin are associated with a widened QRS, either because of rate-related bundle branch block or anomalous antegrade conduction through an accessory connection. Therefore it is most useful to include among SVTs all tachycardias originating from the atrium, the AV node, or both, regardless of whether the ventricles participate primarily (i.e., AV reentry) or merely as a secondary consequence of AV conduction. This broad and inclusive definition appropriately allows inclusion of nonreciprocating mechanisms that need to be included in the differential diagnosis of "SVT," such as intraatrial reentry.

Atrioventricular Reciprocating Tachycardias

AV reciprocating tachycardias use one or more accessory AV connections to allow a reentrant circuit to develop involving both atrial and ventricular tissues. By definition, they display

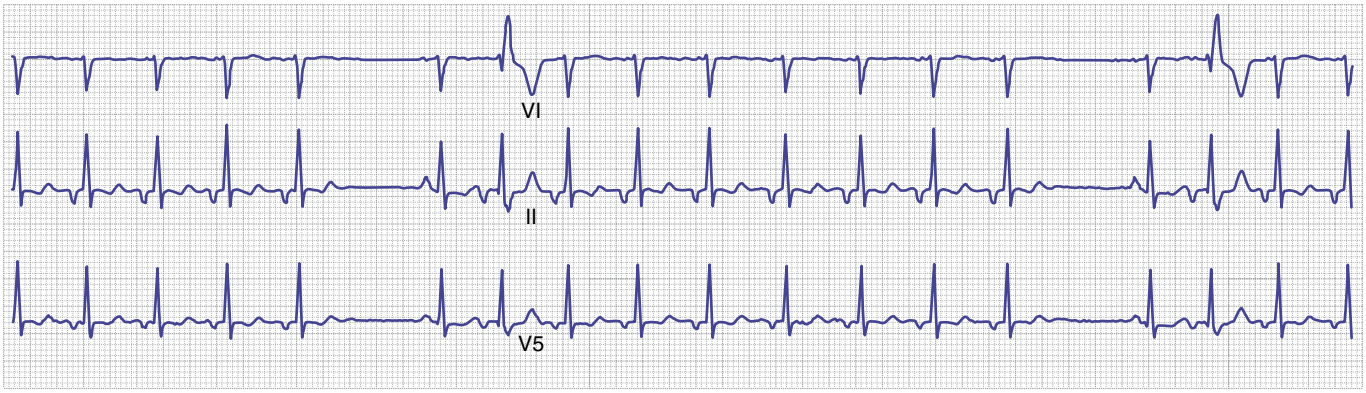

Figure 28–2. Supraventricular tachycardia resulting from the permanent form of junctional reciprocating tachycardia. Note the slow rate, long RP and short PR interval, and inverted P waves in ECG leads II and III. At rest, this rhythm often shows incessantly repetitive termination (with retrograde block), followed by immediate reinitiation (after single, isolated sinus complexes). With exercise, this rhythm often is faster and sustained, rendering it electrocardiographically indistinguishable from the atypical form of nodal reentry.

a fixed 1:1 AV relationship. *Orthodromic reciprocating tachycardia* (ORT) is the most common AV reentrant tachycardia and, in otherwise normal infants, also is the most common mechanism of SVT.[5,6] In ORT, antegrade conduction is over the AV node, whereas retrograde conduction to the atria occurs via an accessory AV connection. QRS morphology and duration usually are normal, with retrograde P waves often evident following each QRS complex. If the accessory connection conducts antegradely during sinus rhythm, ventricular preexcitation occurs prior to conduction over the AV node (Wolff-Parkinson-White [WPW] syndrome). The fusion of preexcited ventricular depolarization with the normal depolarization of the AV node and His-Purkinje system produces the characteristic short PR interval and Δ wave of WPW syndrome. Many patients experiencing ORT have normal QRS morphology during sinus rhythm. In these individuals the accessory pathway may only conduct retrogradely and is thus clinically evident only during tachycardia or during ventricular pacing.

Antidromic reciprocating tachycardia (ART) is a much less common AV reciprocating tachycardia in which the circuit is reversed: antegrade conduction occurs exclusively via the accessory connection and results in a "maximally preexcited" QRS. As a result, ART is not readily distinguishable from ventricular tachycardia by ECG features alone. Retrograde conduction occurs over the AV node (or a second accessory connection), producing a 1:1 ventricular-atrial (VA) relationship. By definition, patients with ART also have the ECG features of WPW syndrome during sinus rhythm. ART should be distinguished from ORT with aberrant conduction.

A specific form of antidromic AV reentry uses Mahaim fibers, which are accessory AV connections with decremental antegrade conduction. Most Mahaim fibers are located on the right ventricular free wall (atriofascicular connections), although some arise from the AV node itself (nodoventricular connections). *Tachycardia using a Mahaim fiber* should be considered in a young patient with a regular tachycardia and left bundle branch block QRS pattern. Typically, ART and tachycardia using Mahaim fibers have a 1:1 VA relationship. However, because retrograde conduction in either case may be supported over a second accessory connection, maneuvers typically resulting in AV nodal block may not terminate these tachycardias, further confusing clinical distinction between these wide QRS complex tachycardias and ventricular tachycardia.

Permanent junctional reciprocating tachycardia (PJRT) is a variant of ORT with retrograde conduction over a slowly conducting accessory AV connection that possesses decremental ("AV nodelike") conduction.[7] The relative conduction and refractory properties of the accessory connection and the AV node are such that the PR interval is short or normal and tachycardia is incessant. In a single-lead rhythm strip, PJRT may mimic sinus tachycardia, although a 12-lead ECG reveals atypical P wave morphology with P-wave inversion in the inferior leads. This tachycardia typically displays repeated spontaneous termination and prompt reinitiation, resulting in incessant tachycardia until it is adequately treated (Figure 28-2).

Atrioventricular Nodal Reentrant Tachycardia

AV nodal reentrant tachycardia (AVNRT) is the most common cause of SVT in older children and young adults without WPW syndrome or structural heart disease. It is seen less commonly in infants.[5,6] Occasionally it is precipitated for the first time by a serious illness or by other secondary factors associated with arrhythmias in the intensive care unit (ICU). This tachycardia can be attributed to so-called "dual AV nodal physiology." Conceptually, one functional "limb" of the AV node typically displays slow conduction and a short refractory period, whereas the other limb typically displays more rapid conduction but a longer refractory period. The differential conduction between the two "limbs" of the AV node (slow and fast pathways) provides the functional substrate for reentry. In actuality, these "limbs" represent differential conduction properties of the fibers inputting the AV node from upper and lower approaches of the atrial septum, representing so-called "fast" and "slow" inputs.

Classically, two electrocardiographically distinct forms of AVNRT may occur. In the "typical" form of AV node reentry, antegrade conduction during tachycardia is over the slow AV node inputs, and the P waves often are obscured by the preceding QRS complex. In the "atypical" form of AV node reentry, antegrade conduction is via the fast inputs of the AV node and retrograde conduction is over the slow limb. This conduction results in a long RP and short PR with an inverted P wave. The typical form of AVNRT can be difficult to distinguish from ORT in which P waves also are often obscured.

The atypical form of AVNRT may be indistinguishable from PJRT (see previous section), except that the tachycardia is paroxysmal rather than incessant. Like PJRT, atypical AVNRT must be carefully distinguished from other tachycardias with a normal PR interval, including sinus tachycardia, intraatrial reentry, or ectopic atrial tachycardias (see next section). Other atypical forms of AV nodal reentry using "intermediate" pathways can occur but are uncommon in children. Other variations of AVNRT can be characterized during the course of formal intracardiac electrophysiologic study.

Primary Atrial Tachycardias

Primary atrial tachycardias represent a diverse group of tachycardias originating solely from atrial tissue. They include tachycardias with discrete P waves (ectopic atrial tachycardia, intraatrial reentry), sawtooth flutter waves (atrial flutter), or disorganized atrial activity (atrial fibrillation, chaotic atrial tachycardia).[8] The ECG appearance alone may not adequately distinguish the underlying mechanism.

In all cases, conduction to the ventricles is over the AV node (except in patients with associated WPW syndrome). The resulting ventricular rate determines the degree of clinical compromise during these tachycardias. If conduction is rapid or occurs over an accessory connection, the QRS morphology may be aberrant and difficult to distinguish from ventricular tachycardias. However, interventions that slow or block AV nodal conduction usually allow the ongoing and faster atrial rhythm to be revealed. It is useful and often necessary to directly record atrial depolarization (via esophageal, epicardial, or intraatrial recordings) to discern atrial activation. Despite the potential ECG similarities of the various primary atrial tachycardias, the varying mechanisms confer important differences in clinical behavior.

Most atrial tachycardias encountered in the intensive care setting are reentrant in nature. Most commonly these atrial tachycardias occur either in neonates, where the classic sawtoothed pattern of atrial flutter is observed, or in postoperative cardiac patients. In patients with congenital heart disease (CHD), the patterns of intra-atrial activation may be quite variable and depend upon the surgical anatomy and resultant scar and conduction slowing. As such, the tachycardia, often referred to as *intra-atrial reentrant tachycardia* (IART), often displays a slower atrial rate with more discrete and sometimes normal-appearing P waves (rather than classic "flutter" waves). Because of the slower atrial rate, 1:1 AV conduction may be especially common. The administration of an AV node–blocking agent may slow AV conduction, and especially if 2:1 AV conduction results, ongoing tachycardia may be mistaken as sinus tachycardia with first-degree AV block. Thus this arrhythmia should be considered with any monotonous and seemingly inappropriate sinus rate with PR prolongation in a patient with CHD. Careful inspection of any transient irregularities that may result from variations in the AV conduction ratio may reveal the diagnosis.

Atrial fibrillation, a very common arrhythmia among the elderly, is far less common in pediatric patients. It may occur as the result of atrial myocarditis,[9] as a result of an underlying reentrant SVT,[10] or sometimes as the result of central venous catheters (Figure 28-3). In patients with WPW syndrome, rapid conduction over the accessory pathway may be life-threatening. When atrial fibrillation is seen, the underlying basis should be sought, because the long-term implications and treatment measures are much different than in adult patients.

Ectopic atrial tachycardia is an automatic arrhythmia that typically presents as an incessant and chronically elevated atrial rhythm that may be mistaken for sinus tachycardia,

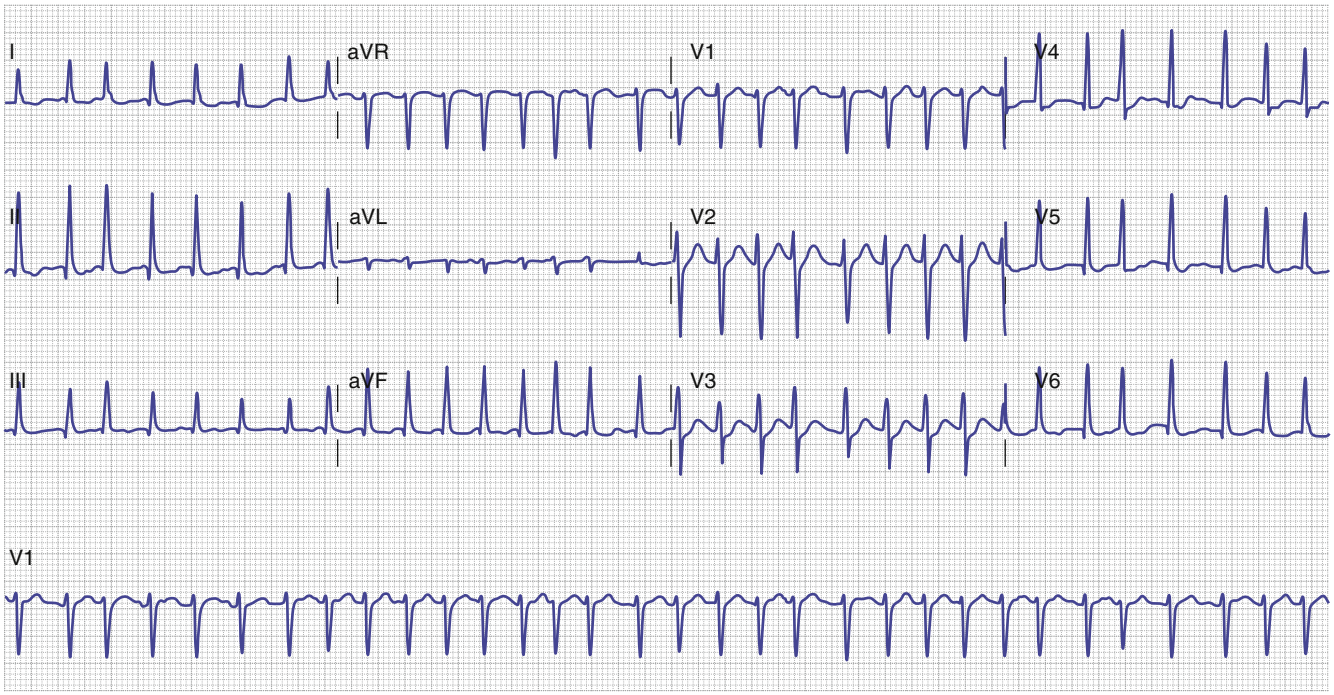

Figure 28–3. Sustained atrial fibrillation in a previously healthy 17-year-old placed on extracorporeal membrane oxygenation for pneumonia and acute respiratory distress syndrome. Review of stored telemetry revealed atrial ectopy soon after cannulation, eventually initiating atrial fibrillation. Following DC cardioversion to sinus rhythm, frequent ectopy persisted until the venous cannula was repositioned. Several months later, the patient remained free of further arrhythmias.

depending on the site of the automatic focus. First-degree AV block may be seen as a result of the inappropriate rate. Patients often experience no overt palpitations but rather present with ventricular dysfunction and sometimes frank congestive heart failure. In such cases, careful scrutiny of the P wave morphology and evaluation of any abrupt changes in rate (as the result of transitions between sinus and the tachycardia) are necessary to establish the diagnosis. Adenosine may inhibit the automatic focus, making this diagnosis especially difficult.

Chaotic atrial tachycardia is an uncommon arrhythmia that is usually observed in infants and toddlers, often in association with a viral respiratory illness.[11] The hallmark features are a rapid and irregular atrial rate, often exceeding 300 bpm, and presence of multiple P-wave morphologies. The resulting ventricular response is irregularly irregular, simulating atrial flutter. However, this rhythm is probably the result of multiple triggered foci within the atria, and thus acute termination measures (i.e., DC cardioversion, adenosine, or pacing) are of little benefit. Usually this arrhythmia resolves within weeks or months of presentation.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) probably arises from an abnormal automatic focus or a protected microreentrant circuit in the region of the AV node or proximal His bundle. Antegrade conduction usually is over the normal His-Purkinje system with a narrow QRS. Retrograde (VA) block or complete VA dissociation with a slower atrial rate aids in the recognition of this mechanism. Variants include a congenital form, the more common postsurgical form, and paroxysmal JET described primarily in adults.[12,13] As in primary atrial tachycardias, atrial depolarization may be obscure, and direct atrial recordings aid the diagnosis. Occasionally JET is associated with 1:1 VA conduction, in which case additional pacing or pharmacologic maneuvers are necessary to distinguish it from other mechanisms of SVT.

Ventricular Tachycardias

Ventricular tachycardias include all tachycardias that arise exclusively within the ventricle(s) and require neither the atrium nor the AV node for perpetuation. Because ventricular depolarization is aberrant, the QRS duration is always prolonged for a given age and heart rate. The QRS morphology may be either uniform or changing (bidirectional, polymorphic). Classically, ventricular tachycardias are associated with VA dissociation (atrial rhythm at a slower rate). However, in children, VA conduction over the AV node (or an accessory connection) may be sufficient to allow intermittent or even 1:1 VA conduction. Thus VA dissociation, when present, is helpful, but when it is absent (or uncertain) it does not exclude ventricular tachycardia as the underlying mechanism. The presence of periodic fusion complexes (QRS morphology intermediate between tachycardia morphology and sinus morphology) is virtually pathognomonic for ventricular tachycardia with VA dissociation.

Although often regarded as a homogeneous group of arrhythmias, ventricular tachycardias actually constitute diverse rhythms, representing each of the underlying tachycardia mechanisms (reentry, automaticity, and triggered activity) with important therapeutic implications.[14] Likewise, although they are sometimes lethal, they may range in complexity and severity from benign accelerated ventricular rhythm to rapid polymorphic ventricular tachycardia and ventricular fibrillation. Both the clinical setting and the QRS morphology during ventricular tachycardia may provide important clues to the mechanism and pathogenesis, anatomic origin or tachycardia focus (see incessant ventricular tachycardias), and treatment strategies, as discussed later.

Approach to Diagnosis

Monitoring and General Assessment

In the intensive care setting, there may be a tradeoff between precision of diagnosis and urgency of therapy. Even so, appropriate diagnosis remains key to ongoing therapy. When an arrhythmia develops, rapid assessment of hemodynamic stability dictates the extent to which diagnostic studies can be pursued relative to the urgency of treatment. This should include assessment of level of consciousness, ventilation, tissue perfusion, and blood pressure. If time allows, determination of acid-base balance or other indicators of tissue perfusion (e.g., mixed venous oxygen saturation and serum lactate levels) is helpful. Minimal initial diagnostic evaluation should always include a timely evaluation of available ECG rhythm strips and a rapid review of drugs being administered, potential toxic exposures, respiratory and acid-base status, and known associated illnesses. Electrolyte assessment (potassium, calcium, and possibly magnesium) and drug screening may provide valuable diagnostic clues and should be obtained. The history of surgical procedures for CHD and trauma (chest and cranial) should be quickly reviewed. Indwelling catheters should be surveyed on radiographs for potential intracardiac position. Concurrent with this brief survey, a differential diagnosis of the rhythm disturbance should be quickly established, followed by the most appropriate emergency therapy. If the patient is sufficiently stable, therapy may be deferred until the arrhythmia can be more precisely characterized.

Surface Electrocardiogram

The surface ECG remains the cornerstone of arrhythmia diagnosis. Certainly in patients with known cardiac abnormalities, and arguably in all patients admitted to the ICU, a baseline ECG should be obtained at admission. This ECG may provide a valuable baseline for later comparison in the event of an arrhythmia. Because these arrhythmias occur in a monitored environment, a strip should be available to assess the rate, regularity, QRS morphology and duration, and AV relationship (Table 28-2), which should provide an initial differential diagnosis (Figure 28-4). Ideally, multiple leads should be inspected. For sustained tachycardias, a full 12-lead ECG should be obtained whenever possible because diagnostic details, such as QRS aberrancy, atrial rate, and P-wave morphology, or hidden features, such as "flutter waves," may be evident only in selected leads (Figure 28-5). Most contemporary monitoring systems now have automatic arrhythmia detection and storage capabilities, allowing discrimination between a gradual versus abrupt change in rhythm or rate. Such distinctions may be key in discriminating between sinus and nonsinus tachycardias in the critical patient. Familiarity with the capabilities and limitations of the specific system available is therefore essential.

For bradycardias, the surface ECG usually is sufficient to characterize the arrhythmia and differentiate between an abnormality in sinus nodal function and AV block, based

Table 28–2 Electrocardiographic Patterns

Pattern	Description
AV BLOCK	
Mobitz I	Shortened PR of first conducted beat after block
Mobitz II	No change in PR before/after block
	Periods of high-grade block
Third-degree	Fixed, rather than variable, RR interval
SUPRAVENTRICULAR TACHYCARDIAS	
AV reentrant supraventricular tachycardia	P waves obscured or buried in ST segment
AV nodal reentrant supraventricular tachycardia	P waves obscured by terminal QRS
	"Pseudo" R′ in lead V_1 during tachycardia, not sinus
Junctional ectopic tachycardia	Narrow QRS tachycardia, VA dissociation
	RR periodically shortened because of sinus capture complexes*
Atrial ectopic tachycardia	Monotonous rate, inappropriately fast
	Abnormal P-wave morphology (may be subtle)
Intraatrial reentrant tachycardia	Inappropriately fast rate, discrete P waves, variable AV conduction in postoperative patient with congenital heart disease
Atrial flutter	Variable RR interval
	Rapid, sawtooth flutter waves (>280 beats/min)
Atrial fibrillation	Irregular ventricular rate
	Coarse baseline with no discernible P waves
Chaotic atrial tachycardia	Three or more P-wave morphologies, irregular atrial rate, variable AV conduction (periods or atrial flutter or fibrillation common)
VENTRICULAR TACHYCARDIAS	
Monomorphic	Wide QRS for age, different from baseline
	Slurred upstroke of QRS
	Variable VA conduction†
	Sinus capture complexes†
Idiopathic types	Left bundle branch block, inferior axis (right ventricular outflow tract origin)
	Right bundle branch block, left superior axis (left ventricular septal origin)
Bidirectional	Alternating QRS axis (beat-to-beat)
Torsades des pointes	Initiation with "short-long-short" sequence
	QT-interval prolongation prior to onset
	"Twisting" of QRS axis

AV, Atrioventricular; *VA,* ventriculoatrial.
*Junctional ectopic tachycardia may be associated with third-degree AV block.
†Helpful when seen; absent if 1:1 VA relationship.

on the ratio of atrial-to-ventricular rate. The diagnosis of tachycardias may not be feasible from the surface ECG alone. Nevertheless, a combination of surface ECG and simple diagnostic maneuvers, sometimes coupled with direct recording of atrial activation, should allow accurate determination of most tachycardias. As with bradycardias, the surface ECG should be inspected for the ventricular rate and regularity, QRS duration and morphology, and atrial-to-ventricular relationship. Too often the apparent atrial-to-ventricular relationship is not clearly reflected on the surface ECG, and direct atrial recording, either with temporary atrial pacing wires or an esophageal ECG, is necessary to facilitate the diagnosis (Figure 28-6).

Bradycardias

In the absence of AV block, bradycardias are characterized by the origin of the initiating impulse as sinus, atrial, junctional, or ventricular. It is important to distinguish junctional or ventricular bradycardia from sinus bradycardia with an underlying junctional or ventricular escape, respectively. Terms such as "nodal rhythm" and "dissociated" are imprecise and demand further characterization. When the atrial rate exceeds the ventricular rate, second-degree or third-degree AV block is present. In complete AV block, the resultant escape rhythm usually is regular; in second-degree AV block, the ventricular intervals vary (see Figure 28-1). Occasionally, sinus node disease and complete AV block coexist, so it is important in the setting of a slow atrial rate to note "sinus capture" complexes when appropriately timed P waves conduct to the ventricle. When atrial pacing is feasible (as in patients with recent cardiac surgery), temporary atrial pacing can be used to demonstrate normal AV conduction, and the maximum rate at which 1:1 conduction can be maintained can be easily determined and followed serially.

The distinction between bradycardia resulting from AV block and sinus nodal dysfunction may have important therapeutic implications. If AV nodal conduction is intact, it usually is most appropriate to pace the atrium only (see AAI mode) rather than perform dual-chamber pacing. In contrast, isolated AV block is best managed by sensing and tracking the intrinsic atrial rate (see DDD mode).

Extrasystoles

Extrasystoles, or premature beats, usually are defined as supraventricular (supraventricular premature beats or premature atrial complexes) or ventricular (premature ventricular complexes, ventricular premature beats [VPBs]) in origin. True junctional extrasystoles are uncommon. When the extrasystole results in an early QRS with normal morphology and duration, a supraventricular extrasystole may be presumed. Usually, an early P wave can be discerned, but it may be obscured by the preceding T wave in certain leads. The ensuing sinus beat usually is advanced by the atrial extrasystole, but entrance block can result in a "full compensatory pause," usually attributed to a ventricular extrasystole.

Isolated premature QRS complexes with prolonged QRS duration may represent either ventricular extrasystoles or aberrantly conducted atrial extrasystoles. Distinguishing the two may be difficult from a single rhythm strip. Premature P waves often may be obscured in a particular lead, or the ventricular extrasystole morphology may appear similar to the sinus QRS in one lead (but totally dissimilar in another). The ECG features favoring ventricular extrasystoles over aberrantly

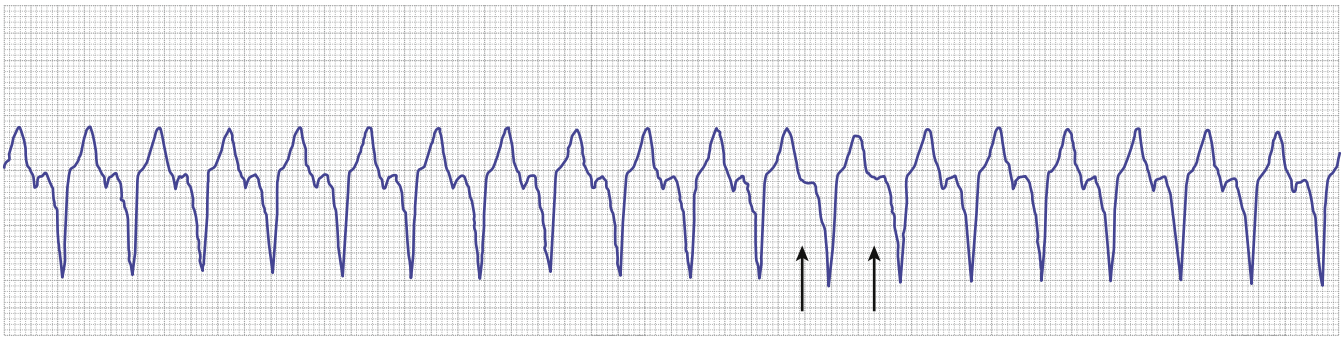

Figure 28–4. Ventricular tachycardia in an 8-year-old with previous muscular ventricular septal defect repair. Note transient VA block *(arrows),* excluding a supraventricular mechanism with aberrant conduction.

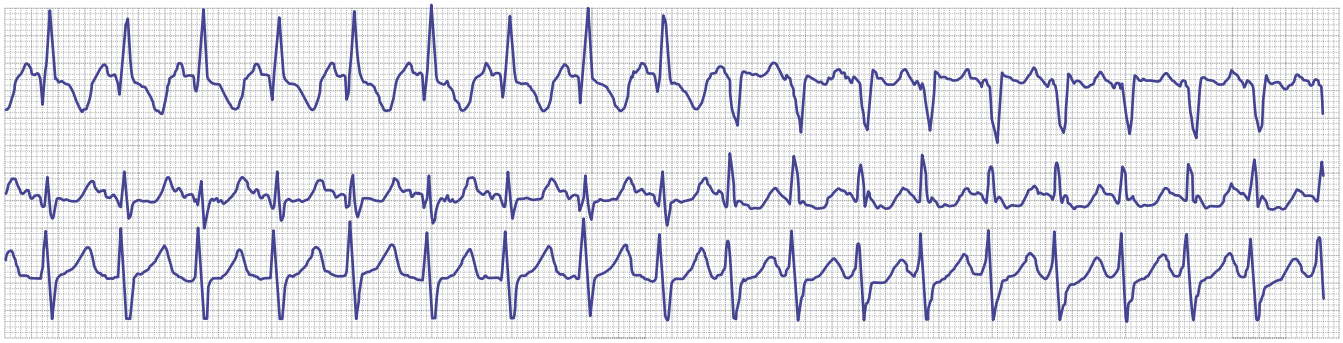

Figure 28–5. Ventricular tachycardia following cardiac surgery. Note similarity between QRS complexes during sinus rhythm and ventricular tachycardia in two of three recorded leads.

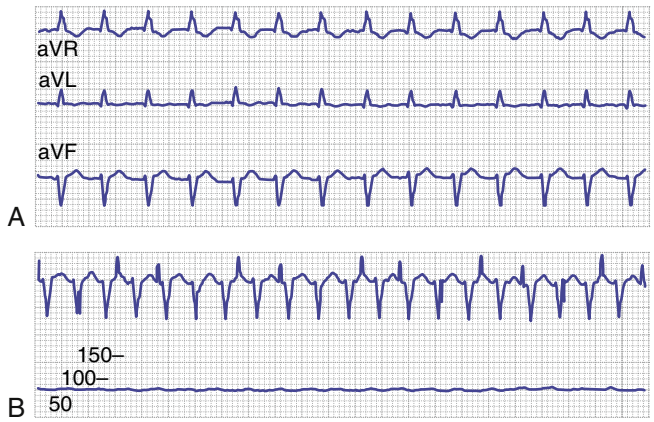

Figure 28–6. A, Narrow QRS tachycardia in an infant following a stage I Norwood operation. Possible AV dissociation is suggested, but P waves are not easily discerned on the surface electrocardiogram. **B,** Atrial recording from the same patient (after rate increased) using an epicardial atrial pacing wire. AV dissociation with faster junctional rate is demonstrated, typical of junctional ectopic tachycardia. Absence of clearly shortened RR intervals because of sinus capture might indicate associated AV block.

conducted atrial extrasystoles include (1) wide QRS morphology, (2) a full compensatory pause, (3) presence of fusion beats, and (4) absence of a discernible premature P wave. In the setting of ventricular preexcitation, variable fusion can occur as a result of exaggerated preexcitation with premature atrial depolarizations. As noted earlier, ventricular extrasystoles usually are followed by a full compensatory pause because the sinus node is not reset by the ventricular depolarization. However, an atrial extrasystole may sometimes fail to reset the sinus node (because of entrance block) or a ventricular extrasystole may occasionally reset the sinus node because of retrograde (VA) conduction. The simultaneous occurrence of both narrow QRS and wide QRS extrasystoles usually favors normally and aberrantly conducted atrial extrasystoles, particularly when the QRS width varies with the degree of prematurity (excluding fusion complexes).

The distinction of atrial versus ventricular extrasystoles may be somewhat academic in otherwise asymptomatic individuals because neither generally warrants therapy. However, either might be a harbinger for underlying myocardial irritability and should prompt a search for underlying causes. Occasionally, measures to suppress ectopy may appear to improve cardiac output by "regularizing" filling time in an otherwise tenuous patient. The relative advantages and risks of any such measure, whether achieved with medications or temporary pacing, need to be considered individually.

Tachycardias with Normal QRS

By definition, all tachycardias with normal QRS represent either sinus tachycardia or a form of SVT. It should be noted that the terms *supraventricular tachycardia, paroxysmal supraventricular tachycardia, and paroxysmal atrial tachycardia* often are used in reference to tachycardias with normal QRS, a regular rate in excess of 200 bpm, and no readily discernible P waves. In otherwise healthy infants, children, and adolescents, these features usually result from either AV reentrant tachycardia or AVNRT (Figure 28-7). Further distinction between

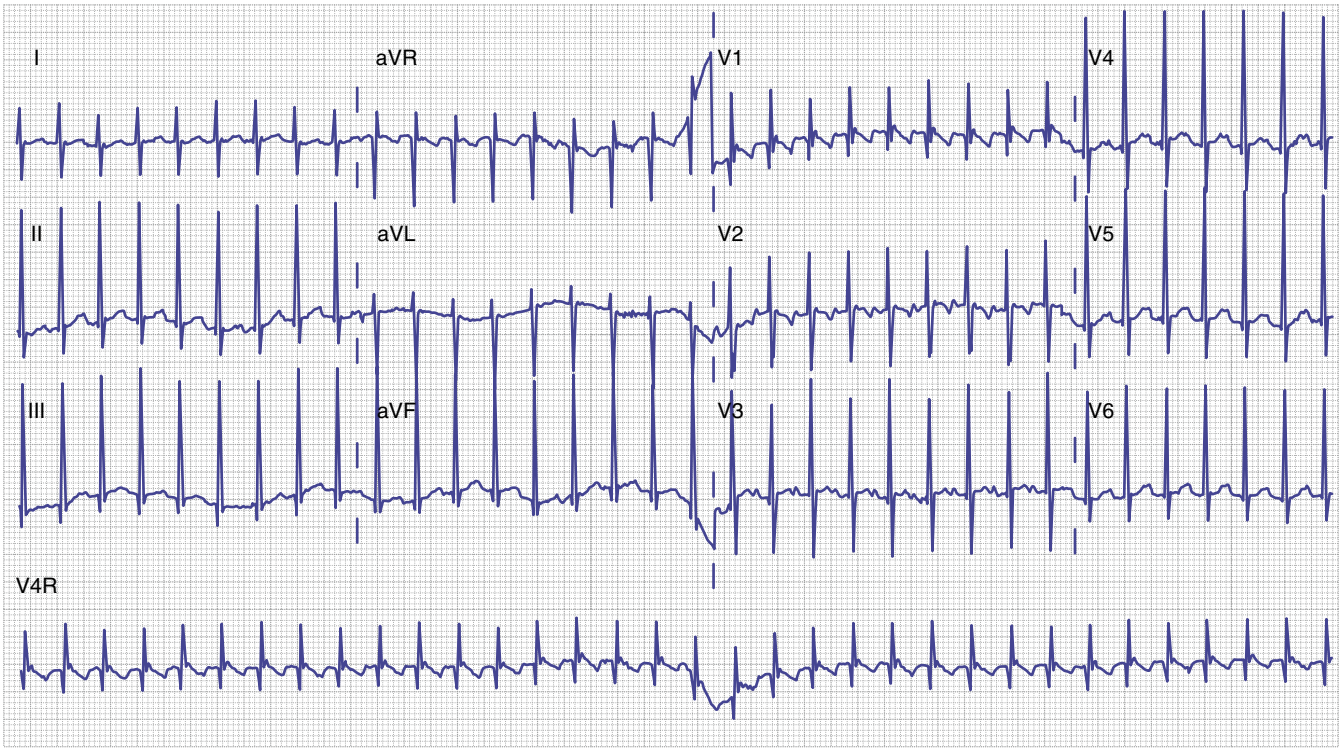

Figure 28–7. Supraventricular tachycardia resulting from AV nodal reentry in an infant. Although considerably less common than orthodromic reciprocating tachycardia in this age group, the P wave on the terminal portion of the QRS complex results in a "pseudo rSr′ pattern." During sinus rhythm, this terminal deflection on the QRS was absent, and the transesophageal recording confirmed the mechanism.

these two mechanisms has little impact on acute management. However, in the ICU setting, primary atrial tachycardias (including sinus tachycardia) and junctional tachycardias also must be considered (particularly following cardiac surgery). Abnormal P-wave morphology (determined by 12-lead ECG), PR interval greater than 50% of the RR interval, or completely obscured P waves favor a nonsinus mechanism. Finally, the QRS duration may appear normal by adult standards but be significantly prolonged for age.

In young patients, intraatrial reentry, atrial flutter, and atrial fibrillation usually are seen following surgical treatment for congenital heart defects involving the atrium (atrial septal defects, atrial repair of transposition of the great arteries, or the Fontan operation).[15] The sawtooth pattern typical of atrial flutter may be absent in these patients, and the term *intraatrial reentrant tachycardia* (IART) may be more appropriate when discrete P waves are present. Because the atrial rate often is relatively slow in comparison with "typical" atrial flutter, a high index of suspicion is required. In some cases, the atrial rate is slow enough that consistent 1:1 conduction (with discrete P waves) further obscures the diagnosis by simulating sinus tachycardia. Similarly, with 2:1 conduction, alternate P waves may be obscured by the T wave, giving the impression of sinus rhythm.

Distinguishing sinus tachycardia from various types of SVT may be difficult. The appropriateness and variation of the rate (or lack thereof) may be particularly helpful in differentiating sinus from nonsinus tachycardias. Observing the heart rate response to interventions such as volume expansion, analgesia, antipyretic agents, and catecholamine infusions often is helpful. Depending on the pattern of atrial activation, P waves may even simulate a normal sinus P-wave morphology during primary atrial tachycardias. In other cases, AV conduction may appear to be 1:1 on the surface electrocardiogram when, in fact, a second P wave is obscured by the QRS complex or T wave. Direct atrial recordings using transesophageal electrocardiography or temporary epicardial atrial pacing wires usually facilitate the diagnosis (see Figure 28-6, *B*). Vagal maneuvers or administration of adenosine to interrupt AV conduction transiently often helps characterize the true AV relationship and determine whether the AV node participates in the tachycardia mechanism.

Tachycardias with Prolonged QRS

Generally, tachycardias with prolonged QRS should be presumed to be ventricular tachycardias until or unless evidence of an alternative diagnosis is demonstrated. VA dissociation, the hallmark ECG feature of ventricular tachycardia, may not be seen in childhood because of rapid retrograde conduction over the AV node (see Figure 28-4). The distinction between ventricular tachycardia and SVT with aberrant conduction can be difficult and may require invasive electrophysiologic study. Prolonged attempts to differentiate the two at the bedside by noninvasive means often are fruitless and may delay treatment. The wrong conclusion may prompt inappropriate and potentially dangerous therapeutic maneuvers. In the acute setting, treatment based on a presumed diagnosis of ventricular tachycardia is rarely deleterious, even when the mechanism subsequently proves to be supraventricular. However, an erroneous presumption of "SVT with aberrant conduction" may have disastrous consequences. When feasible, a full 12-lead ECG may aid in the diagnosis, particularly when a baseline ECG in normal rhythm is available for comparison. Apparent hemodynamic stability should not be mistaken for evidence of SVT rather than ventricular tachycardia, whether in an otherwise healthy child or in a patient with known cardiac disease.

Monitoring of Atrial Depolarization

When the AV relationship during a tachycardia is unclear, sometimes it can be inferred indirectly by other available monitoring. Invasive arterial and venous pressure waveforms can help define atrial contractile action in some situations. For example, cannon A waves commonly are noted in patients with atrial flutter or JET.

Direct recording of atrial activity is necessary when the AV relationship cannot be determined from the surface ECG or otherwise inferred by the means described. Patients recovering from cardiac surgery frequently have temporary atrial epicardial pacing wires in place that can be used to record atrial electrograms directly while simultaneously recording the surface ECG (see Figure 28-6, *B*). Attachment of the atrial wires to a unipolar precordial lead ("V lead") on the monitor is an easy way to observe atrial activation. Otherwise, atrial activity can be readily recorded with a bipolar esophageal catheter inserted in the esophagus behind the left atrium.

Diagnostic Uses of Adenosine

Although most widely used as an acute therapy for terminating SVT that involves the AV node, adenosine administration also may yield important diagnostic clues to the underlying arrhythmia mechanism.[16] By producing transient block in the AV node during tachycardia, it often is possible to distinguish AV reentrant tachycardias and AVNRTs (either of which should terminate) from atrial tachycardias and ventricular tachycardias. However, adenosine's effects are not confined to the AV node. Ectopic (automatic) atrial and junctional tachycardias, intraatrial reentry, and certain ventricular tachycardias also may terminate with adenosine. Extreme caution should be taken when administering adenosine during wide QRS tachycardia. Adenosine produces vasodilatation, which theoretically can result in hemodynamic deterioration and tachycardia acceleration, or even fibrillation, if tachycardia fails to terminate. Ventricular fibrillation has been rarely observed when adenosine is administered in the setting of WPW syndrome, probably as a result of atrial fibrillation that then is conducted rapidly to the ventricles. Prompt defibrillation should always be readily at hand when administering adenosine for diagnostic or therapeutic purposes.

Treatment of Rhythm Disturbances

The approach to treatment of cardiac arrhythmias is influenced by the clinical setting, but several important considerations help guide therapy in any given situation. The first and most important concern is the degree of hemodynamic compromise associated with a particular arrhythmia. Minor rhythm disturbances may be more readily recognized in the intensive care setting than in other situations simply because of the level of monitoring and may prompt undue attention. In contrast, potentially life-threatening arrhythmias may best be treated by acute measures (e.g., cardioversion or temporary pacing) not readily available in other settings. Extracorporeal support and assist devices add another dimension to the equation. Extracorporeal membrane oxygenation support may serve as adjunctive therapy for refractory arrhythmias, whereas other modes of support (e.g., an assist device or balloon pump) may require a regular rhythm for appropriate coordination of the device with spontaneous cardiac activity.

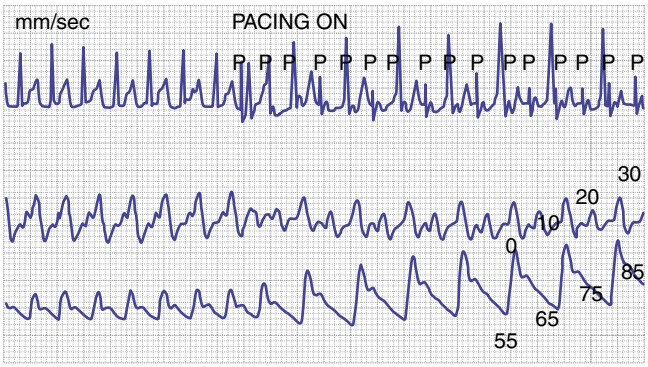

Figure 28–8. Junctional ectopic tachycardia with hypotension immediately improved with faster atrial pacing (in this case, resulting in 2:1 AV block and AV synchrony).

A second important consideration in critically ill patients, particularly those undergoing cardiac surgery, is to favor therapies that maintain appropriate AV synchrony. In the setting of marginal hemodynamics, an otherwise acceptable ventricular rate during arrhythmias such as atrial tachycardias and fibrillation, junctional tachycardia, or AV block may further compromise cardiac output as a result of loss of AV synchrony (see Figure 28-8).

A third consideration in the management of arrhythmias in this setting is the recognition that many arrhythmias in the ICU are iatrogenic. Even minor arrhythmias may herald more serious issues, such as electrolyte disturbances, acidosis, subendocardial ischemia, excessive catecholamine infusions, or increased intracranial pressure. It is important to identify and correct any such underlying causes because therapies directed at the rhythm itself may not protect from more serious rhythm decompensation.

Finally, whenever feasible, acute and short-term measures with limited potential to impair hemodynamics generally should be favored over chronic therapies. Thus nonpharmacologic therapies, such as pacing or cardioversion, or ultrashort-acting drugs, such as adenosine and esmolol, may be preferable to chronic antiarrhythmic therapy. Whether chronic therapy is warranted for a given arrhythmia is determined more by its underlying mechanism, clinical setting, and frequency than by the severity of the arrhythmias encountered in the intensive care setting. Before beginning chronic antiarrhythmic therapy, consultation with a cardiologist versed in the spectrum of arrhythmias seen in childhood is advisable. The impact of acute measures on chronic arrhythmia management becomes increasingly crucial with the emergence of amiodarone use in the ICU and the increasing availability of nonpharmacologic therapies such as radiofrequency catheter ablation and implantable defibrillators for a broader spectrum of arrhythmias and patient populations.[17,18]

Bradycardia Therapies

Whenever treatment is instituted for a rhythm disturbance, an underlying cause should be sought. This course of action is especially important in the treatment of bradycardias that occur in the intensive care setting, where airway compromise and respiratory insufficiency probably are the most common

causes of acute bradycardias. Increased intracranial pressure, hypothermia, or iatrogenic causes also may produce bradycardias that require specific interventions beyond those outlined here. Emergency interventions for AV nodal and sinus nodal dysfunction are essentially identical.

Pharmacologic Treatment of Bradycardias

After appropriate confirmation or restoration of airway integrity and ventilatory function, initial treatment of symptomatic bradycardias usually is pharmacologic, whether the cause is sinus node slowing or AV nodal block. Atropine (0.01-0.04 mg/kg intravenously or, if necessary, intramuscularly or via endotracheal tube) may transiently ameliorate the bradycardic effects of hypoxia (or other vagal stimulants), digoxin, intracranial hypertension, or AV block as a result of Lyme disease. Atropine is less likely to reverse bradycardic effects of β-blocking agents or other antiarrhythmic drugs, particularly in the setting of underlying sinus node disease. Epinephrine (0.1 μg/kg) can be administered by various routes to accelerate the heart rate. Continuous infusions of epinephrine (0.05-0.5 μg/kg/min) or isoproterenol (0.02-0.2 μg/ kg/min) may be instituted. In general, high-dose epinephrine or isoproterenol infusions should be replaced by temporary pacing as soon as feasible. Even if lower doses of these agents prove adequate, temporary pacing should be available as backup. Occasionally, methylxanthines are useful as an alternative to pacing for nonlethal bradycardias. Glycopyrrolate and ketamine may help augment rates in bradycardic patients requiring sedation or anesthesia.

Temporary and Permanent Pacing for Bradycardias

Pacing is an essential adjunct to medical management of arrhythmias in the ICU. Several reviews of pacing in children are available.[19-21] Pacing can be accomplished using a permanently implanted pacemaker and lead systems, temporary leads attached to the heart at the time of cardiac surgery or passed through the venous system to the heart, a lead passed into the esophagus to stimulate the atrium, or through use of transcutaneous patches to stimulate the ventricle. Most pacing is performed for bradyarrhythmias, although temporary pacing may be used to terminate reentrant tachyarrhythmias. Examination of atrial electrograms obtained from epicardial, transvenous, or esophageal pacing leads can be helpful in diagnosing arrhythmias.

Principles of Pacing

All pacing requires a complete circuit with at least one lead on or near each chamber that is to be paced. Often two leads are placed on each chamber (bipolar leads), although sometimes only the cathode is attached to the heart (unipolar leads), with a subcutaneous electrode acting as the anode. The metal can of a permanent pacemaker also can serve as the anode. The intensity of the pacing stimulus is related to the stimulus duration (pulse width) and its amplitude, which can be expressed either as current (mA) or voltage (V). Energy is proportional to the pulse width and the square of the amplitude. Most temporary pacemakers provide a fixed pulse width, with an adjustable current output (mA). Permanent pacemakers generally have both an adjustable pulse width and an adjustable amplitude.

Sensing of intrinsic activity of the heart is important to prevent pacing at inappropriate times. The sensitivity of permanent and temporary pacers is adjustable. The sensitivity setting (mV) actually refers to a sensing threshold for detection of spontaneous cardiac activity. The spontaneous activity must exceed that threshold to be detected. Thus a lower numeric sensitivity setting makes the pacemaker more sensitive to both spontaneous activity of the atrium or ventricle (appropriate sensing) and other electrical signals (oversensing).

The timing circuits of the pacemaker determine when the pacemaker fires and its response to sensed events. A simplification of the North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group (NASPE/BPEG) pacing code uses three letters to describe pacing modes.[22] The first two letters refer to the chamber(s) paced and chamber(s) sensed, respectively (A, atrium; V, ventricle; D, dual). The third letter refers to the response to sensed events (I, inhibit; T, trigger; D, dual). Thus a single-chamber atrial or ventricular pacing demand mode is AAI or VVI mode, whereas dual-chamber pacing is generally DDD mode. In evaluating and adjusting pacemakers, it is helpful to think in terms of intervals rather than rates. Because there are 60,000 ms in 1 minute, to convert a rate (bpm) to an interval (ms) you must divide 60,000 by the rate. For example, a rate of 100 bpm corresponds to an interval of 600 ms. Thus for a ventricular demand (VVI) pacemaker programmed to pace at a rate of 100, the pacemaker stimulates the ventricle 600 ms after the previous paced or sensed ventricular beat unless there is another sensed ventricular beat. If there is another sensed ventricular beat, the pacemaker output is inhibited and another interval of 600 ms is started. Similarly, for dual-chamber pacing with an AV interval of 150 ms, the ventricle is paced 150 ms after an atrial paced or sensed beat unless a ventricular sensed beat occurs during that interval.

Temporary Pacing

In the pediatric ICU, temporary pacing is most commonly used in patients after surgical treatment of CHD. Temporary epicardial pacing wires are usually placed on the atria and ventricles, allowing pacing of either chamber. As previously noted, direct atrial recording (by attaching the wire to an ECG lead) also may aid in the diagnosis of tachyarrhythmias such as JET. Atrial burst pacing can be used to terminate reentrant supraventricular arrhythmias such as IART, AVNRT, and ORT. Pace termination of ORT is shown in Figure 28-9. Although JET generally cannot be terminated with burst pacing, atrial pacing at a rate faster than the JET rate often improves hemodynamics by allowing AV synchrony until the JET resolves or is pharmacologically controlled (see Figure 28-8).

In bradycardic patients who do not have temporary epicardial pacing wires, transcutaneous pacing can be performed.

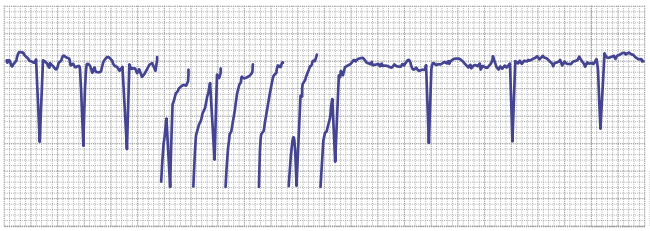

Figure 28–9. Pace termination of orthodromic reciprocating tachycardia with a burst of atrial pacing.

It is important that electrodes and output are appropriate for the patient size, and positioning may be critical to maintaining capture. In general, transcutaneous pacing is used only for a short time while a temporary transvenous pacing lead is placed. At the bedside, placement of a balloon-tipped temporary transvenous lead is best accomplished via the internal jugular or subclavian vein, because the catheter often can be directed to the ventricle "blindly." When fluoroscopy is available, a temporary active fixation may be preferred, allowing more secure positioning and the choice of pacing the atrium, the ventricle, or both (in dual-chamber mode).

Setting Temporary Pacing Parameters

For AAI or VVI demand pacing, the pacemaker usually is initially set at a rate higher than the patient's intrinsic atrial or ventricular rate. The pacemaker's output expressed in mA (current) or V (voltage) is gradually reduced until there is loss of capture and then is increased again. The lowest output that captures the chamber being paced is known as the pacing threshold. Usually the output is set at twice the threshold output. The pacemaker rate is lowered to a rate below the intrinsic rate of the chamber being paced, unless the patient is hemodynamically unstable at that rate. The pacemaker should indicate that it is sensing the intrinsic atrial or ventricular activity, usually with a blinking indicator light. The sensitivity of the pacemaker is adjusted to higher numeric settings (less sensitive) until the pacemaker stops sensing the intrinsic activity. The sensitivity then is reduced to a lower numeric value (more sensitive). The highest numeric value at which the pacemaker senses appropriately is known as the sensing threshold. Ideally, the sensitivity is set to a numeric value that is half the sensing threshold, but this is not always possible, especially for temporary atrial leads. Failure to sense can result in inappropriate pacing, which can induce tachyarrhythmias. Figure 28-10 shows a single inappropriate atrial stimulus initiating sustained ORT.

Dual-chamber pacing is more complex. The atrial and ventricular sensitivity and output are set using basically the same process described for single-chamber pacing. In addition to setting the low rate of the pacemaker, several other timing parameters must be set, including the upper tracking limit (UTL), the AV delay, and the postventricular atrial refractory period (PVARP). UTL defines the fastest rate at which the pacemaker will pace the ventricle. PVARP refers to a period after a ventricular paced event during which the pacemaker is refractory to atrial sensed events and ignores any spontaneous atrial beats. The pacemaker is also refractory to spontaneous atrial events during the AV interval. Thus the total atrial refractory period (TARP) includes both the AV interval and the PVARP. Although TARP is not a programmable parameter (it is the sum of the programmed AV interval and the programmed PVARP), it is an important concept for understanding high rate behavior.

If the spontaneous atrial cycle length (60,000 ms/min divided by the spontaneous atrial rate in bpm) is less than the TARP, only half of the spontaneous atrial beats will be sensed, resulting in 2:1 block. The point at which this occurs is known as the 2:1 block rate. Because abrupt 2:1 block is generally an undesirable situation, most temporary pacemakers will not allow the UTL to be set above the 2:1 block rate. Thus before increasing the UTL, it often is necessary to shorten the AV interval or the PVARP. If the atrial rate exceeds the UTL, the ventricular output will be delayed, producing a rhythm that resembles Wenckebach AV conduction, known as pacemaker Wenckebach. It is important to remember that pacemaker Wenckebach is a desirable response to high atrial rates. The alternatives, tracking rapid atrial rates 1:1 and abrupt 2:1 ventricular tracking of the atrium, are more likely to cause hemodynamic compromise. Occasionally appropriate pacemaker Wenckebach is mistaken for failure to sense the atrium or failure to pace the ventricle. Figure 28-11 shows 1:1 conduction, 2:1 block, and pacemaker Wenckebach at different pacemaker settings in a patient with a dual-chamber pacemaker for high-grade AV block.

When initiating dual-chamber pacing, it is important to be sure that the atrial lead senses appropriately and that the rates, intervals, and refractory periods are set appropriately to allow the pacemaker to track the spontaneous atrial rate. If the intrinsic atrial activity is not appropriately sensed and the dual-chamber temporary pacemaker's low rate is lower than the patient's intrinsic atrial rate, you may falsely assume that dual-chamber pacing is occurring when it is not. The presence of cannon A waves on the central venous pressure tracing may provide a clue that AV synchrony is not occurring. Reversing the atrial leads, lowering the numeric atrial sensitivity, or adjusting the AV interval, UTL, or PVARP may remedy this situation. If the atrium still cannot be sensed appropriately, setting the pacemaker's low rate higher than the patient's own

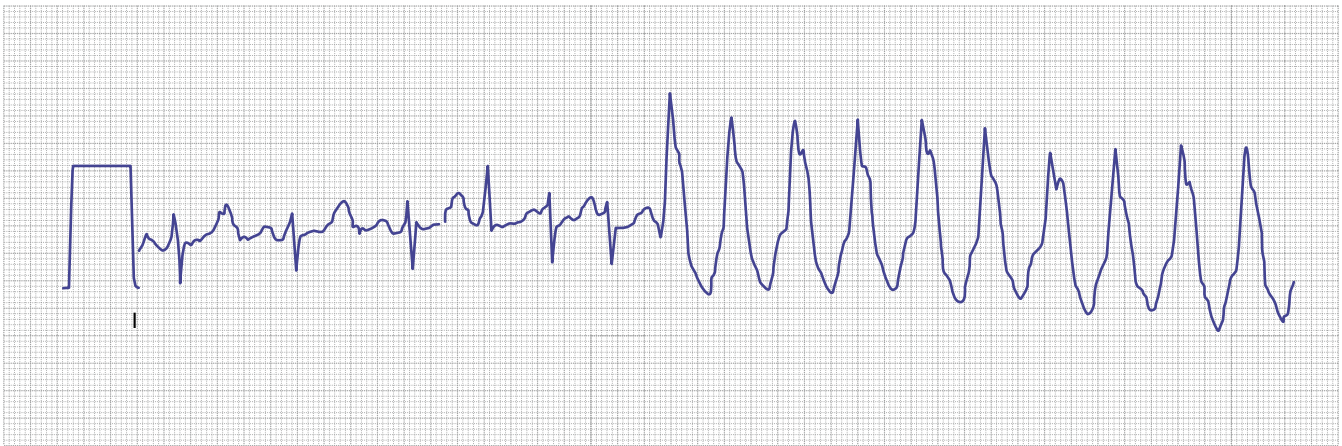

Figure 28–10. Initiation of orthodromic reciprocating tachycardia with a single atrial paced beat that falls at a vulnerable time. After several narrow-complex beats, bundle branch block in tachycardia results in a wide-complex rhythm.

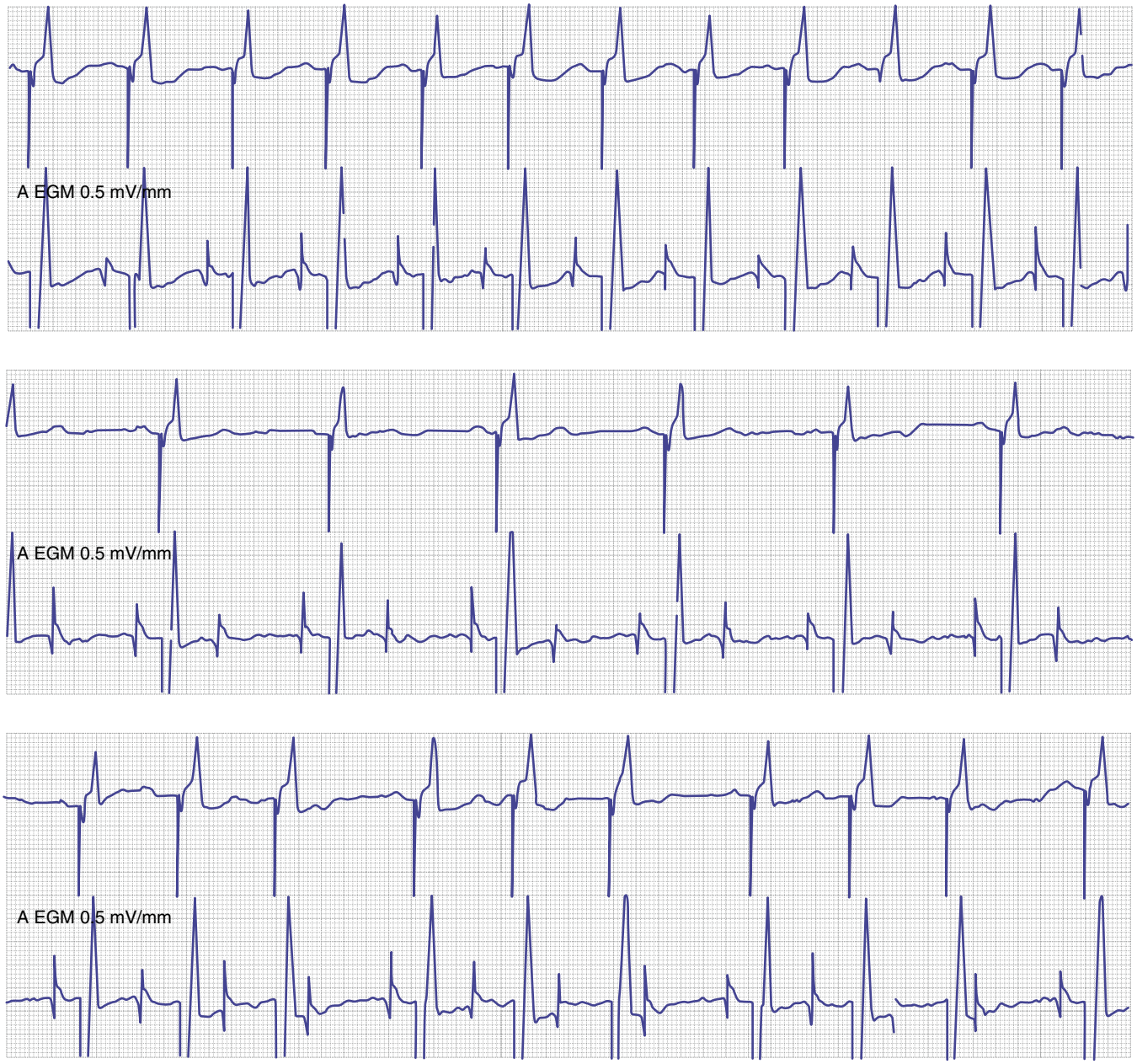

Figure 28–11. Examples of pacemaker high-rate behavior. Each panel shows a surface electrocardiogram with the simultaneous atrial electrogram below. *Top,* 1:1 Atrioventricular conduction. Each sensed atrial event falls outside the total atrial refractory period, resulting in a corresponding paced ventricular event. *Middle,* 2:1 Block occurs when the total atrial refractory period exceeds the spontaneous atrial cycle length. Every other atrial beat falls within the refractory period and fails to trigger a ventricular pacing stimulus. *Bottom,* "Pacemaker Wenckebach" operation occurs when the atrial rate reaches the upper tracking rate. Gradual lengthening of the AV delay ensures that the ventricular pacing does not occur above the upper tracking rate. Eventually, an atrial sensed event falls within the refractory period so that a ventricular pacing stimulus is not triggered. All three recordings were obtained in the same patient over a short period by adjusting the programmable pacemaker parameters. *(From Sliz NB Jr, Johns JA: Cardiac pacing in infants and children,* Cardiol Rev *8:223-239, 2000.)*

atrial rate will allow AV synchrony. In effect, you are pacing in DVI mode, pacing atrium and ventricle, sensing the ventricle, and inhibiting pacemaker output when spontaneous ventricular beats occur. Older temporary dual-chamber pacemakers offered only DVI mode; newer devices allow true DDD pacing as long as atrial sensing can occur.

Occasionally, a reentrant arrhythmia known as pacemaker-mediated tachycardia (PMT) may be seen, in which a DDD pacemaker senses the atrium and paces the ventricle, with the patient's own AV node conducting the impulse up from the ventricle to the atrium and the cycle repeating again. Thus the pacemaker acts as the antegrade limb of the reentrant circuit, while the patient's own AV node acts as the retrograde limb. Usually, PMT can be avoided with careful adjustment of the pacemaker's AV interval and PVARP. Acutely, PMT usually can be terminated by placing a magnet over the pacemaker, which makes the pacemaker pace asynchronously, ignoring any sensed events, thus interrupting the antegrade limb of the reentrant circuit. Figure 28-12 shows initiation of PMT by loss of atrial capture with termination of the tachycardia by a spontaneous ventricular beat.

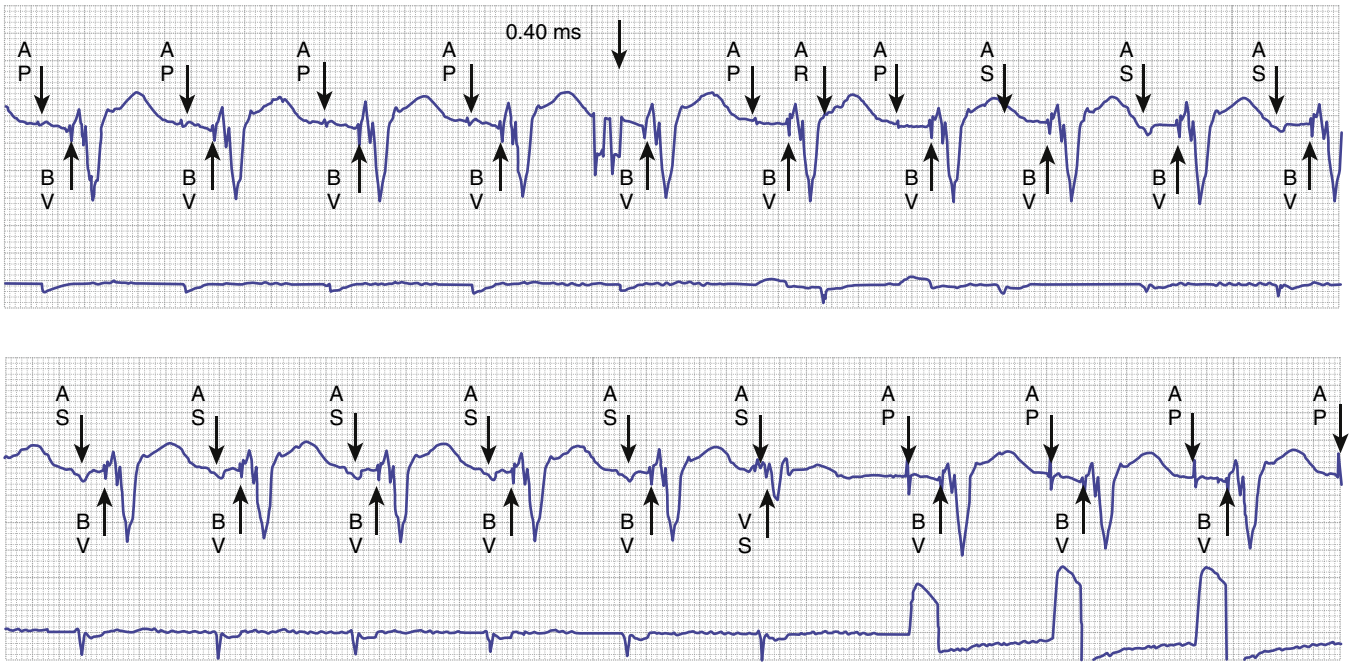

Figure 28–12. Initiation and termination of pacemaker-mediated tachycardia. *Top,* Two atrial pacing stimuli fail to capture, followed by ventriculoatrial conduction of a ventricular paced beat. The resulting atrial beat *(AS)* is sensed and triggers another ventricular beat, and the process repeats. Had the retrograde atrial beat occurred during the postventricular atrial refractory period, it would not have triggered a ventricular paced beat. *Bottom,* Spontaneous ventricular beat inhibits the ventricular pacing, terminating the process. Atrial electrogram tracings are shown at the bottom of each panel. *AP,* Atrial pace; *AR,* atrial refractory; *BV,* biventricular pace; *VS*, ventricular sense.

Permanent Pacing

The two most common indications for permanent pacing are high-grade AV block and sinus nodal dysfunction. AV block may be congenital or acquired, with surgical damage to the conduction system the most common cause of acquired AV block. In patients with surgical AV block, there may be recovery of normal conduction with resolution of edema. In general, permanent pacing is not recommended unless there has been no recovery for 7 to 14 days.[23] Occasionally, if the surgeon is confident that the conduction system has been permanently damaged or if temporary pacing is not reliable, permanent pacemakers may be implanted before 7 days after the initial injury. Elective pacing for congenital AV block in the first decade of life usually is prompted by symptoms, low ventricular rates, or ventricular ectopy. Elective pacing is commonly recommended in the second decade of life even for asymptomatic patients with congenital heart block, based on studies showing that the first symptom in teenagers and adults may be catastrophic.[24] Pacing for sinus nodal dysfunction is most commonly performed in patients with structural heart disease, usually following extensive atrial surgery such as Fontan operation or atrial repair of transposition of the great arteries.

In older children and adults, transvenous pacing is the preferred route for pacing because of better pacing thresholds, easier lead placement, and lower susceptibility to lead fractures than with epicardial leads. In younger children, however, concern about venous occlusion in a patient who will require many decades of pacing often favors placement of epicardial pacemaker leads. The development of epicardial leads that elute a small amount of dexamethasone appears to improve epicardial lead performance,[25] although epicardial lead fractures remain a problem that is cause for concern. In patients requiring a lifetime of pacing, various approaches to allow atrial and ventricular pacing are commonly needed (Figure 28-13).

Newer Indications for Pacing

Data on adults have suggested that biventricular pacing, with independent stimulation of the right and left ventricles, improves ventricular function in some patients with heart failure. Limited data are available in the pediatric population on this approach to heart failure treatment (often referred to as cardiac resynchronization therapy). Certainly, if pacing is otherwise required in a patient with impaired ventricular function, a biventricular pacing system should be considered. However, identifying patients most likely to benefit from this modality and the best technique for optimizing the timing of activation between the ventricles remains unresolved. Ventricular pacing also has been suggested to be helpful in patients with hypertrophic cardiomyopathy.

Tachycardia Therapies

Vagal Maneuvers

"Vagal maneuvers" once were the most commonly used intervention for terminating SVTs. They occasionally terminate ventricular tachycardias as well. Mechanical maneuvers such as the Valsalva maneuver or carotid sinus massage usually produce effective vagal stimulation beyond infancy. In infants, a similar reflex vagal response sometimes can be elicited by applying firm, steady abdominal pressure or by applying an ice pack to the face. These maneuvers should be attempted

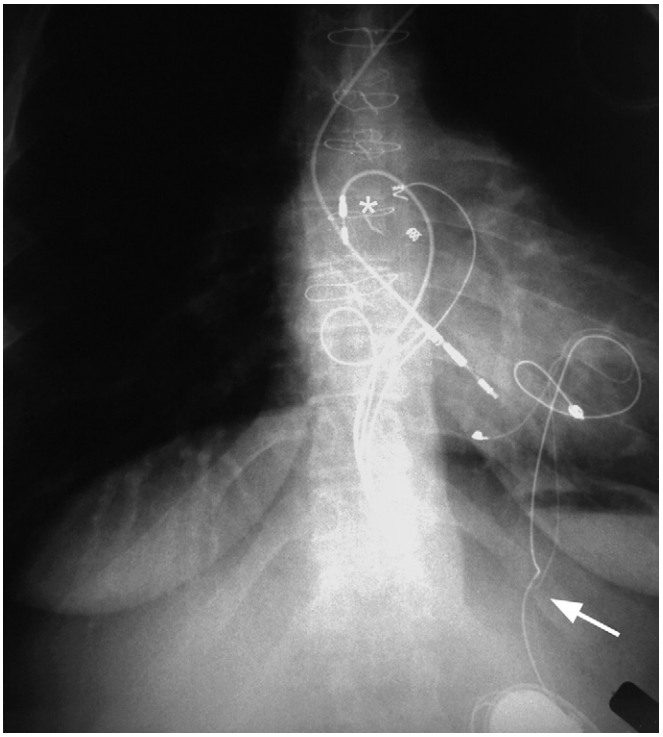

Figure 28–13. Chest x-ray film of a patient with many abandoned pacing leads. There is a bipolar transvenous lead with the tip in the right ventricle. Another bipolar transvenous lead has been used as an epicardial atrial lead *(asterisk).* There are two screw-in epicardial leads, one atrial and one ventricular. The atrial lead has a fractured electrode. There are two other types of epicardial leads more toward the apex, one of which is fractured *(arrow),* and the other of which is kinked. Only the kinked lead is functional. *(From Sliz NB Jr, Johns JA: Cardiac pacing in infants and children,* Cardiol Rev *8:223-239, 2000.)*

for 15 to 30 seconds. Endotracheal suctioning may terminate tachycardias by this mechanism. Although it rarely has been used since adenosine became available, pharmacologic vagal stimulation can be achieved directly with the acetylcholinesterase inhibitor edrophonium (Tensilon, 0.1 to 0.2 mg/kg). Phenylephrine (0.01 to 0.1 mg/kg boluses or continuous infusion of 10 to 100 μg/kg/min) sufficient to raise the systolic blood pressure by at least 50% to a maximum of 180 mm Hg also induces a potent reflex vagal response.

Acute Pharmacologic Therapies

Adenosine. An endogenous nucleoside with profound effects on SA node and AV node conduction, adenosine has become a mainstay in the acute treatment of SVT with normal QRS duration.[16] Administered as a rapid bolus, it produces transient but profound depression of AV nodal conduction and should reliably terminate reciprocating tachycardias (AV nodal reentry, AV reentry). Although less commonly recognized, adenosine also may interrupt AV reentry by directly blocking accessory pathway conduction.

Given the prevalence of AV reentry and AV nodal reentry among otherwise healthy young patients, adenosine often is advocated for wide QRS tachycardias as a therapeutic and/or diagnostic maneuver. Its effects are mediated through specific membrane receptors coupled to inhibitory G proteins modulating K channel function. These receptors are found not only in the AV and SA nodes but also on atrial myocytes. It usually causes transient AV block without terminating most primary atrial tachycardias but instead may transiently suppress atrial automatic tachycardias (ectopic atrial or junctional) and occasionally may terminate intraatrial reentrant tachycardias. Certain ventricular tachycardias may be adenosine sensitive, particularly those originating because of abnormal triggering in the right ventricular outflow tract.

Adenosine must be administered rapidly (50 to 250 μg/kg) because of rapid metabolism by erythrocytes. If tachycardia is not terminated, determination must be made regarding whether a larger dose is warranted, the dose was given too slowly, or VA or AV conduction was altered without terminating tachycardia (see discussion on diagnosis). Therefore it is important to record an ECG strip during adenosine administration so that important diagnostic or therapeutic clues are not missed. Because of its brief effect (a half-life of 8 to 10 seconds), tachycardias sometimes immediately reinitiate following successful termination. If they reinitiate, readministration of the same dose should be attempted rather than increasing the dose further.

In addition to effects on the AV node, adenosine can produce sinus arrest, which may be prolonged in the setting of intrinsic SA nodal dysfunction in the presence of drugs that interfere with its metabolism, such as dipyridamole and diazepam, or with drugs that may exaggerate its effects, such as class I, II, or III antiarrhythmic drugs. High doses should not be used indiscriminately in these situations. The use of adenosine in patients with reactive airway disease may be problematic because adenosine occasionally triggers severe bronchospasm. Conversely, its effects may be antagonized by aminophylline and other methylxanthines the patient may be receiving.

Adenosine produces dramatic but transient chest pain, along with systemic vasodilatation, both of which tend to increase sympathetic tone. As a result, adenosine may paradoxically accelerate tachycardias if termination is unsuccessful or, in the case of primary atrial tachycardias (atrial flutter or fibrillation), may produce more rapid conduction over the AV node (after initially slowing the ventricular rate). Various secondary arrhythmias may occur following administration of adenosine, particularly ventricular ectopy, atrial fibrillation, or, rarely, ventricular fibrillation. Although these effects usually are transient, emergency external cardioversion should always be available whenever adenosine is administered. The appropriateness of adenosine has been questioned in patients with known ventricular preexcitation syndromes (WPW syndrome) or suspected ventricular tachycardias. Nevertheless, its thoughtful and careful use remains invaluable for both diagnosis and treatment of many tachycardias.

Antiarrhythmic Agents. The addition of pharmacologic agents following adenosine administration should be guided by the clinical situation, known or suspected tachycardia mechanism, and response to adenosine administration. In some cases (such as in patients with wide QRS tachycardia or in hemodynamically compromised patients), it may be most appropriate to proceed directly to pacing termination or cardioversion if adenosine is unsuccessful in restoring sinus rhythm. In other instances, acute antiarrhythmic drug therapy may be warranted.[26]

Antitachycardia drugs usually are classified according to their surface ECG effects, which often correlate closely with their cellular electrophysiologic effects. The Vaughan Williams

classification divides drugs into those that block cardiac sodium channels (class I), block β-adrenoreceptors (class II), prolong repolarization (class III), and block calcium channels (class IV). Digoxin and adenosine, which are not included in this classification scheme, exert their primary antiarrhythmic effects on the AV node. Magnesium also has depressant effects on the AV node and suppresses early and late afterdepolarizations (triggered activity). Many of the available drugs manifest properties of more than one class, which contribute collectively to their antiarrhythmic action.[27]

In general, class I drugs (particularly IA and IC) slow conduction in atrial, ventricular, or accessory pathway tissue and class III drugs increase refractoriness in these same tissues. Class IA drugs usually accomplish both effects. β-Adrenergic antagonists, calcium channel antagonists, digoxin, and adenosine act primarily by slowing AV nodal conduction or inhibiting abnormal automaticity. Thus the latter group of drugs is primarily used for reciprocating tachycardias using the AV node (ART, ORT, AVNRT) or to induce second-degree AV block during a primary atrial tachycardia. In contrast, class IA, IC, and III drugs may be more effective in terminating or directly suppressing primary atrial tachycardias and may be effective for reciprocating tachycardias.[5,26]

Despite the various antiarrhythmic agents available for chronic therapy, relatively few are suitable for acute administration to the critically ill patient either because the drugs are not available in intravenous formulation or they have significant negative inotropic effects when administered intravenously (Table 28-3). This discussion is limited to agents suitable for acute and short-term parenteral administration.

All antiarrhythmic agents have the potential for producing bradycardia, particularly when administered acutely, and most have negative inotropic and/or hypotensive effects. Careful observation is required during initial administration and subsequent infusion of all intravenous antiarrhythmic agents. Although many are contraindicated in cases of heart failure or hypotension, therapy may be necessary if the arrhythmia is contributing significantly to the patient's hemodynamic compromise.

Procainamide. Procainamide is useful for various SVTs and ventricular tachycardias in the intensive care setting. Its broad electrophysiologic effects include both conduction slowing and increased refractoriness in atrial tissue, ventricular tissue, and accessory AV connections. Unlike quinidine, procainamide can be administered intravenously. Effective plasma concentrations (6 to 10 μg/dL) can be readily achieved with a total loading dose of 15 mg/kg over 15 minutes (or in small bolus increments at a similar rate). Careful and repeated blood pressure monitoring is required as loading ensues because of potential negative inotropic and direct vasodilator effects. We prefer to administer intravenous procainamide by hand in 1 mg/kg aliquots at 1- to 2-minute intervals, rather than using a continuous infusion on a pump. In a patient not set up for continuous direct arterial blood pressure monitoring, we set the noninvasive blood pressure monitor to measure blood pressure at 1- or 2-minute intervals. An acceptable noninvasive blood pressure measurement is then the cue to give the next aliquot of procainamide. If hypotension results, the administration should be momentarily interrupted until blood pressure returns toward normal. In primary atrial tachycardias, a vagolytic effect may increase the ventricular response over the AV node. Occasionally, atrial tachycardia that is conducting 2:1 to the ventricle slows sufficiently to allow 1:1 conduction, converting a hemodynamically stable rhythm to an unstable rhythm. Thus one should always be prepared to use cardioversion if necessary.

Procainamide, like other class IA and class III drugs, is contraindicated in patients with the congenital or acquired long QT syndromes. Regular monitoring of plasma concentration every 6 to 12 hours is necessary during intravenous administration to maintain levels between 5 and 10 μg/dL. The active metabolite N-acetylprocainamide contributes to the antiarrhythmic action; higher levels of the parent drug may be necessary in patients lacking the enzyme to produce this metabolite.

Lidocaine. Intravenously administered lidocaine is useful for suppressing and sometimes terminating ventricular tachycardias in children. Although somewhat less likely to acutely terminate ventricular tachycardias than procainamide, bretylium, or amiodarone, lidocaine's lack of significant negative inotropic effect often makes it more attractive for this indication. The usual loading dose is 1 to 2 mg/kg acutely or 3 mg/kg over 20 to 30 minutes, followed by a 20 to 50 μg/kg/min infusion. Lidocaine levels should be monitored to prevent central nervous system (CNS) toxicity. With chronic use (4 to 7 days), accumulation of the metabolite glycine xylide may impair drug efficacy by interfering with the parent drug effect at the sodium channel. Despite traditional recommendations for its use in ventricular fibrillation, lidocaine actually increases defibrillation energy requirements. It probably is superior to phenytoin for ventricular arrhythmias related to digitalis toxicity, but more specific therapies are available (see magnesium, pharmacologic, and toxic arrhythmias).

β-Blocking Agents. A limited number of β-blocking agents are useful for intravenous treatment of tachycardias. Acutely, their role is generally limited to incessant tachycardias, which seem to be dependent on sympathetic tone, and ventricular tachycardias related to myocarditis, ischemia/reperfusion injury, or congenital long QT syndromes. In hemodynamically unstable patients, β-blocking agents should be used cautiously because of hypotension and potential sinus bradycardia once tachycardia terminates. All may produce bronchospasm, hypotension, or bradycardia or may depress ventricular function.

Esmolol, a short-acting, nonselective β-blocker with a half-life of 2 to 5 minutes, can be administered as a continuous infusion. A loading dose of 500 μg/kg is followed by an infusion of 50 to 100 μg/kg/min. The infusion can be titrated upward by doubling every 3 to 5 minutes up to 500 μg/kg/min. Repeat loading doses may be useful as the infusion is increased. Its very short half-life is excellent for short-term use, but extended efficacy is limited by tachyphylaxis. For longer-term intravenous administration, propranolol (0.02 to 0.1 mg/kg) and metoprolol (0.05 to 0.10 mg/kg) are administered by slow intravenous infusion every 4 to 6 hours, carefully observing for hypotension (or bradycardia). Metoprolol, a selective β_1-blocker, may be preferable for ventricular arrhythmias and in patients with reactive airway disease.

Amiodarone. Amiodarone is arguably the single-most potent antiarrhythmic drug available, both in the acute, intravenous setting and when administered chronically. At sufficient doses, it is often effective in controlling various tachycardias

Table 28–3 Treatment of Bradycardias, Supraventricular Tachycardias, and Ventricular Tachycardias

	Primary Therapies	Secondary Therapies	Long-Term Therapies
BRADYCARDIAS			
Sinus bradycardia	Atropine 0.01 mg/kg	Temporary pacemaker	Permanent pacemaker (AAIR, DDDR)
	Epinephrine 0.1 mg/kg	Isoproterenol infusion	
	Transcutaneous pacemaker		
AV block (high-grade)	Transcutaneous pacemaker	Temporary pacemaker	Permanent pacemaker (DDDR)
SUPRAVENTRICULAR TACHYCARDIAS			
Sinus tachycardia	Identify cause(s)	Sedation, pain control	β-Blockers, if chronic
		Adjust catecholamines	Consider nonsinus mechanism
		Respiratory support	
Paroxysmal supraventricular tachycardia, AV nodal reentrant tachycardia	Vagal maneuvers	Esmolol	β-Blockers, class I, class III
	Adenosine	Verapamil	Amiodarone
	Transesophageal termination	Procainamide (IV)	Radiofrequency ablation
		Amiodarone (IV)	Radiofrequency ablation
	Procainamide	Class I, class III	
AET and other incessant supraventricular tachycardia	Amiodarone	β-blockers	
	Esmolol	Amiodarone	
	Avoid cardioversion		
Atrial flutter <24 hours	Rate-control (diltiazem IV)	Pace termination	Radiofrequency ablation
	Procainamide	(transesophageal, intracardiac)	Antitachycardia pacemaker
	Pace termination with pacemaker		
	DC cardioversion		
	Ibutilide (transesophageal echocardiography if duration unknown of >24 hours to rule out thrombus)		
Atrial fibrillation <24 hours	Same as above, except pace termination not feasible)		
Chaotic atrial tachycardia	Procainamide, amiodarone	β-Blocker (rate control)	Propafenone, amiodarone
VENTRICULAR TACHYCARDIAS			
Monomorphic (conscious, stable)	Procainamide/lidocaine	Procainamide/lidocaine	Defined by substrate
	DC cardioversion	Amiodarone	
	Pace termination if PM, ICD		
Known heart disease	Same	Amiodarone	ICD, Radiofrequency ablation
			Amiodarone
Known idiopathic	Consider IV verapamil	β-Blocker	Ca-channel blocker
	Avoid cardioversion		β-Blocker
			Radiofrequency ablation
Pulseless (monomorphic, polymorphic)	DC cardioversion	Amiodarone (unless long QT)	ICD
	β-Blocker	β-blocker	
	Amiodarone	Magnesium	
Ventricular fibrillation	Defibrillation	Epinephrine	ICD
		Vasopressin	

AET, Atrial ectopic tachycardia; *AV,* atrioventricular; *ICD,* implantable cardioverter-defibrillator; *IV,* intravenous; *PM,* pacemaker.

refractory to other antiarrhythmic agents.[28] Although typically regarded as a class III agent, its effects are considerably more diverse. It not only prolongs repolarization (by blocking potassium channels), but to varying degrees it blocks some sodium channel (class I effect), calcium channel (class IV effect), and β receptors (class II effect).

Amiodarone is administered as a total loading dose of 5 mg/kg divided into 1 mg/kg aliquots given at 5- to 10-minute intervals. The loading can be truncated if arrhythmia control is achieved. If hypotension ensues, volume expansion or calcium chloride (10 to 30 mg/kg) should be administered. If arrhythmia control is not achieved, a second loading dose can be administered 30 to 60 minutes later. A continuous infusion of 10 mg/kg over 24 hours can be administered if ongoing therapy is desired.

Because of amiodarone's slow elimination and its potential for significant vasodilatation, its usage usually should be limited to arrhythmias truly refractory to other agents or certain arrhythmias recognized as poorly responsive to conventional therapy. Furthermore, because of its slow elimination, the absence of spontaneous arrhythmias following acute administration may obscure the determination of whether ongoing therapy is warranted for several days or weeks. Similarly, amiodarone may obscure subsequent diagnostic efforts and inhibit induction of arrhythmias at electrophysiologic study for days or weeks after ceasing administration. Cessation of intravenous therapy at the earliest possible opportunity is advisable. When necessary, oral therapy should be deferred until necessary diagnostic issues (sometimes including formal electrophysiologic study) have been addressed. Because of the potential for chronic toxicity, dronedarone, a noniodinated analogue to amiodarone, has recently been approved for use in adults as an alternative for treatment of atrial fibrillation. Its use in other arrhythmias and its use in pediatric patients remain to be evaluated.

Calcium Channel–Blocking Agents. Verapamil and, more recently, diltiazem have proved useful for terminating SVT involving the AV node (AV reentry, AV nodal reentry). However, their acute efficacy is no greater than that of adenosine, and both may cause hypotension or cardiovascular collapse in young infants or patients with poor ventricular function.[29] Either drug can be useful as an alternative to adenosine when tachycardias have repeatedly reinitiated following termination with adenosine.

Both agents may help slow the ventricular response over the AV node during atrial flutter or fibrillation. Verapamil is administered as a bolus of 0.15 mg/kg. Diltiazem can be administered as a bolus of 0.15 to 0.35 mg/kg and can be infused continuously at 0.05 to 0.2 mg/kg/hr if ongoing effect is necessary. In addition to vasodilatation and negative inotropic effects, both can accelerate antegrade conduction over accessory pathways in patients with WPW syndrome. Therefore they are contraindicated for patients with WPW syndrome with atrial fibrillation over the accessory pathway, and generally they should not be administered during uncharacterized wide QRS tachycardias. Likewise, oral calcium channel blockers generally should not be used as maintenance therapy for patients with WPW syndrome. If hemodynamic compromise develops, intravenous calcium gluconate should be administered immediately.

Magnesium Sulfate. Magnesium (administered as 25 to 50 mg/kg magnesium sulfate) has proved useful in the treatment of certain ventricular and supraventricular arrhythmias. Its actions appear to be mediated through depression of early and late afterdepolarizations; depressant effects on AV nodal conduction; and, at high doses, indirect inhibition of sodium-potassium adenosine triphosphatase. It has proved most effective in the acute treatment of torsades de pointes and as a temporizing measure in the treatment of arrhythmias associated with digoxin toxicity.[30] Therapeutic efficacy is not restricted to situations where hypomagnesemia is present (although hypomagnesemia may predispose to afterdepolarization-dependent arrhythmias).

Although magnesium has efficacy comparable with that of adenosine in the acute termination of SVT resulting from AV reentry and AV nodal reentry, it has more severe and lasting adverse effects. It has little demonstrable effect in the acute treatment of monomorphic ventricular tachycardias or polymorphic ventricular tachycardias not associated with QT prolongation. Although administration of magnesium for various ventricular arrhythmias has become popular, its usage generally should be restricted to the situations described or for cases of documented severe hypomagnesemia.

Digoxin. Digoxin historically has been used for various supraventricular arrhythmias, including AV reentry, AV nodal reentry, and primary atrial tachycardias. Its therapeutic role has been questioned in numerous situations. Digoxin terminates ORT slowly, is associated with a high recurrence rate in infants, and may increase the risk of rapid antegrade conduction during atrial fibrillation in older patients and possibly infants with preexcitation. Its usage is further confounded by potentially dangerous interactions with other medications likely to be administered concurrently including quinidine, verapamil, amiodarone, flecainide, phenytoin, and warfarin. Even with intravenous loading, the therapeutic effect on the AV node may be unpredictable in onset and often inadequate. Like calcium channel–blocking agents, it should be avoided altogether in the treatment of patients with ventricular preexcitation (WPW syndrome). At toxic dosages, its direct cellular effects may predispose to dangerous tachycardias and bradycardias. Thus given the availability of an increasing number of preferable alternatives, its appropriate usage as an acute antiarrhythmic agent is limited.

Cardioversion and Defibrillation

Cardiovascular collapse or failure of mechanical and pharmacologic interventions for tachycardias may warrant cardioversion. For tachycardias with discrete QRS complexes, synchronization with the QRS should be confirmed (the default mode for most defibrillators is nonsynchronized, and most revert to nonsynchronized shocks after each shock is delivered). Proper synchronization may require changing the ECG lead configuration to achieve an upright QRS complex.

Several factors may determine the success of cardioversion and defibrillation. Energy requirements may vary from 0.25 to 1 J/kg for SVTs to greater than 2 J/kg for ventricular tachycardias. Newer defibrillators with a "biphasic" rather than "monophasic" waveform have reduced defibrillation energy requirements. Electrode (paddle) location is an important variable. If conversion is not achieved with low or moderate energy levels, consideration should be given to changing electrode position before using higher energy levels. Automatic tachycardias are characteristically refractory to cardioversion and may account for treatment failure. Finally, some antiarrhythmic drugs, particularly sodium channel–blocking drugs

(see later discussion), increase defibrillation energy requirements and pacing thresholds, whereas other drugs (QT-prolonging drugs) appear to have a favorable effect.[31]

The availability of automatic external defibrillators injects an additional complexity into the use of external cardioversion and defibrillation. Each ICU should carefully consider how to best configure devices for automatic versus manual defibrillation operation and which electrode system (ECG leads, paddles, and patches) best suits the particular patient population and care team.[32]

Approach to Therapy

Extrasystoles

In general, isolated extrasystoles do not require treatment unless they are sufficiently frequent to impair hemodynamics (e.g., incessant bigeminy or trigeminy with pulse deficit) or they serve as frequent initiating events for tachycardias. In otherwise healthy children and adolescents, extrasystoles may be a benign finding. In other settings, "complex" ventricular extrasystoles may identify patients at increased risk for cardiac arrest. Even in such situations, prophylaxis may not decrease and may actually increase the risk. Effort should instead be directed at identifying possible causes and correcting any predisposing factors, which include ischemia, electrolyte disorders, acidosis, pericarditis, or direct trauma from recent cardiac surgery, blunt or penetrating chest trauma, and intracardiac catheter-induced irritation. Numerous drugs, including digoxin, catecholamines, or drugs associated with the acquired long QT syndrome, may produce extrasystoles. Frequent extrasystoles occasionally are the sole manifestation of myocarditis.

Sustained Tachycardias

Most sustained tachycardias observed in the intensive care setting warrant immediate attention and intervention. Sinus tachycardia may indicate the need for additional sedation and analgesia or may reflect hemodynamic compromise as a consequence of anemia, hypovolemia, or impaired myocardial function. Sinus tachycardia as a consequence of hyperthermia may be poorly tolerated in children already critically ill, especially following cardiac surgery. Sinus tachycardia may reflect an underlying neuroendocrine process such as hyperthyroidism or pheochromocytoma requiring acute medical intervention (β-blocker) while instituting therapy for the underlying disorder.

Nonsinus tachycardias in patients with primary rhythm disturbances (rather than as a complication of another problem) may warrant therapy to prevent life-threatening events, prevent the development of myocardial dysfunction as a consequence of chronic (incessant) tachycardia, or simply alleviate acute tachycardia-related symptoms such as chest pain, lightheadedness, and palpitations. The acuity of the situation dictates the approach to therapy. Tachycardias occurring secondary to other abnormalities (structural heart disease, metabolic derangements, drug toxicity) should always be regarded as high risk for serious hemodynamic deterioration.

Unstable Patients

The approach to patients with tachycardia is determined largely by the degree of hemodynamic compromise (see Table 28-3). Patients who are hemodynamically unstable or in cardiovascular collapse resulting from sustained tachycardia almost always warrant prompt cardioversion or defibrillation. In these patients, measures that otherwise would be appropriate, such as vagal maneuvers, adenosine administration, or attempts to differentiate SVT from ventricular tachycardia, should be deferred. Delaying prompt termination of tachycardia in the unstable patient may further compromise the hemodynamic status and increase the risk of other end-organ damage. Only when tachycardia is known to be incessant or unresponsive to cardioversion (e.g., JET, atrial ectopic tachycardia, chaotic tachycardia, and PJRT) should antiarrhythmic medications (and other supportive measures) replace cardioversion in the unstable patient.

Cardiopulmonary resuscitation should always be instituted in the absence of a pulse or blood pressure, as is typically the case for polymorphic ventricular tachycardia and ventricular fibrillation. Although hemodynamic and ventilatory support should be initiated immediately and maintained following tachycardia termination as necessary, cardioversion (with bag and mask ventilation initially) should take precedence over other interventions.[33] Although congestive heart failure may accompany tachycardias (as in an infant with SVT of several hours' duration), aggressive diuresis should be avoided; patients may benefit initially from fluid resuscitation. Even mild intravascular volume contraction in the face of subsequent tachycardia recurrences further compromises ventricular filling and results in more severe hypotension. Underlying factors contributing to the tachycardia should be sought, including hypoxia, infection (cardiac or systemic), drug toxicities (see later), and electrolyte derangements.

Once tachycardia is terminated, acute therapies may focus on either suppressing recurrences or terminating them when they recur. In critically ill patients, the latter may be preferable, at least initially. Although antiarrhythmic medications eventually may be necessary to suppress recurrences, most have negative inotropic or vasodilating effects, particularly when administered intravenously. Often it is preferable to delay specific therapy after initial termination until ventricular function improves. Most recurrences of SVTs can be safely treated with temporary pacing or adenosine rather than with repeated cardioversions. In the event of frequent recurrences, a transesophageal catheter may be left in place for this purpose, or a transvenous atrial pacing catheter may be warranted in selected patients. Similarly, temporary ventricular pacing may be useful in some circumstances for recurrent ventricular tachycardia. Although adenosine can be administered repeatedly because of its short half-life, the resulting vasodilatation may be poorly tolerated in patients with tachycardia mechanisms unresponsive to adenosine.

Treatment Failure

When seemingly appropriate electrical and pharmacologic interventions fail to terminate tachycardias, three possibilities should be considered: erroneous diagnosis, unrecognized tachycardia reinitiation, or a technical error in the termination technique.

Errors in Diagnosis

As noted previously, automatic atrial tachycardias, JET, and occasionally chaotic atrial tachycardia might be mistaken for tachycardias with reentrant mechanism (ORT, AVNRT, and

primary atrial reentry). Each of these conditions usually is refractory to electrical termination (either pace termination or cardioversion), yet the diagnosis may be subtle if atrial activity is obscured.

Confusion between ventricular tachycardias and SVTs with prolonged QRS probably remains the most frequent diagnostic error. Occasionally the presumption of ventricular tachycardia may lead to ineffective treatments. For example, following cardiac surgery, incessant, monomorphic wide QRS tachycardia that is refractory to cardioversion may actually be JET with postsurgical bundle branch block. Brief atrial pacing at a faster rate may be necessary to confirm the diagnosis.

Certain tachycardias such as torsades de pointes related to long QT syndromes (congenital or drug-induced) or bidirectional ventricular tachycardia resulting from digoxin toxicity must be recognized to provide more appropriate and specific therapies to prevent recurrences following cardioversion.

Unrecognized Reinitiation

Unrecognized reinitiation may occur following medical termination, pace termination, or cardioversion. In some tachycardias (as in PJRT or other incessant forms of SVT), reinitiation is expected, but it also may occur inadvertently as the result of continued pacing beyond the point of termination or may be facilitated by sinus pauses, junctional beats, or ectopic beats following adenosine or cardioversion. Again, measures to decrease the factors favoring reinitiation (e.g., shorter pacing bursts, antibradycardia pacing, and coadministration of an antiarrhythmic drug) should be used rather than further increases in energy or dose of the terminating therapy. With frequent terminations and reinitiations of tachycardia, multiple repeated cardioversions are likely ineffective and may cause myocardial injury.

Improper Technique

Appropriate administration of adenosine is accomplished through an intravenous catheter (peripheral or central) by rapid push followed immediately with ample flush. Because of rapid metabolism by erythrocytes, arterial administration may be ineffective in terminating tachycardia (yet still produce vasodilatation). Errors in cardioversion or pacing technique are generally attributable to insufficient energy or improper electrode (or paddle) placement.[32] For pace termination, the stimulator must be capable of sufficient output for the pacing modality being used (see section on temporary pacing). Intensive care personnel should be familiar with the defibrillation devices available in the ICU, including adjustment of ECG gain and lead selection to allow synchronous cardioversion when appropriate. However, in ventricular fibrillation or polymorphic tachycardia, asynchronous countershock is necessary. Use of excessive energy may damage the myocardium and, when repeated, may lead to preterminal bradycardias, which are refractory to all pacing modalities and progress to complete electromechanical dissociation if hypoxia and acidosis are not corrected.

Specific Arrhythmias

Primary Arrhythmias

Some arrhythmias require unique therapeutic approaches or are seen with sufficient frequency to warrant a brief review (Box 28-1).

Orthodromic Reciprocating Tachycardia in Infancy

Infants with ORT can present with tachycardia in utero, at birth, or within the first weeks to months of life. Intrauterine tachycardia can result in abnormal hemodynamics resulting from limited ventricular filling times accentuated by atrial systole against closed AV valves. Retrograde systemic venous flow during tachycardias may contribute to low cardiac output, congestive heart failure, and nonimmune hydrops fetalis prenatally.[34] Postnatally, tachycardia sustained beyond a few hours may result in congestive heart failure that may progress to shock, acidosis, and complete cardiovascular collapse.[35] In the latter situation, ORT may be terminated during resuscitation efforts such that its causative role remains unrecognized. Thus SVT should be considered in the differential diagnosis of neonatal shock, along with other conditions such as sepsis, aortic coarctation, and congenital adrenal hyperplasia in which sinus tachycardia associated with cardiovascular collapse would be expected.

The transesophageal electrophysiologic (TEP) study is useful in determining tachycardia mechanism[36] and especially for assessing drug efficacy. The negative predictive value of TEP (noninducible with no clinical recurrence) is 89% and

Box 28–1 Rhythm Disturbances

Primary Rhythm Disturbance

Paroxysmal supraventricular tachycardias (AV reentrant tachycardia, AVNRT)
- Congenital AV block
- Congenital long QT syndrome, Brugada syndrome
- Other genetic arrhythmias
- Ventricular tachycardias resulting from Purkinje hamartoma
- Verapamil-sensitive ventricular tachycardias
- Accelerated ventricular rhythm

Secondary Rhythm Disturbances

Early Postoperative Arrhythmias

JET
- Postsurgical AV block
- Early primary atrial tachycardia

Late Postoperative Arrhythmias

Ventricular arrhythmias (postoperative tetralogy of Fallot)
- Sick sinus syndrome

Metabolic Derangements

Electrolyte disturbances
- Endocrine derangements (thyroid)
- CNS injury
- Hypothermia, hyperthermia
- Acute hypoxia (newborns)
- Acute myocardial infarction

Drug Toxicity, Proarrhythmia

Digoxin
- Cocaine
- Tricyclic antidepressants
- Antiarrhythmic drugs
- Quinidine/sotalol
- Flecainide/encainide
- Organophosphates

Infectious

Lyme disease
- Myocarditis, endocarditis

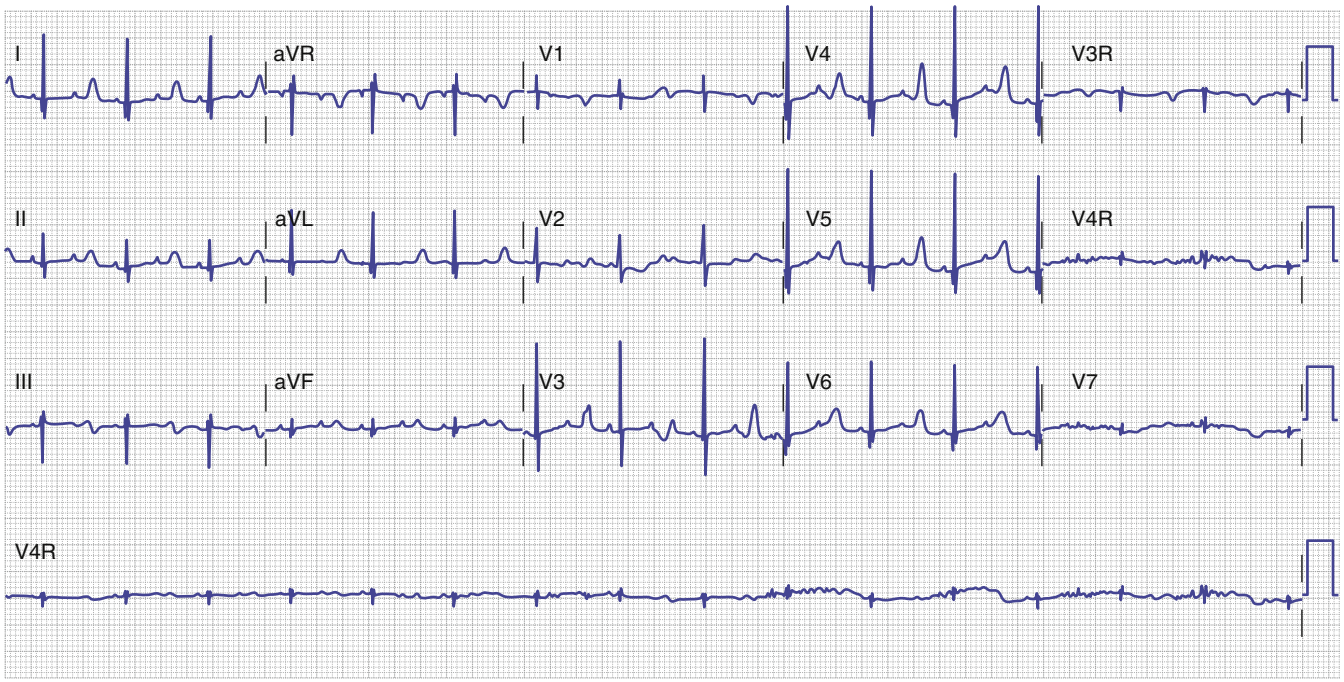

Figure 28–14. Congenital long QT syndrome presenting with 2:1 atrioventricular block. The corrected QT interval is >560 ms, resulting in "functional" block of every other sinus beat in the His-Purkinje system.

increases to 96% when stimulation is also performed after administration of isoproterenol.[37] Long-term drug therapy is not always necessary, because approximately half of infants have no inducible tachycardia at TEP by age 1 year.[38]

Tachycardia-Induced Cardiac Dysfunction

Although most SVTs are paroxysmal or episodic, chronic SVTs pose a unique problem. Many are minimally symptomatic and are recognized only by the inappropriately fast rate. However, with time, varying degrees of congestive heart failure become evident, and ventricular dysfunction may be severe. Even then, the diagnosis may not be immediately evident. As a consequence, chronic tachycardia must be considered in any patient presenting with gradually progressive congestive heart failure. In one series, chronic atrial tachycardia was present in 37% of patients initially diagnosed with "idiopathic" cardiomyopathy and listed for heart transplant.[39]

In patients with structurally normal hearts, the most common incessant SVTs are PJRT and ectopic atrial tachycardia. These conditions may occur throughout infancy, childhood, and adolescence. The rates (often less than 200 beats/min) and normal PR interval during tachycardia may lead to an erroneous diagnosis of sinus tachycardia secondary to the hemodynamic compromise (see Approach to Diagnosis section). An abnormal P-wave axis on 12-lead ECG, determination of the "intrinsic heart rate" following complete autonomic blockade, and Holter monitoring to look for interruptions in the tachycardia with changes in P-wave morphology are helpful.

Electrophysiologic study still may be necessary to establish the diagnosis. In infants, incessant ventricular tachycardias and the rare congenital form of JET also are seen.

In each of these entities, it is important first to recognize the primary role of the tachycardia in producing secondary congestive symptoms and to recognize the futility of acute therapies such as adenosine, pace termination, and cardioversion. Most are catecholamine dependent so that inotropic agents may aggravate the situation and compromise the efficacy of antiarrhythmic regimens, whereas β-blocking agents may be useful despite the presence of heart failure. Once the diagnosis is established, chronic antiarrhythmic therapy is instituted to control or limit the tachycardia. Uncontrolled, severe cardiac symptoms may result, but ventricular dysfunction improves once tachycardia is suppressed medically or treated by catheter ablation.[40] Despite the severity of heart failure, antiarrhythmic medications that depress ventricular function usually are well tolerated.

Congenital Atrioventricular Block

Congenital heart block is usually the result of either maternal connective tissue disease (45%) or structural congenital heart disease (53%), particularly L-transposition of the great arteries or left atrial isomerism. Mothers with connective tissue disease are frequently asymptomatic but may have detectable anti-Ro/SSA antibodies. In a prospective study of mothers with anti-Ro/SSA antibodies, the risk of congenital AV block was 2%.[41] The L-type calcium channel is the likely target of these autoantibodies.[42] Rarely, congenital AV block is the initial manifestation of congenital long QT syndrome (Figure 28-14).[43] Temporary pacing in congenital AV block may be required to treat symptoms or secondary ventricular arrhythmias. In a subset of patients, ventricular dysfunction may develop despite pacing therapy.[44] Guidelines and indications for permanent pacing have been established.[23]

Chaotic Atrial Tachycardia

Chaotic atrial tachycardia is a primary atrial tachycardia characterized by three or more different P-wave morphologies and irregular, rapid atrial rates (Figure 28-15). Although atrial flutter may be associated with it, episodes usually are self-limited, and cardioversion is neither indicated nor effective. Asymptomatic patients with slow or intermittent tachycardia may

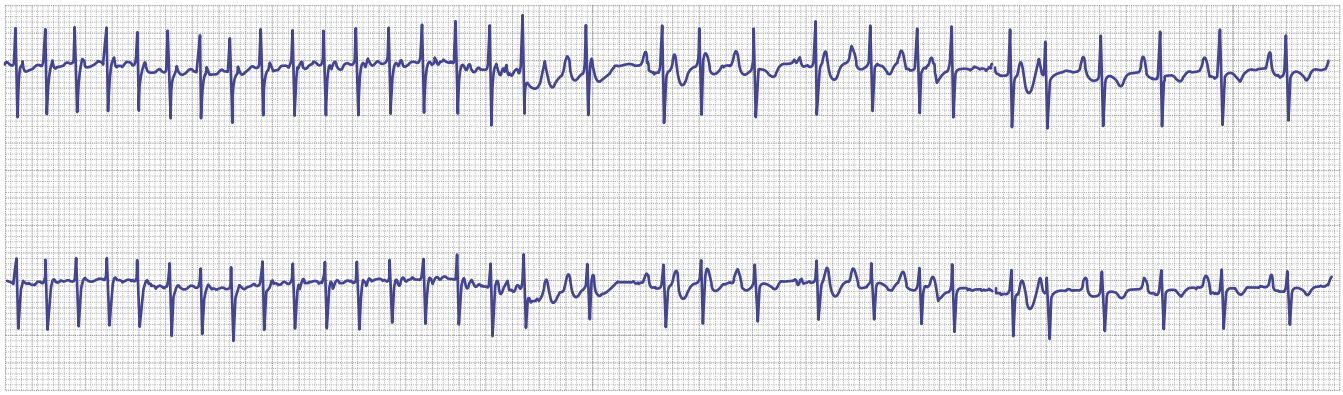

Figure 28–15. Chaotic atrial tachycardia. Note two discrete P-wave morphologies before conversion to sinus rhythm.

require no treatment. Occasionally digoxin is used to limit AV conduction when atrial rates are excessive or to enhance contractility in the setting of tachycardia-induced cardiomyopathy.[45] An association with respiratory syncytial virus has been described in some patients.[11] Various agents have been used in symptomatic cases; amiodarone and propafenone are the most effective.[45,46]

Long QT Syndromes

The long QT syndromes are a diverse group of disorders, both congenital and acquired, in which individuals are at risk for torsades de pointes and sudden death because of abnormalities in ventricular repolarization. In both congenital and acquired forms, the rate-corrected QT intervals usually exceed 0.46 second, and more typically are greater than 0.48 to 0.50 second. Associated anomalies of T-wave morphology, including T-wave alternans, "bifid" T waves, and prominent U waves, are common. It may be difficult to establish the diagnosis of congenital long QT syndrome because QT prolongation may not be severe. In fact, affected individuals sometimes have a normal QTc.[47] Congenital long QT syndrome should be considered in all patients with QT prolongation and a history of syncope, cardiac arrest, or seizures or a family history of unexplained sudden death. The diagnosis should be strongly considered in any child presenting with syncope or sudden death in whom polymorphic ventricular tachycardia or multiform ventricular premature beats are documented. Incidental QT prolongation in an asymptomatic child (with a negative family history) may warrant further scrutiny and possibly serial Holter monitoring. However, unless the QTc is markedly prolonged (longer than 0.48 to 0.50 second), the diagnosis should be withheld until or unless further suggestive features are noted. Finally, all infants presenting with second-degree or third-degree AV block should be evaluated for the possibility of long QT syndrome.[43]

Patients with symptoms or arrhythmias associated with QT prolongation require careful evaluation for secondary causes, which include CNS injury, hypocalcemia, hypokalemia, and drugs that prolong the QT interval. The list of drugs that prolong the QT interval is extensive and includes antiarrhythmic and noncardiac drugs, most of which block I_{Kr}, the rapid component of the delayed rectifier potassium current.[48] Updated lists of these drugs are available at www.qtdrugs.org.

Torsades de pointes is the specific arrhythmia associated with long QT syndromes and is responsible for the symptoms (Figure 28-16). This characteristic arrhythmia is recognized

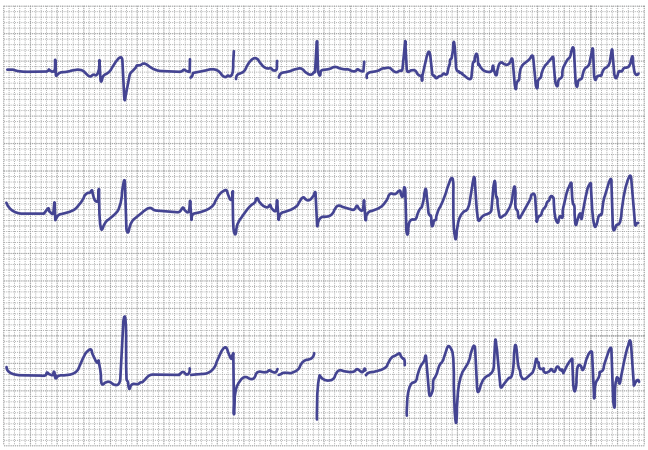

Figure 28–16. Torsades des pointes in a teenage patient with long QT syndrome. This arrhythmia is associated with no pulse and results in syncope. It often terminates spontaneously but otherwise rapidly degenerates to ventricular fibrillation.

by progressive undulation in the QRS axis, resulting in a "twisting" appearance, and usually is associated with a specific initiation with a VPB following a pause (often following a previous VPB). Many episodes are not sustained, and even prolonged episodes may terminate spontaneously. Torsades de pointes that degenerates to ventricular fibrillation requires defibrillation.

Because the stress caused by defibrillation may trigger recurrent arrhythmias, defibrillation should be performed in an unconscious or sedated patient. Treatment of immediate recurrence of torsades de pointes is challenging and includes magnesium sulfate, increasing the heart rate with temporary pacing or isoproterenol, and sedation.[49] For most acquired long QT syndromes (and some congenital forms), increasing the heart rate using isoproterenol or by pacing shortens the QT interval, but isoproterenol may exacerbate some forms of the congenital long QT syndrome.[50] Therefore isoproterenol should be used only when there is underlying bradycardia and cardiac pacing cannot be started immediately. Correcting hypokalemia, hypomagnesemia, or hypocalcemia and removing potentially causative agents may be important in the ICU setting.

The molecular/genetic basis of the congenital long QT syndrome was discovered in the 1990s. To date, mutations have been discovered in twelve genes.[51] Most of these genes encode channels or proteins that regulate potassium and sodium currents, and rarely calcium channel currents. The type and location of

the genetic mutation may determine to some extent the expression of the clinical syndrome. However, as mentioned earlier, this disorder has variable expression of severity (i.e., variable penetrance). This variability in expression in related individuals with the same mutation suggests the influence of environmental factors and/or the presence of other modifier genes.

Genetic Arrhythmias

Other genetic causes of arrhythmias deserve brief mention. Brugada syndrome, the syndrome of ST-segment elevation in the right precordial leads and a high incidence of sudden cardiac death in the absence of cardiac structural abnormalities, was first recognized in 1992.[52] Since then, there has been tremendous advancement in the understanding of the clinical, genetic, cellular, and molecular aspects of this disease.[53] Although relatively rare (incidence 5 per 10,000), it accounts for 4% to 12% of all sudden deaths (20% in patients with structurally normal hearts). Implantation of a defibrillator is the only established effective treatment and is indicated for symptomatic patients.[54]

Catecholaminergic polymorphic ventricular tachycardia is an uncommon arrhythmia occurring in children and adolescents with structurally normal hearts. The characteristic arrhythmia of ventricular tachycardia with beat-to-beat alternation of the QRS axis occurs with physical or emotional stress and can be asymptomatic. Mutations in the cardiac ryanodine receptor gene (*RyR2*) or cardiac calsequestrin (*CASQ2*) underlie catecholaminergic bidirectional ventricular tachycardia, and patients with the disease are at risk for sudden cardiac death and ventricular fibrillation.[55,56] β-blockers can suppress bidirectional ventricular tachycardia, but data suggest they provide incomplete protection from arrhythmias.[57] Flecainide may target the underlying mechanism and provide even greater protection from exercise-induced arrhythmias.[58]

Genetic cardiomyopathies that are associated with sudden death include arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy. Arrhythmogenic right ventricular dysplasia is a disease of autosomal dominant inheritance characterized by fatty replacement of right ventricular myocardium and risk for ventricular tachycardia and sudden death.[59] Linkage analysis has yielded genetic heterogeneity, and currently approximately 50% of symptomatic individuals harbor a mutation in one of the five major components of the cardiac desmosome.[60] Hypertrophic cardiomyopathy is an inherited cardiac muscle disorder disease that affects sarcomeric proteins, resulting in small vessel disease, myocyte and myofibrillar disorganization, and fibrosis with or without myocardial hypertrophy.[61] These features may result in significant cardiac symptoms and are a potential substrate for arrhythmias. Risk stratification for sudden death is an important component in the management of these patients.

Ventricular Tachycardia in Ostensibly Healthy Patients

Accelerated ventricular rhythm is observed occasionally in neonates in the first few days of life at rates only slightly faster than the appropriate sinus rates. The rhythm competes with the sinus mechanism, and alternation between sinus and ventricular rhythm with fusion beats is common. The rhythm is self-limited, does not usually result in hemodynamic compromise, and carries a good prognosis. No specific therapy is necessary unless rates are excessive.[62] A similar rhythm is seen in older children and usually has a similarly benign course.[63] Two other characteristic ventricular tachycardias may be seen in otherwise healthy children and adolescents. One arises from the right ventricular outflow tract, resulting in a left bundle branch block pattern with inferior QRS axis. This pattern may be incessant, in which case the term "repetitive monomorphic ventricular tachycardia" has been used. The other arises from the posterior fascicle of the left-sided conduction system, producing a right bundle branch block pattern with leftward QRS axis (Figure 28-17). This tachycardia has been called fascicular, Belhassen, or verapamil-sensitive ventricular tachycardia. Interestingly, the response to verapamil may result in misclassification as "SVT with aberrant conduction."

Although ventricular tachycardia can be seen without any apparent underlying heart disease, a rigorous search for occult heart disease often is fruitful. Cardiac tumors (rhabdomyomas, fibromas, hamartomas) and myocarditis can be associated with ventricular arrhythmias.[64]

Secondary Rhythm Disturbances

Certain arrhythmias characteristically follow operative treatment of CHD. Among those observed in the early postoperative period are complete heart block, JET, and primary atrial tachycardias. Late postoperative arrhythmias include ventricular arrhythmias following tetralogy of Fallot repair and atrial arrhythmias following the Mustard/Senning and Fontan procedures.

Postoperative Arrhythmias

Postsurgical Atrioventricular Block. Inadvertent damage to the AV conduction system may occur with cardiac surgery, especially after closure of ventricular septal defects (particularly associated with l-loop ventricles), during resection of septal tissue, or after insertion of prosthetic valves in the tricuspid, aortic, or mitral position. Bradycardia from AV block can be initially managed using isoproterenol to accelerate the ventricular rate. When anticipated or recognized in the operating room, temporary pacing wires usually are left in place. Although temporary pacing frequently is necessary for rate support, permanent pacemaker implantation usually should be delayed 7 to 14 days to allow for potential recovery of AV conduction. Most patients who recover AV conduction do so within 9 days of surgery.[65]

Junctional Ectopic Tachycardia. JET immediately following cardiac surgery may be mistaken for third-degree AV block, but on rewarming ventricular rates approach or exceed 200 bpm. Atrial wires or esophageal electrography confirms the key diagnostic features: AV dissociation with normal QRS and the regular ventricular rate faster than the atrial rate. Appropriately timed atrial systoles conducted to the ventricle result in "advancement" of the tachycardia cycle (without a change in QRS morphology or subsequent pause). If the QRS is normal but the RR interval does not shorten with appropriately timed atrial systoles, JET with retrograde (VA) conduction or third-degree AV block with JET as the escape rhythm should be suspected.

Infants with JET usually are severely ill, and β-adrenergic agonists, fever, and endogenous catecholamines accelerate the tachycardia. Initial treatment of postoperative JET includes sedation and analgesia, withdrawal of adrenergic stimulants (to the extent possible), and cooling blankets or cool soaks

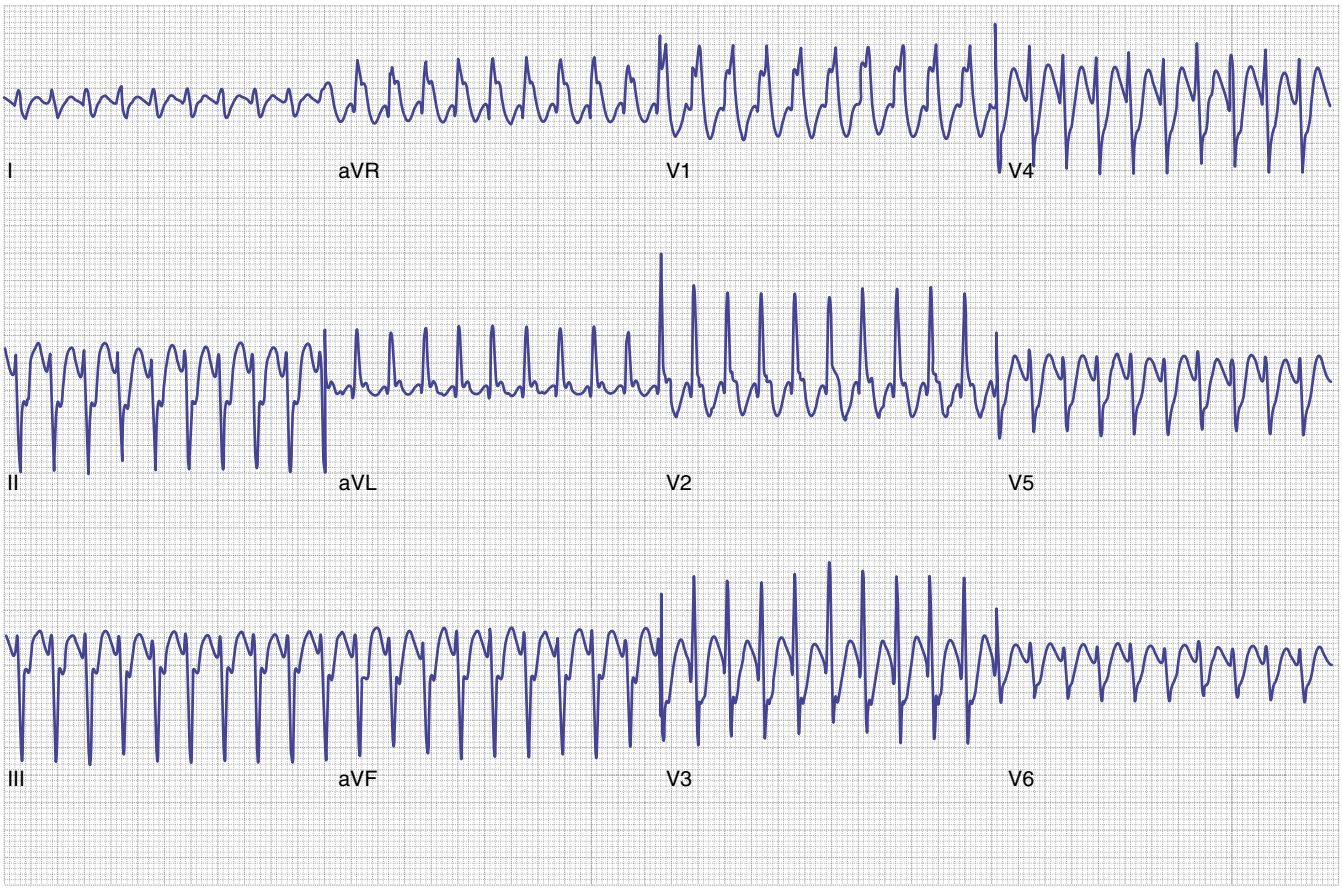

Figure 28–17. Idiopathic ventricular tachycardia in an otherwise healthy 12-year-old. Note right bundle branch block pattern with superior axis, typical of origin within the left posterior fascicle region of the left ventricular septum (sometimes called *Belhassen tachycardia).*

using an electric fan to foster evaporative cooling. The tachycardia may be suppressed by temporary overdrive (atrial) pacing, by pacing at a rate sufficient to produce 2:1 AV block, or by AVT mode pacing to provide AV synchrony.[66] Intravenous amiodarone has been used with perhaps the greatest efficacy.[67] Although emergency radiofrequency ablation has been performed in rare instances, aggressive temporizing measures, including extracorporeal membrane oxygenation, appear warranted given the transient nature of this arrhythmia.

Late Postoperative Arrhythmias

Atrial tachycardia and bradycardia are common late sequelae following the Senning and Mustard operations for D-transposition of the great arteries, atrial septal defect closure, and the Fontan procedure for tricuspid atresia and single ventricle.[68] Patients with these arrhythmias appear to be at increased risk for sudden death, although whether death is the result of atrial tachycardia itself, associated bradycardia, degeneration to ventricular tachycardia, or even nondysrhythmic events remains unclear.

Likewise, in patients with repaired or palliated CHD, ventricular arrhythmias may develop that are associated with risk for sudden death. There seems to be little justification for empirical drug therapy to suppress asymptomatic ventricular arrhythmias in these patients. Earlier repair is believed to decrease the incidence of serious problems. Still, the relative contributions of postoperative hemodynamic abnormalities, the natural history of the unrepaired lesions, and surgical technique to the development of late arrhythmias remain uncertain. Similarly, the roles of pacemaker/defibrillator therapy, prospective electrophysiologic study, and antiarrhythmic drug testing are not well established. Because both bradycardias and tachycardias develop in many patients, the correlation of symptoms with electrophysiologic abnormality is important in guiding therapy.

Metabolic Derangements

Electrolyte Disturbances. Hyperkalemia causes characteristically tall ("peaked" or "tented") t waves with a narrow base with progressive changes at higher concentrations, including decreased P-wave amplitude, QRS prolongation, SA nodal and AV nodal block, and ultimately ventricular fibrillation. Mild to moderate hypokalemia may cause prominent U waves, diminished T-wave amplitude, T-wave inversion, and fusion of the T wave and U wave, along with increased spontaneous ventricular ectopy and inducible ventricular arrhythmias. Arrhythmias caused by hypokalemia are potentiated by catecholamines, and hypokalemia itself potentiates the toxic effects of digoxin and the proarrhythmic effects of drugs associated with drug-induced long QT syndrome.[69] Severe hypokalemia is associated with ventricular fibrillation.

Hypercalcemia produces T-wave inversion and shortens the QT interval. Hypocalcemia prolongs the time to the peak of the T wave (Q-aT) but not the QT interval itself. Isolated calcium abnormalities are uncommon, and arrhythmias caused

by such abnormalities are rare, although hypercalcemia may aggravate digitalis toxicity.[2]

Endocrine Disorders (Thyroid). Hyperthyroidism exerts both sympathetic-like and direct cardiovascular actions that produce sinus tachycardia and atrial fibrillation, but ventricular arrhythmias are uncommon. These arrhythmias respond to β-blockers and resolve when the euthyroid state is restored. Combination treatment with digoxin potentiates AV nodal block while minimizing negative inotropic effects. Hypothyroidism causes sinus bradycardia and AV conduction disturbances; QT interval prolongation is common but rarely associated with torsades de pointes.[70]

Central Nervous System Injury. The most common ECG change associated with CNS trauma and increased intracranial pressure is sinus bradycardia, usually with associated hypertension. These bradycardias appear to be vagally mediated and usually respond to atropine. However, potentially serious arrhythmias may occur within 24 hours following blunt trauma to the head, subdural hematoma, and subarachnoid hemorrhage. QT-interval prolongation is common and, in combination with bradycardia and hypokalemia, may provoke torsades de pointes.

Hypothermia and Hyperthermia. Mild hypothermia can cause a range of reversible ECG changes, including sinus bradycardia; prolongation of the PR, QRS, and QT intervals; and a characteristic secondary deflection on the terminal portion of the QRS (Osborn wave).[71] Severe hypothermia may cause more significant bradycardias, including AV block and asystole or ventricular tachycardias and ventricular fibrillation. Therapeutic hypothermia is associated with QT prolongation, and torsades de pointes has been reported.[72] In contrast, hyperthermia causes sinus tachycardia and may enhance other tachycardias such as PSVT, ectopic atrial arrhythmias, and especially JET in susceptible patients.

Acute Myocardial Infarction. Acute myocardial infarction is uncommon in young patients but may occur in cases of anomalous origin of the left coronary artery, when there is perinatal stress, following Kawasaki disease, with blunt chest wall trauma, and following cardiac transplantation and the arterial switch procedure. It can occur after air embolism in cyanotic CHD or after open heart operations. The diagnosis may be overlooked in infants and children because of the inconsistency of symptoms and relatively poor (60%) clinical recognition by electrocardiography.[73] Nevertheless, acute infarction may result in various rhythm disturbances, including sinus bradycardia (as a result of the Bezold-Jarisch reflex), AV conduction disturbances, intraventricular block, and asystole.

Arrhythmias Resulting from Drug Toxicity

Digoxin. Digoxin toxicity may cause various arrhythmias and should be suspected in any patient in whom a new arrhythmia develops during digoxin therapy. Likewise, digoxin ingestion should be considered in patients with acute arrhythmias, particularly those associated with CNS and gastrointestinal symptoms (although noncardiac adverse effects may be absent with acute ingestion). Accelerated junctional rhythm may be the first arrhythmia seen. Progressive AV block is common. Sinus bradycardia resulting from either SA node exit block or sinus arrest may occur, as can atrial fibrillation (but usually not atrial flutter). Ectopic atrial arrhythmias may occur. Nearly any ventricular arrhythmia may occur, including multiform ventricular extrasystoles, bigeminy, ventricular tachycardia (particularly "bidirectional" VT, otherwise only seen in rare genetic arrhythmia syndromes; Figure 28-18), and ventricular fibrillation.[74]

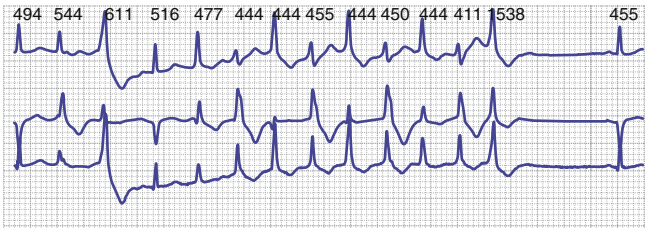

Figure 28–18. Bidirectional ventricular tachycardia. This unusual arrhythmia is only seen in patients with digoxin toxicity and two rare genetic arrhythmia syndromes: Andersen-Tawil syndrome (periodic paralysis and ventricular arrhythmias) and catecholaminergic polymorphic ventricular tachycardia. The patient is asymptomatic during this arrhythmia, but patients appear to be at risk for ventricular fibrillation.

In general, digoxin concentrations less than 2 ng/mL are considered nontoxic. Neonates usually tolerate levels as high as 3.5 ng/mL. Nevertheless, neonates and other intensive care patients may be more susceptible to digoxin toxicity because of renal dysfunction, electrolyte imbalances, and hypoxia. Hypokalemia, excessive calcium infusions, and rapid sinus rates exacerbate digitalis-related arrhythmias.

Purified digoxin-specific Fab antibody fragment, which binds the drug and is eliminated in the urine, is used to treat digoxin toxicity. Prophylactic treatment with this preparation should be gauged according to the quantity ingested, the time since ingestion, and the serum digoxin level. Magnesium sulfate is a useful temporizing treatment while specific antibody treatment is being implemented. Cardioversion should be reserved for life-threatening tachycardias or those unresponsive to these therapies.

Cocaine. Life-threatening ventricular arrhythmias, cardiac arrest, and myocardial infarction can occur in healthy individuals with normal coronary arteries following cocaine ingestion and in prenatally exposed neonates.[75,76] Cocaine produces myocardial ischemia and infarction by inducing severe local coronary vasoconstriction, increasing myocardial-metabolic demand through its potent chronotropic effects, and increasing afterload. In infarct models, cocaine directly potentiates arrhythmias induced by catecholamines.[77] These factors favor the use of β-adrenergic antagonists as first-line treatment for cocaine-related arrhythmias. Additionally, cocaine blocks fast inward sodium channels, similar to class I antiarrhythmic agents.[78] QT prolongation and torsades de pointes have been observed.

Tricyclic Antidepressants and Phenothiazine. Phenothiazines and tricyclic antidepressants produce electrophysiologic (and potentially antiarrhythmic) effects similar to quinidine and procainamide. They slow conduction velocity in atrial and ventricular tissue, prolong repolarization, and exert anticholinergic effects accounting for the observed

ECG changes of conduction disturbances, prolonged QT intervals and QRS duration, and various tachycardias and bradycardias.[79] Sinus tachycardia, atrial and ventricular tachycardias, and AV conduction disturbances distal to the AV node occur occasionally during normal therapeutic administration and may reflect individual susceptibility to QT-prolonging agents. "Unmasking" of the Brugada syndrome has been reported after administration of tricyclic antidepressants.[80]

Arrhythmias commonly follow intentional overdose, resulting in hypotension (due to α-blocking effects), severe anticholinergic effects (neuromuscular and mucosal), seizures, and coma. Quinidine and procainamide are contraindicated for tachycardias because of these agents. In patients manifesting early cardiotoxicity, arrhythmias may develop 3 to 7 days following ingestion, apparently because of release of tissue stores. Therefore ECG monitoring should be continued for at least 24 to 48 hours after apparent ECG and rhythm normalization and longer if severe arrhythmias are observed.

Infections

Myocarditis may cause atrial and ventricular tachycardias or acquired heart block. Lyme disease may produce high-grade acute AV block. Although AV conduction usually normalizes with appropriate antibiotic therapy, temporary pacing may be required.[81] Antibiotic treatment should be instituted based on the history and ECG findings alone while awaiting confirmatory serology. Bacterial endocarditis can cause AV conduction disturbances, particularly when the aortic valve is involved. Unstable or persisting conduction abnormalities (longer than 7 days) carry a high risk of mortality (43% to 80%) and are indications for early valve replacement.[82]

Myocarditis may be responsible for some cases of ventricular tachycardia in otherwise healthy individuals and may range from chronic ventricular ectopy or tachycardia to fulminant and refractory arrhythmias leading to electromechanical dissociation. Chaotic atrial tachycardia may occur in the setting of infection with respiratory syncytial virus, although the cause of this association is unclear. Finally, paroxysmal tachycardias of any etiology may be exacerbated by acute infections that cause fever, dehydration, and increased sympathetic tone. Short-term modifications of chronic therapy may be necessary, particularly when oral administration becomes impractical.

References are available online at http://www.expertconsult.com.

II

Chapter 29

Shock States

Lincoln S. Smith and Lynn J. Hernan

PEARLS

- Shock is recognized by the features of tachycardia, tachypnea, and abnormalities of perfusion, as evidenced by skin perfusion, quality of pulses, mental status, and dysfunction of other organ systems.
- Pediatric patients with shock most often present with myocardial dysfunction ("cold" shock), although older children and adolescents may present with the adult picture of vascular dysfunction ("warm" shock).
- Neonates in shock must be treated for both septic shock and cardiogenic shock resulting from ductal-dependent congenital heart disease until an echocardiogram can confirm the cardiac anatomy. These conditions cannot be ruled out by physical examination. Therefore, all neonates with shock should be given prostaglandin infusion as part of their resuscitation. Pulmonary hypertension, hypocalcemia, and hypoglycemia frequently complicate shock in neonates.
- Pediatric patients in shock generally have absolute or relative hypovolemia, and the first line of resuscitation should be a fluid bolus of 20 mL/kg. Administration of more fluid should be based on rapid assessment of hemodynamic status.
- Early endotracheal intubations allow advantageous redistribution of the compromised cardiac output, and afterload reduces the left ventricle.
- Timely recognition and early aggressive goal-directed therapy reduces mortality in septic shock.

The clinical syndrome of shock is one of the most dramatic, dynamic, life-threatening problems faced by the physician in the critical care setting. Although untreated shock is universally lethal, mortality may be considerably reduced with proper recognition, diagnosis, monitoring, and treatment.

Definition and Physiology

Shock is an acute, complex state of circulatory dysfunction that results in failure to deliver sufficient amounts of oxygen and other nutrients to meet tissue metabolic demands. If prolonged, it leads to multiple organ failure and death. Therefore shock states can be viewed as a state of acute cellular oxygen deficiency. Shock can be caused by any serious disease or injury, but whatever the causative factors, it is always a problem of inadequate cellular sustenance. It is the final common pathway to death.

Delivery of oxygen is a direct function of cardiac output (CO) and arterial oxygen content (CaO_2):

Delivery of oxygen:

$$DO_2 = CO \times CaO_2$$

$$CO = \text{Heart rate (HR)} \times \text{Stroke volume (SV)}$$

$$CaO_2 = (Hgb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$$

Stroke volume is a function of preload, afterload, contractility, and diastolic relaxation. Therefore optimizing heart rate, contractility and diastolic relaxation, and preload and afterload improves cardiac output. Oxygen-carrying capacity can be increased by raising hemoglobin and optimizing its saturation with oxygen. Oxygen delivery can be improved by manipulation of all these factors.

Calculation of oxygen delivery provides a measure of global oxygen delivery and may not reflect regional hypoperfusion and localized ischemia. Inadequate oxygen delivery can result from either limitation or maldistribution of blood flow. Reduced oxygen content (anemia, poor arterial oxygen saturation) necessitates higher cardiac output to maintain oxygen delivery. In certain situations (fever, sepsis, trauma), metabolic demands may exceed normal oxygen delivery. Impairment of the extraction or utilization of oxygen by cells and mitochondria creates a functional arteriovenous shunt and may be the harbinger of multiorgan dysfunction syndrome.[1-3]

When oxygen delivery fails to meet cellular oxygen demands, various compensatory mechanisms are activated. Therefore shock is a dynamic process. The exact cardiorespiratory pattern detected clinically depends on the complex interaction of patient, illness, time elapsed, and treatment provided.

Because of its progressive nature, shock can be divided into phases: compensated, uncompensated, and irreversible. In compensated shock, vital organ function is maintained primarily by intrinsic regulatory mechanisms. Previously healthy children can compensate and maintain normal blood pressure during hypoperfusion states. Therefore identification of the early compensated stage of shock is crucial. Diagnosing a patient as having early compensated shock, rather than mere dehydration, may be the difference between a patient who is appropriately resuscitated and one for whom resuscitative efforts are delayed. As shock progresses, the cardiovascular system's ability to compensate is exceeded, and microvascular

perfusion becomes marginal. Cellular function deteriorates, affecting all organ systems. Terminal or irreversible shock implies damage to key organs of such magnitude that death occurs even if therapy restores cardiovascular function to adequate levels.

The ability to respond to shock states varies with age and depends on developmental aspects of the autonomic nervous, circulatory, respiratory, renal, and immunologic systems, as well as the presence of other medical conditions.

Recognition and Assessment of the Shock State

The early diagnosis of shock requires a high index of suspicion and knowledge of conditions that predispose children to shock. Interviews of the parents, physicians, nurses, and emergency medical services personnel caring for the child provide valuable information. A rapid and focused physical examination of a patient in shock is essential (Box 29-1).

Early signs of compensated shock may be subtle and should not be missed. They include tachycardia, tachypnea, mildly prolonged capillary refill, orthostatic hypotension, and mild alteration of mental status (e.g., lethargy, irritability). In patients with sepsis, other signs of early compensated shock may be plethora, warm extremities, bounding pulses, and a widened pulse pressure.

The contribution of laboratory tests to the initial evaluation of patients in shock is limited. Blood gases and serum lactate levels may quantify the degree of acidosis and are widely used as markers for the effectiveness of treatment. However, an increased understanding of microcirculatory aberrations and cellular hypoxia has raised awareness of the limitations of tests on pooled venous samples. This has stimulated a search for a minimally invasive means of sampling regional circulations.[4] Gastric tonometry,[5,6] near-infrared spectroscopy,[7,8] rectal tonometry,[9] and sublingual capnography[10,11] are methods currently being investigated to evaluate regional circulation. Their clinical utility is unproven at this time.

Repeated evaluation and monitoring of the patient in shock by a competent observer, with appropriate intervention, remains the most effective and sensitive physiologic monitor available.

Treatment of Shock

General Principles

Shock is a clinical syndrome of inadequate tissue oxygenation. In addition to treatment of the primary underlying process, therapeutic efforts involve optimizing and balancing oxygen delivery and oxygen consumption. Efforts to reduce oxygen requirements at a time when oxygen delivery is compromised are important. Intubation, mechanical ventilation, sedation, paralysis, and control of fever are ways to reduce oxygen consumption. Even routine nursing procedures can increase oxygen consumption by up to 20% to 30% in healthy adults.[12]

Intubation and Mechanical Ventilation

Viires et al.[13] studied spontaneously breathing dogs during cardiogenic shock. During a low cardiac output state, blood flow to the diaphragm was substantially increased, while blood flow to the liver, brain, and quadriceps was significantly decreased. Intubation, mechanical ventilation, and paralysis resulted in redistribution of blood flow from the diaphragm to the liver, brain, and quadriceps. A similar study of endotoxic shock in dogs demonstrated that respiratory muscle blood flow rose significantly in spontaneously breathing dogs.[14] During shock states, there is often increased work of breathing and respiratory distress related to capillary leak and acidosis.

Intubation and mechanical ventilation can allow redistribution of cardiac output from the muscles of respiration to vital organs during shock (when cardiac output and oxygen delivery are compromised). Positive pressure ventilation also has the effect of reducing afterload to the left ventricle (potentially improving stroke volume) (see Chapter 26).

Fluid Resuscitation

Regardless of the underlying insult, all patients in shock have an absolute or relative hypovolemia. A primary goal of initial therapy must be restoration of effective circulating volume. Early fluid resuscitation is the cornerstone of immediate therapy.[15,16] In a study of pediatric septic shock patients, Carcillo et al.[15] correlated the volume of fluid given in the first hour of presentation and reversal of hypovolemia to outcome. Patients who received the largest volume of fluid in the first hour of resuscitation had the lowest mortality. Persistent hypovolemia was associated with increased mortality. Fluid resuscitation must be guided by repeated evaluation of the patient's hemodynamic status.

Vasoactive Infusions

Vasoactive infusions are commonly used when patients have been adequately fluid-resuscitated but hemodynamics remain deranged. Infusions of catecholamines (dopamine, dobutamine, epinephrine, norepinephrine), phosphodiesterase inhibitors (inamrinone, milrinone), and vasopressin are most commonly used. The choice of vasoactive infusion is dependent on the physiologic derangement requiring treatment (Table 29-1). Catecholamines work through stimulation of α_1, α_2, β_1, β_2, and dopaminergic receptors to increase intracellular cyclic guanosine monophosphate (cGMP) and cause the appropriate response (Table 29-2). Phosphodiesterase inhibitors increase cGMP by preventing its degradation

Box 29–1 Physical Assessment in Shock

1. State of consciousness: restless, anxious, agitated, comatose
2. Skin: temperature, perfusion, moistness, color, turgor, rash
3. Mucous membranes: color, moistness
4. Nail beds: color, capillary refill
5. Central capillary refill
6. Peripheral veins: collapsed or distended
7. Pulse: rate, rhythm, quality
8. Blood pressure: orthostatic changes, pulse pressure
9. Respiration: rate, depth, effort, crackles, adequacy of aeration
10. Urine: concentration, hourly output

within the cell (see Chapter 25). Vasopressin causes vasoconstriction by direct stimulation of vascular smooth muscle cell V1 receptors.[17-22] Vasopressin also potentiates systemic adrenergic effects.[12,24-26] Vasopressin[20-22] and terlipressin[27-31] (a synthetic analog of vasopressin with a similar pharmacodynamic profile, but with a significantly longer half-life) have also shown some utility in the treatment of catecholamine-resistant shock.

Other Therapies

The finding of hypocalcemia in infants who present in shock should raise the suspicion of left ventricular dysfunction. Hypocalcemia causes left ventricular dysfunction in neonates and is reversible with calcium therapy.[32] Of note, 30% of neonates with DiGeorge syndrome are hypocalcemic.

Neonates, who have low glycogen stores and increased metabolic requirements during shock, may quickly develop hypoglycemia.[32] Shock in neonates is frequently complicated by pulmonary hypertension.

Table 29–1 Therapies for Hemodynamic Patterns in Shock States

	Blood Pressure or Systemic Vascular Resistance		
Hemodynamic Pattern	**Normal**	**Decreased**	**Elevated**
Septic shock			
Stroke index ↑↔	None	α_1, V_1	None
Stroke index ↓	β_1	α_1 and β_1	$\beta_1 + \beta_2$, or PDE
Cardiogenic shock	β_1	α_1 and β_1	$\beta_1 + \beta_2$, or PDE
Myocardial dysfunction (complicating critical illness)*	β_1 and/or β_2	α_1 and β_1	$\beta_1 + \beta_2$, or PDE
Congestive heart failure	β_1 and/or β_2	β_1	$\beta_1 + \beta_2$, or PDE
Bradycardia	None	β_1	None

*For example, acute respiratory distress syndrome or anthracycline therapy.
PDE, Phosphodiesterase inhibitor.

Adrenal insufficiency should be suspected in patients with refractory shock resulting from trauma (head or abdominal), history of steroid use within past 6 months, sepsis, or treatment with etomidate. Direct damage to the hypothalamus, anterior pituitary, or adrenals may result in cortisol deficiency. In septic shock, adrenal hemorrhage has been the paradigm of adrenal insufficiency, but increasing evidence indicates transient relative or functional adrenal insufficiency in septic shock (see section on septic shock).

Extracorporeal membrane oxygenation (ECMO) has been used to support patients of all ages with shock. The Extracorporeal Life Support Organization (ELSO) maintains a database of patients treated with ECMO from member institutions around the world. The registry was searched for data on patients treated with ECMO (from 1985 through January 2010) with any mention of the diagnosis of shock (Lynn Hernan, personal communication, 2010). The registry revealed 1512 pediatric patients (age ≤21 years old) who were treated with ECMO for any diagnosis which included the descriptor shock. The overall mortality was 60%. Sixty-five percent of patients were 1 year of age or younger. Forty-four percent of pediatric patients treated with ECMO for shock were neonates. In patients aged 21 years or younger treated with ECMO, the etiology of shock was cardiogenic in 46%, septic in 22%, hypovolemic in 11%, traumatic or surgical in 1%, and other or unspecified in 20%. The mortality across the groups ranged from 56% to 64%.

Multisystem Effects of Shock

Management of the multisystem deterioration that occurs in shock states is as important as treating the underlying condition. Respiratory, gastrointestinal, central nervous system, renal, and hematologic abnormalities in shock must be identified and treated. Multiple organ dysfunction syndrome (MODS) is the derangement of two or more organs after an insult. The severity of MODS has been associated with increased mortality in PICU patients.[33-35]

Respiratory

Respiratory failure frequently accompanies shock states. It may result from failure of the ventilator pump (i.e., respiratory muscle fatigue) and/or deterioration of lung function (i.e., acute respiratory distress syndrome). For these reasons and

Table 27–2 Vasoactive Medications

	α_1	β_1	β_2	D_1	V_1
Dopamine*	Vasoconstriction	Inotropy, chronotropy	Vasodilation	Renal vasodilation	
Norepinephrine	Vasoconstriction	Inotropy			
Epinephrine†	Vasoconstriction	Inotropy, chronotropy	Vasodilation		
Dobutamine		Inotropy	Vasodilation		
Vasopressin	Potentiates	Potentiates			Vasoconstriction
Inamrinone, milrinone		Non–receptor-mediated inotropy, lusitropy, and vasodilation			

*Dose related: at low infusion rates, D_1 receptor effects predominate; at intermediate rates, β_1 and β_2 receptor effects predominate; at high rates, α_1 effects predominate on peripheral vasculature.
†Dose related: at low infusion rates, β receptor effects predominate; at high rates, α effects predominate on peripheral vasculature.

for maximizing oxygen delivery, increased inspired oxygen is essential in all children with shock. Early tracheal intubation protects the airway, provides relief from respiratory muscle fatigue, facilitates provision of positive airway pressure, redistributes blood flow from the muscles of respiration to core organs, afterload-reduces the left ventricle, and reduces oxygen demands of respiratory muscles. Patients should be ventilated with a lung protective strategy (see Chapter 51).

Renal

Renal failure may develop in association with any of the shock syndromes. Shock-related renal failure is a continuum of acute prerenal azotemia through classic acute tubular necrosis to cortical necrosis. Renal support is essential to prevent prolonged renal shutdown in shock states. Volume augmentation to correct absolute or relative hypovolemia is essential. Although low-dose dopamine (3 to 5 μg/kg/min) improves renal blood flow,[36,37] it also impairs renal oxygen kinetics, inhibits protective feedback loops with the kidney, and may worsen tubular injury.[38,39] It has failed to show benefit in preventing or altering the course of acute renal failure in adults.[38,39] Dopamine may also inhibit secretion of prolactin, growth hormone, and thyrotropin in critically ill children.[40]

Acute anuric renal failure may require treatment with peritoneal dialysis, ultrafiltration, continuous hemofiltration or hemodiafiltration, or hemodialysis (see Chapter 72). High-output renal failure may occur in shock states without previous oliguria. The polyuria associated with this condition may falsely suggest adequate renal perfusion and adequate vascular volume at a time when the patient's intravascular volume is, in fact, depleted. Restoration of renal perfusion pressure remains the standard of care.

Populations for whom early renal replacement therapies result in decreased mortality have not been consistently identified.[41,42] There is evidence that fluid overload is related to mortality in critically ill children with renal dysfunction.[43] If renal dysfunction exists, all medications and therapies should be adjusted for creatinine clearance.

Coagulation

Coagulation abnormalities (e.g., disseminated intravascular coagulation) probably occur to some extent in all forms of shock. Monitoring of prothrombin time, partial thromboplastin time, and platelet count and observation for abnormal bleeding are essential. Replacement therapies specifically designed to replace absent clotting factors seem to be the most advantageous treatments. Use of vitamin K, fresh-frozen plasma, cryoprecipitate, and platelet transfusions should correct most coagulopathies. If general replacement therapy is ineffective, and the patient is at risk for complications, specific factor therapy may be indicated.

Coagulopathy is ubiquitous in all patients with severe sepsis.[44] Recombinant activated protein C has been shown to decrease mortality in adults with severe sepsis (see section on septic shock).

Use of plasmapheresis, plasma exchange, and plasma filtration as therapy for treating sepsis-induced multiple organ system failure and improving outcome remains experimental.[42,45-49]

Hepatic

The degree of hepatic dysfunction may determine a patient's ultimate outcome in severe shock states. Maintaining adequate circulation helps maintain liver function and prevents further hepatocellular damage. Liver function tests should be performed early and followed frequently. If dysfunction exists, drugs requiring hepatic metabolism must be carefully titrated.

Gastrointestinal

Gastrointestinal disturbances after hypoperfusion and stress include bleeding, ileus, and bacterial translocation. Ileus may result from electrolyte abnormalities, administration of narcotic medications, or from shock itself. Abdominal distension from ileus or ascites may cause respiratory compromise, especially in infants. Use of prophylactic medications (H_2 blockers, protein pump inhibitors, sucralfate) to prevent gastrointestinal hemorrhage is unproven.[50] Use of histamine antagonists has been associated with an increased incidence of nosocomial pneumonias.[50,51]

Acute nonocclusive mesenteric ischemia is a devastating condition characterized by intense, prolonged splanchnic vasoconstriction, intestinal mucosal hypoxia, and acidosis. Mesenteric ischemia eventually leads to transmural necrosis of the bowel, bacterial translocation, sepsis, and multisystem organ dysfunction.[52-54] Morbidity and mortality for this condition are high because the signs/symptoms are nonspecific, delaying diagnosis. Prevention of gut ischemia through adequate oxygen delivery may prevent bacterial translocation. Some clinicians advocate the use of selective gut decontamination and early enteral nutrition.[55-56] Most children with shock will tolerate postpyloric enteral feeding, although GI feeding complications are more common than in critically ill patients without shock.[57,58]

Endocrine

Multiple endocrine problems involving fluid, electrolytes, and mineral balance may arise and complicate the management of children in shock. Severe abnormalities of calcium homeostasis can occur during the course of acute hemodynamic deterioration.

Hypoadrenalism may exacerbate the shock state. Patients who have been administered corticosteroids within 6 months preceding the onset of shock should be considered for stress doses of glucocorticoids. Patients in shock because of head or abdominal trauma may have disruption of the hypothalamic-anterior pituitary-adrenal axis. Adrenal hemorrhage has been demonstrated as a manifestation of severe sepsis, but more commonly patients may develop a relative or functional adrenal insufficiency (see section on septic shock).

Functional Classification and Common Underlying Etiologies

Shock states can be classified into six functional categories (Box 29-2). Such tidy classifications imply a degree of precision that will be misleading when approaching an individual patient. Vicious cycles play a prominent role in most shock syndromes. Any given patient, over time, may display features of any functional category or features of multiple categories.

Hemodynamic profiles of these categories are summarized in Table 29-1.

Hypovolemic Shock

Etiology and Pathophysiology

Hypovolemia is the most common cause of shock in infants and children. Hypovolemic shock is best defined as a decrease in the intravascular blood volume to such an extent that effective tissue perfusion cannot be maintained. Etiologies include hemorrhage (see Chapter 112), fluid and electrolyte loss (see Chapter 67), endocrine disease (see Chapter 77), and plasma loss (Box 29-3).

Hypovolemia causes a decrease in preload leading to a decrement of stroke volume and reduction in cardiac output. Activation of peripheral and central baroreceptors produces an outpouring of catecholamines, and the resulting tachycardia and peripheral vasoconstriction are initially adequate to support the blood pressure with little or no evidence of hypotension. Acute losses of 10% to 15% of the circulatory blood volume may be well tolerated in healthy children who have intact compensatory mechanisms. An acute loss of 25% or more of the circulating blood volume, however, frequently results in a clinically apparent hypovolemic state that requires immediate, aggressive management.

The most reliable indicators of early, compensated hypovolemic shock in children are persistent tachycardia, cutaneous vasoconstriction, and diminution of the pulse pressure. The best clinical evidence of decreased tissue perfusion is skin mottling, prolonged capillary refill, cool extremities, and decreased urine output. Systemic arterial blood pressure is frequently normal, the result of increased systemic vascular resistance, making blood pressure measurement of limited value in managing the patient with compensated hypovolemic shock. Neurologic status is normal or only minimally impaired.

With continued loss of blood volume or with delayed or inadequate blood volume replacement, the intravascular fluid losses surpass the body's compensatory abilities, causing circulatory and organ dysfunction. Stroke volume and cardiac output are decreased. The pronounced systemic vasoconstriction and hypovolemia produce ischemia and hypoxia in the visceral and cutaneous circulations. Altered cellular metabolism and function occur in these areas, resulting in damage to blood vessels, kidneys, liver, pancreas, and bowel. Patients become hypotensive, acidotic, lethargic or comatose, and oliguric or anuric. It is important to emphasize that arterial blood pressure falls only after compensations are exhausted, which may occur long after the precipitating event and only after a severe reduction in cardiac output. Terminal phases of hypovolemic shock are characterized by myocardial dysfunction and widespread cell death.

Box 29–2 Shock States

Hypovolemia
Cardiogenic
Obstructive
Distributive
Septic
Endocrine

Courtesy Mark S. McConnell, MD, and Ronald M. Perkin, MD.

Box 29–3 Etiologies of Hypovolemic Shock

I. Whole blood loss
  A. Absolute loss: hemorrhage
    1. External bleeding
    2. Internal bleeding
      a. Gastrointestinal
      b. Intra-abdominal (spleen, liver)
      c. Major vessel injury
      d. Intracranial (in infants)
      e. Fractures
  B. Relative loss
    1. Pharmacologic (barbiturates, vasodilators)
    2. Positive pressure ventilation
    3. Spinal cord injury
    4. Sepsis
    5. Anaphylaxis
II. Plasma loss
  A. Burns
  B. Capillary leak syndromes
    1. Inflammation, sepsis
    2. Anaphylaxis
  C. Protein-losing syndromes
III. Fluid and electrolyte loss
  A. Vomiting and diarrhea
  B. Excessive diuretic use
  C. Endocrine
    1. Adrenal insufficiency
    2. Diabetes insipidus
    3. Diabetes mellitus

Courtesy Mark S. McConnell, MD, and Ronald M. Perkin, MD.

Therapy

Initial treatment of the child in hypovolemic shock is similar regardless of etiology. Therapy begins with the establishment or assurance of adequate oxygenation and ventilation. Oxygen should always be the first drug administered. Once the airway is assured or established (may require intubation) and ventilation is adequate, measures to restore an effective circulating blood volume should begin immediately. Placement of an adequate intravenous or intraosseous catheter and rapid volume replacement are the most important therapeutic maneuvers to reestablish the circulation (see Chapter 15). Central venous catheterization is infrequently necessary during initial resuscitation.

The choice of fluid depends on the nature of the loss. Early correction of hypovolemia is the major factor preventing the later complications of shock. Isotonic crystalloid solutions, which are readily available, safe, and the least expensive, should be used in initial volume resuscitation. The first fluid bolus (20 mL/kg) should be administered as rapidly as possible. Heart rate, pulse pressure, blood pressure, peripheral perfusion, quality of mentation, and volume of urine output should be monitored. Improvement in these measurements should be expected if the blood volume loss is approximately 20%. Under these conditions, a rapid response to resuscitation can be anticipated. Maintenance fluid administration then can be initiated and vital signs monitored. The appropriate maintenance fluid depends on the measurements of serum electrolytes, total protein, and hematocrit.

The end point of fluid resuscitation should be normalization of arterial blood pressure, pulse pressure, peripheral perfusion, and heart rate; establishment of adequate urine output; and a decrease in the metabolic acidosis. If shock persists, continued aggressive fluid resuscitation in aliquots of 20 mL/kg should be initiated with rapid assessment of response to therapy. If the patient does not show improvement after several isotonic fluid boluses, more aggressive monitoring and reevaluation of the diagnosis may be required. Causes of ongoing vascular depletion should be sought. Patients in profound hypovolemic shock will require frequent or continuous monitoring of heart rate, arterial blood pressure, arterial blood gases, central venous pressure (CVP), and urinary output.

Uncomplicated, promptly treated hypovolemic shock usually does not lead to a significant capillary injury and leak. However, severe, prolonged hypovolemic shock, traumatic shock with extensive soft-tissue injury, burn shock, or sepsis complicating hypovolemic shock may seriously impair capillary integrity. Therefore, once adequate circulation and urine output have been restored, fluid administration may be reduced unless there are demonstrable ongoing fluid losses. Continued assessment of hemodynamic status and vascular volume is essential to guide further therapy.

The amount of fluid necessary to restore effective circulating blood volume depends on the amount lost (deficit) and the rate of ongoing loss. The total amount of fluid given often exceeds the total volume lost because of expanded capacitance of the vascular space and dysfunction of cellular membranes. Ongoing fluid losses from chest tube drains, biliary drains, bowel, edema formation, or other losses of bodily fluids may dictate the use of solutions other than crystalloid. Enough fluid must be given to provide adequate cardiac filling pressure. Adequate filling pressure only ensures that one determinant of cardiac performance—preload—has improved. It does not ensure adequate contractility, ejection of blood, and perfusion of tissue beds. A child with nonhemorrhagic hypovolemic shock should respond to 40 mL/kg of crystalloid solution. If a child is unresponsive to this amount of fluid resuscitation, the child must be evaluated for complicating factors. Causes of refractory shock include unrecognized pneumothorax or pericardial effusion, intestinal ischemia (volvulus, intussusception, necrotizing enterocolitis), sepsis, myocardial dysfunction, adrenocortical insufficiency, and pulmonary hypertension.

The first approach to further diagnosis of patients in persistent hypovolemic shock is the establishment of a central venous catheter for measurement of CVP. In the hypotensive patient, a CVP of less than 10 mm Hg, in the absence of pulmonary edema, should be carefully augmented by fluid infusion until that level of preload is reached. If there is no improvement in blood pressure, peripheral perfusion, or urine output, cardiogenic causes of circulatory failure must be considered. Arterial blood gases, hematocrit, serum electrolytes, glucose, and calcium should be reevaluated. Correction of acidosis, hypoxemia, or metabolic derangements is essential. Blood and other appropriate sites must be cultured and broad-spectrum parenteral antibiotic coverage begun if sepsis is suspected. Shock persisting in the face of a CVP exceeding 10 mm Hg may be an indication for placement of a flow-directed thermodilution pulmonary artery catheter and/or an echocardiogram.

Because many factors affect preload measurements, the absolute value of the CVP and pulmonary capillary pressure measurement may be less important than the change in measurement in response to therapeutic interventions. Used this way, these measurements allow detection of limitation in cardiac competence and therefore provide an important guide for volume replacement. Fluid administration should be discontinued when ventricular filling pressure rises without evidence of improvement in cardiovascular performance. At such a time, an inotropic agent may be necessary.

In the case of hemorrhagic hypovolemia, blood must be obtained and transfused if hypotension persists despite early crystalloid infusions. The patient with severe anemia in shock may need emergency transfusion of uncrossmatched blood as part of the initial resuscitation. The hematocrit may be a poor indicator of the severity of hemorrhage because it may not immediately decline in the setting of acute hemorrhagic shock. The possibility of occult intrathoracic or intraabdominal bleeding must be considered. Concomitant with fluid resuscitation of hemorrhagic shock, early surgical intervention may be indicated to control the source of bleeding. In the setting of hemorrhagic shock caused by penetrating trauma in adults, surgical control of the bleeding site may be more important than initial fluid resuscitation in improving patient outcome.[14]

Cardiogenic Shock or Congestive Heart Failure

Etiology and Pathophysiology

Cardiac shock is the pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the cardiovascular system to meet the metabolic needs of tissues. The common denominator is depressed cardiac output, which in most instances is the result of decreased myocardial contractility. Cardiogenic shock or congestive heart failure (CHF) during infancy and childhood is a diagnostic and therapeutic challenge because of its myriad etiologies (Box 29-4).

Cardiac function can be depressed in patients with shock of noncardiac origin. Myocardial dysfunction is frequently a late manifestation of shock of any etiology. Although the cause of myocardial dysfunction in such patients is not completely understood, the following mechanisms have been proposed: (1) specific toxic substances released during the course of shock that have a direct cardiac depressant effect, (2) myocardial edema, (3) adrenergic receptor dysfunction, (4) impaired sarcolemmic calcium flux, and (5) reduced coronary blood flow resulting in impaired myocardial systolic and diastolic function.[20]

Another form of cardiogenic shock is caused by diastolic dysfunction. Impaired myocardial relaxation changes the pressure-to-volume ratio during diastole and increases ventricular pressure at any volume. This lack of myocardial relaxation is hemodynamically unfavorable because increased left ventricular diastolic pressure is transmitted to the lung and results in pulmonary edema and dyspnea. Elevated left ventricular diastolic pressure also decreases myocardial perfusion pressure and can lead to subendocardial ischemia. Such patients present with "heart failure" but may have normal left ventricular systolic function. Diastolic properties of the ventricle appear to be the first to become abnormal in patients with ischemic heart disease or disorders associated with ventricular hypertrophy.[61,62] Therefore when approaching a patient with

Box 29–4 Etiologies of Cardiogenic Shock

I. Heart rate abnormalities
  A. Supraventricular tachycardia
  B. Ventricular dysrhythmias
  C. Bradycardia
II. Cardiomyopathy, carditis
  A. Hypoxic-ischemic events
    1. Cardiac events
    2. Prolonged shock
    3. Head injury
    4. Anomalous coronary artery
    5. Excessive catecholamine state
    6. Cardiopulmonary bypass
  B. Infectious
    1. Viral
    2. Bacterial
    3. Fungal
    4. Protozoal
    5. Rickettsial
    6. Sepsis
  C. Metabolic
    1. Hypothyroid, hyperthyroid
    2. Hypoglycemia
    3. Pheochromocytoma
    4. Glycogen storage disease
    5. Mucopolysaccharidoses
    6. Carnitine deficiency
    7. Disorders of fatty acid metabolism
    8. Acidosis
    9. Hypothermia
    10. Hypocalcemia
  D. Connective tissue disorders
    1. Systemic lupus erythematosus
    2. Juvenile rheumatoid arthritis
    3. Polyarteritis nodosa
    4. Kawasaki disease
    5. Acute rheumatic fever
  E. Neuromuscular disorders
    1. Duchenne muscular dystrophy
    2. Myotonic distrophy
    3. Limb girdle (Erb)
    4. Spinal muscular dystrophy
    5. Friedreich ataxia
    6. Multiple lentiginosis
  F. Toxic reactions
    1. Sulfonamides
    2. Penicillins
    3. Anthracyclines
  G. Tachydysrhythmias
    1. Supraventricular tachycardia
    2. Atrial flutter
    3. Ventricular tachycardia
  H. Other
    1. Idiopathic dilated cardiomyopathy
    2. Familial dilated cardiomyopathy
III. Congenital heart disease
IV. Trauma

Courtesy Mark S. McDonnell, MD, and Ronald M. Perkin, MD.

Box 29–5 Recognition of Congestive Heart Failure in Infants

History	Excessive respiratory effort Prolonged feeding time Poor weight gain Excessive sweating Frequent respiratory tract infections
Physical examination	Tachycardia Tachpnea Gallop rhythm Cold extremities Weak peripheral pulses Wheezing, rales Dyspnea, cough Cyanosis Diaphoresis Hepatomegaly Neck vein distension Peripheral edema Hypotension
Chest radiograph	Cardiomegaly Pulmonary venous congestion Hyperinflation

Courtesy Mark S. McConnell, MD, and Ronald M. Perkin, MD.

cardiogenic shock, it is important to characterize both systolic and diastolic function. Therapy designed to improve systolic function may impair myocardial diastolic function (see Chapter 19).[62]

Clinical Assessment

The appropriate management of CHF in infancy is critically dependent upon the specific etiology; accurate and rapid diagnosis is of prime importance. Recognition begins with a careful history and physical examination (Box 29-5) and is supplemented by chest radiography, electrocardiography, and echocardiography.

Two-dimensional and Doppler echocardiographic studies provide important information about the size, thickness, and performance of the heart and delineation of cardiac malformations. Doppler investigation of the diastolic mitral inflow pattern is useful in assessing the presence of diastolic dysfunction.[62]

As opposed to hypovolemic shock, compensatory responses can have deleterious effects in patients with cardiogenic shock. Compensatory responses are nonspecific and imprecise and may contribute to the progression of shock by further depressing cardiac function. As contractility deteriorates and cardiac output decreases, systemic vascular resistance increases, in response to neurohumoral mediators, in order to maintain circulatory stability.[63] However, this increase in afterload adds to the heart's workload and further decreases pump function. Therefore, in cardiogenic shock, a vicious cycle is established. Because of the self-perpetuating cycle, compensated phases of cardiogenic shock may not be observed. Patients are tachycardic, hypotensive, diaphoretic, oliguric, acidotic, and poorly perfused. Extremities are cool and mental status is altered. Hepatomegaly, jugular venous distension, rales, and peripheral edema may be observed. Cardiac output is depressed, and elevations in CVP, pulmonary capillary wedge pressure, and systemic vascular resistance are observed.

Therapy

Box 29-6 lists the general supportive and pharmacologic measures used in the treatment of severe CHF or cardiogenic shock. These measures are designed to increase tissue oxygen supply, decrease tissue oxygen requirements, and correct metabolic abnormalities. The initial therapy for cardiogenic shock is to support the heart with supplemental oxygen and mechanical ventilation. Preload should be optimized to allow the patient to take advantage of Starling mechanisms.

Although volume expansion and correction of metabolic derangements (e.g., pH, glucose, calcium, magnesium) may enhance cardiac function, pharmacologic interventions are usually necessary to improve cardiac function. This approach to treatment relies on the use of drugs having the ability to restore or augment myocardial contractility, improve cardiac output, and bring about restoration and maintenance of blood flow. The proper choice of drug(s) requires knowledge of the exact hemodynamic disturbance and of the pharmacology of the drugs (see Tables 29-1 and 29-2) (see Chapter 25).

In neonates presenting in shock within the first 2 weeks of life, a lesion with ductal-dependent systemic output should be suspected, and prostaglandin E_1 (PGE_1) (0.05 to 0.1 μg/kg/min) should be infused emergently until a cardiac echocardiogram can be obtained. This is a lifesaving intervention; opening and maintaining ductal patency is the only medical intervention that can restore adequate systemic cardiac output.

Proper use of the various vasoactive drugs often requires the presence of indwelling arterial and central venous catheters. A pulmonary artery catheter may be helpful if the patient is not responding to therapy and shock is not resolving as expected. The presence of these monitoring devices allows the generation of data that will characterize the hemodynamic state, direct appropriate therapy, and allow for evaluation of the response to therapy. There is no usual drug or dose in shock; instead, therapy must be continually tailored to the patient's response.

Box 29–6 General Principles in Management of Cardiogenic Shock or Severe Congestive Heart Failure

I. Minimize myocardial oxygenation demands
   1. Intubation and mechanical ventilation
   2. Maintain normal core temperature
   3. Provide sedation
   4. Correct anemia
II. Maximize myocardial performance
   1. Correct dysrhythmias
   2. Optimize preload: fluid boluses; if congested, appropriate salt and water restriction and appropriate use of venodilators and/or diuretics
   3. Improve contractility: provide oxygen, guarantee ventilation, correct acidosis and other metabolic abnormalities, inotropic and lusitropic drugs
   4. Reduce afterload: provide sedation and pain relief, correct hypothermia, appropriate use of vasodilator
III. Rule out congenital heart or traumatic heart disease
IV. Explore surgical options

Courtesy Mark S. McConnell, MD, and Ronald M. Perkin, MD.

Myocardial Contractility: Inotropic Agents

The catecholamines are the most potent positive inotropic agents available; however, effects are not limited to inotropy. The catecholamines also possess chronotropic properties and have complex effects on vascular beds of the various organs of the body. Consequently, the choice of an agent may depend as much on the state of the circulation as it does on the myocardium.

The most commonly used catecholamines are norepinephrine, epinephrine, dopamine, and dobutamine.[64] Fenoldopam has been used to augment diuresis and improve hemodynamics after cardiac surgery and in septic shock.[65,66]

The digitalis glycosides may augment myocardial contractility, but because of a narrow therapeutic-to-toxic ratio, long half-life, and dependence of clearance on renal (digoxin) or hepatic function, their use in patients with cardiogenic shock should be avoided. These compounds have the advantage of improving contractility without further increasing the heart rate. They can be used once the shock is resolved.

Inamrinone, milrinone, and enoximone 133 belong to a class of nonglycoside, nonsympathomimetic inotropic agents that act via potent and selective inhibition of phosphodiesterase. Intravenous administration of inamrinone or milrinone increases cardiac output and reduces cardiac filling pressures and systemic vascular resistance with minimal effect on the heart rate and systemic blood pressure of adult patients. These drugs are particularly useful in the treatment of cardiogenic shock because they improve diastolic function (lusitropy), increase contractility, and reduce afterload by peripheral vasodilation without a consistent increase in myocardial oxygen consumption. These agents require careful bolus dosing prior to initiating an infusion; a rapid infusion of the bolus dose may cause hypotension. Both of these drugs have relatively long half-lives, and they should be used cautiously in the presence of significant hypotension. Milrinone may be preferred over inamrinone because of inamrinone's tendency to cause thrombocytopenia.

Afterload Reduction: Vasoactive Drugs

Neurohumoral compensatory mechanisms that initially compensate for a fall in output of the failing heart in time become a major part of the problem.[63] The kidney's response to a decrease in cardiac output leads to expansion of extracellular fluid volume which may lead to circulatory congestion and edema. Systemic vasoconstriction raises aortic impedance, which maintains perfusion pressure in the face of declining cardiac output but may impair ventricular function. After resuscitation, therapy is directed to counteract these physiologic responses: for example, use of vasodilators to oppose systemic vasoconstriction, angiotensin-converting enzyme inhibitors to block the renin-angiotensin system, and diuretics to prevent or reverse abnormal fluid retention. They should not be used as first-line therapy to reverse shock.

Numerous vasodilators, representing several different pharmacologic classes, improve cardiac performance and lessen clinical symptoms via arterial and venous smooth muscle relaxation. Arterial relaxation should increase ejection fraction, increase stroke volume, and decrease end-systolic left ventricular volume. Some evidence suggests some vasodilator drugs increase left ventricular compliance, which should improve diastolic function.[62] Venous relaxation should shift

blood into the periphery and reduce right and left ventricular diastolic volume, with attendant beneficial effects on pulmonary and systemic capillary pressure. This ought to be reflected in decreased edema, reduced myocardial wall stress, and improved diastolic perfusion of the myocardium.

For treatment of cardiogenic shock, intravenous vasodilators with rapid onsets of action and short half-lives are preferred. Selection of a vasodilator agent should depend on its principal hemodynamic effects and the specific hemodynamic abnormalities in individual patients. Factors that increase systemic resistance, such as hypothermia, acidosis, hypoxia, pain, and anxiety, should be treated before vasodilator drugs are considered.

Use of vasodilators in shock is generally limited to situations in which cardiac dysfunction is associated with elevated ventricular filling pressures, elevated systemic vascular resistance, and normal or near-normal systemic arterial blood pressure. Occasionally, the combination of vasodilator and inotropic therapy results in hemodynamic improvement not attainable with either approach alone.

There is a growing awareness that right ventricular dysfunction plays a pivotal role in some of the most frequently encountered and important cardiopulmonary disorders in children, including congenital heart disease, acute respiratory distress syndrome, bronchopulmonary dysplasia, and other chronic pulmonary disorders. The ability of the right ventricle to respond to the increased pulmonary vascular resistance seen in these situations often determines outcome. Therefore, measures to decrease pulmonary vascular resistance have become more common in the treatment of many seriously ill pediatric patients. Such measures include supplemental oxygen, hyperventilation, metabolic and respiratory alkalosis, inhaled nitric oxide, prostaglandin E_1, prostacyclin, analgesia, and sedation.[67-69]

Surgical Intervention

A number of congenital cardiac defects may present in severe CHF and cardiogenic shock. Diagnosis of these defects is critical because surgery is the definitive therapy. Prostaglandin E_1 infusion may allow for resuscitation and stabilization until surgery can be accomplished in ductus-dependent obstruction to systemic blood flow (e.g., hypoplastic left heart syndrome, interruption of the aortic arch, coarctation of the aorta).

Cardiac function can sometimes be supported temporarily by mechanical means, including intraaortic balloon counterpulsation, left ventricular assist device, and ECMO. Cardiac transplantation has become an important tool for treating patients with severe myocardial dysfunction who otherwise would die of their heart disease.

Specific Etiologies

Cardiomyopathy

Patients may present in shock with dilated cardiomyopathy. The etiologies of acute dilated cardiomyopathies are listed in Box 29-4. Myocarditis is one of the more common causes of dilated cardiomyopathy in previously healthy children. The clinical presentation of myocarditis in pediatric patients is varied. Carditis may cause myocardial dysfunction or dysrhythmia, or it may be "clinically silent." Tachycardia (in the absence of fever) and tachypnea are usual presenting symptoms. In acute myocarditis, the history of illness is very short (hours to days). Life-threatening dysrhythmias in patients with acute myocarditis include ventricular tachycardia and supraventricular tachycardia. Initial resuscitation of the patient with myocarditis is the same as for other forms of cardiogenic shock; however, patients with myocarditis and other dilated cardiomyopathies may not respond as well to traditional inotropic therapy.[70,71] In addition, catecholamine infusions may promote the development of dysrhythmias.

Once the diagnosis of myocarditis is made, treatment with steroids or intravenous immunoglobulin (IVIg) (1 g/kg/day for 2 days) is recommended to modulate the inflammatory response.[72,73] Use of ECMO has been lifesaving in patients with acute myocarditis whose shock does not reverse with conventional therapy or in whom arrhythmias are unremitting. We queried the ELSO registry for cases of myocarditis treated with ECMO from 1987 through 2009. There were 485 pediatric cases (age 21 years or younger), with a median run time of 6.8 days (range, 0 to 51.9 days). The survival was 62% (Lynn Hernan, personal communication, 2010).

Hypoxic-Ischemic Injury

Shock following a generalized hypoxic-ischemic episode (e.g., near-drowning, sudden infant death syndrome) is frequently encountered in infants and children with no preexisting cardiovascular or pulmonary disease. Data have shown that shock following hypoxic-ischemic events is cardiogenic. This shock is characterized by a low cardiac index, elevated right and left heart filling pressures, elevated systemic and pulmonary vascular resistances, decreased oxygen consumption, and elevated oxygen extraction index. In many patients, the mean systemic arterial blood pressure is elevated, which suggests the increase in systemic vascular resistance is exaggerated. Studies have documented progressive systolic and diastolic myocardial dysfunction immediately after successful cardiac resuscitation.[74] All of these observations have important therapeutic implications because the increased vascular resistance and decreased cardiac output may prevent adequate tissue perfusion following anoxic injury.

Cardiac Injury in Trauma

Blunt cardiac injury can cause myocardial contusion, myocardial concussion, aneurysm, septal defects, chamber rupture, valvular rupture, and bleeding into or damage to the pericardium. Each of these entities has separate presentations, although the lesions often are concurrent. Every pediatric trauma patient deserves a careful cardiac evaluation. Of note, both left and right ventricular function may be impaired significantly in children with isolated head injury. The myocardial injury seen in children with head injury appears to be related to high levels of catecholamines with resultant myocardial ischemia.[75]

Obstructive Shock

Etiology and Pathophysiology

Obstructive shock is caused by the inability to produce adequate cardiac output despite normal intravascular volume and myocardial function. Causative factors may be located within the pulmonary or systemic circulation or associated with the heart itself. Examples of obstructive shock include acute pericardial tamponade, tension pneumothorax, pulmonary or

systemic hypertension, and congenital or acquired outflow obstructions. Recognition of the characteristic features of these syndromes is essential, because most of the causes can be treated provided the diagnosis is made early.

Specific Etiologies

Cardiac Tamponade

Cardiac tamponade is defined as hemodynamically significant cardiac compression resulting from accumulating pericardial contents that evoke and defeat compensatory mechanisms. The pericardium may contain effusion fluid, purulent fluid, blood, or gas.

Clinical manifestations of tamponade may be insidious, especially when it occurs in conditions such as malignancy, connective tissue disorders, renal failure, or pericarditis. In early phases, the symptoms are nonspecific. As cardiac output becomes restricted, the overall picture resembles CHF; however, the lungs usually are clear. Findings on physical examination that suggest cardiac tamponade include pulsus paradoxus, narrowed pulse pressure, pericardial rub, and jugular venous distension. Echocardiography is of particular value in detecting the presence of pericardial effusion and can provide clues about the presence of tamponade. In rapid tamponade caused by hemorrhage, as in trauma, shock dominates the picture. Left untreated, it leads to electromechanical dissociation.

The definitive treatment of cardiac tamponade is removal of pericardial fluid or air by surgical drainage or pericardiocentesis. Removal of even a small volume of fluid can rapidly improve blood pressure and cardiac output. Surgical drainage by either thoracotomy or a subxiphoid limited surgical approach should be considered for traumatic tamponade.

Pericardiocentesis should be performed as soon as possible if the patient is considered to be in a life-threatening condition. Pericardiocentesis is a blind procedure; introduction of the needle should be monitored by echocardiography whenever possible. The subxiphoid approach is generally preferable (see Chapter 15).

Medical management is not a substitute for drainage but may avert a catastrophe until pericardiocentesis or surgical drainage can be safely performed. The principles of medical management include blood volume expansion to maintain venoatrial gradients and inotropic agents. In addition, any anticoagulant or thrombolytic therapy should be withheld or discontinued if pericardiocentesis is anticipated. Diuretics, which reduce blood volume, and digoxin or other agents, which slow the heart, are contraindicated in tamponade.

Coarctation/Interrupted Arch

Infants with aortic arch interruption or juxtaductal coarctation of the aorta may depend on patency of the ductus arteriosus to provide adequate lower body perfusion. In many such infants, the ductus arteriosus constricts after birth, resulting in severe heart failure, poor systemic perfusion, and acidemia. Many of the signs and symptoms of coarctation with shock are indistinguishable from shock of other etiologies.[76] A high index of suspicion must be maintained for infants who present in shock in the first month of life. In severely ill infants in whom the diagnosis of coarctation or interruption of the aorta is clinically suspected, it is appropriate and often lifesaving to start a continuous prostaglandin E_1 infusion before diagnostic evaluation is performed.

Distributive Shock

Etiology and Pathophysiology

Distributive shock results from maldistribution of blood flow to the tissue. Abnormalities in distribution of blood flow may result in profound inadequacies in tissue oxygenation, even in the face of a normal or high cardiac output. Such maldistribution of flow generally results from widespread abnormalities in vasomotor tone. Distributive shock may be seen with anaphylaxis, spinal or epidural anesthesia, disruption of the spinal cord, or inappropriate administration of vasodilatory medication.

Treatment generally includes reversal of the underlying etiology and vigorous fluid administration. In severe cases of distributive shock unresponsive to fluids, vasopressor infusions may be necessary.

Septic Shock

The incidence of pediatric septic shock in the United States is approximately 0.56 cases per 1000 population.[77] The incidence is highest in infants (5.16 cases per 1000 population) and falls rapidly after the first year. There are an estimated 42,000 cases per year with a case fatality rate of 10.3% (or approximately 4400 deaths per year). The average cost per case of pediatric sepsis in the U.S. is estimated to be greater than $40,000. The estimated national total annual cost is $1.97 billion.[77] Sepsis and septic shock are significant causes of mortality in children and consume a significant amount of U.S. health care dollars.

Etiology and Pathophysiology

Septic shock is the most complex and controversial type of shock and merits independent classification. Septic shock is often a combination of multiple problems, including infection, relative or absolute hypovolemia, maldistribution of blood flow, myocardial depression, and multiple metabolic, endocrine, and hematologic problems. Thus shock in sepsis contains many elements of the other types of shock discussed previously (hypovolemic, cardiogenic, and distributive shock) (see Chapters 91 and 103).

Septic shock encompasses a cascade of metabolic, hemodynamic, and clinical changes resulting from invasive infection and the release of microbial toxins in the bloodstream. Correlation of clinical findings with the type of invading microorganism has been attempted. However, the systemic inflammatory response is independent of the type of invading organism (bacterial, virus, fungus, *Rickettsia*) and is a host-dependent response.[78]

The pathophysiology of septic shock is incompletely understood. A combination of the direct effects of microbial agents, microbiologic toxins, the patient's inflammatory response to infection, and activation of endogenous mediators results in the cardiovascular instability and multisystem organ failure.[79] Septic shock is a constellation of signs and symptoms that reflect multiple organ system derangement at the subcellular level. Mediator release seems to be the final common pathway

to the development of this shock state regardless of etiology.[78] Some mediators are cytokines, tumor necrosis factor, interleukin-1, interleukin-6, kinins, eicosanoids, platelet activating factor, and nitric oxide.

The clinical pattern and presentation of septic shock vary greatly and are dependent on the dynamic interplay of the invading organism, time to treatment, and the host response to the infection and treatment. All patients present with an absolute or functional hypovolemia. Several factors may contribute to hypovolemia. Increased microvascular permeability, arteriolar and venular dilation with peripheral pooling of intravascular volume, inappropriate polyuria, and poor oral intake all combine to result in reduced effective blood volume. Volume loss secondary to fever, diarrhea, vomiting, or sequestered third space fluid also contributes to hypovolemia.

Abnormal hemodynamic responses constitute a primary hallmark of septic shock.[80] The most common presentation (80%) in children is low cardiac index with or without abnormalities of vascular tone.[25] These children present with tachycardia, mental status changes, diminished peripheral pulses, mottled cold extremities, and prolonged capillary refill (more than 2 seconds). Adults and some children (20%) present in a hyperdynamic state characterized by an elevated (or normal) cardiac output and decreased systemic vascular resistance. On physical examination, patients appear plethoric with warm extremities. They have tachycardia, bounding (or collapsing) pulses, and a widened pulse pressure. High fever, mental confusion, and hyperventilation may be present. At this stage the inexperienced observer may fail to recognize shock. Paradoxically, hypotension may occur in the presence of a normal or elevated cardiac output. In either case, hypotension is not necessary to make the diagnosis of shock.

Progression of sepsis is characterized by a loss of cardiac compensation for diminishing systemic vascular resistance, possibly as a result of inflammatory-mediated capillary leak, vasodilation, and/or toxin-mediated cardiac depression. Some patients die of refractory hypotension as a result of a low systemic vascular resistance.[82]

The progression from high to low cardiac output may occur rapidly. As cardiac output decreases, the physical symptoms change to those of a hypoperfused state. The patient has tachypnea, tachycardia, hypotension, weak thready pulses, mottled cold extremities, and delayed capillary refill. As tissue perfusion worsens, anaerobic metabolism ensues and lactic acid accumulates.

Progressive deterioration in oxygen consumption and oxygen extraction portends a poor prognosis. In pediatric patients with septic shock, oxygen consumption is dependent on oxygen delivery.[83] This is similar to the physiologic relationship seen in pediatric patients with cardiogenic shock, suggesting that these two groups could be resuscitated with the same physiologic principles. In addition to oxygen, impaired use of other metabolic substrates has been demonstrated in septic shock. Prior to the onset of cellular hypoxia,[1-3] dysregulation of glucose, fat, and amino acids occurs. Changes in glycolysis and gluconeogenesis are possibly the earliest metabolic manifestation of sepsis.[84] Insulin responsiveness,[85] intracellular calcium,[86] glucose distribution,[87] and adrenergic effects[88] have all been implicated.

Although most adults present with hyperdynamic septic shock, most children and especially infants, who have limited cardiac reserve, present with a low cardiac output state clinically indistinguishable from cardiogenic shock.[81] Even during the hyperdynamic state seen in adults, myocardial contractility is depressed because of myocardial depressant factor, diffuse myocardial edema, adrenergic receptor dysfunction, and impaired sarcolemmic calcium flux.[89] Survival of children in septic shock is related to the speed and adequacy of resuscitation. When resuscitation is delayed or inadequate, cellular hypoxia and multiple system organ failure ensue and are the final common pathway to death.

In recognition that pediatric septic shock differs from adult septic shock, and that the clinical presentation is similar to shock from other etiologies, standardized definitions for SIRS, sepsis, septic shock (Box 29-7), and organ dysfunction (Box 29-8) were developed in an attempt to allow comparison within and across clinical trials.[90] While complete and detailed, the clinical utility of these definitions is questioned.[91]

Therapy

Primary therapeutic goals for the initial treatment of septic shock are identification of the shock state, rapid reversal of cardiovascular dysfunction, and control of the infection.

Removal or control of microorganisms by surgical debridement, drainage, and antibiotic therapy is a crucial component of treatment of septic shock. Antibiotic treatment is appropriate in patients with circulatory shock whenever an infectious etiology cannot be ruled out. Choice of antibiotic therapy is determined by the clinical scenario, likely organisms, and local antibiotic sensitivities. Whenever possible, blood, urine, and samples from other potential infected sites should be sent

Box 29–7 Definitions for Sepsis and Septic Shock

Bacteremia	**Presence of Viable Bacteria in Blood**
Infection	Proven infection (culture, stain, PCR) or clinical syndrome with high probability of infection (e.g., lobar pneumonia with negative culture, purpura fulminans in meningococcemia)
Systemic inflammatory response syndrome	At least 2 of 4 of the following criteria (one must be abnormality of temperature or WBC count) 1. Core temperature >38.5° C or <36° C 2. Tachycardia (HR >2 SD for age) or bradycardia (HR <10th percentile for age) if <1 year old 3. Tachypnea (RR >2 SD for age) 4. WBC count elevated or depressed, or >10% band forms
Sepsis	SIRS + infection
Severe sepsis	Sepsis + ≥1 of the following organ dysfunctions: 1. Cardiovascular dysfunction or 2. Respiratory dysfunction or 3. Two other organ dysfunctions
Septic shock	Sepsis + cardiovascular dysfunction

PCR, Polymerase chain reaction; *WBC,* white blood cell; *HR,* heart rate; *SD,* standard deviation; *RR,* respiratory rate.
Modified from Goldstein B, Giroir B, Randolph A, et al: International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics, *Pediatr Crit Care Med* 6:2-8, 2005.

Box 29–8 Organ Dysfunction Criteria

Cardiovascular	After isotonic fluid bolus ≥40 mL/kg in 1 hour: Hypotension: BP <5th percentile for age *or* systolic BP <2 SD below normal age *or* Need for vasoactive drug to keep BP in normal range *or* ≥2 of the following: 1. Unexplained metabolic acidosis: base deficit >5.0 mEq/L 2. Lactic acidosis more than twice the upper limit of normal 3. Oliguria: urine output <0.5 mL/kg/hr 4. Prolonged capillary refill: >5 sec 5. Core to peripheral temperature gap >3° C
Respiratory	PaO_2/FiO_2 <300 in absence of cyanotic congenital heart disease or preexisting lung disease *or* $PaCO_2$ >65 torr or 20 torr over baseline *or* FiO_2 = 0.50 to keep saturations ≥92% *or* Need for invasive or noninvasive mechanical ventilation
Neurologic	GCS score ≤11 *or* Acute mental status change: decrease in GCS ≥3 points from abnormal baseline
Hematologic	Platelet count <80,000/mm^3 or 50% decline in platelet count (for hematology/oncology patients) *or* INR > 2
Renal	Serum creatinine ≥twice the upper limit of normal for age or twofold increase in baseline creatinine
Hepatic	Total bilirubin ≥4 mg/dL (outside neonatal period) *or* ALT twice upper limit of normal

BP, Blood pressure; *SD,* standard deviation; *GCS,* Glasgow Coma Scale; *INR,* international normalized ratio; *ALT,* alanine aminotransferase.
Modified from Goldstein B, Giroir B, Randolph A, et al: International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics, Pediatr Crit Care Med 6:2-8, 2005.

for culture and susceptibility testing before broad-spectrum antibiotic therapy is initiated. It may be necessary to give antibiotics before obtaining cultures.

Cardiovascular Support

The primary goal in the initial management of septic shock is to restore hemodynamic stability. Increasing oxygen delivery by maximizing cardiac output and arterial oxygen content and minimizing oxygen requirements are fundamentals of management.[15,116]

Restoration of preload by volume resuscitation is the first therapeutic measure.[16] Early and effective expansion of the circulating blood volume may enhance oxygen delivery and prevent progression of the septic shock state. Patients in septic shock have an enormous fluid requirement caused primarily by peripheral vasodilation and capillary leak. Initial fluid requirements of septic patients frequently exceed 60 mL/kg,[16] and patients may require as much as 200 mL/kg. Fluids must be given incrementally, with attention to clinical signs of volume overload, and the administration of pressors may mask hypovolemia.[92] Placement of a thermodilution pulmonary artery catheter may be indicated in children who demonstrate a sluggish response to fluid infusion, show clinical or echocardiographic evidence of myocardial dysfunction, or fail to respond to appropriate cardiovascular support.

There continues to be debate regarding the use of crystalloid or colloid solutions for volume expansion in sepsis.[93] Packed red blood cells may be used if the hematocrit is less than 30% because red blood cell transfusion increases oxygen delivery to the tissues. However, expansion of oxygen-carrying capacity may not improve oxygen consumption.[94] Transfusion of pRBCs as part of a strategy to increase mixed venous oxygen saturation (SVO_2) to greater than 70% resulted in improved outcome in pediatric septic shock.[95]

Some patients respond to fluid resuscitation alone, but many patients require therapy with vasoactive infusions (inotropes, pressors, or dilators). Inotropy with catecholamines or phosphodiesterase inhibitors may be effective in reversing myocardial depression and improving contractility. An evidence-based guideline for the management of resuscitation and support of children and neonates with septic shock was issued in 2009.[16] Updated evidence-based algorithms for resuscitation for children (Fig. 29-1) and neonates (Fig. 29-2) are easy to use and have been shown to improve outcomes across diverse patient populations.[16] The emphasis remains on the first hour of fluid resuscitation and use of vasoactive infusions directed to goals of threshold HR, normal BP, and capillary refill time 2 seconds or less. Severity of shock states has been categorized according to hemodynamic reponses (Table 29-3).[16]

Aggressive use of goal-directed therapies, which emphasize rapid recognition of shock and aggressive resuscitation in the first hours of shock, have been shown to improve mortality in both the pediatric[16,96] and adult patient populations.[97]

A significant advance in the treatment of severe sepsis has emerged from the finding that the immune/inflammatory cascade and the coagulation pathways are closely intertwined.[44,98] Cytokines activate coagulation and inhibit fibrinolysis, and the procoagulant thrombin can activate inflammation. Patients with severe sepsis may be coagulopathic, and several studies have demonstrated acquired protein C deficiency in up to 90% of adult septic patients.[44] This deficiency is associated with poor outcome.[99] Phase III trials of recombinant human activated protein C (rhAPC) demonstrate significant reductions in morbidity[101] and mortality rates in adults.[101]

Doubt about the effectiveness of activated rhAPC in both pediatric and adult patients has been expressed.[102,103] An increased incidence of significant bleeding was seen in adult and pediatric trials of rhAPC.[101,103] The RESOLVE study of the use of rhAPC in pediatric septic shock was stopped for lack of efficacy.[103]

Nutrition

Septic patients develop protein/caloric malnutrition as a principal manifestation of their metabolic response to sepsis.[104] In patients who were previously malnourished or remained hypermetabolic, this rapidly developing malnutrition is believed to contribute to morbidity and mortality. However, the abnormalities in intermediary metabolism (see the

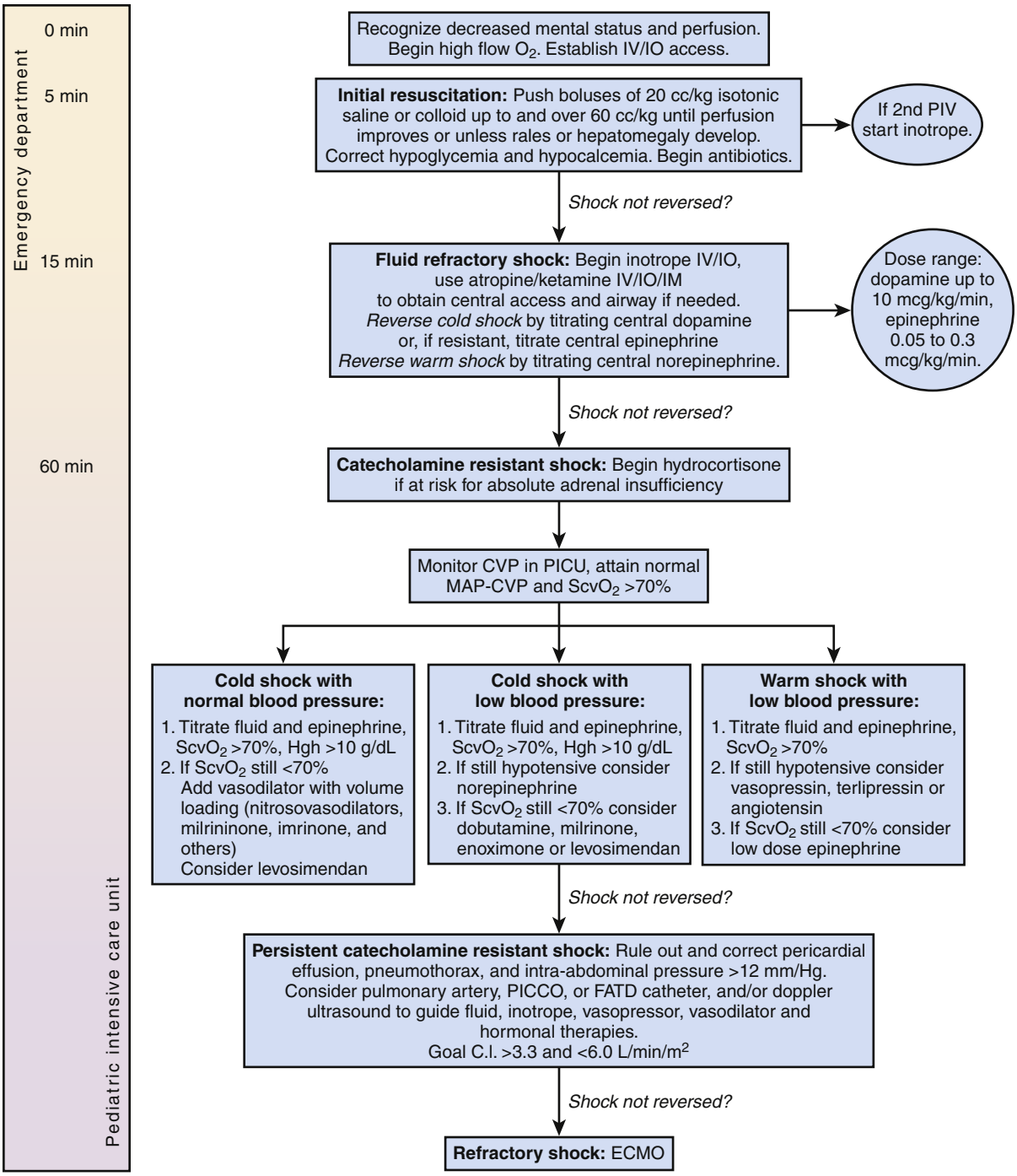

Figure 29–1. Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children. Proceed to next step if shock persists. (1) First hour goals: restore and maintain heart rate thresholds, capillary refill ≤2 sec, and normal blood pressure in the first hour/emergency department. Support oxygenation and ventilation as appropriate. (2) Subsequent intensive care unit goals: if shock is not reversed, intervene to restore and maintain normal perfusion pressure (mean arterial pressure [MAP], central venous pressure [CVP]) for age, central venous O_2 saturation >70%, and CI >3.3, <6.0 L/min/m^2 in pediatric intensive care unit (PICU). *Hgb,* Hemoglobin; *PICCO,* pulse contour cardiac output; *FATD,* femoral arterial thermodilution; *ECMO,* extracorporeal membrane oxygenation; *CI,* cardiac index; *CRRT,* continuous renal replacement therapy; *IV,* intravenous; *IO,* intraosseus; *IM* intramuscular. *(Modified from Brierley J, Carcillo JA, Choong K, et al:* International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics, Crit Care Med *37:666-688, 2009.*

Multisystem Effects of Shock section) make the provision of an adequate level of metabolic support challenging. Parenteral or enteral nutrition should begin as soon as cardiovascular stability is achieved. Many clinicians advocate the early use of enteral feedings to prevent gut mucosal atrophy and bacterial translocation.[57,58,105]

Experimental/Unproved Therapies

ECMO has been used to support myocardial and/or pulmonary function during sepsis. We queried the ELSO registry (1976 through January 2010) for ECMO use in all (neonatal, pediatric, and adult) patients with sepsis or septic shock. A total of 2960 patients were identified: 2409 neonates (81%)

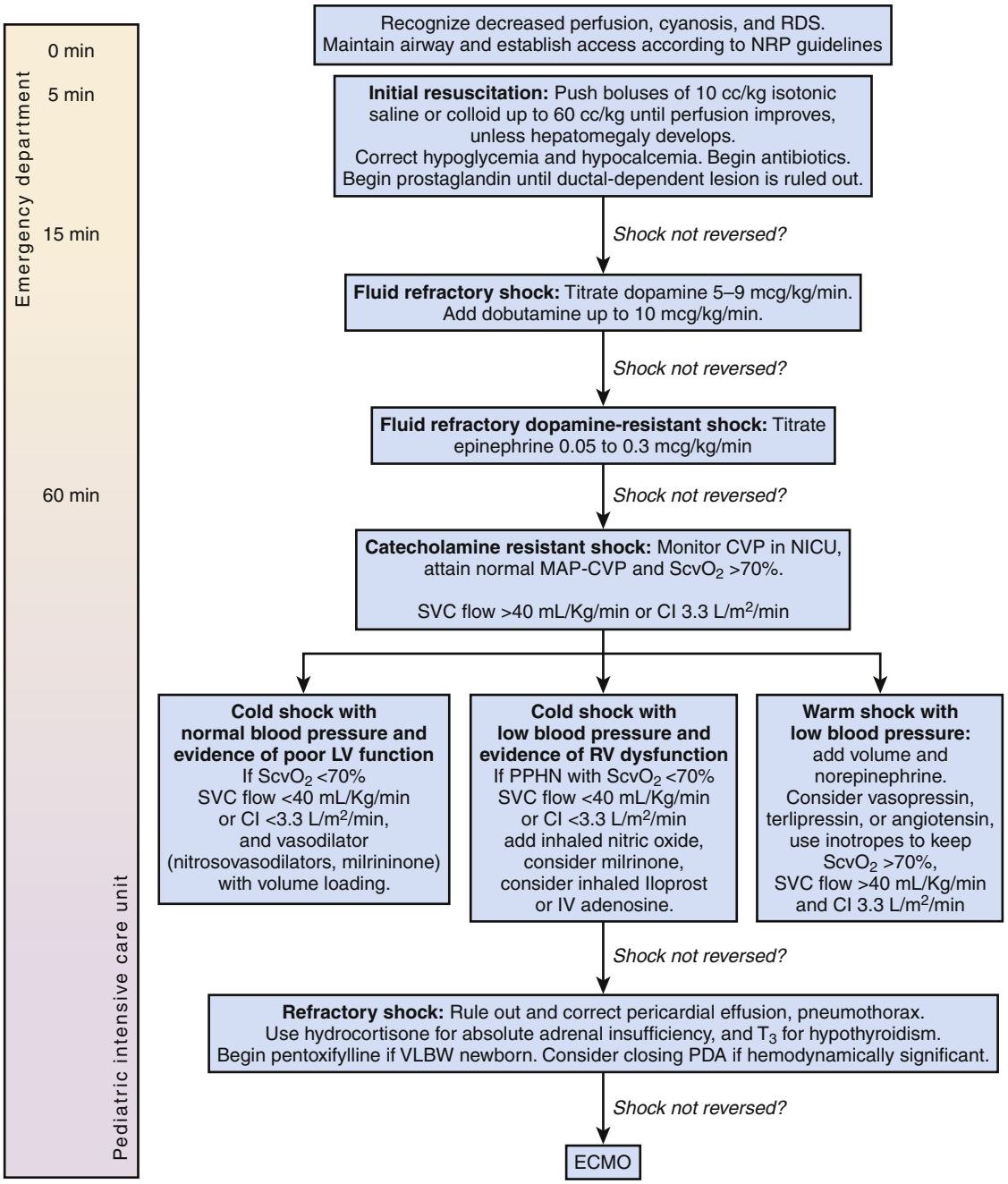

Figure 29–2. Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in newborns. Proceed to next step if shock persists. (1) First hour goals: restore and maintain heart rate thresholds, capillary refill ≤2 sec, and normal blood pressure in the first hour. (2) Subsequent intensive care goals: restore normal perfusion pressure (mean arterial pressure [MAP], central venous pressure [CVP]), preductal and postductal O_2 saturation difference <5%, and either central venous O_2 saturation ($ScvO_2$) >70%, superior vena cava (SVC) flow >40 mL/kg/min, or cardiac index (CI) >3.3 L/min/m^2 in the neonatal intensive care unit (NICU). *RDS,* Respiratory distress syndrome; *NRP,* Neonatal Resuscitation Program; *PDA,* patent ductus arteriosus; *ECMO,* extracorporeal membrane oxygenation. *(Modified from Brierley J, Carcillo JA, Choong K, et al:* International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics, Crit Care Med *37:666-688, 2009.)*

and 551 patients older than 1 month (19%). Overall survival was 67%, but there was a significant difference in the survival of neonates versus other patients. Survival in the neonatal group was 74% versus 40% in all other patients.

The presence of adrenal insufficiency in septic shock has been widely studied. Meta-analyses of early studies using a short course of high-dose ("shock") glucocorticoids found no benefit and possibly increased mortality rate.[106,107] Subsequent observations of adrenal hemorrhage and cytokine-mediated adrenal insufficiency identified a select group of patients who benefit from glucocorticoid replacement (50 mg intravenously every 6 hours) over a prolonged period (7 days).[108,109] Increased knowledge of the close intertwining of the hypothalamic-pituitary-adrenal axis with inflammatory mediators led to the concepts of "functional adrenal insufficiency" or "relative adrenal insufficiency."[109] In many cases, the insufficiency is temporary.[108,109] A random cortisol level of 25 μg/dL or less in hypotensive septic adult patients is more sensitive and

Table 29–3 ACCM Hemodynamic Definitions of Shock

Cold or warm shock	Hypoperfusion manifested by: ↓ Mental status or capillary refill >2 sec (cold shock) or flash capillary refill (warm shock) *or* ↓ (cold shock) or ↑ (warm shock) peripheral pulses *or* mottled cool extremities (cold shock) or ↓ urine output <1 mL/kg/h
Fluid-refractory dopamine-resistant shock	Persistent shock after: ≥60 mL/kg fluid resuscitation (when appropriate) and dopamine to 10 μg/kg/min
Catecholamine-resistant shock	Persistent shock after use of direct-acting catecholamines: epinephrine and norepinephrine
Refractory shock	Persistent shock despite goal-directed use of inotropes, vasopressors, vasodilators, and maintenance of metabolic (glucose, calcium) and hormonal (thyroid, hydrocortisone, insulin) homeostasis

From Brierly J, Carcillo JA, Choong K, et al: International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics, *Crit Care Med* 37:666-688, 2009.

specific than low-dose or high-dose corticotropin stimulation tests at identifying a group of septic patients as steroid-responsive. Responsiveness was defined as cessation of the need for pressor support within 24 hours of initiation of steroids (100 mg every 8 hours). Sixty-one percent of adult patients had relative adrenal insufficiency as defined by the random cortisol level or response to steroid therapy.[110]

A randomized, double-blind, crossover study of a continuous infusion of low-dose (100 mg loading dose over 30 minutes followed by 10 mg/h) hydrocortisone in septic adults showed improved hemodynamics and an antiinflammatory benefit without evidence of immunosuppression.[111]

The incidence of adrenal dysfunction in pediatric sepsis may be as high as 52% and is associated with increased vasopressor requirement and longer duration of shock.[112]

The use of stress-dose steroids for general adjunctive therapy for pediatric septic shock remains controversial. Steroids should be given to patients with known adrenal insufficiency or who are at risk for adrenal insufficiency (chronic or recent steroid use; purpura fulminans; etomidate or ketoconazole administration; and hypothalamic, pituitary, or adrenal disease).[16,130] The safety and efficacy of stress-dose steroids administered to pediatric patients with relative adrenal insufficiency is unproven, and poses potential risks to patients.[130]

Many pharmacologic agents and therapies have been evaluated as adjunctive treatments in sepsis and septic shock. They include inhibitors of arachidonic acid metabolism and inhibitors of thromboxane and leukotriene formation; exchange transfusion and plasmapheresis[45,46,113,114,131]; white blood cell transfusions; passive immunotherapy; toxic oxygen scavengers; inhibitors of myocardial depressant factors; and fibronectin administration.[80,115] Although these therapies have significant potential therapeutic usefulness, further study is required before they can be recommended.

The recognition of sepsis as the systemic inflammatory response to an invading microorganism led to therapies targeted at modulating inflammation, such as the administration of antagonists or antibodies to various cytokines (e.g., tumor necrosis factor).[115,116] In preliminary studies, monoclonal antibodies and therapies directed toward lipid A of endotoxin appeared to favorably affect the outcome of patients with gram-negative sepsis. Further trials demonstrated no improvement in survival in patients given these antibodies.[117] Anticytokine therapies directed at tumor necrosis factor and interleukin-1 similarly demonstrated no benefit or worsened survival in patients with septic shock.[116,118] However, reevaluations of studies using anti–tumor necrosis factor-α may have revealed subpopulations for whom there is a survival benefit.[119]

Therapies designed to modulate the immune response,[120,121] inhibit neutrophil function, or inhibit synthesis of nitric oxide (endothelial-derived relaxing factor) have demonstrated no clinical benefit in septic shock.[118] Other areas being explored with regard to the pathophysiology and treatment of septic shock include factors that promote apoptosis,[116,121,122] use of insulin to maintain tight glucose control and normoglycemia,[123-125,132] and use of vasopressin[20-22,126-129] or terlipressin[27-31] in sepsis. These therapies have shown some promise but remain unproven.

Summary

Shock is a life-threatening condition that has a myriad of causes. In order to survive shock, recognition of the shock state and resuscitative efforts must be achieved early, the etiology elucidated, and ongoing monitoring and therapy instituted. The astute clinician who recognizes shock, institutes therapy, and continuously assesses response to therapy offers the child the best chance for a quality survival.

References are available online at http://www.expertconsult.com.

Cardiac Bypass for Repair of Congenital Heart Disease in Infants and Children

J. William Gaynor and Darryl H. Berkowitz

PEARLS

- Pediatric patients are not small adults with respect to their physiology, responses to cardiopulmonary bypass (CPB) and the conditions under which repairs are performed. Many pediatric heart operations are performed under conditions of deep hypothermia (with or without circulatory arrest). Dilutional effects of CPB may enlarge circulating blood volume by 200% to 300%. Blood gas management usually makes use of pH-stat methodology during cooling.
- Neurologic abnormalities or injuries may occur prior to operation and CPB. Preoperative risk factors include episodes of decreased cerebral blood flow, ductal-dependent blood flow with low diastolic pressures, history of balloon atrial septostomy, ongoing systemic inflammation, genetic polymorphisms, a congenital syndrome, low birth weight or a history of preoperative extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD).
- CPB will affect the brain, myocardium, lungs, kidneys, endocrine, and gastrointestinal systems through its generation of nonpulsatile flow. It causes hypoperfusion secondary to hypothermia and lower than normal perfusion pressures. CPB triggers the inflammatory cascade and increases extracellular fluid. Unfortunately, there is lack of agreement surrounding preventive therapies and thus research continues.
- Efforts to limit inflammation include design of smaller circuits to reduce requirements for blood in the prime; the use of biocompatible circuits, the addition of steroids to the prime; and the use of modified ultrafiltration (MUF) at the termination of bypass. These maneuvers are intended to limit blood-circuit interactions, decrease the production of mediators, and filter inflammatory mediators out of the circulation.
- Termination from bypass in the pediatric patient is complicated by the effects of deep hypothermia on organ function and coagulation. The repair can cause heart block. Malignant supraventricular tachycardia can occur. There may be residual intracardiac shunts and outflow tract obstructions. Abnormal pulmonary vascular reactivity may result in hypoxia, acidosis, and acute right ventricular failure.
- In the adult, postbypass acute ventricular failure may be treated with an intraaortic balloon pump or VAD. In the pediatric patient, acute ventricular failure, malignant rhythm, or pulmonary failure is often treated with ECMO.

The history of surgery for congenital heart disease is relatively brief. The first successful intracardiac operation took place less than 60 years ago. The groundwork for the performance of cardiac surgery began in two very different arenas. Clinically, surgeons had gained valuable experience in the battle theaters of World War II with removal of foreign bodies from inside the heart.[1] Experimentally, DeBakey devised a hand-driven pump in 1934. Later, rudimentary bubble or film oxygenators were added to this device. Another important line of experimentation was pursued by Bigelow and colleagues, who described the application of hypothermia to cardiac surgery in 1950. Although two groups successfully performed surgery to repair atrial septal defects, these were performed without the assistance of cardiopulmonary bypass. F. John Lewis successfully closed an atrial septal defect under deep hypothermic arrest in 1951[2] and a group led by Gross and Wilkins described the atrial well technique in 1953, whereby they opened the right atrium and sewed to it a silo, which then filled with blood, enabling them to operate on the beating heart by feel.[3] Between 1951 and 1954, other groups described various forms of cardiopulmonary bypass. Collectively, there were 18 described operations with only one survivor (operated on May 18, 1953, by J.H. Gibbon). Interestingly enough, the survivor was the first in his series after which he recorded five consecutive deaths, resulting in his abandonment of the technique.[4] Failures were attributable to incorrect preoperative diagnoses, ventricular dysfunction at termination of bypass, hypovolemia, surgical errors, and ventricular failure within the convalescence period. During this same period, C. Walton Lillehei and colleagues described a technique known

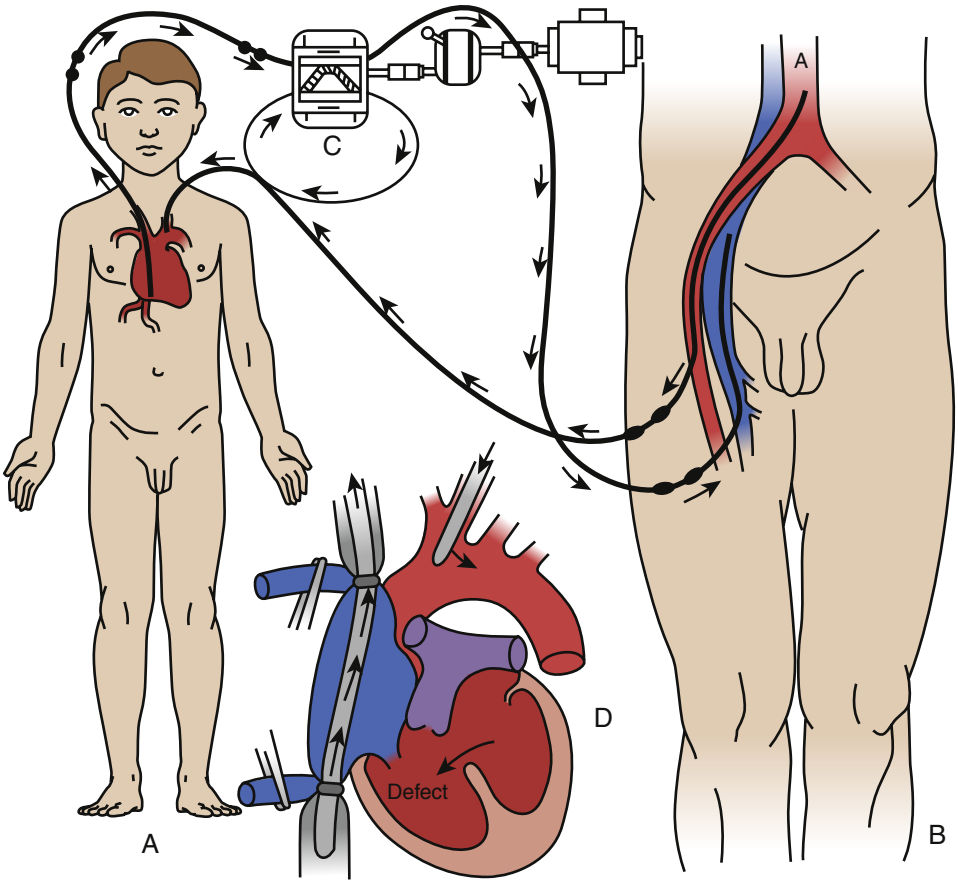

Figure 30–1. Controlled cross circulation. *(Modified from Lillehei CW: Controlled cross circulation for direct-vision intracardiac surgery: correction of ventricular septal defects, atrioventricularis communis, and tetralogy of Fallot,* Post Grad Med [Minneapolis] *17:288-396, 1955.)*

as controlled cross-circulation whereby a "donor," usually one of the patient's parents, functioned as a pump/oxygenator (Figure 30-1). The first case was described in 1954. After this, they described 45 patients, with 18 patient and no donor deaths. Although clearly an extremely high mortality, this represented a great improvement.[5] Interestingly enough, after this data was published, some commentators suggested abandonment of further research into the bypass machine. In May 1955, a team lead by Kirklin of the Mayo Clinic published an initial series of 8 patients who were operated on by a machine similar to that of Gibbon. Despite a mortality rate of 50%, this was clearly an improvement over the early bypass patients. In conclusion, Kirklin declared that "Use of this system established excellent conditions for precise, unhurried intracardiac surgery."[6] Thus began the modern age of cardiac surgery. What followed over the next few decades was experimentation with different types of oxygenators, culminating in the formulation of microporous hollow-fiber membranes. These oxygenators were made of hollow fibers within a hard plastic shell. They had a large surface area/volume ratio, thus making them extremely efficient for gas exchange. Other advantages included being easy to produce in large numbers, in different sizes, and with noncompliant blood/gas compartments. These collective advantages made them ideal for pediatric cardiac surgery.

Over the last three decades, surgeons have been able to offer improved palliations for diseases that were uniformly fatal up until that point. Teams routinely used deep hypothermic circulatory arrest to perform complex repairs. This chapter outlines present understanding of cardiopulmonary bypass: attempts that are made to protect vital organs and our present day options for myocardial support postbypass. Looking forward into the next decade, the issues of functional survival into midlife; neurologic outcomes; and such technical questions as blood conservation, further decreasing the inflammatory response to bypass, and circuit miniaturization will come to the forefront of research.

Cardiopulmonary Bypass in Infants Versus Adults

The management of CPB in the pediatric patient is very different from that of the adult (Table 30-1). The most important of these are the routine use of hypothermia with or without circulatory arrest, the use of low perfusion pressures, and, of great clinical importance, marked hemodilution. Thus pediatric patients are exposed to the extremes of physiologic tolerance. These factors, coupled with immature organ systems, place pediatric patients at great risk during the period of cardiopulmonary bypass. In addition to these differences, which are directly attributable to the differences between the two age groups, there are additional factors unique to the pediatric patient that further complicate the management strategy. Box 30-1 lists some of these factors. From the surgical perspective, several technical challenges exist. Venous and arterial cannulae have potential effect on hemodynamics. Collateral vessels may

Table 30–1 Differences Between Adult and Pediatric Cardiopulmonary Bypass

Parameter	Adult	Pediatric
Hypothermic temperature	Rarely <25-32° C	Commonly 15-20° C
Circulatory arrest	Uncommon	Common
Pump prime		
Dilutional effect on blood volume	25%-33%	200%-300%
Additional additives	Blood, albumin	
Perfusion pressure	50-80 mm Hg	20-50 mm Hg
Influence of pH management	Minimal at moderate hypothermia	Marked at deep hypothermia
Measured $PaCO_2$ differences	30-45 mm Hg	20-80 mm Hg
Glucose regulation		
Hypoglycemia	Rare; requires liver injury	Common ↓ glycogen stores
Hyperglycemia	Frequent; insulin bolus/infusion	Less common; rebound ↓↓ glucose

From Dinardo JA: Physiology and techniques of extracorporeal circulation in the pediatric patient. In Lake CL, Booker PD: *Pediatric cardiac anesthesia,* Philadelphia, 2005, Lippincott Williams & Wilkins, p 229.

Box 30–1 Unique Pediatric Characteristics

Smaller circulating blood volume
Higher oxygen consumption
Reactive pulmonary vascular bed
Intracardiac and extracardiac shunting
Altered thermoregulation
Poor tolerance for micoroemboli

allow blood return to the heart during bypass (making visibility a challenge). Collaterals may also steal blood away from vital organs making organ preservation difficult.[7] Coronary anomalies that accompany many congenital cardiac lesions complicate repair, and the multiple suture lines required for repair may bleed after surgery in patients with coagulopathy.

Physiology of Cardiopulmonary Bypass

The safe conduct of CPB in the neonate and infant requires a comprehensive understanding of the physiologic effects that occur. Variables include circuit design, hemodilution, choice of cannulae, degree of hypothermia, acid-base strategies, and flow rates, and include the decision to use deep hypothermic circulatory arrest.

Hypothermia

The reason for the use of hypothermia during CPB is protection of the myocardium and other vital organs. To this end, three distinct methods are used: moderate hypothermia (25° to 32° C), deep hypothermia (18° to 20° C), and deep hypothermic circulatory arrest (DHCA) where circulation is shut down completely at 16° to 18° C.

Normothermia and moderate hypothermia are used in cases where the surgeon is able to safely cannulate both vena cavae in order to operate within the heart. This, of cours,e can be done even on the smallest of patients, bearing in mind that the cannulae may cause vena caval obstruction and impaired drainage that can adversely affect both cerebral and abdominal perfusion, independent of perfusion pressure. Deep hypothermia with reduced pump flow to as low as 25 to 50 mL/kg/min will allow the surgeon to perform corrective surgeries with only minimal return of blood to the surgical field while at the same time maintaining vital organ perfusion. DHCA is used for the repair of complex intracardiac lesions as well as reconstruction of the aorta. Once circulation has ceased, the surgeon is able to remove all cannulae and work in a completely bloodless and unobstructed field. An alternative for aortic surgeries is DHCA with low-flow antegrade cerebral perfusion with an arterial cannula in the innominate artery and drainage via a suction catheter or venous cannula in the right atrium/superior vena cava. Flow rates of between 20 and 50 mL/kg/min to a perfusion pressure of 30 to 50 mm Hg are used.[8]

The principal clinical effect of hypothermia is to reduce metabolic rate and molecular movement. As temperature is lowered, both basal and functional cellular metabolism are reduced, and the rate of adenosine triphosphate consumption is decreased. Whole body oxygen consumption decreases directly with body temperature. The cerebral metabolic rate ($CMRO_2$) has been found to exponentially decrease as temperature decreases throughout the clinically relevant temperature range of 37° to 18° C.[9,10] The reduction in $CMRO_2$ has been calculated to be between 82% and 87% of baseline in both the canine model and the pediatric population.[9] The relationship between temperature and metabolic rate is quantified experimentally by calculating a temperature coefficient known as the Q10. It is defined as the ratio of metabolic rates at two different temperatures separated by 10° C. In the adult population, this has been found to be 2.4 to 2.8, while in the pediatric population it is 3.65. This shows that in the pediatric population there is a greater decrease in metabolic rate as the core body temperature drops. Clinically, this translates to potentially greater brain and organ protection with hypothermic temperatures.

In contrast to the role that hypothermia plays in cerebral protection, it has less importance in protection of the myocardium; indeed, it has been suggested that electrical quiescence accounts for approximately 90% of myocardial protection at normothermia.[11] It has been found that a decrease in perfusion temperature has a possible deleterious effect on the myocardium, as it leads to abnormal calcium and sodium handling. As Na^+/K^+ ATPase inhibition occurs with a falling temperature, it gives rise to an increase in intracellular sodium. This may then result in an increased activity of the Na^+/Ca^{2+} exchanger, with an increase in intracellular calcium.[12] This may play an important part in the development of an entity described as rapid cooling contracture, which is thought to play a role in postbypass myocardial dysfunction. This effect of cooling on myocardial performance may be felt more in neonates and infants, as their lower total body and cardiac masses make them susceptible to more rapid temperature changes.[13]

The adverse effects of rapid cooling have been demonstrated experimentally in the kidneys, liver, and lungs as well. In clinical practice, however, many variables are involved and there does not seem to be readily apparent injury to the patient from rapid cooling.[14,15] It does appear that the neonate is able to tolerate the stress of profound hypothermia without difficulty. The reason for this may be the fact that neonates possess differential ionic channel density or have different membrane function when compared to older subjects. These theories remain speculative.

The use of hypothermia in pediatric cardiac surgery is commonplace. It aids in organ function during ischemia, it allows the surgeon to operate in a bloodless surgical field in the case of DHCA, and CPB is safer.

Pulsatile Versus Nonpulsatile Flow

The question whether pulsatile flow could improve outcome compared to nonpulsatile flow remains unanswered. The basis for this concern stems from the suggestion that nonpulsatile perfusion may be associated with microcirculatory dysfunction and thus may be important in the genesis of post-CPB myocardial, cerebral, and renal dysfunction.[16] The desirability of pulsatile perfusion has been contemplated and studied since the introduction of extracorporeal circulation in the 1950s.

The difference between these two modes of perfusion is not simply the generation of a pulse pressure. Pulsatile flow also depends upon creation of an energy gradient and thus pump flow as well as arterial pressure must be included.[17] This relationship was described by Shepard in 1966[18] and is known as the Energy Equivalent Pressure Formula:

$$\text{EEP} = (\int fp\,\text{dt}) / (\int f\,\text{dt})$$

Thus it is the ratio of the area under the hemodynamic power curve ($\int \text{fp}dt$) and the area under the pump flow curve ($\int \text{f}dt$), where f is the pump flow rate, p is the arterial pressure (in mm Hg), and dt indicates that the integration is performed over time (t). EEP is measured in mm Hg, and therefore a comparison can be made between it and mean arterial pressure (MAP). The difference between these two measurements is the energy generated by the bypass machine, be it a pulsatile or nonpulsatile device.[17] This difference must then be applied to the surplus hemodynamic energy (SHE) formula:

$$\text{SHE} = 1332(\text{EEP} - \text{MAP})$$

The unit of measure of this formula is the erg, which measures energy. Pulsatile flow is best represented by an energy gradient rather than a pressure gradient. Pulsatile perfusion produces greater SHE units than nonpulsatile perfusion.[19] This improved generation of energy units may translate into improved regional and global blood flow to vital organs.[20] The converse is also true, that when there is no difference in energy level generated between pulsatile and nonpulsatile flow then there is no difference in vital organ blood flow (see Figure 30-2).[21]

Pulsatile flow appears to improve organ flow during CPB and function in the post-CPB period. In a pilot study of 50 patients, Alkan et al.[22] described improved myocardial function in the pulsatile group based upon the observation that this group of patients required less inotropic support. The same investigators found equivalent findings in a follow-up study of 215 patients.[20] This was similar to experimental findings of improved myocardial blood flow and function even after up to 60 minutes of DHCA.[23]

Cerebral blood flow patterns have also been studied and experimental animal models have been used to find differences in flow techniques. It is noted that both methods of perfusion show decreased flow when compared to pre-CPB. The findings showed that cerebral hemispheric, basal ganglia, brainstem, and cerebellar flows were better maintained in the pulsatile group. This was found at normothermic CPB, pre-DHCA, post-DHCA and even post-CPB. An important factor related to these findings is that cerebral vascular resistance is found to be lower under pulsatile perfusion during and after normothermic CPB.[19] Interestingly, authors involved in the aforementioned work have performed other studies that do not agree with these findings but, despite this, they make a point of concluding that in their opinion pulsatile flow remains a better choice based upon its ability to generate more hemodynamic energy, which in turn may maintain the microcirculation to a greater degree.[21,24]

Postoperative ventilation and the effects of CPB on pulmonary function are important clinical markers in patients undergoing cardiac surgery. In their large clinical study, Alkan et al.[20] found that time to extubation and length of ICU stay were significantly shorter in the pulsatile perfusion group, from which it can be concluded that pulmonary function was improved in this group. Renal function was also a marker analyzed in this study, and it was found that urine output was significantly improved in the pulsatile group, although the serum creatinine was similar in both groups. Indeed, it has been shown that pulsatile perfusion increased renal, and specifically renal cortical, flow. Pulsatile perfusion also played a role in decreasing edema and ischemic changes found in renal tubules, as compared to nonpulsatile flow.[25]

One of the biggest problems faced by clinicians when patients are placed on CPB is the inflammatory cascade that is initiated secondary to the exposure of patient's blood to the foreign surface of the bypass circuit, surgical trauma, ischemia/reperfusion, hemodilution, hypothermia, and possibly changes related to the artificial nature of perfusion. The end result is organ dysfunction that affects the myocardial, pulmonary, hepatic, and renal systems. The release of cytokines from damaged endothelium is increased. The use of pulsatile cardiopulmonary bypass has been associated with a lower concentration of interleukin-8 (IL-8), leading authors to speculate that this may improve outcomes with regard to function and microcirculation of vital organs.[22,26]

Despite encouraging experimental and clinical results with the use of pulsatile flow, broad use of this technique has not yet occurred. Multicenter trials have been called for but as yet, these have not occurred. The result is that nonpulsatile flow remains the perfusion technique most widely used in pediatric cardiac surgery.

Strategies for Blood Gas Management: Alpha-Stat and pH Stat

Another topic of considerable debate in pediatric CPB is the question of interpretation and management of pH, most specifically at deep hypothermia. In adult patients undergoing CPB, the commonest cause of brain injury is related to the

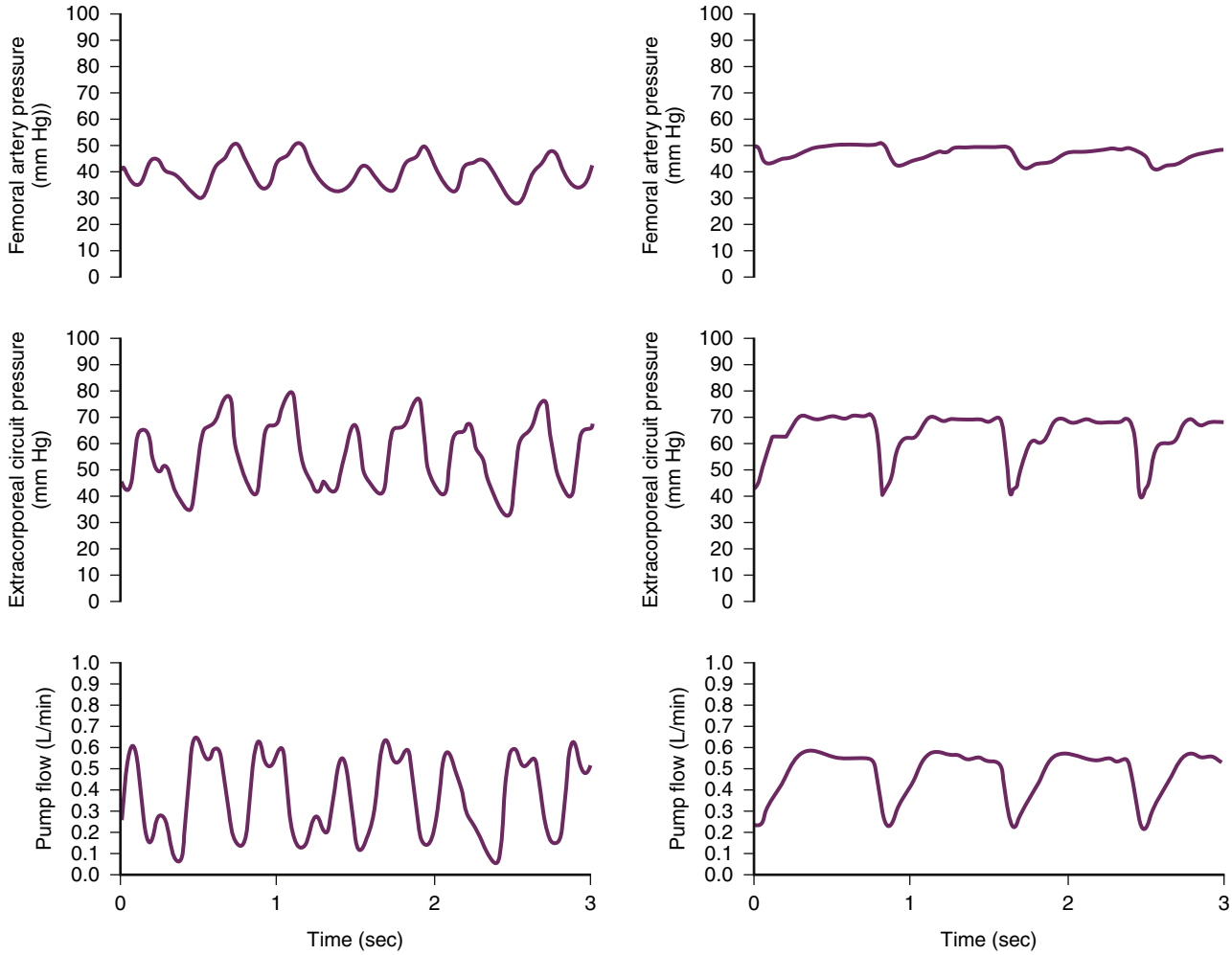

Figure 30–2. Pressure wave differences between pulsatile and nonpulsatile flow. *(Modified from Undar A, Masai T, et al: Effects of perfusion mode on regional and global organ blood flow in a neonatal piglet model,* Ann Thorac Surg *68:1336-1343, 1999.)*

delivery of embolic material to the cerebral vasculature. The etiology of brain injury in children is thought to result from hypoperfusion with cerebral hypoxia/ischemia during periods of low flow or DHCA.[26] As has been mentioned in prior discussion, many pediatric cardiac operations are performed under conditions of decreased flow rates with moderate to deep hypothermia, with the aim of protecting against vital organ injury. It would thus follow that strategies that result in the lowest cerebral rate of oxygen consumption ($CMRO_2$) would offer the best protection.

The temperature at which the pH is reported is of fundamental importance. Within the body, maintenance of electrochemical neutrality is necessary to ensure that cellular protein and enzymes function optimally. This neutrality occurs when there are equal concentrations of positively and negatively charged ions within aqueous solutions. As the temperature begins to drop, the dissociation constant of aqueous systems will increase, and thus the concentration of H^+ begins to decrease. As pH is the inverse log of H^+ and electrochemical neutrality must be maintained, the pH of the solution will increase. Electrochemical neutrality is also maintained within cells, and thus we can hypothesize that the pH within cells is a pH of neutrality. Hence we would then assume that the intracellular pH would change with a change in temperature to maintain neutrality. Analysis on ectothermic animals shows that intracellular pH remains at or near this pH of neutrality even as body temperature drops. For this to occur, there are two additional processes that occur. The first is a buffer system with a pK value close to that of the intracellular pH and whose pK changes as temperature changes. The buffering capacity of the imidazole of the amino acid histidine has these characteristics. Histidine is found commonly within intracellular proteins as well as enzymes. The term alpha refers to the degree of dissociation of the imidazole, i.e., the ratio of unprotonated to total imidazole; under normal conditions within the intracellular compartment, this has a value of 0.55. This dissociation (and hence the alpha value) will remain constant over a range of temperatures, as there is a proportional change of the neutral pH of water, the pKa of imidazole, and the tissue pH. The second necessary process is that the CO_2 content of the blood must remain constant as body temperature drops. This is the alpha-stat condition. If, however, during hypothermia the pH remains constant, then the alpha number of the imidazole will change and thus there may be a change in protein structure or enzyme function. This is known as the pH-stat condition. In this management technique, in order for the pH to remain constant through the range of hypothermic temperatures, CO_2 is added (Figure 30-3).

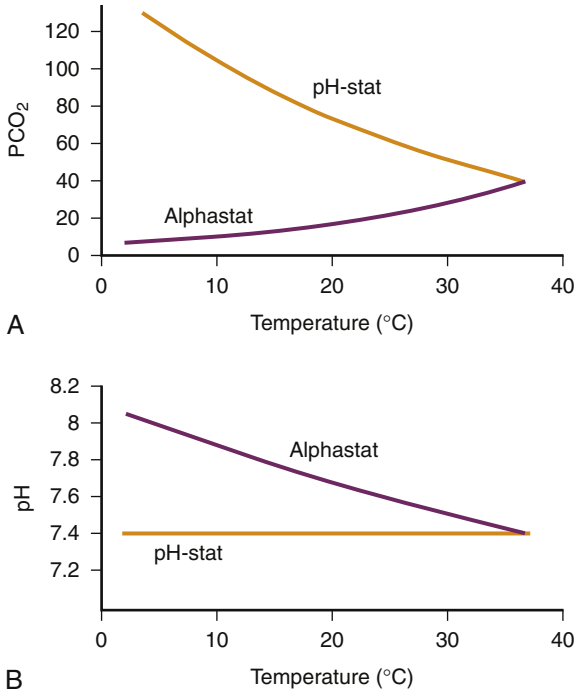

Figure 30–3. The effect of temperature on blood plasma pCO_2 and pH. *(Modified from Tallman RD: Acid-base regulation, alpha-stat, and the emperor's new clothes,* J Cardiothorac Vasc Anesth *11:282-288, 1997.)*

Into the 1990s, based upon adult studies and strategies, the alpha-stat technique was thought to have a better neuroprotective outcome. Despite the lack of prospective data, it gained widespread use amongst institutions performing cardiac surgery on children.[26] In a neurodevelopmental follow up of 16 patients who had undergone Senning operations, Jonas and colleagues reviewed perfusion techniques and pH strategy. They found that the use of alpha-stat strategy prior to DHCA was associated with poorer developmental scores. The authors postulated that the lower cerebral blood flow associated with alpha-stat might result in inadequate cooling. This study, despite having the groups at different ages at the time of assessment and being underpowered with respect to numbers, hinted at a possible need to change strategies in the pediatric population.[27] Another more devastating neurologic complication of pediatric cardiac surgery is the development of choreoathetosis. In two studies, including one from the above group, patients underwent DHCA and later went on to develop choreoathetosis. After analysis, apart from having the use of DHCA in common, it was found that all of the affected patients were managed using alpha-stat.[28,29] Laboratory studies have demonstrated that the use of pH-stat appears to offer better cerebral protection. Neonatal piglets were used in these studies, with DHCA times varying from 60 to 90 minutes. In the studies referenced, the markers used to compare the two management strategies included microvascular diameter during cooling and rewarming, cerebral tissue oxygenation, brain cooling, and metabolic markers of ischemia, such as extrastriatal dopamine production.[31,32] The effects on brain cooling include a faster rate of cooling which is uniform across all regions of the brain, especially the cortical white matter.[33] The results of these showed pH-stat to be superior in all of the aforementioned categories in the cooling phases of DHCA as well as in the recovery phase. In the first prospective trial on the use of pH-stat management in the cooling phases of DHCA, du Plessis and colleagues found that there was a greater degree of cerebral cooling, as measured by tympanic membrane temperature, in the pH-stat group. This they attributed to increased cerebral blood flow, which appeared to be equally distributed throughout the brain. In keeping with these data, this group also had more rapid recovery of electroencephalographic (EEG) activity compared to those in whom alpha-stat management had been used. EEG-confirmed seizures were also increased twofold in the alpha-stat group.[26] Although a section in this chapter will be dedicated to the discussion of monitoring with near-infrared spectroscopy (NIRS), studies suggest that the use of alpha-stat is associated with lower signals during cooling, indicating that this method results in insufficient cerebral blood flow and oxygenation.[34,35] The next question to be answered will be whether this improved brain perfusion and cooling seen with pH-stat will translate into improved neurologic outcomes. Patients enrolled in this trial underwent neurodevelopmental testing at 1 year of age, using standardized tests. There was no difference in scores based on treatment group assignment. The authors concluded that the "use of alpha-stat versus pH-stat acid-base management strategy during reparative infant cardiac operations with deep hypothermic cardiopulmonary bypass was not consistently related to either improved or impaired early neurodevelopmental outcomes."

The effects of pH/CO_2 on other organ systems have also been studied. Myocardial protection is also obviously of great concern to the entire care team. In a study performed by Nagy et al. in which troponin I was used as the marker of myocardial injury, it was found across a spectrum of patients, including some with pulmonary hypertension and cyanotic congenital heart disease, that those in whom pH-stat was used had better myocardial performance after CPB.[36] They postulated that pH-stat might induce a more even myocardial temperature during cooling due to hypercapnia-induced vasodilation. Oxygen delivery may also be improved as the oxygen-hemoglobin dissociation curve shifts rightward with the increase in CO_3. Lastly, they suggested that the hypercapnia-induced inhibition of pyruvate dehydrogenase, which leads to a decrease in lactate production, may also be of great benefit. As a secondary outcome, their study also suggested that postoperative ventilation and length of ICU stay may be shorter in the pH-stat group. Improved myocardial performance had also been found in the du Plessis study, where there appeared to be a higher cardiac index within the first 18 hours after CPB with lower inotropic use, less hypotension, and less metabolic acidosis compared to the alpha-stat group. These patients also had significantly less mechanical ventilation and shorter ICU stays.[26]

Despite these advantages, there is concern that the use of pH-stat may result in a change in the internal pH (pHi) of cells that would lead to a prolonged depletion of high energy phosphates during rewarming, which in turn would lead to cellular damage. Experimental evidence, however, seems to suggest that the pHi of cells is regulated independently of the extracellular environment. Hiramatsu et al. showed that the pHi was alkalotic irrespective of the use of alpha-stat or pH-stat strategies during the cooling phase, but that it tended towards acidosis with the onset of DHCA.[30] The data then suggested that there was a quicker recovery of both pHi and ATP using the pH-stat technique. As mentioned before, this was on the basis of a greater oxygen reserve secondary to increased

blood flow and oxygen delivery in the cooling phase. In conclusion, it would seem that the evidence presented here would undoubtedly indicate that a prudent approach would be for the use of pH-stat management during the cooling phase of deep hypothermic CPB; indeed, there is also some evidence from these studies that this strategy should be employed in the rewarming phases as well. Many centers, including our own, use alpha-stat during rewarming with good clinical outcome

Neurologic Injury and Protection

The last 30 years have seen the advent of surgical techniques and management strategies that have changed a diagnosis from universally fatal to one that can be palliated well into adulthood. The challenge we now face is the long-term effects that these very techniques and strategies have on neurodevelopmental outcomes. In contrast to the adult population where neurologic injury commonly involves thromboembolic stroke, in the pediatric population the injury results in more subtle effects such as attention-deficit problems and difficulties with fine and gross motor control, visual motor integration, and executive functioning. The end result of these problems is school failure and low self-esteem. This "developmental signature" is similar to that seen in very low birth weight premature infants.[37]

It is quite alarming to note that long-term follow-up has found that neurodevelopmental impairment occurs in more than 50% of children who have cardiac surgery as newborns or young infants.[38] Many studies of neurodevelopmental outcome after cardiac surgery in infancy have focused on injury during the intraoperative period as the likely cause of adverse outcomes. However, there is increasing evidence that brain development is abnormal in children with congenital heart disease (CHD), and injury can often be identified prior to surgery. Patient-specific factors such as genetic abnormalities, socioeconomic status, and maternal education are more important determinants of neurodevelopmental outcomes than are intraoperative management strategies.[39] Box 30-2 highlights a number of factors that influence neurologic outcome.

Box 30–2 Factors Influencing Neurologic Injury

Fixed Factors

Genetic syndromes
Structural CNS malformations
Socioeconomic status
Genetic predispositions

Modifiable Factors

Preoperative
Hypotension
Glycemic control
Hyperthermia

Operative
Emboli; gaseous/particulate
CPB circuit/inflammation
Modified ultrafiltration
pH-stat blood gas management
Cerebral ischemia
Steal
Hemodilution
Free radicals/reoxygenation

From Hsai T-J, Gruber PJ: Factors influencing neurologic outcome after neonatal cardiopulmonary bypass: what we cannot control, *Ann Thorac Surg* 81: S2381-8, 2006.

Preoperative Factors

Neonates with CHD have a higher incidence of cerebral dysgenesis than those in the general population.[40] The era of staged reconstruction of hypoplastic left heart syndrome began in the late 1970s. The diagnosis was fatal prior to that time. In a series of postmortem examinations from the early- to mid-1980s, 29% of the patients had either minor or major central nervous system (CNS) abnormalities. The absence of dysmorphic features did not preclude CNS abnormalities.[41]

Periventricular leukomalacia (PVL) is one of the most frequent and severe neuronal injuries specific to the neonatal brain. It is caused by necrosis of deep white matter adjacent to the lateral ventricles. The mechanism is thought to be related to hypoxic/ischemic injury to immature oligodendrocytes, the very cells responsible for myelination throughout the central nervous system. In early life, the brain undergoes an intensive period of neuronal development and axonal growth; thus the white matter of the brain is particularly susceptible to injury.[40] It is during this period that the brain is susceptible to ischemia-reperfusion injury due to its fragile vascularity, high metabolic activity, and immature autoregulation. PVL occurs not only in the period surrounding CPB but also in premature infants and after such insults as hypoxia, hypoglycemia, and meningitis. The incidence in infants with CHD prior to cardiopulmonary bypass has been estimated to be between 16% and 25%,[42,43] with this rate increasing to between 54% and 73%[43,44] post-CPB, based upon magnetic resonance imaging (MRI) studies. Studies have been performed using both MRI and fetal ultrasound and have demonstrated altered cerebral blood flow in fetuses with congenital heart disease; this may therefore be a basis of abnormal brain development. MRI studies have also found alarmingly low cerebral blood flow in infants with CHD prior to surgery, in some cases less than 10 mL/100 g/min.[45] Other associated factors include the presence of ductal-dependent blood flow with resultant diastolic hypotension that lowers cerebral perfusion, balloon atrial septostomy with possible embolic phenomena,[46] and ongoing systemic inflammation due to endotoxemia from mesenteric hypoperfusion.[38]

An interesting genetic association has also been found. Apolipoprotein E (APOE) is an important lipoprotein that aids in cholesterol metabolism as well as being an important cofactor in neuronal repair. There are three common forms of APOE (E2, E3, and E4), which are encoded by three alleles (ε2, ε3, and ε4). Research has shown that the APOE genotype has a strong association as a determinant of neurologic recovery following CNS injury. The presence of the APOE ε2 allele is associated with lower Psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI) scores when compared to age-matched normals. Other associated risk factors include a confirmed genetic syndrome, lower birth weight, small head circumference at 1 year, preoperative intubation, and history of ECMO or ventricular assist device.[47,48]

The intraoperative period is a time of great risk to the child. In two contrary sets of data, two apparently different neurologic outcomes were found. In a study performed in patients undergoing atrial septal defect closure either surgically or via

catheter, there was a significant decrease in intelligence quotient in those undergoing surgery.[49] However, preliminary data from another cohort failed to show a decrease in neurocognitive function in 41 patients with age ranges from 5 to 18 years exposed to CPB for closure of simple atrial or ventricular defects, or for simple valve surgery.

Factors that likely result in poorer neurodevelopmental outcomes include anesthetic-related issues encompassing a decrease in cardiac output with decreased oxygen delivery at the time of transition from negative to positive pressure ventilation, and also the negative inotropic effects of anesthetic agents. Hypoxia may worsen prior to establishment of CPB, particularly in those with ductal-dependent flow, as the surgeon dissects around the ductus causing vasospasm. Once on CPB, numerous factors may occur that may have an adverse effect. These include malposition of both the arterial and venous cannulae with resultant poor flow characteristics and venous drainage leading to cerebral hypoperfusion; embolic phenomena including air and thrombus (may occur despite meticulous circuit check, adequate anticoagulation, and deairing of the heart once repair is undertaken); the inflammatory response induced by CPB; the effects of DHCA with ischemia-reperfusion injury and uneven cerebral cooling; hemodilution; pH management; and the effect of collateral steal of blood away from vital organs.[38,40] Once weaning from CPB has taken place, it is the effect of continued myocardial dysfunction with decreased oxygen delivery and hypoxia that may lead to ongoing brain injury. The need for ECMO for postcardiotomy support (2% to 5% of patients)[50] carries significant morbidity and mortality, with up to 50% of survivors showing neurodevelopmental problems.[51]

Postoperative Factors

In the postoperative period, ongoing low cardiac output and hypoxia may result in continued neurologic damage. Other factors that may play an important part in the genesis of injury during this period include hyperthermia, endocrine abnormalities, acid-base disturbance, and disruption of cerebral vasoregulation. Cerebral vascular autoregulation is disrupted after CPB, and thus it is important to maintain adequate cerebral perfusion pressure. Longer postoperative length of stay has consistently been shown to be associated with worse neurodevelopmental outcomes, suggesting that events in the postoperative period modify the risk of an adverse outcome.

Neuromonitoring and Neuroprotection

A multitude of factors can result in neurologic injury, either independently or in combination. Neuroprotection should begin from birth. In the preoperative period, clinicians should be aware that severe hypoxia, low perfusion pressure in the form of low diastolic pressure, low cardiac output states, respiratory alkalosis, and hyperthermia may be variables in neurologic injury. In the transition to the operating room and controlled ventilation, clinicians should be attentive to changes that result in the aforementioned factors. How then can we protect the brain?

In recent years, interest has been focused on neurologic monitoring with near-infrared spectroscopy (NIRS), transcranial Doppler, EEG, and jugular venous saturation alone or in combination, as opposed to using surrogate markers of perfusion pressure, mixed venous saturation, and acid-base status.[52]

NIRS provides a real-time, noninvasive assessment of regional cerebral oxygenation and has been validated with jugular venous saturation.[52] In this method, a venous-weighted approximation of tissue oxygen saturation is measured with a venous:arterial blood ratio of 85:15. This technology uses modifications of Beer's equation. Infrared light passes through the skin, penetrates through tissue, and then returns, whereupon allowing assessment of the oxyhemoglobin saturation of tissues at a depth of 2 cm. Subtraction of the shallow light path from the deep light path allows assessment of brain oxygenation.[52] The INVOS 5100 (Somanetics, Inc, Troy, Mich.), which is approved by the FDA for use in adults and children, calculates a regional cerebral saturation index (rSO_2i) by computing the ratio of oxyhemoglobin to total hemoglobin. It has a range of 15% to 95%. These monitors are best used as trend monitors, with a fall of 20% from baseline being significant.[53] Factors that affect cerebral oxyhemoglobin saturation include cerebral perfusion pressure, cerebral blood flow, arterial oxyhemoglobin saturation, $PaCO_2$, and cerebral metabolic rate. The baseline values have been quantified, with 70% being normal in adults. Studies of single-ventricle patients, and laboratory studies, have suggested that a saturation below 30% suggests dependence on anaerobic metabolism.[54,55]

NIRS has thus been used to guide a safe duration of DHCA, proper placement of CPB cannulae, and also to guide optimal flow during low-flow cerebral perfusion during deep hypothermia.[56-58] Some authors have even suggested that the placement of a NIRS probe over the anterior abdominal wall or renal bed will give an idea of somatic flow that in conjunction with cerebral NIRS will give invaluable data with respect to adequacy of perfusion.[59,60] EEG monitoring is theoretically attractive for the detection of hypoperfusion or ischemia on the basis of altered signals. It is, however, not routinely feasible, as the technology is bulky and the signals may be affected by electrical interference from electrocautery, patient temperature, anesthetic agents used, and CPB itself. EEG is, however, useful for quantification of anesthetic depth, occurrence of electrical silence with DHCA, and of course the presence of epileptiform activity in the postoperative period that may indicate neuronal damage.[53]

Transcranial Doppler (TCD) provides a real-time monitor of cerebral blood flow velocity and the occurrence of embolic phenomena during CPB. The instrument uses pulsed-wave ultrasound, usually at 2 MHz frequency. The units display the frequency of the Doppler signals; peak systolic and mean flow velocities (in centimeters per second); and the pulsatility index, which is the peak velocity minus the end-diastolic velocity divided by the mean velocity.[61] The added advantage of the device is the identification of microemboli via high intensity transient signals displayed as an audible click for each event. The most consistent and reproducible technique is to monitor the middle cerebral artery through the temporal window, which is located superior to the zygoma and anterior to the tragus. Clinically, either an inflow arterial obstruction, which will be seen by a drop in the peak Doppler signal, or an outflow obstruction, which is diagnosed by a decrease in the diastolic flow signal, can be appreciated. The etiologies include malposition of the arterial cannula, arterial line obstruction, changes to perfusion pressure, and changes in the flow rates,

or alternatively obstruction to venous drainage from the head by superior vena caval cannula malposition, kinking of the venous line, or after the creation of a superior cavopulmonary anastomosis.[52]

Jugular venous bulb saturation (SjO_2), as its name implies, measures the saturation of the venous blood by the placement of a retrograde catheter into the jugular venous bulb located, approximately, just cephalad of the C1-C2 disc. The jugular veins drain almost all blood from the brain, but up to 6.6% of this blood comes from extracranial sources including the emissary and frontal veins and the facial vein, which contributes the most extracranial blood.[62] Another potential anatomic problem with this monitoring technology is that blood does not drain equally into the two jugular venous bulbs. In the pediatric population, the use of SjO_2 has been studied in the context of optimal cooling time in those undergoing DHCA. As the temperature drops, the brain will extract less oxygen as its metabolic demands fall. Under optimal conditions, as the temperature falls, the SjO_2 rises, until the difference between the arterial saturation and the jugular venous saturation becomes minimal.[63] At this point, it can be concluded that the metabolic rate of the brain has reached a nadir at which maximal protection is occurring. This technique is clearly invasive and thus studies have been performed comparing this technique to NIRS. These studies demonstrate that although there is a good correlation, certain limitations occur.[64-67] These involve the accuracy of NIRS at low SjO_2; NIRS may have difficulty reading values greater than 90% when cerebral metabolism is slowing, and has questionable accuracy at low flow rates. The best correlations between the modalities occur in patients who weigh less than 10 kg, because of their lesser scalp and skull thickness.[65,66]

Some centers use triple monitoring; that is, NIRS, EEG, and TCD. The advantage of this is that the monitoring is noninvasive and relatively easy to apply. Once an abnormality is detected, adjustments in patient positioning, cannula position, blood pressure, hemoglobin, $PaCO_2$, and depth of anesthesia may be needed in the prevention of potential neurologic injury.[38,52,53,61] In a study of triple monitoring on 250 patients, at first the investigators did not treat any changes that were observed, as this phase was an attempt to validate this triple monitoring. Twelve (26%) of 46 of these patients developed early postoperative neurologic problems inclusive of seizures, coma, hemiparesis, movement, vision or speech disorder. In the group in which an intervention was performed when a problem was found, the complication rate decreased to 7 out of 130 patients (6%). Of note in the study was that in the remaining 74 patients in whom no changes were detected, 5 patients had adverse outcomes. Of the monitoring modalities, EEG found 5% of the abnormalities, while NIRS and TCD found 58% and 37%, respectively.[68] A recent meta-analysis of NIRS monitoring alone found it to be a useful adjunct, but that greater clinical relevance can be achieved by combining modalities. However, despite measuring regional cerebral saturation, there is a paucity of data suggesting improved neurologic outcome based upon these numbers alone.[69]

Box 30-3 illustrates a suggested strategy for neuroprotection and monitoring during CPB. A recent study failed to demonstrate an association between a low rSO_2 during CPB and neurologic outcome.[70] It did, however, show that there appeared to be an association between preoperative MRI findings of brain immaturity and outcome. This led the authors to suggest that the preoperative MRI finding of immaturity, which results in vulnerability to injury, may be a useful marker for long-term outcome.[70]

Box 30–3 Comprehensive Strategy for Brain Protection

CPB Factors

Adequate perfusion pressure
Adequate DO_2 as measured by SvO_2/ABG
Limit inflammatory response: steroids/leukocyte–depleting filters/heparin-coated circuitry
Use of filters to avoid air/particulate emboli
Ensure adequate anticoagulation
pH-stat management for any temperature ≤ normothermia
Hematocrit ≤30 (≤1 year of age) or ≥25 (≥1 year of age)
Hyperglycemia
Hypothermia

DHCA

Adequate cooling times of at least 20 minutes
Hyperoxygenation prior to arrest
Limit time to ≤40 minutes
Alternative perfusion strategies:
  Intermittent cerebral perfusion
  Low-flow CPB
  Antegrade cerebral perfusion

Monitoring

Near-infrared spectroscopy
Electroencephalography
Transcranial Doppler

Neuroprotection must be continued well into the postoperative phase. We know that cerebral autoregulation is not normal in the immediate postoperative period and thus adequate perfusion is reliant on MAP. Important management strategies include avoiding alkalosis and hypocarbia as these may further decrease cerebral blood flow, and early treatment of hypoxia, hyperthermia, acid-base disturbance, and electrolyte abnormalities. It has been suggested that continued NIRS monitoring in the postoperative phase may be useful at guiding therapy to protect the brain, but its impact on neurodevelopmental outcomes remains unclear.[38]

Myocardial Protection

Experimental evidence suggests that neonatal and infantile myocardium will have an earlier accumulation of lactate that in turn inhibits glycolysis and the generation of ATP. The decreased ATP will prevent the uptake of calcium by the sarcoplasmic reticulum. As such, the immature myocardium that relies on glucose as its major energy substrate and extracellular calcium for excitation coupling is at a major disadvantage.[71-73] The end result is earlier ischemic damage compared to the adult. Unfortunately, most patients operated on in infancy have associated cyanosis, myocardial hypertrophy, hypoxia, volume and pressure overload, and acidosis. Thus it is obvious that these factors, coupled with immature myocardial physiology, place these patients at an enormous disadvantage. The presence of large amounts of collateral flow associated with a number of congenital abnormalities will result in increased flow to the left heart that can result in the washing away of cardioplegia and constant myocardial warming. Either of these

factors can result in inadequate myocardial protection.[74] It has been found that up to 90% of patients who do not survive the perioperative period show some form of myocardial necrosis that exists in the absence of coronary artery obstruction. This necrosis may affect the entire subendocardium and lead to endocardial fibrosis with late myocardial dysfunction.[75]

The major factors that will aid in myocardial protection are electrical quiescence achieved by the infusion of cardioplegia into the aortic root after aortic crossclamping or directly into the coronary arteries, hypothermia, and the prevention of myocardial distension. Cardioplegia solution is infused, under the direction of the surgeon, by the perfusionist. The principles that guide the composition of the solution include (1) ability to produce rapid cardiac arrest, (2) hypothermia, (3) metabolic substrates, (4) appropriate pH, and (5) membrane stabilization (i.e., low Ca^{2+}, Mg^{2+}, steroids, O_2 radical scavengers).[76] Historically, crystalloid cardioplegia has been used. Apart from the high concentration of potassium that is responsible for the electrical quiescence, the concentrations of both calcium and magnesium have been found to be important. Ideally the solution should be hypocalcemic and hypermagnesemic. Experimental studies have shown that under hypoxic conditions (cyanotic heart disease), hypocalcemic cardioplegia allows for improved recovery from hypoxic damage. It has been found that high levels of intracellular Ca^{2+} during ischemia and reperfusion lead to increased cellular injury.[76] The importance of high levels of magnesium is twofold: the prevention of calcium entry into hypoxic myocardial cells and the prevention of arrhythmia in the immediate post-bypass period.[76] The two most widely used crystalloid cardioplegia solutions are the del Nido and St. Thomas solutions. The del Nido solution contains Na^+ of 153 mmol/L, K^+ of 24 mmol/L, Cl^- of 132 mmol/L, Ca^{2+} of 0.4 mmol/L, Mg^{2+} of 6.2 mmol/L, lidocaine of 140 mg/L, and mannitol of 2.6 g/L. St. Thomas' solution contains Na^+ of 129 mmol/L, K^+ of 16 mmol/L, Cl^- of 140 mmol/L, Ca^{2+} of 1.2 mmol/L, Mg^{2+} of 16 mmol/L, and no mannitol or lidocaine. Each solution has its proponents and opponents.

Three phases of cardioplegia have been described: induction, maintenance, and reperfusion. Induction of cardioplegia covers the initial dose that results in electrical silence soon after initiation of CPB. All hearts receive noncoronary collateral blood flow via pericardial connections and, in some patients with aortopulmonary collaterals, this may be more significant. The presence, size, and number of these vessels may be variable, and thus the flow may be of sufficient volume to wash out the cardioplegia. This will result in an increase in myocardial temperature, as the collateral flow will bring blood to the heart that is at the temperature of the systemic perfusate and also, importantly, a possible return of electrical activity. This is the rationale to give intermittent doses of cardioplegia every 10 to 30 minutes.[75-77] The periodic cardioplegia will result in 1) maintenance of arrest, 2) restoring myocardial hypothermia, 3) buffering acidosis and washing away acidic metabolites, 4) replenishing high-energy phosphates, and (5) counteracting edema with hyperosmolarity[75,76] This is the maintenance phase of cardioplegia. The reperfusion phase is a critical time, as the mode of reperfusion appears to be more important than the duration of ischemia. In a study performed on 103 patients with both cyanotic and acyanotic congenital heart disease, one group received intermittent boluses of cold cardioplegia, while the second group received the same cardioplegia strategy, to which was added 300 mL/m^2 of the same cardioplegia solution at 35° C, just prior to aortic crossclamp removal. This is known as terminal warm blood cardioplegia (TWBCP) and is often used in adult cardiac surgery. The use of TWBCP was associated with higher numbers of patients resuming spontaneous sinus rhythm, decreased inotropic use to wean from CPB (although nearly all patients in the study required inotropic support postoperatively in the ICU), improved lactate extraction, decreased troponin T, and decreased heart-type fatty acid binding protein. The latter two markers are indicative of cellular damage and necrosis. It would thus appear that the use of TWBCP may provide additional protection by improving myocardial aerobic energy metabolism and decreasing cellular damage.[77]

Three additional factors are of importance in optimal cardioplegia: adequate coronary distribution, the delivery pressure of cardioplegia solution, and whether one uses crystalloid versus blood cardioplegia. Although the pediatric patient generally does not suffer from coronary artery disease, the presence of aortic insufficiency, severe septal and ventricular hypertrophy, and the need to move the coronaries (arterial switch operation) are important considerations. Despite the requirement that the cardioplegia be delivered at a certain pressure to ensure adequate distribution, care must be taken not to perfuse the myocardium at too high a pressure as this may itself lead to myocardial and vascular endothelial cell damage, increased edema, and decreased ATP levels. A pressure of between 30 and 50 mm Hg has been shown to be adequate.[75] The use of blood cardioplegia results in myocardial arrest in an oxygenated state, with no loss of ATP in the period of electrical activity prior to arrest. This is contrasted to the use of crystalloid where there is a high loss of ATP during this same period. Several authors and commentators have concluded that there appears to be a distinct advantage in the use of blood cardioplegia over crystalloid, be it at cold or warm temperatures.[75-77,79-82] Some of these advantages included lower coronary sinus lactate, improved cardiac index, better echocardiographic evidence of left ventricular function, increased heat-shock protein (produced in myocardial cells in response to stress), and decreased troponin I release, which may correlate with less myocardial injury.

In addition to these factors, meticulous surgical technique that prevents myocardial tissue injury secondary to tissue trauma, heart block, coronary kinking, and coronary air is of great importance. Anesthesia factors that may aid myocardial protection include a thorough understanding of the underlying physiology both prior to and after surgical intervention, ventilator settings that will aid and not impede myocardial function (e.g., attempts to keep pulmonary artery pressures low so as to off-load the right ventricle), and precise use of inotropic, vasodilator, or antiarrhythmic therapies.

Pulmonary Effects of Cardiopulmonary Bypass

The institution of CPB may have deleterious effects on the lungs. It is, however, important to note that there is a group of patients who present to the operating room with preexisting abnormal pulmonary physiology. This is often caused by their preexisting cardiac condition. Some patients exhibit the ill effects of increased pulmonary blood flow due to unrestricted left-to-right shunt. The presentation at surgery is thus

a spectrum of patients who have been successfully medically palliated with antifailure therapy, those who have failed medical therapy, and, worst case scenario, those with established pulmonary hypertension. This latter possibility is commonly found in those with trisomy 21 who are operated upon at or after 6 months of age. The pulmonary hypertension occurs due to unrestricted pulmonary blood flow that results in hypertrophic changes to the media of the pulmonary arteries. This places these patients at a clear disadvantage at the weaning phase of CPB. In some, this may be severe enough that the patient may suffer acute right ventricular failure, resulting in a failure to wean from CPB and thus necessitating the use of acute extracorporeal support. Other patients in whom vascular reactivity and pulmonary hypertension may be an issue during weaning and separation from cardiopulmonary bypass include neonates, by virtue of their pulmonary vasoreactivity, a carryover from the fetal circulation, and those patients in whom there is an obstruction to pulmonary venous drainage, be it at the level of the pulmonary veins or due to restrictive atrial septae associated with left-sided obstructive lesions. The lungs may be a source as well as a target of the inflammatory response associated with CPB.[83] The result of this is capillary leak and extravasation of fluid into the alveolar spaces with resultant poor oxygen exchange and a detrimental effect on pulmonary mechanics. Etiologic factors associated with capillary leak include hemodilution with resultant decrease in oncotic pressure, ischemia-reperfusion injury, and the sequestration of activated neutrophils, cytokines, complement, and leukotrienes within the pulmonary vascular bed during the period of CPB. At the onset of CPB, perfusion will cease through the pulmonary bed, and that in turn leads to a decrease in alveolar stability.[84] Clinical studies have also shown that there are changes to functional residual capacity (FRC) during CPB. Initially there is an increase in FRC as the chest cavity is opened. This will, however, change to a decrease with the cessation of pulmonary flow and alveolar collapse. There is a further decease in FRC with chest closure, continued inflammatory effects, and the presence of extravasated fluid.[84] It can thus be appreciated that all these factors lead to the inevitable decrease in PaO_2 encountered in the immediate postbypass period.

Although the use of steroids has been shown to improve postoperative pulmonary function by decreasing the inflammatory effects on the lung, it is the use of modified ultrafiltration (MUF) that has greatly improved pulmonary function and oxygenation/ventilation in the immediate post-CPB phase. The use of MUF has two apparent effects:

1. The reduction of total body water and, with this, an associated decrease in lung water that leads to improved lung compliance and decreased airway pressure[85]
2. A decrease in inflammatory markers, which leads to a decrease in capillary leak.[86]

The clinical result is decreased mechanical ventilation, faster time to extubation, and decreased ICU time.[85,87] The use of MUF has allowed the practice of early extubation at many institutions. The patient population in which early extubation is key to further management is the single-ventricle population after the cavopulmonary anastomosis and Fontan completion. In those patients, the flow through the pulmonary bed is entirely passive and can be adversely affected by positive-pressure ventilation, leading to a decrease in cardiac output that is clearly detrimental. Early extubation, for the purposes of this discussion, is defined as extubation upon arrival to the ICU immediately postoperatively. This strategy is also commonly applied to patients undergoing such diverse procedures as coarctation surgery, shunt procedures, ASD, VSD, and conduit revision, to name a few.

Renal Function and Protection on Cardiopulmonary Bypass

The development of acute kidney injury (AKI) is multifactorial and can be subdivided into preoperative, intraoperative, and postoperative causes. The etiologies of the preoperative injury are mainly associated with neonates and infants as their renal physiology is immature. Glomerular filtration rate (GFR) is lower in this age group due to lower mean arterial pressure and high renovascular resistance with GFR maintained by postglomerular efferent arteriolar vasoconstriction that is dependent on high levels of angiotensin II activity. It is for this reason that the angiotensin-converting enzyme inhibitors are used in these patients with extreme caution.[88]

Preventive and treatment strategies aim to maintain systemic oxygen delivery, maintain perfusion pressure to vital organs, and prevent any further deterioration in function. Thus, in the preoperative phase, careful attention must be paid to balancing pulmonary and systemic perfusion (Qp/Qs). Soon after birth the pulmonary resistance begins to fall, and thus in patients with ductal-dependent systemic flow, pulmonary blood flow may increase. The increase in pulmonary blood flow results in a concomitant decrease in systemic flow. This may decrease perfusion of vital organs. Management at this time will therefore include prostaglandin infusion to maintain ductal-dependent systemic flow, low inspired FiO_2 to increase PVR, support of cardiac function, and early corrective or palliative surgery. Intraoperative aims include many of the factors that are discussed elsewhere in this chapter including dampening the inflammatory response, decreasing DHCA time, the effects of nonpulsatile versus pulsatile CPB, decreasing circuit size, and limiting the exposure to blood products. After the completion of CPB, the aims of preventative management include decreasing total body water and inflammatory mediators by means of modified ultrafiltration; ensuring that there are no residual lesions that may impact Qp/Qs or directly affect cardiac function; and ensuring appropriate and ongoing cardiac support in the form of inotropic drugs, vasopressors, vasodilators, and diuretics.

The incidence of AKI varies depending on surgical procedure, ranging from 0.7% for short, uncomplicated operations such as atrial septal defect closure, to 59% for longer, more complicated operations such as the arterial switch. Across the entire spectrum of procedures the incidence varies from 6% to 17%. Renal replacement therapy is required in 2.3% to 11.5%.[89-91] Mortality rates in this subgroup of patients may be as high as 79%.[90] Box 30-4 describes the risk factors associated with the development of acute kidney injury (AKI) in the immediate post-CPB period. Although this has been collated from data collected over the last 10 to15 years, it seems that the incidence of acute post-CPB renal failure is decreasing.[90] It is unknown whether this can be ascribed to improved perfusion techniques, improved surgical technique, improved drug therapies, or improved understanding and management in the ICU. The development of AKI is a risk factor for mortality as well as for prolonged hospital stay and an associated

Box 30–4 Risk Factors for the Development of Acute Renal Failure

Age ≤1 year
Elevated Aristotle/RACHS-1 (categories 4-6) surgical complexity scores
Long bypass time
Long crossclamp time
Deep hypothermic circulatory arrest
Increased use of blood products
Low post-CPB cardiac output
Inotropic support (especially epinephrine and isoproterenol)
Low trough blood pressure on postoperative day 1

increase in hospital costs. Despite these alarming numbers, the diagnosis may prove difficult, as consensus as to the definition is not clear. The important factor to remember is that by the time the laboratory values begin to change significantly, damage may already have occurred. A number of attempts have been made to find a reliable marker. Candidates include the use of p-RIFLE (pediatric risk, injury, failure, loss, and end-stage renal disease) which estimates the decrease in creatinine clearance[92]; renal neutrophil gelatinase-associated lipocalin (NGAL), which is expressed during ischemic injury, sepsis, and posttransplant[93]; and interleukin 18 (IL-18).[94] The advantage of early detection is the early institution of therapy. Two forms of therapy have been used in this setting: peritoneal dialysis (PD) and continuous renal replacement therapy (CRRT). Advantages of CRRT include rapid removal of excess body fluid, treatment of life-threatening hyperkalemia, and the ease in which the circuit can be placed in parallel with an ECMO circuit. In this setting, CRRT is usually achieved by a venovenous circuit with the utilization of the internal jugular, subclavian, or femoral veins. In one study using this approach, up to 90% of patients were discharged with normal renal function.[89]

Endocrine Response to Cardiopulmonary Bypass

The use of CPB, with and without the use of DHCA, is associated with considerable endocrine stress.[95] In a study of 22 infants ranging in age from 2 days to 18 months with a mix of both cyanotic and acyanotic conditions who all underwent repair utilizing DHCA, the authors found that there was an increase in both endogenous epinephrine and norepinephrine. This increase persisted from the cooling phase through the warming phase and up to the end of the study, which unfortunately ended with chest closure. These findings led the authors to conclude that there is considerable sympathoadrenal stress associated with CPB and DHCA, despite what appeared to be adequate anesthesia and analgesia. The nonlinear relationship between duration of arrest and the postarrest values possibly indicated that the tissues were beginning to become hypoxic; thus trending these values could suggest a safe time for DHCA.[96] Clinically, however, these elevations in catecholamines are of unknown significance.

The end point of the hypothalamic-pituitary-adrenal axis, that is, the secretion of glucocorticoids, is important in the setting of cardiac surgery, as studies suggest that the effect of these glucocorticoids include: 1) enhanced vascular sensitivity to catecholamines, 2) increased myocardial β-adrenergic receptors, 3) increased renin substrate and calcium availability, 4) inhibition of vasodilation and catecholamine degradation. The end result of these factors may be that glucocorticoids enhance myocardial and vascular responsiveness to catecholamines. In studies performed on critically ill neonates, infants, and children with hypotension refractory to volume resuscitation as well as inotropic support, adrenal insufficiency was found, with clinical improvement upon administration of corticosteroids.[97] Despite these findings, there is still considerable disagreement in the literature as to the optimal dosing and timing, or whether corticosteroids should even be administered.[98-101]

Thyroid hormone levels have been found to become suppressed after critical illness and surgical procedures. This has the potential to cause a number of problems in the post-CPB period including prolonged ventilation, increased inotropic requirements, and increased need for diuretic therapy.[102] Endogenous mediators including glucocorticoids, tumor necrosis factor, and IL-6 are released in response to CPB and lead to low postoperative triiodothyronine (T_3). Interestingly, there is an initial surge of free hormone after the institution of CPB, followed by low total and free T_3/T_4 levels. The nadir of this effect occurs between 12 and 48 hours after bypass and lasts up to 5 days.[102,103] At a cellular level, the effect of thyroid hormone is to influence the entry and extrusion of calcium from the cardiac myocyte via the sarcoplasmic reticulum and cell membrane. Thus low T_3 has a profound effect on myocardial function and may be manifest by both systolic and diastolic dysfunction and by increased vascular resistance, which collectively are seen clinically as a low cardiac output state.[103] Treatment with T_3 either as repeated bolus therapy or infusion in the immediate postoperative period has been shown to improve systolic and mean arterial blood pressure and cardiac output, which in turn leads to improved renal perfusion and negative fluid balance.[104,105]

Hyperglycemia in the critically ill adult patients is known to be associated with higher morbidity and mortality.[106-108] Hyperglycemia is a normal response to stress. Surgery, with its associated stress response, results in an increase in counterregulatory hormones (epinephrine, glucagon, growth hormone, and cortisol). The result is increased hepatic glucose mobilization, impaired peripheral glucose utilization, relative insulin deficiency, and thus hyperglycemia.[108] This is further complicated by the insulin resistance found in cardiac surgery patients. It has been found that during hypothermia, glucose levels increase and insulin decreases. On rewarming, glucose levels continue to rise, with an associated rise in insulin. In addition to these etiologic factors, the administration of corticosteroids and inotropes also plays a role. Three retrospective studies in the pediatric population showed similar findings to the adult studies, namely that hyperglycemia was associated with increased morbidity and mortality.[109-111] The differences, however, were that in contrast to the adult experience (where initial glucose level was associated with mortality), in the pediatric group, the peak level as well as continued elevation were associated with complications. The morbidities described in these studies included prolonged ventilation, prolonged ICU stay, and increased rates of infection. In a study performed on neonates who underwent arterial switch operations, it was found that in a group of patients whose blood sugar averaged over 200 mg/dL, there was no increased risk of adverse event.[112] Another concern for clinicians is the effect of posttherapy hypoglycemia and the possibility of associated

neurologic damage. A clinical study performed by Ballweg et al. demonstrated that there was no associated worsening of neurodevelopmental outcome at 1 year in those patients who demonstrated early postoperative hyperglycemia.[113] There is currently insufficient evidence to support a beneficial effect of tight glycemic control during cardiac surgery in infants. There is, however, strong evidence of the adverse effects of persistent hyperglycemia in this patient population.

Systemic Inflammation

The perioperative period is a potentially deleterious time, as the combination of anesthesia, the stress of surgery, and the immune-stimulating effects of the CPB circuit combine to result in a systemic inflammatory response. Indeed, it has been found that certain patients, including those with single-ventricle physiology, may have an activated inflammatory response prior even to the commencement of CPB.[114] Possible etiological factors include: 1) cellular activation with contact of blood products with the surface of the bypass circuit; 2) mechanical shear stress as the blood passes through suction systems and filters; 3) tissue ischemia and reperfusion; 4) hypotension and hemodilution; 5) administration of blood products; and 6) hypothermia (mild, moderate, and deep hypothermia).[83] These factors will result in the activation of both humoral and cellular immune responses that generate the activation of the complement, coagulation, and fibrinolytic pathways. Collectively, these pathways result in endothelial damage, capillary leak, and organ dysfunction. In the literature, up to 50% of children have pulmonary and cardiovascular dysfunction attributable to this proinflammatory response in the post-CPB period.[115] The pediatric population may be at increased risk compared with the adult population, as the body surface area to circuit size is greater.

Figure 30-4 demonstrates the effects of surgical trauma and CPB. Complement activation occurs by both the alternative (contact with foreign surfaces, that is, bypass circuitry) and classical pathways (protamine-related). These two pathways result in the elevation of C3a and C5a, and C4a with additional C3a respectively. Elevations of C3a and C5a lead to activation and degranulation of neutrophils, release of histamine from mast cells and basophils, and platelet aggregation. These elevations have been associated with poor outcomes, with severe organ dysfunction, prolonged mechanical ventilation, and poor outcome.[83,116] Contact activation of clotting factor XII results in the eventual activation of kallikrein and bradykinin. The effect of increased kallikrein is the positive feedback on the activation of more factor XII, while the increased bradykinin results in the stimulation of B_1 and B_2 receptors. The effect of their stimulation is the production of nitric oxide, free radicals,

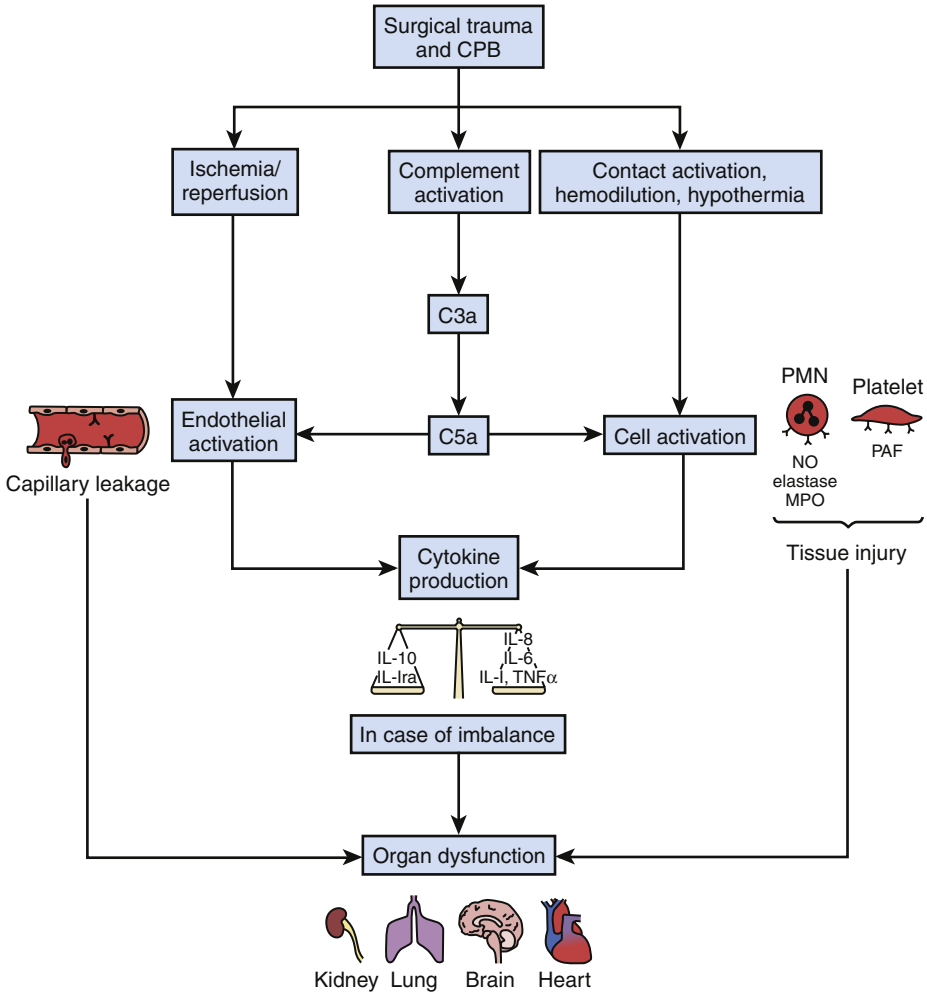

Figure 30–4. Illustration of the effects of surgical trauma and CPB. *(Modified from Brix-Christensen V: The systemic inflammatory response after cardiopulmonary bypass in children,* Acta Anaesthesiol Scand *45:671-679, 2001.)*

eicosanoids, and cytokines. This will result in vasodilation and increased capillary permeability, which in turn may lead to organ dysfunction.[114,117] B_2 receptors have also been found in the brain and this may play a role in the genesis of ischemia-reperfusion injury.[94] Cytokines are produced by a wide range of cells including monocytes, macrophages, lymphocytes, and endothelial cells. These factors are either proinflammatory in the form of interleukins (IL) 6 and 8 and tumor necrosis factor α (TNF-α), or antiinflammatory in interleukin 10 and interleukin-1 receptor antagonist. An increase in TNF-α has been demonstrated to be associated with increased capillary leak[117]; however, other studies have failed to show any significant increase.[115,118] Elevations in IL-6 and IL-8 have been shown to correlate with compromised postbypass cardiopulmonary function with increased inotropic requirements, severe capillary leak syndrome, and an increase in mortality.[83,114,115,118] The balance therefore between the proinflammatory and antiinflammatory responses may thus be altered in those who demonstrate an aggressive systemic inflammatory response. In uncomplicated cases, the systemic inflammatory response is self-limited and is only of a few days duration.[115]

The more important question is what can be done to prevent initiation of this inflammatory process. Several therapeutic maneuvers have been proposed including the addition of steroids to the pump prime; the use of indomethacin or aprotinin; heparin-coated CPB circuitry; and the use of ultrafiltration.[101] The administration of steroids into the pump prime seems a logical therapeutic measure. However, data supporting this were derived from adult patients undergoing coronary artery bypass grafting.[119] Studies in the pediatric population have demonstrated variable results, and indeed there does not appear to be agreement on timing or dosing of steroids.99 In one study, there were measurable differences in the degree of inflammatory markers found between the 15 test subjects and the 14 controls. In this study, although the age at the time of surgery, the CPB times, and aortic crossclamp times were similar, they did not reach statistical significance. The authors found that in the steroid group there was a decrease in the concentrations of IL-6 and TNF-α. They noted, however, that these decreases were after the initiation of bypass and prior to MUF in the TNF-α group, and after the removal of the crossclamp in the IL-6 group. The concentration of C3a, however, was not different between groups. In terms of clinical effect, the steroid-treated group had lower alveolar arterial oxygen differences, lower temperatures (due to lower cytokine levels), required less supplemental fluid in the first 24 hours, had better renal function, and had less ICU time.[120] A further study looking into the effects of administration of steroids (methylprednisolone 30 mg/kg) 4 hours before surgery as well as intraoperatively, compared to a cohort that received only intraoperative steroids, found that the group who received two doses had reduced levels of IL-6 and IL-10, and a clinical advantage as outlined in the first study.[121] Results of other studies have, however, not shown positive results. In a study that included patients 3 months of age or older, but weighing no more than 7 kg, 24 patients were given steroids while 26 were not. An obvious weakness of the study was that the dose and timing of the steroids were not mentioned. Investigators found no differences in the inflammatory or clinical markers between the groups.[119] As has been indicated elsewhere in this discussion, a large, randomized, prospective study is essential in order to properly elucidate this question.

Aprotinin, a serine protease inhibitor, was reported to help preserve platelet function, to decrease bleeding diatheses associated not only with CPB but also other procedures including spinal surgery, and also to have antiinflammatory effects. Studies concluded that its use had beneficial effects on post-CPB organ function and improved hemodynamic stability. However, after published data in the adult literature suggested that there was a thrombosis and renal failure risk with its use, the drug was voluntarily removed from the market in November of 2007.[122,123] In the pediatric literature, safety studies looking at these effects failed to concur with the adult studies[124,125] As with many clinical questions in the literature, some studies even questioned the drug's efficacy.[125,126]

Exposure of blood to the bypass circuit itself is probably the main factor in initiation of the inflammatory cascade. Two strategies have been used to attenuate this response: miniaturization of bypass circuits, and coating the circuit in an attempt to make it more biocompatible. Other strategies that have been used by clinicians in an attempt to minimize the inflammatory effects include ultrafiltration and the use of biocompatible circuits. It appears that a multimodal strategy is essential to decrease the deleterious effects of the multisystem inflammatory cascade that is incited by CPB.

Management of Cardiopulmonary Bypass

The trend in modern pediatric bypass equipment is to reduce the size of the extracorporeal circuit in order to reduce the prime volume. The priming volume may actually exceed the blood volume of the neonate by as much as 200% to 300%. This is in contrast to the adult CPB patient where the priming volume accounts for only between 25% and 33% of the patient's blood volume. The effects of CPB have led surgeons to perform operations without the use of CPB and interventional cardiologists to close atrial and ventricular septal defects in the catheterization laboratory.[127-132] Indeed, some undertake a hybrid approach for closure of ventricular septal defects and other procedures such as stenting of the pulmonary arteries, in which the surgeon obtains direct access to the heart and the procedure is performed using transcatheter techniques by an interventional cardiologist.[133]

Hemodilution

Research into the effects of CPB on the inflammatory cascade and organ dysfunction that occur in the postbypass period have also found that the use of blood products plays a significant role in the inflammatory response. These effects include an elevation in complement and inflammatory cytokines.[134] The use of blood in the pump prime, especially in neonates, infants, and patients who will undergo DHCA and hypothermic low-flow bypass, is based upon earlier published data that suggested that a hematocrit between 20% and 25% was associated with acute and long-term sequelae.[135] Acutely, there appeared to be a lower minimum cardiac index in the post-CPB phase, higher serum lactate levels at 60 minutes post-CPB, and a greater increase in total body water in the first postoperative day. At 1 year of age, this same group tested lower on the Psychomotor Development Index both in absolute number and also in a greater number of subjects who tested 2 standard deviations from the population mean.

Although these authors suggested that a hematocrit below 25% was associated with worse outcomes, both acutely and at 1 year follow-up, they could not identify a target hematocrit that was optimal. A later study comparing a hematocrit of 25% to one of 35% was also undertaken. Apart from a greater intraoperative fluid accumulation with the lower hematocrit there were no reported differences between groups both in the early postoperative period and at 1-year neurodevelopmental follow-up.[136] Thus it appears that a hematocrit of 25% or more may be adequate. At our institution we keep the hematocrit at least at 30% in patients younger than 1 year and at least 25% in those older than 1 year, irrespective of congenital abnormality. Based on these targets, blood is added into the prime volume as needed.

Circuit Miniaturization

The desire to maintain hematocrit at the aforementioned levels and the discrepancy between patient size and circuit volume has led researchers to attempt to miniaturize circuits. This has the advantage of not only decreasing the total surface area the patient will contact but also raises the possibility of a bloodless prime. Methods that may be used to achieve this include using biocompatible coated circuitry and oxygenators, the use of vacuum-assisted venous drainage, the ability to decrease circuit length by bringing the pump as close to the patient as possible, and finally, the exclusion of certain circuit components, for example, arterial line filters and in-line cardioplegia.[137]

Biocompatible Circuits

The initiation of CPB results in the activation of the five proteolytic plasma systems (coagulation, fibrinolysis, complement activation, kallikrein-kinin, and contact systems) as well as leukocytes, platelets, and endothelial cells. One option is to modify the surface of the circuit and dampen the response.

Box 30-5 describes the ideal biocompatible circuit.[137] Surface modification can be achieved by four techniques: coating, chemical modification, attachment of macromolecules, and blending of polymers.[138] Studies using these modified circuits have found modification of the inflammatory response by some (e.g., polymethoxyethylacrylate or PMEA, a polymer blend; and heparin-coated circuits)[139-142] and improvement in platelet count (phosphorylcholine, a circuit coating) in others.[143] Some studies have also suggested that these modified circuits may even improve urine output postoperatively and decrease the time that ventilation is required.[141,142] It would seem that these latter effects are on the basis of a decrease in the inflammatory response and capillary leak, but evidence of a significant clinical benefit is still lacking.

Box 30–5 Properties of the Ideal Circuit

Inability to initiate thrombogenesis
Inability to initiate hemolysis
No complement activation
No toxicity of products extracted from the circuit by the blood
Chemical inertness so that no toxic metabolites are generated

From Janvier G, Baquey C, et al: Extracorporeal circulation, hemocompatibility, and biomaterials, *Ann Thorac Surg* 62:1926-1934, 1996.

Circuit Design

The use of smaller circuit size, and thus prime volume, is aimed at decreasing hemodilution, which might decrease transfusion requirements, and decreasing the severity of the inflammatory response, thus reducing hospital costs because of improved outcomes.[144] Techniques that investigators have used in order to create these smaller circuits have included: low prime volume oxygenators, reservoirs, and arterial filters; shorter extracorporeal circuitry; remote pump heads; use of venous vacuum (which can, in turn, result in the use of smaller venous tubing), and, in certain configurations, removal of parts of the classic circuit, most frequently the arterial line filter.[134,144-149] Such devices have been shown to be safe, even in the neonatal population, with priming volumes as low as 110 mL. Other descriptions have included configurations where the bypass circuit is placed as close to the operating table as possible with either the surgeon or assistant straddling the circuitry.

A wide range of operations have been described using these adjustments. They range from ASD and VSD surgery to such complex procedures as the arterial switch operation and even the stage 1 palliation of hypoplastic left heart syndrome. With changes to the circuitry comes a permissible degree of hemodilution, requiring that patients be continuously monitored by means of hemoglobin concentration, mixed venous oxygen saturation, regional cerebral oxygenation, and pump plasma lactate. Values of less than 7 g/dL, less than 70%, less than 50% and greater than 4 mmol/L, respectively, have been used as transfusion triggers.[146,148]

Animal experimentation using circuit miniaturization with deep hypothermia and asanguineous prime has found a decrease in the inflammatory cascade. Tumor necrosis factor was decreased and primed neutrophils from donor blood were obviously absent. These donor-originated neutrophils are key factors in the genesis of the CPB-induced inflammatory cascade and capillary leak leading to organ dysfunction. Further analysis found improved right ventricular cardiac index, improved pulmonary vascular resistance index, and improved dynamic pulmonary compliance in animals exposed to asanguineous prime. The authors concluded that these could be attributed to a decrease in total lung water associated in turn with decreased inflammation.[150] A separate study found that there was improved postbypass cerebral blood flow. The authors postulated that this might lead to improved long-term neurologic outcome.

Oxygenators

In the pediatric population, oxygenators must provide efficient gas exchange over a wide range of temperatures (10° C to 40° C), pump flow rates (0 to 200 mL/kg/min) , line pressures, gas flow rates, and hematocrits as low as 15%. Both bubble and membrane oxygenators can achieve effective gas exchange under these diverse conditions. Historically three different types of oxygenators have been used, namely the film-type, bubble-type, and membrane-type. In the film-type, a thin blood film is created, with gas exchange taking place on the surface of the film. In this method, there is no mechanical introduction of gas into the blood and thus trauma to red blood cells is minimal. However, a large surface area is necessary, with a large priming volume. The bubble oxygenator

uses bubbles that are introduced directly into the blood. It has advantages in that the effective surface area for gas exchange is large due to the surface area of the bubbles. The obvious disadvantage, however, is that the introduction of the bubbles causes red cell trauma. In addition to this, the bubbles must clearly be removed from the circuit and this requires a settling chamber, which may in turn require added volume in the circuit.

The third oxygenator is the membrane type, the one that is most widely used today. In this technique, the blood is exposed to oxygen through a gas-permeable membrane and thus, because there is no direct contact between gas and blood, trauma is minimal.[151] Refinements in early membrane oxygenator design occurred in the 1980s, with the introduction of microporous hollow fibers with blood flowing over the outside of the fiber and gas flowing down the fiber lumen. This increased the efficiency of gas exchange and, at the same time, decreased manufacturing costs to be in line with the cheaper bubble oxygenators.[152]

Common to all CPB circuits is the presence of gaseous microemboli. These may be caused by pulsatile bypass, low venous reservoir levels, vacuum-assisted venous drainage, venous line air, field suckers, drug administration, and blood sampling. Perfusionists may utilize a number of methods to decrease this, ranging from filtration at the time of circuit setup, ensuring adequate volumes within the venous reservoir, and the placement of arterial line filters.

Unfortunately, the arterial line filter may add as much as 20% to 40% to the prime volume.[153] Arterial line filters are used in 96% of North American centers, whereas in Europe, they have not been commonplace for a number of years.[153]

The first oxygenator specifically designed for pediatrics was the Dideco Kids D100 neonatal oxygenator (Sorin Group, Mirandola, Italy). It was first evaluated at Duke on a series of 6 neonates: two underwent Norwood procedures, two truncus arteriosus repairs, and two, arterial switch operations. The investigators noted that the total priming volume for the oxygenator was only 31 mL and this enabled the priming volume of the circuit to be decreased by 12.5%. The change to this oxygenator did not compromise oxygenation, and apart from the 1 unit of packed red blood cells and fresh frozen plasma originally added as the prime, no further blood products were used to maintain a hematocrit greater than 35%.[154] The Terumo Medical Corporation, Tokyo, Japan has manufactured a miniature oxygenator with an incorporated arterial line filter. The total prime volume is only 43 mL. In clinical evaluations, it was found to be easy to use, decreased the number of gaseous emboli, and was easily incorporated into their miniature circuit setup.[153] It can thus be appreciated that newer generation neonatal oxygenators have an advantage in that they are specifically designed for this patient population, are easy to use, and have the benefit of small prime volumes, which enable teams to attempt to achieve the goal of asanguineous prime.

Initiation of Cardiopulmonary Bypass

Prior to the initiation of cardiopulmonary bypass, the entire team must plan a strategy for the safe undertaking of the planned procedure. The surgical team ensures that the proper instrumentation is available, that the lines that will be used for the bypass are appropriately sized, and that they are cut to appropriate length under the direction of the surgeon. In addition to this, the surgical team assembles the appropriate mechanical or tissue valves and thaws homograft tissue patches that may be required by the surgeon for specific repairs (e.g., pulmonary artery patches or aortic augmentation). A major concern for the anesthesia team is the smooth transition from spontaneous to controlled ventilation. This transition may lead to changes in intrathoracic pressure, heart rate, and pulmonary:systemic blood flow that may be poorly tolerated. The question of whether the patient is to be intubated orally or nasally is practitioner and institution dependent. In addition, the anesthesia team will place peripheral intravenous lines, and invasive monitoring in the form of an arterial line, with or without a central venous line. Central venous catheters are also institution-dependent, with some groups avoiding them in favor of direct intracardiac lines placed by the surgeon prior to the termination of CPB. The reasoning is to avoid stenosis or thrombosis of the central veins, particularly in single-ventricle patients whose venous drainage from the head and neck is integral to survival. Other preparations include the placement of Foley catheters, the adjustment of the temperature of under-body cooling blankets, institution of topical cooling in the form of ice bags to the head (in those undergoing DHCA), and the placement of further monitoring (e.g., EEG, cerebral oximeters, or transcranial Doppler).

Specific surgical factors that need to be considered include the potential for the use of DHCA, accessing defects through the right side of the heart, whether or not an aortic cross clamp will be necessary, and whether the size of the child being operated on will influence cannulation strategy. Options available to the surgeon include dual caval cannulation for patients having repairs of ASD, VSD, atrioventricular canal defects, tetralogy of Fallot, and transposition of the great vessels with VSD; and single venous cannulation, mainly for those cases in which DHCA will be used, including augmentation of the aortic arch, Norwood stage 1 palliation, cavopulmonary anastomosis, and Fontan completion, to name a few. In these cases, CPB is used to decrease patient temperature. Cooling is usually performed over a 20-minute period down to a target temperature of 18° C. Once the target temperature has been achieved, circulation is shut down and the cannulae are removed so that the repair may take place in a bloodless field. Meticulous de-airing of the circuit is critical to this population to avoid cerebral air embolus, remembering that air may cross any of the intracardiac shunts.

It is essential to check that the cannulae are appropriately positioned prior to going on to CPB. This will include the correlation of the pressure in the aorta with the invasive arterial line and making sure that the venous cannulae are in the correct direction and that they are not potentially abutting the wall of either the vena cava or right atrium. Once the patient is placed on to CPB, ventilation will cease and it is thus important to observe the oxygenation difference between the venous and the arterial cannulae, as well as the SvO_2 that is measured from the bypass circuit. Box 30-6 lists both direct and indirect measures of adequate perfusion. Based upon this list of measures, there are a number of management strategies that may be employed should there be indications of decreased perfusion. The perfusionist will ensure that the cardiac index is adequate based on the patient's weight or increase mean arterial pressure with the use of vasopressor agents. In the event that the cerebral saturations or jugular venous bulb saturation

Box 30–6 Measures of Adequate Perfusion on CPB

Direct measures
- Cardiac index generated by pump
- Mean arterial blood pressure generated by pump
- Cerebral oximetry
- Jugular bulb saturation
- SvO_2

Indirect measures
- Acid-base status
- Plasma lactate
- Urine output

Box 30–7 Factors Related to Coagulopathic Complications in Neonates and Infants

Procedure-independent factors
- Ductal-dependent flow
- Cyanosis
- Prematurity
- Low cardiac output
- Neurologic injury
- Sepsis
- Malnutrition

Procedure-dependent factors
- Hemodilution
- Hypothermia
- DHCA
- Redo surgery
- Prolonged CPB
- Use of prosthetic material
- Low cardiac output

From Jaggers J, Lawson JH: Coagulopathy and inflammation in neonatal heart surgery: mechanism and strategies, *Ann Thorac Surg* 81:S2360-S2366, 2006.

decreases, it is imperative that the surgeon check for correct placement of both arterial and venous cannulae. The arterial cannula may be directing blood away from the head vessels, and the venous cannula may be positioned so that it is causing obstruction to venous drainage from the head and thus decreasing cerebral perfusion pressure. Cerebral perfusion pressure (CPP) is calculated from the following calculation: CPP = MAP − ICP (or jugular venous pressure) and thus we see that alterations of either the arterial inflow or obstruction to outflow may result in the aforementioned decrease in perfusion pressure. Other important factors that must be assessed are adequacy of hemoglobin/hematocrit and oxygenation.

Anticoagulation

At birth, concentrations of the vitamin K-dependent clotting factors (II, VII, IX, X), contact factors (XI and XII) and the anticoagulant and inhibitory factors (antithrombin III, protein C, protein S, CI esterase inhibitor, and plasminogen) are all reduced. The mechanisms may include decreased hepatic synthesis or increased clearance secondary to increased metabolic rate.[155,156] Despite these apparent abnormalities, normal neonates have preserved coagulation function. The same, however, cannot be said for patients with cyanotic heart disease. This group is known to have impaired coagulation prior to surgery on the basis of polycythemia, abnormal platelet count and function, decreased factor concentration (V, VII, and VIII), and increased fibrinolysis.[156,157] Box 30-7 lists factors that are associated with coagulopathy in neonates and infants presenting for surgery with cardiopulmonary bypass.

The institution of CPB will result in activation of the clotting cascade, and thus therapeutic anticoagulation is vital to prevent the formation of clot within the circuit and the disastrous effects of possible thromboembolism into the arterial tree. The anticoagulant universally used in both adult and pediatric CPB is heparin. At the Children's Hospital of Philadelphia, the patient is given 200 U/kg, either by the surgeon as a direct injection into the right atrium, or by the anesthesiologist into a peripheral intravenous site. Some institutions use between 300 and 400 U/kg. The goal is for activated clotting time (ACT) to be no less than 480 seconds. This is based upon early work by Bull and colleagues who formulated a heparin-protamine dose-response curve in the attempt to avert the use of either excess heparin or protamine.[158] The mechanism by which heparin works is by binding to antithrombin III (ATIII), resulting in a conformational change in the enzyme and enhancing its activity. Under normal conditions, there is a continuous balance between coagulation and anticoagulation within the body. ATIII functions to inactivate thrombin and other proteases, most notably factor Xa, thus preventing ongoing propagation of the clotting cascade. The effect of heparin on ATIII is to increase its efficacy by a factor of a thousand. As mentioned earlier, the level of ATIII is decreased in neonates and will only reach adult levels by 3 to 6 months. Despite this, it has been found that there are two other thrombin inhibitors, namely heparin cofactor II and α_2-macroglobulin. In neonates and infants, the concentration of α_2-macroglobulin is twice as high as that of ATIII. In a study by Guzzetta et al., it was found that, despite these concerns, there was a statistically significant prolongation in ACT and that a heparin dose-response relationship occurred in the neonatal group. The authors postulated that this could be on the basis that either neonates generate less thrombin or that ACT is a poor indicator of anticoagulation in this age group.[159] The problem in the neonatal and early infant population is what to make of the ACT and whether or not there is sufficient anticoagulation despite ACT prolongation. Based upon these misgivings, some authors have suggested that using a heparin concentration protocol may be more effective.[160,161] Using this technique, despite decreased thrombin and preserved factor VIII levels which indicate improved anticoagulation, there was increased bleeding and increased blood requirement.[160]

A concern in patients presenting for repeat cardiac surgery is the possibility of these patients developing heparin-induced thrombocytopenia (HIT). The syndrome itself is an immune-mediated phenomenon of platelet activation resulting in thrombocytopenia and diffuse venous and even arterial thrombosis. Thrombocytopenia will occur some days after the exposure to unfractionated heparin .with platelet counts dropping to between 20 and 100×10^9/L. It is important, however, to be mindful of any drop in the platelet count. A drop in the count by 50%, even if still in the normal range, is considered to of significance. There are two forms of HIT. HIT 1 is a transient early onset of a nonimmune-mediated decrease in platelet count that does not require the discontinuation of heparin. HIT 2 is immune-mediated with a decrease in platelet count by at least 50%.[162] In the adult literature, the

incidence is reported to be 1% to 3% post-CPB, with a thrombotic morbidity of between 38% and 81% and a mortality of 28%.[163] The antibodies are formed against platelet factor 4 (PF4), which is found on the surface of activated platelets as well as on endothelial cell surfaces secondary to heparin exposure. The presence of these antibodies occurs in up to 50% of adult cardiac surgery patients, but only the quoted 1% to 3% will go on to develop the syndrome.[163] This suggests that, although the platelet antibody is itself common after CPB, in and of itself it does not confer increased risk. A pediatric series including neonates, infants, and young children revealed an incidence of 1.3%.[164] As in the adult population, a study of older children looking at positive antibody screen found the same incidence as in the adult population of 50%.[165]

The question then is what to do with patients who have a history of HIT or HIT-associated thrombosis. There are three alternatives: 1) the use of an alternative anticoagulant with the complete avoidance of all heparin both intraoperatively and postoperatively; 2) standard heparin anticoagulation with a platelet antagonist; and 3) waiting until the disappearance of HIT antibodies and proceeding with heparin anticoagulation.[162] Box 30-8 lists the alternatives to heparin. Of this list of drugs, only the thrombin inhibitors lepirudin and argatroban have been used to any degree. Argatroban has the advantage that it is metabolized in the liver, can be monitored by ACT, and has a half-life of less than 60 minutes. The problem, however, is that there are no standardized dosing protocols. Initial bolus dosing was inconsistent across the literature with a range of 35 to 750 μg/kg and infusion rates between 2 and 65 μg/kg/min. Further bolus doses for inappropriate ACT were on the order of 20 μg/kg.[167-169] Problems included no reversal drug and the use of nonstandardized protocols that resulted in increased bleeding and blood use. Lepirudin is more difficult to use based upon its longer $T^{1/2}$ at 40 to 80 minutes, the need for ecarin clotting time (ECT), and renal excretion. It is also possible to monitor lepirudin with the aPTT but this test would take too long in the setting of CPB. Just as with argatroban, there is no reversal agent. Dosing of this agent follows the adult dosing of a bolus of 0.25 mg/kg and 0.2 mg/kg into the CPB circuit, although a single group suggested increasing these doses due to a greater volume of distribution.[170-172]

At the termination of CPB, as the cannulae are being removed, protamine will be administered to reverse the anticoagulation due to heparin. As with many areas in practice, there is a range of dosing used in the clinical arena. As mentioned, at the Children's Hospital of Philadelphia the heparin dosing is 200 IU/kg, and for reversal the protamine dosing is 4 mg/kg, with a maximum of 100 mg. This works out to be a ratio of protamine to heparin of 2:1 based on 1 mg of protamine to 100 IU (sometimes referred to as 1 mg) of heparin. In a survey of units within Great Britain and Ireland, there was a reported ratio of 0.3:1 to 2:1 after a uniform heparin dose of 300 IU/kg. In adult cardiac surgery, adverse reactions to the administration of protamine are common and include anaphylactic and anaphylactoid reactions as well as pulmonary hypertensive events. These reactions range from minor hypotensive events to fatal cardiovascular collapse. Although catastrophic events are rare, adverse events occur in up to 2.6% of adult patients.[173] Risk factors for adults include the use of protamine-containing insulin, previous drug reaction or exposure, vasectomy, rate of infusion, and allergy to protamine or fish. A study looking at the incidence in the pediatric population under16 years of age found that in a series of 1249 anesthesias, the incidence of hypotension that persisted for greater than 5 minutes was 1.76%. The authors noted that this might have included causes other than protamine reaction, due to the proximity to termination of CPB. Of interest in this study were the associated risk factors for hypotension, namely female sex, large dose of protamine, and small heparin doses.[174] Vigilance for pulmonary hypertension, hypoxemia, and cardiovascular collapse cannot be overemphasized at the time of protamine reversal.

Box 30–8 Alternative Drugs to Heparin for Anticoagulation

Glycoprotein IIb/IIIa inhibitors
- Abciximab
- Eptifibatide
- Tirofiban

Direct thrombin inhibitors
- Hirudin
- Lepirudin
- Bivalirudin
- Argatroban

Defibrinogenating enzymes
- Ancrod

Termination of Cardiopulmonary Bypass

To terminate CPB, a number of important criteria must be met. These must be identified and treated concomitantly at a time when the patients' clinical condition may be tenuous.

General Principles

Prior to the termination of CPB, an adequate cardiac rhythm must be established, and, if the native rhythm is inadequate either by rate or rhythm itself, the heart will need external stimuli in the form of atrial and/or ventricular epicardial pacing. The use of inotropic support will obviously depend on the case, the presence of preexisting myocardial dysfunction, and the duration of CPB. In the pediatric setting, this may take the form of dopamine, epinephrine, and milrinone, but under certain circumstances vasopressin may be necessary. Concomitant with this will be the reexpansion of the lungs and resumption of ventilation. It is important that the lungs are fully reexpanded, as atelectasis will lead not only to hypoxemia but also to direct compression of the pulmonary vascular bed. The combination of these two factors will lead to an increase in pulmonary vascular resistance and pulmonary artery pressure. In the neonate who already has an extremely reactive pulmonary bed, this may precipitate a spiral of increasing hypoxia, worsening pulmonary artery pressure, and subsequent right ventricular failure, which may necessitate placing the patient back onto CPB or even ECMO. The principles of preventing this phenomenon include adequate ventilation, ensuring adequate oxygenation, avoiding hypothermia, avoiding acidosis, the use of the phosphodiesterase inhibitor milrinone, and using inhaled nitric oxide as a direct pulmonary artery vasodilator.

Anatomical Considerations and the Use of Transesophageal Echocardiography

Essential to the termination of CPB is an anatomically sound repair. This is true from a simple repair such as a secundum atrial septal defect to the complexities of a stage I Norwood reconstruction for the single ventricle. The effects of CPB on the myocardium are well known. The longer the bypass time, the worse its effects of failure to establish electrical quiescence, unequal myocardial cooling, and ongoing inflammation may become. A myocardium recovering from these insults will not function well should there be residual outflow tract obstruction, abnormal coronary flow, or abnormal flow through intracardiac baffles. The role of the intraoperative transesophageal echocardiography (TEE) is vital in diagnosing these problems in patients who are difficult to wean from CPB or who are possibly more cyanotic than expected. In the early days of TEE, probe size limited use in small patients and neonates—precisely the group of patients undergoing the most complex of procedures. Fortunately, in recent years, probes have been developed that can be used in patients down to approximately 2.5 kg.[175] The incidence of post-CPB residual defects diagnosed by TEE that will go on to require a second CPB run is approximately 7% to 9.6%.[176-178] This is clearly a significant number of patients who might otherwise have required later reoperation or even postoperative emergent ECMO cannulation due to acute cardiac failure. Complications associated with passage of the TEE probe include failure to pass the probe, esophageal trauma that includes laceration or even perforation, airway compression, and hemodynamic compromise. The hemodynamic issues are related to compression of structures, including the ascending and descending aorta, left atrium, pulmonary artery and veins, and superior vena cava.[178] Fortunately, these more serious complications are rare. In a study of 22 patients between 2 and 5 kg who underwent TEE examination before and after CPB, no differences in lung function or arterial blood gas were found. In two patients, the probe was removed because of concerns about ventilation that were unrelated to the TEE probe. The aforementioned parameters did not change before or after the removal of the probe.[179]

Another study performed by the same authors, looking at hemodynamic parameters, found that there was an incidence of compromise in 1.7% of patients.[178] Despite the theoretical concerns in the smallest of patients, TEE examinations can be performed safely.

Hypothermia

If the procedure was performed at anything but normothermia, the patient needs to be rewarmed back to normal temperature. Hypothermia may result in a wide range of abnormalities. Experimental evidence suggests that hypothermia will result in a negative inotropic effect at the atrial level, an effect that may be detrimental at the termination of CPB, as normal atrial function is an important contributor of ventricular preload.[180] Hypothermic effects on ventricular function include bradycardia, heart block, reduction of fibrillation threshold, and increase in pacing threshold. These effects may occur even at moderate hypothermia.[174] Termination of CPB necessitates an adequate heart rate, which may require external pacing, and thus normothermia is vital. Another important problem related to hypothermia in the cardiac surgery patient is the effect that it has on bleeding. It appears that hypothermia will affect both platelet function and the coagulation cascade. The defect in platelet function is related an impaired release of thromboxane A_2 which is necessary for the formation of the platelet plug. Coagulation is affected by a temperature-dependent decrease in enzyme function. These effects may occur at even 1° to 2° C below normal.[181,182] Even if patients are normothermic on termination of CPB, for obvious reasons it is imperative to keep patients warm thereafter, as temperature may drift downwards soon after resumption of spontaneous circulation, placing them at risk once again.

Bleeding

The origins of the ongoing coagulopathy upon termination of bypass are multifactorial and include complement cascade activation due to CPB, therapeutic hypothermia as part of CPB, dilution, consumption of circulating clotting factors, and ongoing bleeding from the surgical site. Obviously, strategies to prevent blood loss must start at the beginning of CPB. These attempts focus on limiting hemodilution, the use of antifibrinolytic agents, and use of fresh whole blood in the prime volume.

The antifibrinolytics that have been used are the serine protease inhibitor aprotinin and the lysine analogs ε-aminocaproic acid and tranexamic acid. Aprotinin inhibits kallikrein and plasmin with resultant decrease in hemostatic activation, inhibition of fibrinolysis, inhibition of the inflammatory cascade, and preservation of platelet function. It is eliminated via the kidneys, reabsorbed in the proximal tubule, and then enzymatically broken down in phagolysosomes. Attempts have been made to establish the overall effects of the drug; this has been difficult, however, as published studies have included small groups of patients, nonheterogeneous groups, and inconsistent dosing. It does appear that there were trends toward less bleeding, improved transpulmonary pressure gradients suggesting decreased inflammation and capillary leak, improved myocardial function, and decreased postoperative ventilation.[183] As mentioned previously, problems were identified in adult cardiac patietns with respect to postoperative renal failure and thrombosis risk following aprotinin. This drug is no longer used, even in pediatric cardiac surgery, despite pediatric data which may suggest that there is no statistically significant renal failure, need for dialysis, worsened neurologic outcome, or mortality (early or late) in the pediatric group.[184-188] At this time, there is no plan to reintroduce the drug to market. The role of the lysine analogues has also long been studied. The mechanism of action is to interfere with the binding of plasminogen to fibrin that is necessary for the activation of plasminogen to plasmin. Both drugs are eliminated via the kidneys with terminal T½ of 2 hours. The apparent advantages in comparison to aprotinin include the lack of an immunological response, low cost, suggestion of platelet protection, and similar efficacy to aprotinin with respect to bleeding. A meta-analysis containing over 1000 patients found decreased bleeding in both cyanotic and acyanotic patients, decreased transfusion requirements, decreased sternal closure time, and improved reexploration rates with the use of the lysine analogues. In two of the reviewed articles there was no improvement in postoperative ventilation time, suggesting that these drugs have no

antiinflammatory effect.[183] In another meta-analysis including all three of the aforementioned drugs, the effect on bleeding was found to be similar comparing aprotinin to tranexamic acid with insufficient data to draw conclusions about the use of ε-aminocaproic acid.[189] In a further randomized study, the two lysine analogues were compared in a cohort of patients ranging in age from 2 months to 14 years, all with cyanotic heart disease. Both drugs had similar efficacy in decreasing postoperative blood loss as well as the use of blood products.[190]

Introduced into the adult world in the late 1980s with investigations in pediatrics in the early 1990s, the use of fresh whole blood in the priming volume (between 24 hours and 48 hours old) carried a theoretical advantage over stored blood or reconstituted blood (made of packed red cells, FFP, and platelets) in that the coagulation factors and platelets had little time to degrade due to cold storage, thus improving postbypass hemostasis. Other advantages cited by proponents are the decrease in systemic inflammation, manifested as decreased edema and improved organ function.[191] A study involving patients under 21 years of age with either cyanotic or acyanotic conditions had one group receive very fresh whole blood (less than 6 hours old), another group receive fresh whole blood, and a third group receive reconstituted blood. All subjects who required blood in the prime solution received whole blood. Once the heparin was reversed, any further bleeding and/or volume requirements were met with the assigned blood. It was found that patients who received the reconstituted blood had significantly more bleeding in comparison to the other two groups and that the most significant decrease in bleeding was in patients who were transfused fresh whole blood and were less than 2 years of age undergoing complex repairs. Another interesting finding from this was that despite theoretical advantages of the very fresh whole blood, there was no significant difference in bleeding between the two whole blood groups.[192] Further investigation into the question of fresh whole blood has looked at comparing reconstituted fresh whole blood versus banked blood and also into reconstituted blood versus fresh whole blood.[191,193] A head-to-head comparison of fresh whole blood versus reconstituted blood (packed red cells and FFP) in circuit prime had outcomes in favor of the reconstituted blood. Although there was no difference in chest tube output and requirements for transfusions between the two groups, the fresh whole blood was associated with increased perioperative fluid overload, increased ventilation, and prolonged ICU stay. The authors concluded that although the reconstituted blood group required more donor exposure (four donors as compared with three and a half in the fresh whole blood group), in their opinion the clinical hazards of fresh whole blood outweighed the risk of increased exposure. Despite these findings, there is ongoing debate and, as further research is performed into circuit size, this debate may be resolved by the use of asanguineous prime.[193] Proponents of fresh whole blood would also suggest that there is a decrease in bleeding observed when it is administered after CPB, on the basis of preservation of clotting factors and platelets in the fresh blood.

Ongoing bleeding despite the above strategies occurs after a wide variety of operations especially in patients with cyanotic heart disease, patients having long bypass times, after DHCA, and with operations that involve multiple suture lines. In these patients, it is useful to perform coagulation studies, platelet counts, and fibrinogen levels to better guide therapy. The problem, however, comes in that there are not many institutions that can perform these tests quickly enough so that the results are still clinically relevant. Ongoing bleeding is treated with packed red cells or fresh whole blood, with component therapy transfused as needed in the form of cryoprecipitate, platelets, or even FFP. Desmopressin (DDAVP) has been used because it decreases platelet dysfunction after CPB. Desmopressin will increase the release of von Willebrand factor (vWF) multimers and factor VIII from endothelial storage sites. Factor VIII levels increase immediately and levels of vWF peak in 30 to 60 minutes. The net effect in adults is to augment platelet adhesion and aggregation.[194] Comparable results have not been seen in pediatric patients, with studies finding no improvement in coagulation in patients who have been given the medication as a prophylactic measure.[194,195]

In patients who continue to bleed despite attempts to correct coagulopathy with blood products, recombinant factor VII may be administered. Unfortunately, as with many drugs, pediatric dosing is extrapolated from adults. The dose thus is between 90 and 120 μg/kg, given every 2-3 hours. Studies have demonstrated that the half-life of factor VII in pediatrics may be half of that in the adult and that clearance is faster, suggesting the need for higher doses.[196] It has also been suggested that transfusion of coagulation factors, fibrinogen, and platelets prior to the administration of factor VII may also affect the dosing regimen.[196] Pediatric experience has suggested it to be extremely efficacious but with some limitations and potential complications. The cost is extremely high, with a 1- to 2-mg vial costing around $1000, and with some patients obviously requiring more than just the one vial. The other concerns surround clot formation and thrombosis. Case reports have described mediastinal clot formation that in some cases has required emergency evacuation.[197] Recombinant factor VII has also been used successfully in patients with intractable bleeding on ECMO. In this subgroup of patients, there is obviously concern for circuit thrombosis that would have catastrophic consequences and it has been suggested that the dosing be reduced to 30 to 50 μg/kg.[196] Yet another study has demonstrated no complications using the standard dose of 90 to 120 μg/kg in a group of ECMO patients.[198] Despite its very important place in the management of the post-CPB patient, there is still much investigation around the use of this drug with respect to remain questions about optimal dosing and administration interval.

Modified Ultrafiltration

The net effect of the proinflammatory state caused by CPB is a capillary leak, increase in total body water, and edema formation. This phenomenon, although affecting the entire body, will be especially problematic for the lungs, myocardium, and brain. Pulmonary compliance will decrease, and the end result of myocardial edema is both systolic and diastolic dysfunction.[199,200] First described in 1991 by Naik and colleagues, modified ultrafiltration (MUF) was formulated to improve the removal of this excess body fluid after the termination of CPB. These authors described that their new technique was better able to remove body water and elevate hematocrit when compared to conventional ultrafiltration that is employed while the patient is still on bypass.[201] The perfusionist employs a number of forms of filtration, during and after CPB, all of which are aimed at limiting the inevitable increase in total

body water, as well as removal of electrolytes and inflammatory mediators. Prime ultrafiltration (PUF) is used when packed red cells are added to the prime volume. The aim of this filtration technique is to prevent unfavorable electrolyte elevations associated with stored blood, increase the pH toward the physiologic range, and decrease the inflammatory response.[202] Conventional ultrafiltration (CUF) is employed throughout CPB, with a common use being the removal of extra volume and electrolytes added to the circuit after the use of cardioplegia. In zero-balance ultrafiltration (ZBUF), crystalloid is added to the circuit at the time of ultrafiltration. A complication of ultrafiltration during CPB is depletion of the venous reservoir volume, and thus ZBUF is an attempt to counter this hypovolemia. Dilutional ultrafiltration is the last method of ultrafiltration used with the patient on CPB. The aim of this method is the dilution of a given electrolyte whose concentration is elevated. Dilution is achieved by the addition of hypotonic fluid (e.g., half-normal saline) into the circuit at the time of the ultrafiltration. The common goal of these methods is removal of excess free water and inflammatory mediators and maintaining the hematocrit at a safe level during CPB.

Since the description of the technique of MUF, studies have shown that it improves both cardiac and pulmonary function, increases hematocrit, and removes inflammatory mediators, and that these effects are more potent than with other ultrafiltration techniques. The technique of MUF includes the following modifications to the CPB circuit upon weaning from bypass. A clamp is applied which functionally disconnects the venous line from the venous reservoir. A line is then brought up to connect the ultrafilter directly onto the venous line (as shown in Figure 30-5). A roller pump is then interposed between the blood source and the filter to ensure blood moves toward the patient at a rate of approximately 200 mL/min. Suction is also applied to the filter at about −125 mm Hg to achieve a filter rate of approximately 100 to 150 mL/min.[203,204] Saline is used to chase the blood still in the venous reservoir through the circuit (allowing reinstitution of CPB, if necessary) and also to maintain right atrial filling pressure at the desired level. The end points are time (usually 15 to 20 minutes), the desired hematocrit of at least 40%, replacement of the venous reservoir with crystalloid, or the patient's inability to tolerate the procedure.

Box 30-9 shows the positive effects of MUF. The advantages of MUF with respect to cardiac function have been studied across the spectrum of patients.[203,206] The improvement in myocardial performance appears to result from a reduction of myocardial edema. It has been shown that after MUF there is an increase in systolic function coupled with an increase in end-diastolic length and a decrease in end diastolic pressure. These improvements in diastolic function indicate improvement in left ventricular compliance.[203] This is in agreement with earlier clinical observations made by Naik and his team in their original description. They observed that there was a universal rise in blood pressure and an apparent decrease in the myocardial dimension.[202] Overall, MUF leads to improved left and right heart function. MUF has been shown to also improve pulmonary vascular resistance, even in those patients who had elevated pulmonary pressure in the preoperative phase, an effect that lasts into the postoperative phase.[204,205] The patient with single-ventricle physiology is potentially at risk during the process of MUF because blood is drawn away from the aorta and coronaries as well as from pulmonary flow (in those patients with a modified Blalock-Taussig shunt). In a study by Gaynor and colleagues, however, this was shown to be a safe procedure after the Norwood procedure, with similar improvements in myocardial function as noted earlier.[206]

Improving pulmonary function is important not only for myocardial function but for ventilation and oxygenation,

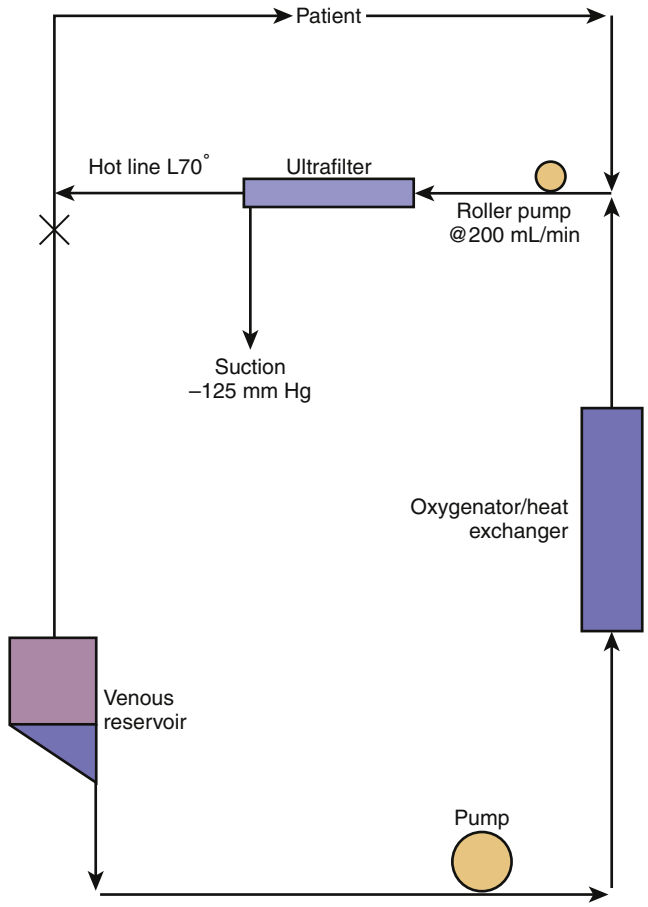

Figure 30–5. Setup for modified ultrafiltration. *(Modified from Davies MJ, Nguyen K, Gaynor JW, et al: Modified ultrafiltration improves left ventricular systolic function in infants after cardiopulmonary bypass,* J Thorac Cardiovasc Surg *115:316-370, 1998.)*

Box 30–9 Effects of Modified Ultrafiltration

General effects
- ↓ Total body water
- ↓ Inflammatory markers

Cardiac effects
- LV: improved systolic and diastolic function
- RV: improved function due to ↓ pulmonary arterial pressure

Pulmonary effects
- ↓ Interstitial water
- ↑ Compliance
- ↑ Ventilation/oxygenation
- ↓ Pulmonary artery pressure

Hematological effects
- ↑ Clotting factors/fibrinogen
- ↑ Plasma protein
- ↓ Transfusion requirements

translating into a decreased need for postoperative mechanical ventilation. Pulmonary dysfunction after CPB is manifest as lowered compliance, increased pulmonary vascular resistance, and a decrease in gas exchange. This pulmonary dysfunction is caused by hemodilution that decreases plasma oncotic pressure, resulting in an increase in interstitial fluid. This is coupled with the atelectasis that occurs secondary to absence of ventilation during CPB. Furthermore, the lung is obviously ischemic during bypass, which leads to the production of oxygen free radicals once the lung is reperfused. Lastly, other factors such as hypothermia and foreign body contact of blood with the CPB circuit result in the release of inflammatory mediators that may further worsen pulmonary damage.[204] The effects of MUF are thus secondary to a decrease in interstitial fluid, which in turn leads to increased pulmonary compliance, improved oxygenation, and a decrease in pulmonary artery pressure. All these positive factors will also lead to improvement of right ventricular function.[204,205] MUF has also been shown to improve the coagulopathy associated with CPB and to decrease transfusion requirements. CPB will lead to a hemodilutional state that affects hematocrit and coagulation factors, as well a separate effect on platelet number and function. The effect of MUF will lead to an increase in hematocrit (which in patients with single ventricle physiology will improve oxygen saturation and oxygen-carrying capacity) and improvements in the level of coagulation factors by clearing the dilutional volume. This will in turn lead to improved coagulation, decreased bleeding, and a decrease in blood requirements. These effects have been shown in neonates and in those with prolonged CPB, two groups associated with increased bleeding. Despite these obvious advantages, MUF has no effect on platelets.[204-208]

Creation of a superior cavopulmonary anastomosis and Fontan completion will increase venous pressure. This is the primary etiological association found in a subgroup of these patients who develop postoperative pulmonary or pericardial effusions. In an early study looking in to the effect of MUF on associated morbidities, it was found that there was a significant reduction in effusions. The difference was found to be most significant in the Fontan group where the incidence was 48.5% in the control group versus 10.5% in the MUF group. In those patients undergoing cavopulmonary anastomosis, 11.5% of those in the control group had effusions versus 4.9% in the MUF group.[208] The morbidity and mortality associated with ongoing effusions include chronic hypoxia and ongoing protein loss resulting in anasarca and immune suppression. These findings have been supported by other studies.[205,209] Clearly, the use of MUF plays an important role in decreasing this morbidity and mortality. Recent advances have also included the creation of a fenestration in the Fontan baffle that serves as a pressure release from the now high-pressure venous system into the atrial chamber.

The systemic inflammatory response that is generated by CPB can prove deleterious to organ function. Huang et al. showed that the use of continuous ultrafiltration and MUF will lead to a decrease in the concentration of IL-6 but had no effect on endothelin-1 (ET-1).[210] Contrary to this study, Bando and colleagues showed that a combination of dilutional ultrafiltration with MUF will result in a decrease in ET-1, thus decreasing the pulmonary/systemic pressure ratio and also reducing ventilatory requirements.[211] In a third study, the addition of a polysulfone ultrafilter to the MUF circuit for both conventional ultrafiltration and MUF improved the removal of IL-6 and tumor necrosis factor.[212]

Despite all these positive effects of MUF, there are important safety concerns. These include inadvertent cooling during the procedure; hypotension if too much blood is drawn off via the arterial line; and varying technical difficulties with the circuit, such as air cavitating out of solution in the arterial line, clotted MUF circuit, and exsanguination due to unclamping of the oxygenator circuit.

The effect of hypoperfusion/reperfusion has the potential to cause a breakdown in the normal gastrointestinal mucosal barrier. The translocation of endotoxins into the bloodstream may result in hypotension, fever, hypermetabolism, tissue damage, and coagulopathy, all factors that can cause problems as patients are being weaned from CPB. In a study by Yngaard et al.,[213] it was found that the endotoxin load significantly increased during cardiopulmonary bypass, peaking at the end of CPB. The use of MUF significantly decreased the load from 24.2 ng at the peak to 9 ng after MUF, with the majority of the load found in the ultrafiltrate. In a separate study quoted by these authors, it was found that an endotoxin load greater than 4 ng/kg may depress myocardial function. The conclusion of the study was that despite not fully removing the endotoxin load, MUF may aid in the modification of the inflammatory response seen.[213]

The use of MUF has become standard in congenital cardiac surgery. In most centers, patients undergo continuous ultrafiltration in one form or another during CPB, and MUF is performed on weaning from bypass.

Delayed Sternal Closure

In some patients, there is an apparent period of hemodynamic and ventilatory stability that is followed by instability of varying degrees upon sternal closure. This may necessitate that the sternum remain open for a period ranging from a few hours up to a few days. This is achieved by placing a tube strut between the two sternal edges (a rigid tube, e.g., a size 4 to 5 mm ETT may suffice) and then closing the skin with a Gore-Tex patch. Concerns for this technique are obviously the risk of infection, tamponade due to inadequate drainage, and the inability to perform standard CPR in the face of cardiopulmonary arrest. Sternal closure can subsequently be achieved either in the ICU or in the operating room. At the Children's Hospital of Philadelphia, this is routinely performed in the ICU with good results.

Conclusions

The management of the cardiac surgery patient has improved greatly over the past 6 decades, with patients who as little as 30 years ago would have had no management options now living and sometimes thriving into adulthood. The treatment and successful outcomes of these potentially complex patients is dependent on a team approach. The management often begins in the ICU or cardiologist's office and runs the full spectrum of anesthesia, perioperative nursing, perfusionists, surgeons, and intensivists. Looking forward over the next decade, the questions of circuit miniaturization, neurocognitive outcome, and intrauterine interventions will be in the forefront of research.

References are available online at http://www.expertconsult.com.

Critical Care After Surgery for Congenital Cardiac Disease

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PEARLS

- Echocardiography is the preferred imaging modality for assessment and delineation of intracardiac anatomic features before surgery in children. Accurate anatomic diagnosis is now routine, so most children can have surgery without preoperative cardiac catheterization.
- A typical and predictable decrease in cardiac index typically occurs 6 to 12 hours after separation from cardiopulmonary bypass.
- Milrinone administered during the early postoperative period plays a significant role in decreasing the likelihood of low cardiac output syndrome.
- Patients with restrictive physiology from hypertrophy and diastolic dysfunction of the right ventricle, such as those after tetralogy of Fallot repair, require high right-sided filling pressures to achieve adequate cardiac output. Consequently, these patients are more prone to hepatic congestion, anasarca, pleural effusions, and ascites.
- Inhaled nitric oxide plays an important role in the management of postoperative pulmonary hypertension in the cardiac intensive care unit. It is particularly effective in the postoperative course of patients with venous hypertensive disorders, such as total anomalous pulmonary venous connection and congenital mitral stenosis.
- Hyperglycemia is a frequent occurrence in the cardiac intensive care unit and has been associated with increased morbidity and mortality during the postoperative period. Careful glycemic control with insulin administration might improve outcomes, but one must be aware of the risk of iatrogenic hypoglycemia.
- Hypoxemia after bidirectional cavopulmonary anastomosis generally is a sign of decreased cardiac output, is poorly responsive to nitric oxide, and tends to improve with maneuvers that increase venous return through the superior vena cava, such as head elevation and controlled hypoventilation/mild hypercapnia.
- Liberation from positive pressure mechanical ventilation should be accomplished as soon as feasible in patients after a Fontan operation, because spontaneous breathing improves pulmonary blood flow, arterial oxygen saturation, and ventricular preload.
- Ventricular ectopy and elevated atrial pressures after the arterial switch operation should raise suspicion of myocardial ischemia from insufficient coronary blood flow.
- Postoperative care of the patient with hypoplastic left heart syndrome after stage I palliation (Norwood procedure) requires adequate balancing of the pulmonary and systemic blood flows. A high arterial oxygen saturation denotes excessive pulmonary blood flow and is generally accompanied by decreased systemic blood flow, acidosis, and end-organ dysfunction.

Congenital anomalies account for the largest diagnostic category among causes of infant mortality in the United States.[1] Structural heart disease leads the list of congenital malformations. Of the more than 4 million children born each year in the United States, nearly 40,000 have some form of congenital heart disease (CHD). Approximately half of these children appear for therapeutic intervention within the first year of life, and the vast majority of them require critical care expertise. Patients with congenital or acquired heart disease compose a major diagnostic category for admissions in large pediatric intensive care units (ICUs) across the country, representing 30% to 40% or more of ICU admissions in many centers.

Newborn Considerations

Care of the critically ill neonate requires an appreciation of the special structural and functional features of immature organs, the interactions of the "transitional" neonatal circulation, and the secondary effects of the congenital heart lesion on other organ systems.[2-4] The neonate appears to respond more quickly and profoundly to physiologically stressful circumstances, which may be expressed in terms of rapid changes in pH, lactic acid, blood glucose, and temperature. Neonates have diminished fat and carbohydrate reserves compared with older children. The higher metabolic rate and oxygen consumption of the neonate play a significant role in

the rapid onset of hypoxemia when these patients become apneic. Immaturity of the liver and kidney may be associated with reduced protein synthesis and glomerular filtration such that drug metabolism is altered and hepatic synthetic function is reduced. These issues may be compounded by the normal increased total body water of the neonate compared with the older patient, along with the propensity of the capillary system of the neonate to leak fluid from the intravascular space. This is especially prominent in the lung of the neonate in whom the pulmonary vascular bed is nearly fully recruited at rest, and lymphatic recruitment required to handle increased mean capillary pressures associated with increases in pulmonary blood flow may be unavailable.[4] The neonatal myocardium is less compliant than that of the older child, is less tolerant of increases in afterload, and is less responsive to increases in preload. Younger age also predisposes the myocardium to the adverse effects of cardiopulmonary bypass (CPB) and hypothermic ischemia implicit in support techniques used during cardiac surgery. These factors do not preclude intervention in the neonate but simply dictate that extraordinary vigilance be applied to the care of these children and that intensive care management plans take into account their immature physiology.

The observed benefits of neonatal reparative operations in patients with two ventricles are numerous (Box 31-1). They continue to dictate that care of the newborn with complex CHD after CPB be a central feature of cardiac intensive care. Elimination of cyanosis and congestive heart failure (CHF) early in life optimize, conditions for normal growth and development. Palliative procedures such as pulmonary artery bands and systemic-to-pulmonary artery shunts may not fully address cyanosis or CHF and may introduce their own set of physiologic and anatomic complications. Some examples of improved outcomes with a single reparative operation rather than staged palliation as a newborn are well known, are supported by published literature, and evoke little controversy. Approaches that have been abandoned include banding the pulmonary arteries in truncus arteriosus,[5] staging repair of type B interrupted aortic arch (IAA),[6] and staging rather than repairing in a single session transposition of the great arteries with IAA.[7] In other conditions (e.g., severely cyanotic newborn with tetralogy of Fallot [TOF]), the risks and benefits of neonatal repair versus a palliative shunt are debatable.[8]

Whereas the neonate may be more labile than the older child, there is ample evidence that this age group is more resilient in its response to metabolic or ischemic injury. In fact, the neonate may be particularly capable of coping with some forms of stress. Tolerance of hypoxemia in the neonate is characteristic of many species,[9] and the plasticity of the neurologic system in the neonate is well known. Neonates with obstructive left heart lesions often present with profound metabolic acidosis but can be effectively resuscitated without persistent organ system impairment or sequelae as the rule rather than the exception. The pliability and mobility of vascular structures in the neonate improve the technical aspects of surgery. Reparative operations in neonates take advantage of normal postnatal changes, allowing more normal growth and development in crucial areas such as myocardial muscle, pulmonary parenchyma, and coronary and pulmonary angiogenesis. Postoperative pulmonary hypertensive events are more common in the infant who has been exposed to weeks or months of high pulmonary pressure and flow.[5,10] This seems especially true for such lesions as truncus arteriosus, complete atrioventricular (AV) canal defects, and transposition of the great arteries with ventricular septal defects (VSDs). Finally, cognitive and psychomotor abnormalities associated with months of hypoxemia or abnormal hemodynamics may be diminished or eliminated by early repair. However, if early reparative surgery results in more exposures to CPB (e.g., repeated conduit changes) and any associated cognitive or subtle adverse effects on motor function, then the risk-to-benefit assessment needs to be modified accordingly.

Box 31–1 Advantage of Neonatal Repair

Early elimination of cyanosis
Early elimination of congestive heart failure
Optimal circulation for growth and development
Reduced anatomic distortion from palliative procedures
Reduced hospital admissions while awaiting repair
Reduced parental anxiety while awaiting repair

Preoperative Care

Optimal preoperative care involves (1) initial stabilization, airway management, and establishment of adequate vascular access; (2) complete and thorough noninvasive delineation of the anatomic defect(s); (3) evaluation and treatment of secondary organ dysfunction, particularly the brain, kidneys, and liver; (4) cardiac catheterization if necessary, typically for (A) physiologic assessment, (B) interventional procedures such as balloon atrial septostomy or valvotomy, or (C) anatomic definition not visible by echocardiography (e.g., coronary artery distribution in pulmonary atresia with intact ventricular septum or delineation of aortopulmonary collaterals in TOF with pulmonary atresia); and (5) surgical management when cardiac, pulmonary, renal, and central nervous systems (CNS) are optimized.

Physical Examination and Laboratory Data

A complete history and physical examination are required, with special attention directed to the extent of cardiopulmonary impairment, airway abnormalities, and associated extracardiac congenital anomalies.[11] Intrathoracic and extrathoracic airway problems in patients with Down syndrome, disorders of calcium homeostasis and immunologic deficiencies in patients with aortic arch abnormalities, and renal abnormalities in patients with esophageal atresia and CHD are a few of the associated congenital abnormalities with which the anesthesiologist should be familiar. Intercurrent pulmonary infection is a common and significant finding in chronically overcirculated lungs. The presence, degree, and duration of hypoxemia are important details that, in the absence of iron deficiency, are reflected in the hematocrit. The nadir of physiologic anemia during infancy may contribute to left-to-right shunting by decreasing the relative pulmonary vascular resistance (PVR).[12]

Chest radiography can be used to asses heart size, pulmonary vascular congestion, airway compression, and areas of consolidation or atelectasis. The electrocardiogram (ECG) may reveal rhythm disturbances and demonstrate ventricular

strain patterns (ST and T-wave changes) characteristic of unphysiologic pressure or volume burdens on the ventricles. Electrolyte abnormalities caused by CHF and forced diuresis also must be evaluated preoperatively. Severe hypochloremic metabolic alkalosis may occur in some patients. It is important to discontinue digoxin preoperatively and to avoid hyperventilation and administration of calcium to these patients during induction of anesthesia, because the alkalotic hypokalemic, hypercalcemic, hypotensive, dilated, digoxin-bound myocardium fibrillates with ease.

Echocardiographic and Doppler Assessment

Advances in echocardiographic imaging have had an enormous impact on the diagnosis of CHD.[13] Accurate anatomic diagnosis now is routine in children without the need for cardiac catheterization. Echocardiography is the preferred imaging modality for assessment of intracardiac anatomic features in young children. However, one should be aware of the current limitations of echocardiographic and Doppler techniques so that alternative diagnoses can be considered when intraoperative or postoperative findings are inconsistent with the working echocardiographic diagnosis.

Skilled echocardiographers accurately interpret the alignment of cardiac chambers and great vessels but cannot always visualize an atrial septal defect (ASD) or VSD, although color flow mapping techniques have vastly improved diagnostic capabilities. An ASD can be indirectly inferred from right ventricular (RV) volume overload and interventricular septal shift. Distal pulmonary artery architecture and conduits between a ventricle and a great artery are poorly imaged by echocardiography, and pressure gradients in these areas are not always measurable with Doppler techniques. Quantification of AV valve regurgitation may be subjective and nonquantitative. Accuracy of echocardiographic diagnosis is limited by an inadequate window for imaging in obese patients, older children, and some postoperative patients. Techniques for three-dimensional echocardiography that may improve diagnostic capabilities, such as defining the mechanism of valve regurgitation or visualization of complex anatomic features, are now available and are gradually gaining popularity among selected services.

Doppler measurements add greatly to noninvasive diagnostic capabilities. Measurements of pressure gradients across semilunar valves and other obstructions frequently are accurate but may not always correlate with peak systolic ejection gradients measured at catheterization. As good as echocardiographic diagnosis of anatomic defects and Doppler measurements of pressure gradients and valve function have become, the standard for assessment of physiology when other clinical information is ambiguous or contradictory remains cardiac catheterization.

Cardiac Catheterization

When echocardiographic analysis with Doppler measurements and color flow mapping is complete and unambiguous, preoperative assessment may no longer require cardiac catheterization. Catheterization typically is not performed before infant or neonatal operations for VSDs, complete AV canal defects, TOF, IAA, hypoplastic left heart syndrome (HLHS), or coarctation of the aorta. However, in older patients with complex anatomy, such as a single ventricle, physiologic data from catheterization may be essential. This technique allows description of the direction, magnitude, and approximate location of intracardiac shunts. Intracardiac and intravascular pressures are measured to determine the presence of obstructions and whether shunt orifices are restrictive or nonrestrictive. Pressure gradients across sites of obstruction must be considered in light of simultaneous blood flow; a small pressure gradient measured at a time of low cardiac output is misleading.

Normal intracardiac pressure and saturation values in children are described in Chapter 24. Normally, there is no significant change in oxygen saturation from vena cava to pulmonary artery. In the child with CHD, the superior vena cava (SVC) gives the best indication of true mixed venous oxygen saturation; a 5% or greater step-up in saturation downstream suggests the presence of a left to right shunt.[14] It would occur at the level of the right atrium with an ASD, in the right ventricle with a VSD, and in the pulmonary artery with a patent ductus arteriosus (PDA). The magnitude of the left-to-right shunt can be calculated from the Fick equation. The oxygen consumption of the patient usually is measured, as are the saturation values, but subsequent flow and resistance calculations can be in error. The frequently used term Q_p/Q_s (pulmonary-to-systemic blood flow ratio) can be derived simply from the measured oxygen saturation values.

The patient whose aortic blood is fully saturated can be safely assumed to have no significant right-to-left shunting. However, when a right-to-left shunt is present, aortic blood is hypoxemic. Blood samples should also be obtained from the pulmonary veins, left atrium, and left ventricle for oxygen saturation determination and ascertainment of the source of desaturated blood. Pulmonary venous desaturation implies a pulmonary source of venous admixture (e.g., pneumonia, atelectasis, other pulmonary disease). Intrapulmonary shunting may substantially alter the anesthetic plan and the postoperative ventilatory requirements of the patient.

In the presence of a left-to-right shunt and elevated PVR, pressure and saturation measurements often are repeated, with the patient breathing 100% oxygen to assess both the reactivity of the pulmonary vascular bed and any contribution of ventilation-perfusion abnormalities to hypoxemia. If breathing 100% oxygen increases pulmonary blood flow and dramatically increases Q_p/Q_s (with a fall in PVR), potentially reversible processes such as hypoxic pulmonary vasoconstriction probably are contributing to the elevated PVR. The patient with a high, unresponsive PVR and a small left-to-right shunt despite a large shunt orifice may have extensive pulmonary vascular damage from irreversible obstructive pulmonary vascular disease. If so, surgical repair usually is contraindicated if the child is older than 1 year.[15]

During cardiac catheterization, anatomic abnormalities are identified angiographically. Special angled views provide specific information about the location and extent of congenital defects.[16] Ventricular function is assessed angiographically and physiologically (e.g., by pressure measurements). The calculated size of a cardiac chamber may have an important bearing on its ability to support the circulation of a child with hypoplastic ventricles.

Magnetic Resonance Imaging and Angiography

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) have emerged as important diagnostic modalities in the evaluation of the cardiovascular system after the development of ECG-gated MRI. Image acquisition is triggered to the patient's ECG to counter motion artifacts and to acquire cine sequences that allow imaging of cardiac structures and visualization of blood flow throughout the cardiac cycle. In addition to providing excellent anatomical and three-dimensional images, particularly of the pulmonary veins and thoracic aorta, it also is possible with MRA to qualitatively assess valve and ventricular function and to quantify flow, ventricular volume, mass, and ejection fraction.[17,18] Whereas ferromagnetic implants near the region of interest might produce artifact, sternal wires and vascular clips produce relatively minor disturbances; therefore MRI can be performed in patients who have undergone previous cardiac surgery. Contraindications include patients with pacemakers, recently implanted endovascular or intracardiac implants, and aneurysm clips on vessels that will be exposed directly to the magnetic field.

Assessment of Patient Status and Predominant Pathophysiology

Frequently, congenital heart defects are complex and can be difficult to categorize or conceptualize. Rather than trying to determine the management for each individual anatomic defect, a physiologic approach can be taken. The following questions should be asked:

1. How does the systemic venous return reach the systemic arterial circulation to maintain cardiac output? What intracardiac mixing, shunting, or outflow obstruction exists?
2. Is the circulation in series or parallel? Are the defects amenable to a two-ventricle or single-ventricle repair?
3. Is pulmonary blood flow increased or decreased?
4. Is there a volume load or pressure load on the ventricles?

Appropriate organization of preoperative patient data, preparation of the patient, and decisions about monitoring, anesthetic agents, and postoperative care are best accomplished by focusing on a few major pathophysiologic problems, beginning with whether the patient is cyanotic, in CHF, or both. Most pathophysiologic mechanisms in the patient's disease that are pertinent to the perioperative plan and to optimal preparation of the patient focus on one of the following major problems: severe hypoxemia, excessive pulmonary blood flow, CHF, obstruction of blood flow from the left heart, and poor ventricular function. Although some patients with CHD present with only one problem, many have multiple interrelated problems.

Severe Hypoxemia

Many of the cyanotic forms of CHD present in the ICU with severe hypoxemia (Pao_2 <50 mm Hg) during the first few days of life, but without respiratory distress. Infusion of prostaglandin E_1 (PGE_1) in patients with decreased pulmonary blood flow maintains or reestablishes pulmonary flow through the ductus arteriosus. This may also improve mixing of venous and arterial blood at the atrial level in patients with transposition of the great arteries.[19] Consequently, neonates rarely require surgery while they are severely hypoxemic. During preoperative preparation with PGE_1, neurologic examination and blood chemistry analysis of renal, hepatic, and hematologic function are necessary to assess the effects of severe hypoxemia during or after birth on end-organ dysfunction.

Cyanotic patients who present for surgery after infancy require adequate preoperative and postoperative hydration to prevent the thrombotic problems caused by polycythemia. Adequate quantities of blood products for treatment of the coagulopathies also are needed, as outlined earlier. Premedication must be given cautiously so as not to cause hypoventilation in these patients.

PGE_1 dilates the ductus arteriosus of the neonate with life-threatening ductus-dependent cardiac lesions and improves the patient's condition before surgery. PGE_1 can reopen a functionally closed ductus arteriosus for several days after birth, or it can maintain patency of the ductus arteriosus for several months postnatally.[19,20] The common side effects of PGE_1 infusion—apnea, hypotension, fever, CNS excitation—are easily managed in the neonate when normal therapeutic doses of the drug (0.02–0.05 μg/kg/min) are used.[21] However, PGE_1 is a potent vasodilator, so intravascular volume frequently requires augmentation. Patients with intermittent apnea resulting from administration of PGE_1 may require mechanical ventilation preoperatively.

PGE_1 usually improves the arterial oxygenation of hypoxemic neonates who have poor pulmonary perfusion as a result of obstructed pulmonary flow (critical pulmonic stenosis or pulmonary atresia). By providing pulmonary blood flow from the aorta via the ductus arteriosus, an infusion of PGE_1 improves oxygenation and stabilizes the condition of neonates with these lesions. The improved oxygenation reverses the lactic acidosis that may have developed during episodes of severe hypoxia. PGE_1 administration for 24 hours usually markedly improves the condition of a severely hypoxemic neonate with restricted pulmonary blood flow.[22]

Excessive Pulmonary Blood Flow

Excessive pulmonary blood flow is frequently the primary problem of patients with CHD. The intensivist must carefully evaluate the hemodynamic and respiratory impact of left-to-right shunts and the extent to which it contributes to the perioperative course in the ICU. Children with left-to-right shunts may have chronic low-grade pulmonary infection and congestion that cannot be eliminated despite optimal preoperative preparation. If so, surgery should not be postponed further. Respiratory syncytial viral infections are particularly prevalent in this population, but improvements in intensive care have markedly improved outcome with this and other viral pneumonias.[23]

Aside from the respiratory impairment caused by increased pulmonary blood flow, the left heart must dilate to accept pulmonary venous return that might be several times normal. If the body requires more systemic blood flow, the heart responds inefficiently. Most of the increment in cardiac output is recirculated to the lungs. Eventually, symptoms of CHF appear.

Children with failing hearts increase endogenous catecholamine production and redistribute cardiac output to favored organs by their increased heart rate and decreased extremity perfusion. In the most severe cases, the evaluation reveals a child whose body weight is below the third percentile for

age and who is tachypneic, tachycardic, and dusky in room air. The child may have intercostal and substernal retractions and skin that is cool to the touch. Capillary refill may be prolonged. Expiratory wheezes usually are audible. Medical management with digoxin and diuretics may improve the patient's condition, but the diuretics may induce profound hypochloremic alkalosis and potassium depletion that often persist after surgery.

Obstruction of Left Heart Outflow

Patients who require surgery to relieve obstruction to outflow from the left heart are among the most critically ill children for whom the intensivist must care. These lesions include interruption of the aortic arch, coarctation of the aorta, aortic stenosis (AS), and mitral stenosis or atresia as part of the HLHS. These neonates present with inadequate systemic perfusion and profound metabolic acidosis. The initial pH may be below 7 despite a low $Paco_2$. Systemic blood flow is largely or completely dependent on blood flow into the aorta from the ductus arteriosus.

Ductal closure in the neonate with these problems causes dramatic worsening of the patient's condition. The patient becomes critically ill or even moribund and requires PGE_1 infusion (see previous section) for survival. PGE_1 allows blood flow into the aorta from the pulmonary artery because it maintains the patency of the ductus arteriosus.[22,24] PGE_1 infusion improves perfusion and metabolism in neonates with acidosis, metabolic derangements, and renal failure because of inadequate systemic perfusion, so surgery generally can be deferred until the patient's condition improves. Ventilatory and inotropic support and correction of metabolic acidosis, along with calcium, glucose, and electrolyte abnormalities are often indicated preoperatively. The stabilization period also allows assessment of the magnitude of end-organ dysfunction caused by the preceding period of inadequate systemic perfusion. Adequacy of resuscitation, rather than severity of illness at presentation, appears to influence postoperative outcome.[25]

Ventricular Dysfunction

Ideally, the intensivists should participate in the care of all preoperative patients who have a planned admission to the ICU. Understanding the extent of ventricular dysfunction preoperatively provides considerable insight into intraoperative and postoperative events. Although patients with large shunts may have complete mixing of systemic and venous blood and only mild-to-moderate hypoxemia as a result of their excessive pulmonary blood flow, the price paid for near-normal arterial oxygen saturation is chronic ventricular dilation and dysfunction and pulmonary vascular obstructive disease. Consequently, narrowing the shunt or a staged approach to single-ventricle repair may be indicated before any other elective surgery can be undertaken. Older patients with CHD and poor ventricular function as a result of chronic ventricular volume overload (aortic or mitral valve regurgitation or long-standing pulmonary-to-systemic arterial shunts) present a different problem, amenable to some extent by afterload reduction. However, in all of these circumstances, when the heart is dilated and volume overloaded, there is a propensity for ventricular fibrillation during sedation, anesthesia, and/or intubation of the airway.

Assessment should include an estimation of the patient's functional limitation as an indicator of myocardial performance and reserve, quantification of the degree of hypoxia and the amount of pulmonary blood flow, and evaluation of PVR. For patients with increased Q_p/Q_s, systemic blood flow should be optimized without further augmenting pulmonary flow during induction of anesthesia in the ICU or in the operating room. However, during maintenance and emergence from anesthesia, retraction of the lung, positional changes, and abdominal distension may increase the hypoxemia and compromise the function of a dilated, poorly contractile ventricle. If this sequence occurs during surgery, patient management must be altered to improve pulmonary blood flow.

In addition, systolic function of the ventricle may be impaired by intrinsic myopathic abnormalities related to drug toxicity (e.g., doxorubicin [Adriamycin]), inborn enzyme deficiencies, or acquired inflammatory or infectious disease. Patients with such dilated cardiomyopathies require optimization of ventricular performance with emphasis on inotropic support and afterload reduction. In many centers, these patients are admitted to the ICU for inotropic support and optimization of hemodynamic state before a planned surgical intervention.

Postoperative Care

Assessment

When the clinical course of patients after cardiac surgery deviates from the usual expectation of uncomplicated recovery, our first responsibility is to verify the accuracy of the preoperative diagnosis and the adequacy of surgical repair. For example, a young infant who is acidotic, hypotensive, and cyanotic after surgical repair of TOF may tempt us to ascribe these findings to the vagaries of ischemia/reperfusion injury of CPB or transient, postoperative stiffness of the right ventricle. However, the real culprit may be an additional VSD undetected preoperatively and therefore not closed, a residual VSD around the surgical patch, or residual RV outflow obstruction. Any of these anatomic issues and more can produce serious adverse outcomes. Getting the right postoperative assessment is imperative and treatment follows accordingly. Evaluation of the postoperative patient relies on examination, monitoring, interpretation of vital signs, or other bedside data and imaging (Box 31-2). When the accuracy of the diagnosis and adequacy of the repair are established, then a low cardiac output

Box 31–2 Ten Intensive Care Strategies to Diagnose and Support Low Cardiac Output States

1. Know in detail the cardiac anatomy and its physiologic consequences
2. Understand the specialized considerations of the newborn and implications of reparative rather than palliative surgery
3. Diversify personnel to include experts in neonatal and adult congenital heart disease
4. Monitor, measure, and image the heart to rule out residual disease as a cause of postoperative hemodynamic instability or low cardiac output
5. Maintain aortic perfusion and improve the contractile state
6. Optimize preload (including atrial shunting)
7. Reduce afterload
8. Control heart rate, rhythm, and synchrony
9. Optimize heart lung interactions
10. Provide mechanical support when needed

state can be presumed and treatment optimized. Treating low cardiac output states and preventing cardiovascular collapse often are the central features of pediatric cardiac intensive care and are the focus of this chapter.

Optimizing preload involves more than just giving volume to a hypotensive patient. There are numerous considerations to fluid balance involving types of isotonic fluid, ultrafiltration in the operating room, optimal hematocrit, and use of furosemide, thiazides, and possibly newer drugs such as fenoldapam or nesiritide. Fluid itself can be detrimental if excess extravascular water results in interstitial edema and end-organ dysfunction of vital organs such as the heart, lungs, and brain. Perhaps permitting a right-to-left shunt at the atrial level would optimize preload to the left ventricle in some conditions (see the following section). Maintaining aortic perfusion after CPB and improving the contractile state of the heart with higher doses of catecholamines are reasonable goals, but may have particularly deleterious consequences in the newborn myocardium after hypothermic CPB. The benefits of afterload reduction are well known, but in excess it results in hypotension and cardiovascular collapse or renal or cerebral insufficiency. Pacing the heart can stabilize the rhythm and hemodynamics, but it also may contribute to dyssynchronous, inefficient contraction of the heart or induce other arrhythmias. Mechanical support of the failing myocardium, in the form of extracorporeal membrane oxygenation (ECMO) or ventricular assist devices, although lifesaving in many instances, has its own set of time limitations and morbid complications. Almost every treatment approach has its own set of adverse effects that may be damaging. Supporting cardiac output in the postoperative patient is a balance between the promise and poison of therapy.

The initial assessment after cardiac surgery begins with review of the operative findings. This includes details of the operative repair and CPB, particularly total CPB or myocardial ischemia (aortic cross-clamp) times; concerns about myocardial protection; recovery of myocardial contractility; typical postoperative systemic arterial and central venous pressures; findings from intraoperative transesophageal echocardiography, if performed; and vasoactive medication requirements. This information guides subsequent examination, which should focus on the quality of the repair or palliation plus clinical assessment of cardiac output (Box 31-3). In addition to a complete cardiovascular examination, a routine set of laboratory tests should be obtained, including a chest radiograph, 12- or 15-lead ECG, blood gas analysis, serum electrolytes and glucose, ionized calcium and lactate measurements, complete blood count, and coagulation profile.

Monitoring

Monitoring central venous pressure is routine for many patients after cardiac surgery, except those who undergo the least complex procedures. For example, we do not routinely place a central venous catheter in patients undergoing thoracic procedures, such as coarctation of the aorta, vascular ring, or PDA ligation, or in patients undergoing cardiotomy with a short period of mildly hypothermic CPB, such as an ASD repair. Intracardiac or transthoracic left atrial (LA) catheters are often used to monitor patients after complex reparative procedures. Pulmonary arterial (PA) catheters now are seldom used but may be particularly useful if the postoperative management anticipates a problem such as (1) a residual lesion producing an intracardiac left-to-right shunt (e.g., multiple VSDs); (2) residual RV outflow tract obstruction, as a catheter "pullback" can be performed to measure the RV-to-PA pressure gradient; and (3) pulmonary hypertension, thereby allowing rapid detection of pressure changes and assessment of the response to interventions.

LA catheters are especially helpful in the management of patients with ventricular dysfunction, coronary artery perfusion abnormalities, and mitral valve disease. The mean LA pressure typically is 1 to 2 mm Hg greater than mean right atrial (RA) pressure, which generally varies between 1 and 6 mm Hg in nonpostoperative pediatric patients undergoing cardiac catheterization. In postoperative patients, mean LA and RA pressures both are often greater than 6 to 8 mm Hg. However, they generally should be less than 15 mm Hg. The compliance of the right atrium is greater than that of the left atrium except in the newborn, so pressure elevations in the right atrium of older patients with two ventricles typically are less pronounced.

Possible causes of abnormally elevated LA pressure are listed in Box 31-4. In addition to pressure data, intracardiac catheters in the RA (or a percutaneously placed central venous catheter), LA, and PA can be used to monitor the oxygen saturation of systemic venous or pulmonary venous blood.

Table 31-1 lists the causes of abnormally high or low RA, LA, and PA oxygen saturations, which can be measured at the bedside in the ICU. After reparative surgery, patients with no intracardiac shunts and adequate cardiac output may have a mild reduction in RA oxygen saturation to approximately 60%. Lower RA oxygen saturation does not necessarily indicate low cardiac output, if a patient has arterial desaturation (common mixing lessons, lung diseases, etc.) and the arteriovenous oxygen difference is normal at 25%, there may be appropriate oxygen delivery and extraction. Elevated RA oxygen saturation often is the result of left-to-right shunting at the atrial level (e.g., from the left atrium, anomalous pulmonary vein, or left ventricular [LV]-to-RA shunt). Blood in the left atrium normally is fully saturated with oxygen (i.e., approximately 100%). The two chief causes of reduced LA oxygen saturation are an atrial level right-to-left shunt and pulmonary venous desaturation from abnormal gas exchange.

Box 31–3 Signs of Heart Failure or Low Cardiac Output States

Signs

Cool extremities/poor perfusion
Oliguria and other end-organ failure
Tachycardia
Hypotension
Acidosis
Cardiomegaly
Pleural effusions

Monitor and Measure

Heart rate, blood pressure, intracardiac pressure
Extremity temperature, central temperature
Urine output
Mixed venous oxygen saturation
Arterial blood gas pH and lactate
Laboratory measures of end-organ function
Echocardiography

In the absence of left-to-right shunts, PA oxygen saturation is the best representation of the "true" mixed venous oxygen saturation because all sources of systemic venous blood should be thoroughly combined as they are ejected from the right ventricle. When elevated, this saturation is useful in identifying residual left-to-right shunts after repair of VSD(s). The absolute value of the PA oxygen saturation is a predictor of significant postoperative residual shunt. In patients after TOF or VSD repair, PA oxygen saturation greater than 80% within 48 hours of surgery with supplemental O_2 at a fractional inspired oxygen concentration (Fio_2) less than 0.5 is a sensitive indicator of significant left-to-right shunt (Qp/Qs >1.5) 1 year after surgery.[26] Determination of PA oxygen saturation also can be useful in patients with systemic-to-pulmonary artery collaterals because flow from these vessels into the pulmonary arteries can increase oxygen saturation.

Box 31–4 Common Causes of Elevated Left Atrial Pressure After Cardiopulmonary Bypass

1. Decreased ventricular systolic or diastolic function
   Myocardial Ischemia
   Dilated cardiomyopathy
   Systemic ventricular hypertrophy
2. Left atrioventricular valve disease
3. Large left-to-right intracardiac shunt
4. Chamber hypoplasia
5. Intravascular or ventricular volume overload
6. Cardiac tamponade
7. Arrhythmia
   Tachyarrhythmia, junctional rhythm
   Complete heart block

Table 31–1 Causes of Abnormal Right Atrial, Left Atrial, or Pulmonary Artery Oxygen Saturation

Location	Elevated	Reduced
RA	Atrial level left-to-right shunt	↑Vo_2 (e.g., low CO, fever)
	Anomalous pulmonary venous return	↓Sao_2 saturation with a normal A-V O_2 difference
	Left ventricular-to-right atrial shunt	Anemia
	↑Dissolved O_2 content	Catheter tip position (e.g., near CS)
	↓O_2 extraction	
	Catheter tip position (e.g., near renal veins)	
LA	Does not occur	Atrial level right-to-left shunt
		↓Pvo_2 (e.g., parenchymal lung disease)
PA	Significant left-to-right shunt	↑O_2 extraction (e.g., low CO, fever)
	Small left-to-right shunt with incomplete mixing of blood	Sao_2 saturation with a normal A-V O_2 difference
	Catheter tip position (e.g., PA "wedge")	Anemia

A-V, Arteriovenous; *CO,* cardiac output; *CS,* coronary sinus; *LA,* left atrium; *PA,* pulmonary artery; *Pvo_2,* pulmonary vein oxygen tension; *RA,* right atrium; *Sao_2,* arterial oxygen saturation; *Vo_2,* oxygen consumption.

Low Cardiac Output Syndrome

Although some causes of low cardiac output after CPB are attributable to residual or undiagnosed structural lesions, progressive low cardiac output states do occur. Several factors have been implicated in the development of myocardial dysfunction after CPB including (1) the inflammatory response associated with CPB, (2) the effects of myocardial ischemia from aortic cross-clamping, (3) hypothermia, (4) reperfusion injury, (5) inadequate myocardial protection, and (6) ventriculotomy (when performed). The expression and prevention of reperfusion injury after aortic cross-clamping on CPB is the subject of intense investigation. The typical decrease in cardiac index in newborns after an arterial switch operation (ASO) has been well characterized (Figure 31-1).[27] In a group of 122 newborns, the median maximal decrease in cardiac index that typically occurred 6 to 12 hours after separation from CPB was 32%. One fourth of these newborns reached a nadir of cardiac index that was less than 2 L/min/m^2 on the first postoperative night. Low cardiac output syndrome (LCOS) does occur in the postoperative patient, but appropriate anticipation and intervention can do much to avert morbidity or the need for mechanical support. Signs of low cardiac output are listed in Box 31-3. Mixed venous oxygen saturation, whole blood pH, and lactate are laboratory measures commonly used to evaluate the adequacy of tissue perfusion and hence cardiac output.

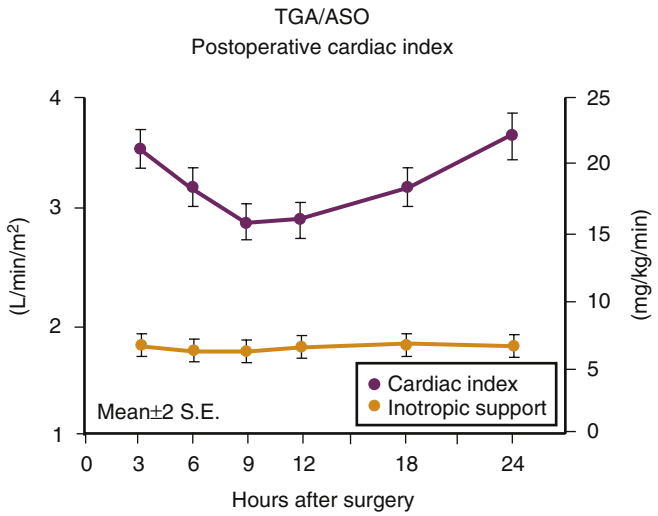

Figure 31–1. Cardiac index (*left axis*) measured in infants after the arterial switch operation declines during the first 12 hours and was not the result of any reduction in inotropic support (*right axis*). One fourth of the patients reach a value less than 2 L/min/m^2. The median reduction in cardiac index the first night is 33%. *(From Wernovsky G, Wypij D, Jonas RA, et al: Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest,* Circulation *92:2226-2235, 1995.)*

Volume Adjustments

After CPB, the factors that influence cardiac output, such as preload, afterload, myocardial contractility, heart rate, and rhythm, must be assessed and manipulated. Volume therapy (increased preload) is commonly necessary, followed by appropriate use of inotropic and afterload-reducing agents. Atrial pressure and the ventricular response to changes in atrial pressure must be evaluated. Ventricular response is judged by observing systemic arterial pressure and waveform, heart rate, skin color, peripheral extremity temperature, peripheral pulse magnitude, urine flow, core body temperature, and acid-base balance.

Preserving and Creating Right-to-Left Shunts

Selected children with low cardiac output may benefit from strategies that allow right-to-left shunting at the atrial level in the face of postoperative RV dysfunction. A typical example is early repair of TOF, when the moderately hypertrophied, noncompliant right ventricle has undergone a ventriculotomy and may be further compromised by an increased volume load from pulmonary regurgitation secondary to a transannular patch on the RV outflow tract. In these children it is very useful to leave the foramen ovale patent to permit right-to-left shunting of blood, thus preserving cardiac output and oxygen delivery despite the attendant transient cyanosis. If the foramen is not patent or is surgically closed, RV dysfunction can lead to reduced LV filling, low cardiac output, and ultimately LV dysfunction. In infants and neonates with repaired truncus arteriosus, the same concerns apply and may even be exaggerated if RV afterload is elevated because of pulmonary artery hypertension.

Right Ventriculotomy and Restrictive Physiology

RV "restrictive" physiology in infants and children who have undergone congenital cardiac surgery has been demonstrated by echocardiography as persistent antegrade diastolic blood flow into the pulmonary circulation after reconstruction of the RV outflow. This occurs in the setting of elevated RV end-diastolic pressure and RV hypertrophy, and the right ventricle demonstrates diastolic dysfunction with an inability to relax and fill during diastole. The right ventricle usually is not dilated in this circumstance, and pulmonary regurgitation is limited because of the higher diastolic pressure in the right ventricle.[29]

The term *restrictive RV physiology* is also commonly used in the immediate postoperative period in patients who have a stiff, poorly compliant, and sometimes hypertrophied right ventricle. The elevated ventricular end-diastolic pressure restricts filling during diastole, and therefore stroke volume and preload to the left ventricle, causes an increase in RA filling pressure and therefore causes systemic venous hypertension. Because of the phenomenon of ventricular interdependence, changes in RV diastolic function and septal position in turn affect LV compliance and function. Factors contributing to diastolic dysfunction include lung and myocardial edema after CPB, inadequate myocardial protection of the hypertrophied ventricle during aortic cross-clamp, coronary artery injury, residual outflow tract obstruction, volume load on the ventricle from a residual VSD or pulmonary regurgitation, and dysrhythmias.

A low cardiac output state with increased right-sided filling pressure (usually >10 mm Hg) is the common feature of neonatal restrictive RV physiology. As a result of the low cardiac output state, patients often have cool extremities, are oliguric, and may have a metabolic acidosis. As a result of the elevated RA pressure, hepatic congestion, ascites, increased chest tube losses, and pleural effusions may be evident.

These patients may be tachycardic and hypotensive with a narrow pulse pressure. Preload must be maintained despite elevation of RA pressure. Significant inotropic support often is required (typically dopamine 5-10 μg/kg/min and/or low-dose epinephrine 0.05-0.1 μg/kg/min). A phosphodiesterase inhibitor, such as milrinone, is beneficial because of its lusitropic properties. Sedation and paralysis often are necessary for the first 24 to 48 hours to minimize the stress response and associated myocardial work.

Patients may be desaturated initially after surgery (typical range, 75% to 85%) because of this shunting. As RV compliance and function improve (usually within 2 to 3 postoperative days), the amount of shunt decreases and both antegrade pulmonary blood flow and arterial oxygen saturation (Sao_2) increase.

Mechanical ventilation may have a significant impact on RV afterload and the amount of pulmonary regurgitation. In addition, an increase in PVR because of hypothermia, acidosis, and either hypoinflation or hyperinflation of the lung also increases afterload on the right ventricle and pulmonary regurgitation. Synchronized intermittent positive pressure ventilation with the lowest possible mean airway pressure should be the aim, as discussed previously.

This concept has been extended to older patients with single-ventricle physiology who are at high risk for Fontan operations.[30] The Fontan circulation relies on passive flow of blood through the pulmonary circulation without benefit of a pulmonary ventricle. If an atrial septal communication or fenestration is left at the time of the Fontan procedure, the resulting right-to-left shunt helps to preserve cardiac output. These children have fewer postoperative complications.[31] It is better to shunt blood right to left and accept some decrement in oxygen saturation but maintain ventricular filling and cardiac output rather than have high oxygen saturation but low blood pressure and cardiac output.

Pharmacologic Support

Catecholamines

Preload adjustments often do not provide adequate cardiac output. Use of pharmacologic agents to support cardiac output is common.[32,33] Table 31-2 lists common vasoactive drugs used in the ICU and their actions. Many prefer to use dopamine first in doses of 3 to 10 μg/kg/min. Dosages greater than 15 μg/kg/min are rarely used because of the known vasoconstrictor and chronotropic properties of dopamine at very high doses. However, extreme biologic variability in pharmacokinetics and pharmacodynamics defies placing narrow limits on recommended dosages. Dobutamine's chronotropic and vasodilatory advantages recognized in adults with coronary artery disease have not always proved equally efficacious in clinical studies in children. The significant chronotropic effect

Table 31–2 Summary of Selected Vasoactive Agents

Agent	Doses (IV)	Peripheral Vascular Effect	Cardiac Effect	Conduction System Effect
Noncatecholamines				
Digoxin (total digitalizing dose)	20 μg/kg premature	Increase peripheral vascular resistance 1 to 2+; acts directly on vascular smooth muscle	Inotropic effect 3 to 4+; acts directly on myocardium	Slows sinus node slightly; decreases AV conduction more
	30 μg/kg neonate (0–1 mo)			
	40 μg/kg infant (<2 yr)			
	30 μg/kg child (2-5 yr)			
	20 μg/kg child (>5 yr)			
Calcium chloride	10–20 mg/kg/dose (slowly)	Variable; age dependent; vasoconstrictor	Inotropic effect 3+; depends on ionized Ca^{2+}	Slows sinus node; decreases AV conduction
Gluconate	50–100 mg/kg/dose (slowly)			Reflex tachycardia
Nitroprusside	0.5–5 μg/kg/min	Donates nitric oxide group to relax smooth muscle and dilate pulmonary and systemic vessels	Indirectly increases cardiac output by decreasing afterload	
Nitroglycerin	0.5–10 μg/kg/min	Primarily venodilator; as a nitric oxide donor, may cause pulmonary vasodilation and enhance coronary vasoreactivity after aortic cross-clamping	Decreases preload; may decrease afterload; reduces myocardial work related to change in wall stress	Minimal
Milrinone	50–75 μg/kg loading dose	Systemic and pulmonary vasodilator	Diastolic relaxation (lusitropy); measurable inotropic effect	Minimal tachycardia
	0.25–1.0 μg/kg/min maintenance			
Vasopressin	0.003–0.002 μg/kg/min	Potent vasoconstriction	No direct effect	None known
Thyroid hormone	0.05–0.10 μg/kg/min	Vasodilation	Positive inotropy	Tachycardia
Triiodothyronine (T3)				
Natriuretic peptide (nesiritide)	0.01–0.03 μg/kg/min	Natriuresis; little experience in children; diuretic effects controversial	Positive inotropy; diastolic relaxation	

	Peripheral Vascular Effect						*Cardiac Effect*
Agent	**Dose Range**	α	β_2	Δ	β_1	β_2	**Comment**
Catecholamines							
Phenylephrine	0.1–0.5 μg/kg/min	4+	0	0	0	0	Increases systemic resistance, no inotropy; may cause renal ischemia; useful for treatment of TOF spells
Isoproterenol	0.05–0.5 μg/kg/min	0	4+	0	4+	4+	Strong inotropic and chronotropic agent; peripheral vasodilator; reduces preload; pulmonary vasodilator; limited by tachycardia and oxygen consumption
Norepinephrine	0.1–0.5 μg/kg/min	4+	0	0	2+	0	Increases systemic resistance; moderately inotropic; may cause renal ischemia
Epinephrine	0.03–0.1 μg/kg/min 0.2–0.5 μg/kg/min	2+ 4+	1–2+ 0	0 0	2–3+ 4+	2+ 3+	β_2 effect with lower doses; best for blood pressure in anaphylaxis and drug toxicity
Dopamine	2–4 μg/kg/min 4–8 μg/kg/min > 10 μg/kg/min	0 0 2–4+	0 2+ 0	2+ 2+ 0	0 1–2+ 1+	0 1+ 2+	Splanchnic and renal vasodilator; may be used with isoproterenol; increasing doses produce increasing α effect
Dobutamine	2–10 μg/kg/min	1+	2+	0	3–4+	1–2+	Less chronotropy and arrhythmias at lower doses; effects vary with dose similar to dopamine; chronotropic advantage compared with dopamine may be be apparent in neonates
Fenoldapam	0.05–1 μg/kg/min (see text; little experience in children)						Powerful D_1 agonist; little chronotropic or inotropic effect but may redistribute flow to renal bed and improve urine output

AV, Atrioventricular; IV, intravenous; *TOF,* tetralogy of Fallot.

and increased oxygen consumption induced by isoproterenol have also increasingly limited its use in neonates and infants. Epinephrine is occasionally useful for short-term therapy when high systemic pressures are sought, provided the temporary increase in peripheral vascular resistance can be tolerated. High doses of epinephrine occasionally are necessary to increase pulmonary blood flow across significantly narrowed systemic-to-pulmonary artery shunts when oxygen saturations are low and falling. Arginine vasopressin has been advocated for states of refractory vasodilation associated with low circulating vasopressin levels as may rarely occur after CPB in children.[34] Vasopressin has been used to treat low systemic blood pressure in postoperative pediatric cardiac patients with pulmonary hypertension where it may ameliorate hypoxic pulmonary vasoconstriction and not exacerbate pulmonary hypertension.[35]

In the past, the side effects of inotropic support of the heart with catecholamines seemed a lesser concern in children than in adults with an ischemic, noncompliant heart. Tachycardia, an increased end-diastolic pressure and afterload, and increased myocardial oxygen consumption, despite their undesirable side effects, were tolerated by most children in need of inotropic support after CPB. However, with increasing perioperative experience in neonates and young infants, the adverse effects of vasoactive drugs have become more evident. The less compliant neonatal myocardium, such as the ischemic adult heart, may raise its end-diastolic pressure during higher doses of dopamine infusion or may develop even more extreme noncompliance. Actual myocardial necrosis caused by high doses of epinephrine infusions has been identified in neonatal animal models after CPB.[36,37] Although these agents do increase the cardiac output, the concomitant increase in ventricular filling pressure is less well tolerated by the immature myocardium than it is in older children. Many of the complex corrective procedures performed in neonates and small infants are accompanied by transient postoperative arrhythmias that are either induced or exacerbated by catecholamines, which can have a profound adverse effect on the patient's recovery after surgery. Diastolic function is crucial in older patients with single ventricles and can be adversely affected by catecholamines. Nevertheless, the predictable and often significant decrease in cardiac output documented by many investigators after CPB in infants and older children continues to justify the practice of judiciously using catecholamines to support the heart and circulation while weaning them from CPB and during the immediate postoperative period.

Type III Phosphodiesterase Inhibitors

Milrinone has emerged as an important inotropic agent for use in children after open heart surgery.[38-40] It is a nonglycosidic, noncatecholamine inotropic agent with additional vasodilatory and lusitropic properties used extensively in adults for treatment of heart failure and now also abundantly used in pediatric practice. This class of drugs exerts its principal effects by inhibiting phosphodiesterase III, the enzyme that metabolizes cyclic adenosine monophosphate (cAMP). By increasing intracellular cAMP, calcium transport into the cell is favored, and the increased intracellular calcium stores enhance the contractile state of the myocyte. In addition, reuptake of calcium is a cAMP-dependent process, and these agents may enhance diastolic relaxation of the myocardium (lusitropy) by increasing the rate of calcium reuptake after systole. The drug also appears to work synergistically with low doses of β-agonists and has fewer side effects than other catecholamine vasodilators, such as isoproterenol. In critically ill postoperative newborns, milrinone increases cardiac output, lowers filling pressures, and reduces pulmonary artery pressures.[39]

The Prophylactic Intravenous Use of Milrinone after Cardiac Operation in Pediatrics (PRIMACORP) trial investigated the efficacy and safety of prophylactic milrinone use to prevent LCOS after cardiac surgery in high-risk pediatric patients.[40] The study was a multicenter, randomized, double-blind, placebo-controlled trial using three parallel treatment groups (low-dose: 25 μg/kg bolus over 60 minutes followed by a 0.25 μg/kg/min infusion for 35 hours; high-dose: 75 μg/kg bolus followed by 0.75 μg/kg/min; or placebo). The composite endpoint of death or the development of LCOS was evaluated at 36 hours and at the follow-up visit. Among 238 treated patients, the prophylactic use of high-dose milrinone significantly reduced the risk of death or the development of LCOS relative to placebo with a relative risk reduction of 55% ($P = .023$) in the treated patients (Figure 31-2). Patients who developed LCOS had a significantly longer cumulative duration of mechanical ventilation and hospital stay in comparison with those who did not develop LCOS. The authors concluded that the prophylactic use of high-dose milrinone after pediatric congenital heart surgery reduces the risk of LCOS. Dopamine and milrinone have emerged as our most commonly used inotropic agents, often used in combination to achieve increased cardiac output, maintain arterial perfusion pressure, and improve diastolic relaxation.

Thyroid Hormone

LCOS typically overlaps with the time that free and total triiodothyronine (T_3) levels are significantly suppressed after surgical reconstruction, namely, during the first 24 to 48 hours postoperatively. This is a significant observation, as T_3 is the predominant form of biologically active thyroid hormone and is known to improve cardiac output by improving the inotropic state of animal and human hearts while decreasing systemic vascular resistance. Limited studies of T_3 supplementation after cardiac surgery have been performed in children. Mainwaring et al.[41] gave two bolus doses of T_3 after the Fontan

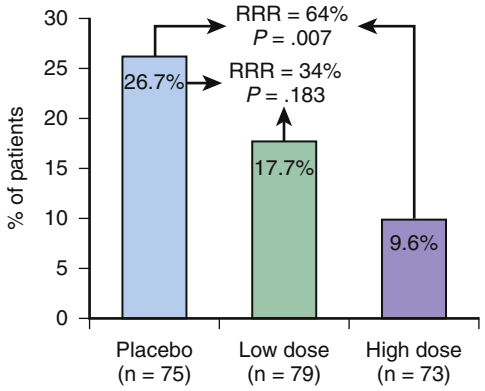

Figure 31–2. Primary end point: development of low cardiac output syndrome (LCOS) or death in the first 36 hours. *(From Hoffman TM, Wernovsky G, Atz AM, et al: Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease,* Circulation *107:996-1002, 2003.)*

procedure to 10 children ages 19 to 42 months. Compared with a historical control group, the T_3 patients had a significantly shorter period of mechanical ventilation. Bettendorf et al.[42] randomized 40 children undergoing a wide variety of cardiac procedures to receive bolus dosing of T_3 or placebo. Cardiac output reportedly was higher in the treatment group but was estimated by echocardiography. Chowdhury et al.[43] randomized 28 children aged 0 to 18 years to a 5-day continuous infusion of T_3 (0.05-0.15 μg/kg/hour) or placebo. Among neonates, the T_3 group had lower severity of illness scores and lower inotrope requirements. The T_3 group also had a trend toward higher mixed venous oxygen saturations, fewer days of mechanical ventilation, and a shorter postoperative length of stay. No adverse effects of T_3 administration were recorded in any of these small series.

Thus the current literature demonstrates that infants undergoing cardiac surgery experience significant depression of T_3 levels and that supplementation of T_3 may have an impact on physiologic variables if not other measures of improved outcomes. Larger trials with more rigorous trial designs are under way and may address whether certain subgroups at particular risk for LCOS may benefit from T_3 administration. At this time, the routine use of T_3 is not supported by the existing literature.[44]

Other Afterload-Reducing Agents

When systemic blood pressure is elevated and cardiac output appears low or normal, a primary vasodilator is indicated to normalize blood pressure and to decrease the afterload on the left ventricle. This is especially true for the newborn myocardium, which is particularly sensitive to changes in afterload and tolerates elevated systemic resistances poorly. Although nitroprusside has no known direct inotropic effects, this potent vasodilator has the advantage of being readily titratable and possessing a short biologic half-life. Use of nitroglycerin avoids the toxic metabolites cyanide and thiocyanate associated with nitroprusside use (especially in hepatic and renal insufficiency), but its potency as a vasodilator is less than that of nitroprusside. Inhibitors of angiotensin-converting enzyme have proved to be important adjuvants to chronic anticongestive therapy in pediatric patients. Intravenous (IV) forms are available and may be useful in treatment of systemic hypertension immediately after coarctation repair or when afterload reduction with these inhibitors would benefit patients unable to receive oral medications. Sudden hypotension with the IV forms may limit use among infants.

The natriuretic hormone system is an important regulator of neurohumoral activation, vascular tone, diastolic function, and fluid balance. Preliminary data suggest that the endogenous biologic activity of the natriuretic hormone system is decreased after pediatric CPB. In theory, infusions of brain natriuretic peptide could oppose the neurohumoral mechanism associated with vasoconstriction and fluid retention after pediatric CPB. In randomized adult studies after CPB, natriuretic hormone infusions suppress the renin-angiotensin-aldosterone axis and improve cardiac loading conditions, cardiac index, and urine output.[45,46] Several services in North America have now accrued experience with nesiritide infusions in children.

Fenoldapam is a new dopaminergic agent useful in the treatment of systemic hypertension. It may have salutary effects on renal blood flow. It has no known chronotropic or inotropic effects on the heart but reduces afterload and may augment urine output in critically ill newborns after cardiac surgery.

Levosimendan is a calcium sensitizer that enhances the contractile state of the ventricle by increasing myocyte sensitivity to calcium and induces vasodilation. Levosimendan increases cardiac output by increasing stroke volume. It is independent of cAMP pathways that characterize the mechanism of action of both the catecholamines and the type III phosphodiesterase inhibitors. With its positive inotropic effects, levosimendan may be of value as adjunctive therapy to other inotropic drugs in patients who are refractory or tachyphylactic to other forms of inotropic support. Its hemodynamic effect in children is uncertain, but its pharmacokinetic profile seems similar to adults.[47]

Other Strategies

Newer strategies to support low cardiac output associated with cardiac surgery in children include use of atrioventricular pacing for patients with complete heart block or prolonged interventricular conduction delays and asynchronous contraction.[48] Appreciation of the hemodynamic effects of positive and negative pressure ventilation may assist cardiac output. Avoidance of hyperthermia and even induced hypothermia may provide end-organ protection during periods of low cardiac output. Antiinflammatory agents including monoclonal antibodies, competitive receptor blockers, inhibitors of compliment activation, and preoperative preparation with steroids are being actively investigated in an effort to prevent and protect major organs from ischemic injury imposed by CPB and the reperfusion injury associated with the recovery period.

Diastolic Dysfunction

Occasionally there is an alteration of ventricular relaxation, an active energy-dependent process, which reduces ventricular compliance. This is particularly problematic in patients with a hypertrophied ventricle undergoing surgical repair, such as TOF or Fontan surgery, and after CPB in some neonates when myocardial edema may significantly restrict diastolic function (i.e., "restrictive physiology").[28,29] The ventricular cavity size is small, and the stroke volume is decreased. β-Adrenergic antagonists and calcium channel blockers add little to the treatment of this condition. In fact, hypotension or myocardial depression produced by these agents often outweigh any gain from slowing the heart rate. Calcium channel blockers are relatively contraindicated in neonates and small infants because of their dependence on transsarcolemmal flux of calcium to both initiate and sustain contraction.

A gradual increase in intravascular volume to augment ventricular capacity, in addition to the use of low doses of inotropic agents, has proved to be of modest benefit in patients with diastolic dysfunction. Tachycardia must be avoided to optimize diastolic filling time and decrease myocardial oxygen demands. If low cardiac output continues despite treatment, therapy with vasodilators can be carefully attempted to alter systolic wall tension (afterload) and thus decrease the impediment to ventricular ejection. Because the capacity of the vascular bed increases after vasodilation, simultaneous volume replacement is often indicated. Milrinone or enoximone is

useful under these circumstances because these agents are noncatecholamine so-called inodilators with vasodilating and lusitropic (improved diastolic state) properties, in contrast with other inotropic agents. Nesiritide also may play a particularly important role in lowering LV filling pressures in patients with heart failure.

Managing Acute Pulmonary Hypertension in the Intensive Care Unit

Children with many forms of CHD are prone to develop perioperative elevations in PVR.[49] This situation may complicate the postoperative course, when transient myocardial dysfunction requires optimal control of RV afterload.[50]

Although postoperative patients with pulmonary hypertension often are presumed to have active and reversible pulmonary vasoconstriction as the source of their pathophysiology, the critical care physician is obligated to explore anatomic causes of mechanical obstruction that impose a barrier to pulmonary blood flow. Elevated LA pressure, pulmonary venous obstruction, branch pulmonary artery stenosis, or surgically induced loss of the vascular tree all raise RV pressure and impose an unnecessary burden on the right heart. Similarly, a residual or undiagnosed left-to-right shunt raises pulmonary artery pressure postoperatively and must be addressed surgically. Extended use of pulmonary vasodilator strategies only augments residual or undiagnosed shunts and increases the volume load on the heart.

Several factors peculiar to CPB may raise PVR: Pulmonary vascular endothelial dysfunction, microemboli, pulmonary leukostasis, excess thromboxane production, atelectasis, hypoxic pulmonary vasoconstriction, and adrenergic events all have been suggested to play a role in postoperative pulmonary hypertension. Postoperative pulmonary vascular reactivity has been related not only to the presence of preoperative pulmonary hypertension and left-to-right shunts but also to the duration of total CPB. Treatment of postoperative pulmonary hypertensive crises has been partially addressed by surgery at earlier ages, pharmacologic intervention, and other postoperative management strategies (Table 31-3).

Table 31–3 Critical Care Strategies for Postoperative Treatment of Pulmonary Hypertension

Encourage	Avoid
Anatomic investigation	Residual anatomic disease
Opportunities for right-to-left shunt as "pop-off"	Intact atrial septum in right heart failure
Sedation/anesthesia	Agitation/pain
Moderate hyperventilation	Respiratory acidosis
Moderate alkalosis	Metabolic acidosis
Adequate inspired oxygen	Alveolar hypoxia
Normal lung volumes	Atelectasis or overdistention
Optimal hematocrit	Excessive hematocrit
Inotropic support	Low output and coronary perfusion
Vasodilators	Vasoconstrictors/increased afterload

Pulmonary Vasodilators

Many IV vasodilators have been used with variable success in patients with pulmonary hypertensive disorders requiring critical care. Older style vasodilators such as tolazoline, phenoxybenzamine, nitroprusside, or isoproterenol had little biologic basis for selectivity or enhanced activity in the pulmonary vascular bed.[51] However, if myocardial function is depressed and the afterload reducing effect on the left ventricle is beneficial to myocardial function and cardiac output, then these drugs may be of some value. However, in addition to drug-specific side effects, they all have the limitation of potentially profound systemic hypotension, critically lowering right (and left) coronary perfusion pressure and simultaneously increasing intrapulmonary shunt. Even with selective infusions of rapidly metabolized, intravenously administered vasoactive drugs into the pulmonary circulation, systemic drug concentrations and systemic hemodynamic effects can be appreciable.

Prostacyclin appears to have somewhat more selectivity for the pulmonary circulation but at high doses can precipitate a hypotensive crisis in unstable postoperative patients with refractory pulmonary hypertension. It is best suited for chronic outpatient therapy in severe forms of primary pulmonary hypertension.[52-54] Agents that improve ventricular function in addition to reducing afterload (e.g., type III phosphodiesterase inhibitors) are more appealing when cardiac output is low.

As an alternative approach to nonspecific vasodilators, it seems logical to target vasoconstrictors known to be associated with pathologic states or critical events. In this regard, endothelin, a potent vasoconstrictor, is elevated in persistent pulmonary hypertension of the newborn, in children with CHD, and in patients after CPB, and seems a likely candidate for investigation of specific receptor blockers. Petrossian et al.[55] showed promising amelioration of postoperative pulmonary hypertension associated with CPB in animal models of increased pulmonary blood flow (from intracardiac shunts) when pretreated with endothelin-A receptor blockers. Undoubtedly, because the causes of pulmonary hypertension in the intensive care setting frequently are multifactorial, our "best" therapy will be multiply targeted. Adding phosphodiesterase inhibitors to prostacyclin infusions, endothelin blockers, thromboxane inhibitors, and inhaled nitric oxide (NO) all may have individual and combined merit with synergism enhancing efficacy.

NO is a selective pulmonary vasodilator that can be breathed as a gas and distributed across the alveoli to the pulmonary vascular smooth muscle.[56] It is formed by the endothelium from L-arginine and molecular oxygen in a reaction catalyzed by NO synthase. It then diffuses to the adjacent vascular smooth muscle cells where it induces vasodilation through a cyclic guanosine monophosphate-dependent pathway.[57] Because NO exists as a gas, it can be delivered by inhalation to the alveoli and then to the blood vessels, which lie in close proximity to ventilated lung. Because of its rapid inactivation by hemoglobin, inhaled NO may achieve selective pulmonary vasodilation when pulmonary vasoconstriction exists. It has advantages over intravenously administered vasodilators that cause systemic hypotension and increase intrapulmonary shunting. Inhaled NO lowers pulmonary artery pressure in a number of diseases without the unwanted effect of systemic

hypotension. This effect is especially dramatic in children with cardiovascular disorders and postoperative patients with pulmonary hypertensive crises.[50,58,59]

Therapeutic uses of inhaled NO in children with CHD abound in the ICU. For example, newborns with total anomalous pulmonary venous connection (TAPVC) frequently have obstruction of the pulmonary venous pathway as it connects anomalously to the systemic venous circulation. When pulmonary venous return is obstructed preoperatively, pulmonary hypertension is severe and demands urgent surgical relief. Increased neonatal pulmonary vasoreactivity, endothelial injury induced by CPB, and intrauterine anatomic changes in the pulmonary vascular bed in this disease contribute to postoperative pulmonary hypertension. Inhaled NO dramatically reduces pulmonary hypertension without change in heart rate, systemic blood pressure, or vascular resistance.

Patients with TAPVC, congenital mitral stenosis, and other pulmonary venous hypertensive disorders associated with low cardiac output appear to be among the most responsive to NO. These infants are born with significantly increased amounts of smooth muscle in their pulmonary arterioles and veins. Histologic evidence of muscularized pulmonary veins and pulmonary arteries suggests the presence of vascular tone and capacity for change in resistance at both the arterial and venous sites. The increased responsiveness to NO seen in younger patients with pulmonary venous hypertension may result from pulmonary vasorelaxation at a combination of precapillary and postcapillary vessels.

Several groups have reported successful use of inhaled NO in a variety of other congenital heart defects after cardiac surgery. It may be especially helpful when administered during a pulmonary hypertensive crisis.[59] NO use after Fontan procedures,[60] after VSD repair, and with a variety of other anatomic lesions has been described. Prophylactic use of inhaled NO in patients at risk for developing postoperative pulmonary hypertensive crises is thought by some to reduce the duration of mechanical ventilation.[61] Oxygen saturation in response to inhaled NO generally does not improve in very young infants who are excessively cyanotic after a bidirectional Glenn anastomosis. Increasing cardiac output and cerebral blood flow may have much greater impact on arterial oxygenation. Elevated pulmonary vascular tone is seldom the limiting factor in the hypoxemic patient after the bidirectional Glenn operation.[62]

Inhaled NO can be used diagnostically in neonates with RV hypertension after cardiac surgery to discern those with reversible vasoconstriction. Failure of the postoperative newborn with pulmonary hypertension to respond to NO successfully discriminated anatomic obstruction to pulmonary blood flow from pulmonary vasoconstriction. Failure of the postoperative newborn to respond to NO should be regarded as strong evidence of anatomic and possibly surgically remediable obstruction.[63]

If withdrawal of NO is necessary before resolution of the pathologic process, hemodynamic instability can be expected. The withdrawal response to inhaled NO can be attenuated by pretreatment with the type V phosphodiesterase inhibitor sildenafil.[64] Sildenafil inhibits the inactivation of cyclic guanosine monophosphate within the vascular smooth muscle cell and has the potential to augment the effects of endogenous or exogenously administered NO to effect vascular smooth muscle relaxation. Sildenafil can be administered in an oral or IV form and has a somewhat selective pulmonary vasodilating capacity while lowering LA pressure and providing a modest degree of afterload reduction in some postoperative children. Chronic oral administration of sildenafil to adults with primary pulmonary hypertension improves exercise capacity, which suggests an important therapeutic application of the IV preparation in postoperative congenital heart surgery.

Cardiac Tamponade

Chest closure is a time of particular instability after operations for CHD. The small infant's mediastinum makes compression of the heart and cardiac tamponade ever-present possibilities after chest closure, despite patent drainage tubes and surgical resection of the anterior pericardium. The warning signs of tamponade frequently are subtle in small children, even minutes before cardiovascular collapse from tamponade. Any significant deterioration in hemodynamics after chest closure first should be attributed to tamponade if ventilation and cardiac rhythm are adequate. The signs of tamponade include tachycardia, hypotension, narrow pulse pressure, and high filling pressures on both the left and right sides of the heart.

Acute myocardial perforation with tamponade occasionally occurs during interventional cardiac catheterization procedures. Prompt support of the circulation with volume infusions and pressor support, along with immediate catheter drainage of the pericardial space, are essential in the event of this complication. Hemopericardium after ventricular puncture usually is self-limited, as the muscular ventricle seals the perforation after the responsible wire or catheter is removed. However, laceration of the more thin-walled atrium may require suture repair under direct vision in the operating room.

Other causes of cardiac tamponade are seen in patients with CHD, and treatment frequently requires the assistance of an intensivist for either pericardiocentesis or sedation and monitoring for that definitive procedure. Postoperative tamponade from bleeding immediately after operation, as discussed earlier, is best handled by facilitation of chest tube drainage or reopening the sternotomy. These patients usually are still anesthetized and mechanically ventilated so that new anesthetic considerations and choices are limited. However, some children develop pericardial effusions during other phases of their illness because of hydrostatic influences (e.g., patients with modified Fontan operations) or postpericardiotomy syndrome. Fluid in the pericardial space may accumulate under considerable pressure, and filling of the heart is impaired. If this problem is left unattended, the transmural pressure in the atria diminishes as intraatrial pressures rise, and diastolic collapse of the atria can be observed echocardiographically. Patients become symptomatic with a narrow pulse pressure, pulsus paradoxus, tachycardia, respiratory distress, abdominal pain progressing to decreased urine output, hyperkalemia, metabolic acidosis, and hypotension with tremendous endogenous catecholamine response.

In summary, aggressive identification and treatment of low cardiac output conditions after cardiac surgery is central to the critical care of children with CHD. Successful application of these strategies and thoughtful use of pharmacologic intervention undoubtedly has contributed to the remarkable decline in mortality associated with congenital heart surgery in the past two decades. However, despite these interventions, additional (mechanical) support is sometimes necessary as a bridge to recovery.

Mechanical Support of the Circulation

Despite the expanding options for pharmacologic support, the circulation cannot be adequately supported in some patients in both preoperative and postoperative situations. Mechanical assist devices have an important role in providing short-term circulatory support to enable myocardial recovery and the potential for longer term support while the patient is awaiting cardiac transplantation. Although a variety of assist devices are available for adult-size patients, ECMO is the predominant mode of support for children.

More than 300 children per year who receive ECMO for cardiac support are reported to the Extracorporeal Life Support Registry, with the majority of patients placed on ECMO after cardiotomy.[65] Although more than 60% of these patients are decannulated from ECMO, the overall survival to discharge has been only 42% of reported cases.

At Riley Hospital for Children, Indiana University, ECMO has been used to support the circulation in more than 130 patients. Neonates comprise 52% of all our cardiac ECMO patients, with a survival rate to discharge of 50% in the last 5 years. The pediatric group (infant through 16 years) comprises 48% of our total experience with a survival rate to discharge of 48% in the same period.

Substantial institutional variability in patient selection for ECMO makes comparison of published experience difficult. Centers with an efficient and well-established ECMO service are more likely to use this form of support in patients with low cardiac output. Furthermore, surgical technique and bypass management are additional confounding factors that make comparisons of the use and indications for ECMO between institutions difficult to interpret. Nevertheless, this form of mechanical support can be demonstrated to be lifesaving, and it can be argued that it should be available when needed for selected patients after congenital heart surgery General indications and contraindications for ECMO support of the circulation in patients with CHD are summarized in Box 31-5 and Box 31-6.

Preoperative Stabilization

Extracorporeal membrane oxygenation may be useful for critically ill neonates before cardiac surgery, thereby enabling preoperative stabilization and limiting end-organ dysfunction before repair. Indications include severe low output state (e.g., critical AS), pulmonary hypertension (e.g., obstructed totally anomalous pulmonary venous return), and severe hypoxemia (e.g., transposition with pulmonary hypertension). These have been relatively rare indications for ECMO at Riley Hospital for Children, Indiana University, and other major centers.

Failure to Wean from Cardiopulmonary Bypass

Patients who fail to wean from CPB may be connected directly to an ECMO circuit in the operating room and brought to the ICU in the hope of recovering myocardial function. These children typically had poorer survival rates for many reasons, including severity and complexity of disease and increased bleeding. A critical decision for using ECMO in this circumstance is whether the patient is a suitable candidate for cardiac transplantation if there is no significant recovery of function. Clearly, patient selection can have an enormous influence on outcomes in this category. As practitioners gained experience with and acceptance of mechanical support, its successful use in the transition from CPB increased.[66]

Box 31–5 Typical Indications for ECMO

I. Inadequate oxygen delivery
   A. Low cardiac output
      1. Chronic (cardiomyopathy)
      2. Acute (myocarditis)
      3. Weaning from cardiopulmonary bypass
      4. Preoperative stabilization
      5. Progressive postoperative failure
      6. Pulmonary hypertension
      7. Refractory arrhythmias
      8. Cardiac arrest
   B. Profound cyanosis
      1. Intracardiac shunting and cardiovascular collapse
      2. Acute shunt thrombosis
      3. Acute respiratory failure exaggerated by underlying heart disease
      4. Congestive heart disease complicated by other newborn indications for ECMO, such as meconium aspiration syndrome, PPHN, pneumonia, sepsis, respiratory distress syndrome
II. Support for intervention during cardiac catheterization

Box 31–6 Relative Contraindications for ECMO

End-stage, irreversible, or inoperable disease
Family, patient directives to limit resuscitation
Significant neurologic or end-organ impairment
Uncontrolled bleeding within major organs
Extremes of size and weight
Inaccessible vessels during resuscitation

Postcardiotomy

In general, ECMO appears to be most effective as a therapeutic option for patients who have a period of relative stability after reparative cardiac surgery but then develop progressive myocardial or respiratory failure or have a sudden cardiac arrest. This typically occurs during the first 24 hours after surgery, and subsequent survival may be better in this group of patients after a period of myocardial rest and decompression.

Bridge to Transplantation

Although ECMO can be used to resuscitate the circulation and prevent end-organ dysfunction while the patient is awaiting potential myocardial recovery, it also can be used as a bridge to transplantation.[67] However, with limitations related to donor availability and the potential complications while the patient is on ECMO, in particular bleeding, end-organ dysfunction, and sepsis, the decision to proceed with listing for transplantation should be made early during the ECMO run. If there is no discernible recovery of myocardial function after 48 to 72 hours on ECMO support, transplant evaluation should be completed for appropriate patients.[68] Selected prospective transplant recipients experiencing waiting times longer than 2 or 3 weeks should be considered for longer term devices such as the Berlin Heart.

Resuscitation

The rapid deployment of ECMO during active CPR (E-CPR) in a pulseless circulation remains a contentious issue. The underlying premise is that survival after a sudden cardiac

arrest and standard resuscitation in children is poor irrespective of the resuscitation setting.[69-73] Therefore a number of pediatric institutions have developed a rapid response system to provide early deployment and cannulation for ECMO. A recent review of the Extracorporeal Life Support Organization database[65] showed that E-CPR accounted for only 2.6% of all reported ECMO runs (696 of 26,242 runs). Survival to hospital discharge was 38%. In a multivariable model, pre-ECMO factors such as cardiac disease and neonatal respiratory disease, white race, and pre-ECMO arterial blood pH >7.17 were associated with decreased odds of mortality. During ECMO, renal dysfunction, pulmonary hemorrhage, neurologic dysfunction, CPR during ECMO, and arterial blood pH <7.2 were associated with increased odds of mortality. Nevertheless, E-CPR rescued one third of patients in whom death was otherwise certain.[74]

The ability to efficiently and rapidly support the circulation or respiration in patients after cardiac surgery (and in children with cardiac disease in general) has improved our ability to salvage a group of children who previously most likely would have died. This type of support is believed to account for a substantial part of the decline in surgical mortality during the end of the 1990s.

The rapid deployment system for E-CPR during cardiopulmonary arrest and resuscitation can be used in a variety of locations throughout the hospital, including the ICU, cardiac catheterization laboratory, emergency department, and noncardiac operating rooms. Typically, one should wait only moments (i.e., after two or three rounds of resuscitation medications) before determining that return of cardiovascular stability during CPR is unlikely and that ECMO should be deployed. Many centers have an ECMO circuit ready and saline primed at all times in the ICU. A neonatal membrane is generally used in this setup (size 0.8-1.5 m^2; appropriate for patients 2-15 kg). For older children and adults, a fresh circuit with a hollow-fiber membrane can be used that takes little time to deair and can be established within 15 minutes. After the patient is stable on ECMO, the hollow fiber can be changed out for a conventional membrane if longer term support is necessary. Blood products are added when they are available (typically after cannulation), and crystalloid is removed by direct withdrawal from the circuit into a syringe or by a volume-matched amount of ultrafiltration. Surgeons trained in cannulation techniques for open chest, groin, or neck routes, ECMO specialists, and cardiac ICU physicians should be immediately available in-house 24 hours per day.

Extracorporeal Membrane Oxygenation Cannulation, Stabilization, and Evaluation

Depending on the circumstances of hemodynamic decompensation (impending or actual cardiac arrest; nonoperated or postoperative cardiac patient) and surgeon preference, vascular access is obtained either by transthoracic approach with direct cannulation of the right atrium and aorta or peripherally through the neck or femoral vessels. Medical support and resuscitation (i.e., airway stabilization with hand ventilation, intravascular volume replacement, catecholamine infusions, correction of electrolyte imbalance, sodium bicarbonate administration, arrhythmia suppression, cardiac pacing, core temperature cooling, and cardiac massage) are continued throughout the cannulation procedure and commencement of venoarterial extracorporeal support until a stable circulation is achieved.

The ECMO circuit is a "closed" circuit, which is an important distinction to a CPB circuit in which cardiotomy suction is used during cardiac surgery. There is very limited ability to handle any air in the venous limb of the ECMO circuit, and careful deairing of both the arterial and venous cannulas is essential when connecting to the ECMO circuit. In our institution, blood flow is driven by a roller pump using a servoregulatory mechanism. This system permits high flow rates with minimal hemolysis and protects against air entrainment. Priming volumes are determined by the surface area of the oxygenator membrane. The circuit is initially vacuumed with carbon dioxide to eliminate nitrogen, which leads to bubble formation after introduction of the saline priming solution. Normosol solution (Abbott Laboratories, Abbott Park, Ill.) is used to displace the CO_2, and after the system has been debubbled, 5% albumin is added to decrease adsorption of fibrinogen to the circuit components during the subsequent blood priming.

After cannulation, the patient is connected to the ECMO circuit and the roller pump is adjusted to gradually achieve the desired flow rates of approximately 100 to 150 mL/kg, depending on the underlying cardiopulmonary physiology. Intracardiac and arterial blood pressures, including waveform characteristics, are noted. Usually, vasopressor infusions are used to maintain mean arterial blood pressure greater than 45 mm Hg in neonates and greater than 60 to 70 mm Hg in children and adults. A chest radiograph is obtained to check cannulas, line position, endotracheal tube, and lung parenchymal status.

Elevated premembrane pressures (i.e., >350 mm Hg) at normal flows without change in postmembrane pressure and evidence of blood-to-gas leak constitute membrane oxygenator dysfunction and may dictate oxygenator replacement. Extensive thrombus or consumptive coagulopathy with hypofibrinogenemia and thrombocytopenia are other indications for circuit replacement. When ECMO flow appears inadequate to meet the needs of the patient and limited venous drainage restricts additional flow, interpretation of arterial and atrial pressures may aid the formulation of a differential diagnosis (Table 31-4). Low flow states and/or significant hypotension require immediate analysis and intervention.

Assessing the adequacy of flow soon after initiation of ECMO is of paramount importance. Answering a checklist of questions assists this assessment.

1. **Is the systemic ventricle adequately decompressed?** Venting the left atrium may be necessary to lower the LA pressure and decrease LV wall stress, thereby minimizing ongoing myocardial injury. Adequate decompression and signs of pulmonary edema can be assessed early by echocardiography. If not decompressed, strategies include (1) placing a vent in the left atrium by direct placement via the atrial appendage or pulmonary veins through an open chest or by a transcatheter approach in the catheterization laboratory[75] and (2) augmenting ventricular ejection by judicious use of inotropic agents.
2. **Are the perfusion pressure and flow adequate?** This determination can be made by assessment of perfusion pressure, patient color and appearance, presence of acidosis, adequate clearance of lactate, and appropriately sized and positioned cannulas. Hypotension with mean arterial blood pressure less than 30 mm Hg in neonates or less than 50 mm Hg in larger children and adults requires prompt evaluation and treatment.

Table 31–4 Assessment of Low Flow States During ECMO

Problem	Observations	Treatment Options
Inadequate oxygen delivery and organ perfusion	Tachycardia, mottled skin, cool extremities, poor capillary refill, hypotension, oliguria, metabolic acidosis, hyperlactatemia, rising serum creatinine, and liver function test results	Check cannula position Increase ECMO flow Increase native cardial output
Inadequate ECMO flow; circuit chatters, bladder collapse, inadequate venous return, or high postmembrane pressure	Atrial pressures normal: Venous cannula malposition Venous cannula too small Venous thrombus formation Excessive runoff through aortopulmonary shunt	Reposition venous cannula Replace or add second venous cannula Surgically remove thrombus or thrombolysis Narrow shunt, embolize collaterals
	Atrial pressures low: Bleeding	Surgically explore, administer coagulation factors and blood, administer antifibrinolytics, reduce heparin
	Systemic vasodilation	Treat sepsis, administer vasoconstrictors
	Atrial pressures high: Tamponade Left ventricular overdistension	Surgically explore, evacuate blood and clot
		Place vent in left atrium, support ejection with catecholamine
	Aortic regurgitation	Reposition aortic cannula, assess need for aortic valve replacement
	Membrane pressures high: Arterial cannula malposition Arterial cannula too small	Reposition cannula Replace or add second arterial cannula (bifemoral arterial cannulation)

Is hemostasis achieved? This is not an uncommon problem in the immediate postoperative period. Prompt control of bleeding has a direct influence on subsequent outcome. Tamponade physiology affects venous return, circuit line pressure, and ECMO flows; mediastinal reexploration may be necessary to evacuate clot and control bleeding. In addition to surgical exploration, replacement of coagulation factors and use of antifibrinolytics must be considered (e.g., aminocaproic acid bolus 100 mg/kg followed by 30 mg/kg/hour infusion). Initial guidelines include transfusion of packed red blood cells to maintain the hematocrit at greater than 35%, cryoprecipitate to keep the serum fibrinogen level greater than 150 mg/dL, and concentrated platelet transfusions to maintain the platelet count greater than 100,000/mm^3. A heparin bolus (50 U/kg) usually is given at the time of cannulation, followed by infusion (20-30 U/kg/hour) adjusted to maintain an activated clotting time of 180 to 200 seconds.

3. **Are there specific considerations based on underlying pathology?** Management of an aortopulmonary shunt is critical in patients with single-ventricle physiology. Systemic and pulmonary flow should be balanced by either partially clipping the shunt or by using high ECMO flows. On ECMO, circuit flows up to 200 mL/kg/min or more usually are necessary to maintain adequate systemic perfusion while accounting for runoff into the pulmonary circulation through the shunt. Although partial temporary narrowing of the shunt may be advisable in some circumstances, it is unwise to completely occlude the only source of pulmonary blood flow to the pulmonary endothelium. It is possible to bypass the membrane oxygenator in patients after the Norwood procedure with a Blalock-Taussig shunt without lung disease if higher flows are maintained and the shunt is patent.[76] This maneuver simplifies the circuit and may permit less use of heparin. Thus ECMO effectively becomes a ventricular assist device.

   Problems related to cannula placement and adequacy of venous drainage must be considered in patients with single-ventricle physiology and complex venous anatomy, such as heterotaxy syndrome or possible vessel occlusion from prior catheterizations, and in patients with a cavopulmonary connection. The site of cannulation is affected by vessel patency, and the underlying physiology might influence the number of venous cannulae used. For example, patients with a superior cavopulmonary anastomosis (bidirectional Glenn shunt [BDG]) as the primary source of pulmonary blood flow often require separate venous drainage of the SVC and inferior vena cava (IVC), unless there is congenital interruption of the infrahepatic IVC with drainage of lower body blood to the azygos vein. In the latter case, a single venous cannula in the SVC might be sufficient. On the other hand, placement of a cannula in the SVC may be detrimental in patients with BDG physiology because of the potential for reduced cerebral venous drainage and therefore decreased cerebral perfusion. This also is a concern for patients with Fontan physiology. Although it may be possible to achieve adequate drainage with a venous cannula placed in the Fontan baffle, an additional SVC catheter often is necessary to achieve the desired or necessary flows on ECMO.[77]

4. **Is there adequate end-organ perfusion?** After stable flows and perfusion have been achieved, the ventricles have been decompressed, and hemostasis has been secured, potential end-organ injury should be evaluated. For patients who have long-standing cyanotic heart disease, it may be preferable to start ECMO using a lower oxygen concentration (closer to room air) to attenuate the potential ischemia/reperfusion injury and potential for injury from reactive

oxygen species. Neurologic protection must be considered. For patients placed on ECMO during active resuscitation, mild hypothermia (34° C) should be maintained for the first 12 to 24 hours on ECMO to prevent secondary neurologic injury. Assessment with head ultrasound, electroencephalography, or computed tomographic (CT) scan should be considered early. Muscle relaxants should not be given and sedation minimized to allow an appropriate daily clinical assessment. In addition, renal function, liver function, risk for sepsis, and possible gut ischemia should be frequently evaluated.

5. **Residual cardiac defects.** If a patient fails to wean from ECMO or if there is a delay in anticipated recovery of myocardial function, the possibility of a residual surgical problem must always be considered. This usually is difficult to diagnose by echocardiography alone, and cardiac catheterization (i.e., diagnostic or interventional) should be considered.

Daily Management

The daily management of a patient on ECMO or other forms of extracorporeal life support requires meticulous assessment of cardiorespiratory function, end-organ perfusion and injury, evolving complications such as bleeding or sepsis, and the mechanics of the ECMO circuit. After ECMO cannulation and initial resuscitation, high flow rates (100-200 mL/kg/min depending on the underlying pathophysiology) are used to "rest" the heart and decompress the ventricle(s). However, in contrast to the concept of "resting the lungs" for patients who are placed on ECMO for respiratory failure and lung injury, it is important that the heart regain contractile function and conduction as soon as possible to maintain a workload and avoid involution of the myocardial mass. For this reason, inotropic support may be reintroduced earlier in cardiac patients compared with those on ECMO purely for respiratory support. Atrioventricular synchrony should be established as soon as possible. This can be achieved with external pacing if necessary. It is very important that dysrhythmias occurring on ECMO be treated promptly. Although it may be possible to maintain adequate systemic perfusion and ECMO flows, the heart may overdistend in the presence of certain dysrhythmias, particularly ventricular fibrillation, resulting in irreversible myocardial injury.

Transient endothelial dysfunction is common after ECMO is established, identical to the injury resulting from CPB, and causes an elevated PVR and ventilation/perfusion abnormalities.[78] Permitting or promoting the heart to eject some blood into the pulmonary circulation while on ECMO may help endothelial recovery and prevent pulmonary hypertension when weaning from ECMO. It is important to remember that the pulmonary venous blood entering the left ventricle and ejected into the coronary circulation may be significantly desaturated, which could cause myocardial ischemia or delay myocardial recovery. For this reason, mechanical ventilation is continued on cardiac ECMO to ensure pulmonary venous blood is well saturated. Ventilator settings are adjusted primarily according to lung compliance, which may reflect the degree of preexisting cardiac-related or parenchymal lung disease. Tidal volumes of 7 to 9 mL/kg with peak inspiratory pressures not exceeding 25 to 28 cmH_2O, positive end-expiratory pressure (PEEP) of 5 to 10 cmH_2O and FIo_2 of 0.3 to 0.4 usually are maintained in patients with normal lung compliance. Changes in ventilator settings are guided by physical examination, assessment of compliance based on hand ventilation and lung volumes, and appearance of the lung fields on daily chest radiographs. Fluid retention and body wall edema are very common in cardiac patients on ECMO because of (1) endothelial dysfunction and capillary leak associated with reperfusion injury and inflammatory response,[79] (2) changes in oncotic pressure depending on the priming solution, and (3) decreased urine output secondary to alterations in perfusion and the influence of antidiuretic hormone, renin-angiotensin, and atrial natriuretic factor production.[80] Diuretic therapy is started early to achieve a negative fluid balance and treat anasarca as soon as possible; fluid overload is one of the most important factors that will determine eventual successful weaning from cardiac ECMO and longer-term survival. Furosemide bolus (1 mg/kg) followed by continuous infusion (0.2-0.3 mg/kg/hour) usually is the first choice to induce diuresis, provided adequate renal perfusion has been achieved with ECMO flow and no significant or irreversible renal injury occurred before starting ECMO. Chlorothiazide (10 mg/kg per dose every 12 hours) is added if the response to furosemide is suboptimal. Ultrafiltration is used in the setting of excessive fluid retention despite maximal diuretic therapy and circulatory support. Suspension of ultrafiltration is advisable in the setting of low atrial pressures with hypotension and frequent circuit shutdown because of low volume or pressure sensing within the bladder, at least until hemodynamics stabilize.

Neurologic assessment, although difficult in patients on ECMO, must be performed regularly. Abrupt changes in heart rate, blood pressure, skin perfusion, and pupillary size could indicate seizure activity in paralyzed patients. Findings of concern should be promptly evaluated by cranial ultrasound, head CT scan, or electroencephalography because changes or abnormalities will impact the decision to continue ECMO support. Sedation and analgesia also must be continually reassessed. Muscle relaxation is advisable in unstable patients but can be used intermittently as needed once the patient and ECMO flows are stable enough to allow neurologic evaluation. Parenteral nutritional support should be initiated within 1 to 2 days after establishing ECMO, although it can be deferred if the ECMO course likely will be relatively short (i.e., <4 days), and introduction of enteral nutrition soon after discontinuing ECMO is anticipated. Patients receiving mechanical support are at high risk for nosocomial infection, especially from skin flora with a direct portal of entry through catheters, chest sites, and open or closed sternotomy wounds. Patients with unexplained hemodynamic instability, coagulopathy, and elevated white blood cell count or fever should be pan-cultured and broad-spectrum antibiotic cover initiated.

Weaning from Extracorporeal Membrane Oxygenation

The strategies for weaning from cardiac ECMO often are quite different from those used for weaning patients who are on ECMO for respiratory support. A thorough understanding of the underlying cardiac physiology and cardiorespiratory interactions and an appreciation for the expected range of oxygen saturations is important. Because of the high risk of complications and substantial mortality in cardiac patients associated with duration of mechanical circulatory support beyond 1 week, consideration as to when and how to wean

cardiac patients from ECMO should begin soon after cannulation once circulatory stability has been established. The disease process and circumstances resulting in hemodynamic failure or cardiac arrest may influence the expected duration of mechanical support. For example, patients who fail to separate from CPB after cardiac surgery because of severe pulmonary hypertension usually respond to a 24- to 48-hour period on ECMO with inhaled NO therapy and inotropic support of the right heart. Similarly, patients who have a low cardiac output state or suffer cardiac arrest after cardiac surgery may have residual defects that allow rapid weaning and decannulation soon after reoperation. The likelihood of recovery of ventricular function should be decided within the first 48 to 72 hours so that cardiac transplantation status can be ascertained. ECMO instituted for catheter intervention or arrhythmia ablation procedures may be discontinued within hours of patient cannulation.[81] In contrast, patients with severe cardiomyopathies or those awaiting heart transplantation may require mechanical assistance for a much longer period. Patients with severe bronchiolitis as a result of respiratory syncytial virus complicating repair of CHD on CPB typically require 2 to 3 weeks of ECMO support for respiratory failure.

Patients requiring cardiovascular support with ECMO are partially weaned within the first 48 hours to assess myocardial function by echocardiography and hemodynamic evaluation. An acceptable Pao_2 obtained while the ECMO circuit is clamped, varies substantially according to the underlying anatomy and pathophysiology. If transthoracic cannulation was used and bleeding problems occurred during the ECMO run, the mediastinum may require exploration before or during the weaning process. If only a short period of reconditioning of the myocardium is anticipated, the patient frequently is sedated and paralyzed, dopamine infusion is increased to 5 to 10 μg/kg/min, intravascular volume status is optimized, and ventilator settings are adjusted according to lung compliance and expected arterial O_2 saturation. ECMO flow is decreased by 25% to 50% over a period of several hours until the circuit is clamped. Volume is infused to achieve appropriate preload. Echocardiographic assessment of ventricular systolic function, valvar function, systemic and pulmonary outflow obstruction, and location and direction of intracardiac shunts is useful before weaning and when a change in hemodynamics occurs after the circuit has been clamped. Arterial blood gases, serum lactate levels, and systemic (mixed) venous saturation are important guides to the stability of the circulation, ventilation, and adequacy of perfusion after the circuit has been clamped. Decannulation from ECMO is undertaken once the patient has maintained a stable circulation and acceptable gas exchange for up to 4 hours.

Cardiovascular Interactions with Other Organs

Respiratory Function and Heart-Lung Interaction

Altered respiratory mechanics and positive pressure ventilation may have significant influence on hemodynamics after congenital heart surgery. Therefore the approach to mechanical ventilation should not only be directed at achieving a desired gas exchange but also should be influenced by the potential cardiorespiratory interactions of mechanical ventilation. Ventilation strategy must be matched to the hemodynamic status of each patient to achieve adequate cardiac output and gas exchange. Frequent adjustments may be necessary during the postoperative period, with attention to changes in lung volume and airway pressure. Changes in lung volume have a major effect on PVR, which is lowest at the lung's functional residual capacity (FRC), whereas both hypoinflation or hyperinflation may result in a significant increase in PVR because of altered traction on alveolar septa and extraalveolar vessels.

Positive pressure ventilation influences preload and afterload on the heart (Table 31-5).[82-84] Increased lung volume and intrathoracic pressure decrease preload to both the right and left atria. The afterload on the pulmonary ventricle is increased during a positive pressure breath secondary to the changes in lung volume and increase in mean intrathoracic pressure. If this is significant or there is limited functional cardiac reserve, RV stroke volume may be reduced and end-diastolic pressure increased. This in turn may contribute to a low cardiac output state and signs of RV dysfunction, including tricuspid regurgitation, hepatomegaly, ascites, and pleural effusions. In contrast to the right ventricle, the afterload on the systemic ventricle is decreased during a positive pressure breath secondary to a fall in the ventricle transmural pressure. The systemic arteries are under higher pressure and are not exposed to radial traction effects during inflation or deflation of the lungs. Therefore changes in lung volume will affect LV preload, but the effect on afterload is dependent on changes in intrathoracic pressure alone rather than changes in lung volume. Therefore positive pressure ventilation and PEEP may have a significant beneficial effect in patients with LV failure.

Patients with LV dysfunction and increased end-diastolic volume and pressure can have impaired pulmonary mechanics secondary to increased lung water, decreased lung compliance, and increased airway resistance. The work of breathing is increased, and neonates can fatigue early because of limited respiratory reserve. A significant proportion of total body oxygen consumption is directed at the increased work of breathing

Table 31–5 Cardiorespiratory Interactions of a Positive Pressure Mechanical Breath

	Afterload	Preload
Pulmonary ventricle	Elevated	Reduced
	Effect: ↑ RVEDp	Effect: ↓ RVEDV
	↑ RVp	↓ RAp
	↓ Antegrade PBF	
	↑ PR and/or TR	
Systemic ventricle	Reduced	Reduced
	Effect: ↓ LVEDp	Effect: ↓ LVEDV
	↓ LAp	↓ LAp
	↓ Pulmonary edema	
	↑ Cardiac output	

LAp, Left atrial pressure; *LVEDp,* left ventricular end-diastolic pressure; *LVEDV,* left ventricular end-diastolic volume; *PBF,* pulmonary blood flow; *PR,* pulmonary regurgitation; *RAp,* right atrial pressure; *RVEDp,* right ventricular end-diastolic pressure; *RVEDV,* right ventricular end-diastolic volume; *RVp,* right ventricular pressure; *TR,* tricuspid regurgitation.

in neonates and infants with LV dysfunction, contributing to poor feeding and failure to thrive. Therefore positive pressure ventilation has an additional benefit in patients with significant volume overload and systemic ventricular dysfunction by reducing the work of breathing and oxygen demand.

The use of PEEP in patients with CHD has been controversial. It initially was perceived not to have a significant positive impact on gas exchange, and there was concern that the increased airway pressure could have a detrimental effect on hemodynamics and contribute to lung injury and air leak. Nevertheless, PEEP increases FRC, enabling lung recruitment, and redistributes lung water from alveolar septal regions to the more compliant perihilar regions. Both of these actions improve gas exchange and reduce PVR. Therefore PEEP should be used in mechanically ventilated patients after congenital heart surgery. However, excessive levels of PEEP can be detrimental by increasing afterload on the right side of the circulation. This may be especially true in the Fontan circulation. Usually 3 to 5 cmH_2O of PEEP helps maintain FRC and redistribute lung water without causing hemodynamic compromise. Of course the optimal condition for the Fontan circulation occurs when the patient can breathe spontaneously, generating negative pleural and intrathoracic pressures that assist systemic venous return. If lung volume can be maintained and work of breathing minimized without any positive pressure ventilation, then the Fontan circulation is best served. Early transition to a pressure-support mode of breathing and aim to extubation during the first few postoperative hours is our goal.

Special Respiratory Problems for the Cardiac Patient

Diaphragmatic paresis (reduced motion) or paralysis (paradoxical movement) may precipitate and promote respiratory failure, particularly in the neonate or young infant who relies on diaphragmatic function for breathing more than older infants and children (who can recruit accessory and intercostal muscles if diaphragmatic function proves inadequate). Injury to the phrenic nerve, usually the left, may occur during operations that require dissection of the branch pulmonary arteries well out to the hilum (e.g., TOF, ASO), arch reconstruction from the midline (e.g., Norwood operation), manipulation of the SVC (Glenn shunts), takedown of previous systemic-to-pulmonary shunts, or after percutaneous central venous access. Phrenic injury may occur more frequently at reoperation, when adhesions and scarring may obscure landmarks. Topical cooling with ice during deep hypothermia may also cause transient phrenic palsy. Increased work of breathing on low ventilator settings, increased P_{CO_2}, and a chest radiograph revealing an elevated hemidiaphragm are suggestive of diaphragmatic dysfunction. The chest x-ray film may be misleading, however, if it is taken during at the end of inspiration when lung volume is at its highest. Ultrasonography or fluoroscopy is useful for identifying diaphragmatic motion or paradoxical excursion. Recovery of diaphragmatic contraction usually occurs; however, if a patient fails to tolerate repeated extubations despite optimizing cardiovascular and nutritional status and diaphragmatic dysfunction persists with volume loss in the affected lung, then the diaphragm may require surgical plication. Although only a temporary effect is gained, the prevention of collapse and volume loss in the affected lung may provide the critical advantage needed for liberation from positive pressure ventilation.

Pulmonary edema, pneumonia, and atelectasis are the most common causes of lower airway and alveolar abnormalities that interfere with gas exchange. If a bacterial pathogen is identified, therapy includes antibiotics and pulmonary toilet. If the cause is pulmonary edema, therapy is aimed at lowering the LA pressure through diuresis and pharmacologic means to reduce afterload and improve the lusitropic state of the heart. For infants, fluid restriction frequently is incompatible with adequate nutrition; therefore an aggressive diuretic regimen is preferable to restriction of caloric intake. Adjustment of end-expiratory pressure and mechanical ventilation serve as supportive therapies until the alveoli and pulmonary interstitium are cleared of the fluid that interferes with gas exchange.

Pleural effusions and ascites may occur in patients after a Fontan operation or reparative procedures requiring a right ventriculotomy (e.g., TOF, truncus arteriosus) with transient RV dysfunction. Especially in young patients, pleural effusions and increased interstitial lung water may be a manifestation of right heart failure. This seems logically related to raised systemic venous pressure impeding lymphatic return to the venous circulation. The lymphatic circuit often is functioning at full capacity in these children. Fluid in the pleural space or peritoneum and intestinal distension compete with intrapulmonary gas for thoracic space. Evacuation of the pleural space or drainage of ascites and decompression of the intestinal lumen allow the intrapulmonary gas volume to increase.

Weaning from Mechanical Ventilation

Early tracheal extubation of children after congenital heart surgery is not a new concept but has received renewed attention with the evolution of "fast track" management for cardiac surgical patients. Early extubation generally refers to tracheal extubation within a few hours (i.e., 4-8 hours) after surgery, although in practice it means the avoidance of routine overnight mechanical ventilation. Factors to consider when planning early extubation are given in Table 31-6. For any patient, a thorough review of the preoperative clinical status and surgical procedure is necessary immediately upon admission to the ICU, followed by a detailed examination and assessment of monitoring and laboratory data. Although procedures vary from patient to patient, carefully constructed postoperative order sheets are useful for directing initial management and planning.

A number of published reports have described successful tracheal extubation in neonates and older children after congenital heart surgery, either in the operating room or soon after in the cardiac ICU.[85] This has been possible without significant compromise of patient care, and a low incidence of reintubation or hemodynamic instability has been reported. This fast track strategy has been extended to routine early (within 24 hours of surgery) discharge from hospital. Although overzealous attempts to achieve this goal can have a negative impact on patients and families (e.g., discharge at 24 hours to hotel with chest tube still in place), the practice has streamlined the care of these children and highlights the advances in perioperative care that now permit hospital discharge of infants and older children within 24 hours of repair of congenital heart defects on CPB.[86]

Table 31–6 Considerations for Planned Early Extubation After Congenital Heart Surgery

Patient factors	Limited cardiorespiratory reserve of the neonate and infant
	Pathophysiology of specific congenital heart defects
	Timing of surgery and preoperative management
Anesthetic factors	Premedication
	Hemodynamic stability and reserve
	Drug distribution and maintenance of anesthesia on bypass
	Postoperative analgesia
Surgical factors	Extent and complexity of surgery
	Residual defects
	Risks for bleeding and protection of suture lines
Conduct of bypass	Degree of hypothermia
	Level of hemodilution
	Myocardial protection
	Modulation of the inflammatory response and reperfusion injury
Postoperative management	Myocardial function
	Cardiorespiratory interactions
	Neurologic recovery
	Analgesia management

Central Nervous System

The dramatic reduction in surgical mortality in recent decades has been accompanied by a growing recognition of adverse neurologic sequelae in some survivors. Central nervous system abnormalities may be a function of coexisting brain abnormalities or acquired events unrelated to surgical management (e.g., paradoxical embolus, brain infection, effects of chronic cyanosis), but central nervous system insults appear to occur most frequently during or immediately after surgery. In particular, support techniques used during neonatal and infant cardiac surgery (e.g., CPB, profound hypothermia, circulatory arrest) have been implicated as important causes of brain injury.[87]

During hypothermic CPB, multiple perfusion variables may influence the risk of brain injury. These variables include (but probably are not limited to) (1) the total duration of CPB and the duration and rate of core cooling, (2) pH management during core cooling, (3) duration of circulatory arrest, (4) type of oxygenator, (5) presence of arterial filtration, and (6) depth of hypothermia. Undoubtedly, there is interaction between these various elements, and central nervous system injury after CPB most likely is multifactorial. Early postoperative studies (in the ICU) revealed a higher incidence of neurologic issues in patients undergoing circulatory arrest, including a higher incidence of clinical and electroencephalographic (EEG) seizures, a longer recovery time to the first reappearance of EEG activity, and greater release of the brain isoenzyme of creatine kinase.

Seizures are the most commonly observed neurologic consequence of cardiac surgery with an incidence in older studies of 4% to 25%. Although the incidence of seizures in the ICU has dramatically declined in recent years, when seizures occur they should be treated aggressively with benzodiazepines, phenobarbital, or phenytoin. Importantly, one should limit practices that may have been associated with brain injury after CPB: rapid cooling on CPB and use of prolonged hypothermic circulatory arrest, extreme alpha-stat strategy of intraoperative pH management, extreme hemodilution to hematocrits less than 20, applying heat lamps to infants on arrival in ICU, hypocapnic hyperventilation, and prolonged muscle relaxation (masking seizure observations). We are especially loath to permit hyperthermia to any degree in the early postoperative period.

Intraventricular hemorrhage may occur as a consequence of perinatal events or circulatory collapse in the first few days of life. It is commonly associated with prematurity. Our approach has been to screen all premature infants or asphyxiated babies with a head ultrasound before CPB, which involves extensive anticoagulation, hemodynamic perturbation, and risk for bleeding extension. Surgical intervention is delayed for several days if intraventricular bleeding is documented. The strategy of deferring operations in very premature newborns for several days after birth is associated with a low incidence of intraventricular hemorrhage in these high-risk patients despite use of CPB.[88]

Renal Function and Postoperative Fluid Management

Risk factors for postoperative renal failure include preoperative renal dysfunction, prolonged bypass time, low cardiac output, and cardiac arrest. In addition to relative ischemia and nonpulsatile flow on CPB, angiotensin II–mediated renal vasoconstriction and delayed healing of renal tubular epithelium have been proposed as one mechanism for renal failure. Postoperative sepsis and nephrotoxic drugs may further damage the kidneys.

Because of the inflammatory response to bypass and significant increase in total body water, fluid management in the immediate postoperative period is critical. Capillary leak and interstitial fluid accumulation may continue for the first 24 to 48 hours after surgery, necessitating ongoing volume replacement with colloid or blood products. A fall in cardiac output and increased antidiuretic hormone secretion contribute to delayed water clearance and potential prerenal dysfunction, which could progress to acute tubular necrosis and renal failure if a low cardiac output state persists.

During CPB, optimizing the circuit prime, hematocrit, and oncotic pressure; attenuating the inflammatory response with steroids; and use of modified ultrafiltration techniques have been recommended to limit interstitial fluid accumulation.[89] During the first 24 hours after surgery, maintenance fluids should be restricted to 50% of full maintenance and volume replacement titrated to appropriate filling pressures and hemodynamic response.

Oliguria in the first 24 hours after complex surgery and CPB is common in neonates and infants until cardiac output recovers and neurohumoral mechanisms abate. Although diuretics are commonly prescribed in the immediate postoperative period, the neurohumoral influence on urine output is

powerful. Time after CPB and enhancement of cardiac output through volume and pharmacologic adjustments are the most important factors that will promote diuresis.

Peritoneal dialysis, hemodialysis, and continuous venovenous hemofiltration provide alternate renal support in patients with severe oliguria and renal failure. Besides enabling water and solute clearance, maintenance fluids can be increased to ensure adequate nutrition. The indications for renal support vary but include blood urea nitrogen greater than 100 mg/dL, life-threatening electrolyte imbalance such as severe hyperkalemia, ongoing metabolic acidosis, fluid restrictions limiting nutrition, and increased mechanical ventilation requirements secondary to persistent pulmonary edema or ascites.

A peritoneal dialysis catheter can be placed into the peritoneal cavity at the completion of surgery or as a bedside procedure later in the ICU. Indications include the need for renal support or for reducing intraabdominal pressure from ascites that may compromise mechanical ventilation. Drainage may be significant in the immediate postoperative period as third space fluid losses continue, and replacement with albumin and/or fresh-frozen plasma may be necessary to treat hypovolemia and hypoproteinemia.

Gastrointestinal Issues

After cardiac surgery in neonates and children, adequate nutrition is exceedingly important. These critically ill children often have decreased caloric intake and increased energy demand after surgery; the neonate, in particular, has limited metabolic and fat reserves. Total parenteral nutrition can provide adequate nutrition in the hypercatabolic phase of the early postoperative period.

Upper gastrointestinal bleeding and ulcer formation may occur after the stress of cardiac surgery in children and adults. There are limited reports of the efficacy of histamine H_2 antireceptors, sucralfate, or oral antacids in pediatric cardiac patients, although their use is common in many ICUs. Hepatic failure may occur after cardiac surgery (particularly after the Fontan operation and typically is characterized by elevated liver enzymes and coagulopathy).

Necrotizing enterocolitis, although typically a disease of premature infants, is seen with considerable frequency in neonates with CHD. Risk factors include (1) left-sided obstructive lesions, (2) umbilical or femoral arterial catheterization/angiography, (3) hypoxemia, and (4) lesions with wide pulse pressures (e.g., systemic-to-pulmonary shunts, PDA, especially in transposition of the great arteries and severe aortic regurgitation) producing retrograde flow in the mesenteric vessels during diastole. Frequently, multiple risk factors exist in the same patient, making a specific etiology difficult to establish. Treatment includes continuous nasogastric suction, parenteral nutrition, and broad-spectrum antibiotics. Bowel exploration or resection may be necessary in severe cases.

Infection

Low-grade (<38.5° C) fever during the immediate postoperative period is common and may be present for up to 3 to 4 days, even without a demonstrable infectious etiology. However, there are several reports of increased susceptibility to infection after CPB. CPB may activate complement and other mediators of inflammation but also can lead to derangements of the immune system and increase the likelihood of infection. A centrally mediated etiology of fever after CPB has been postulated.

Sepsis and nosocomial infection after cardiac surgery contribute substantially to overall morbidity. Despite the recent increased use of broad-coverage, third-generation cephalosporins, these agents do not seem to be more effective in decreasing postoperative infections. Meticulous catheter insertion and daily care routines, along with early removal of indwelling catheters in the postoperative patient, may reduce the incidence of sepsis.[90]

Mediastinitis occurs in up to 2% of patients undergoing cardiac surgery. Risk factors include delayed sternal closure, early reexploration for bleeding, or reoperation. Mediastinitis is characterized by persistent fever, purulent drainage from the sternotomy wound, instability of the sternum, and leukocytosis. *Staphylococcus* is the most common offending organism. Treatment usually involves debridement and irrigation with parenteral antibiotic therapy. Duration of therapy seldom exceeds 2 weeks.

Hyperglycemia

Hyperglycemia is a frequent occurrence in the pediatric cardiac intensive care unit.[91,92] As many as 97% and 78% of patients exhibit at least one blood glucose measurement above 125 mg/dL and 200 mg/dL, respectively, after surgical repair of congenital cardiac defects.[91,92] The duration of postoperative hyperglycemia in these patients has been strongly and independently associated with increased morbidity and mortality rates. [91,92]

Strict glycemic control with insulin administration has been shown to reduce morbidity and mortality rates significantly for adult patients admitted to a surgical ICU.[93] A recent report of the first glycemic control outcome trial conducted in children with a sample largely comprised of postoperative cardiac patients showed decreased mortality, shorter ICU length of stay, and decreased markers of inflammation in patients treated with insulin to maintain fasting blood glucose levels.[94] Of significant concern in that trial, however, was the finding that 24.9% of children undergoing strict glycemic control had at least one episode of severe hypoglycemia (blood glucose <40 mg/dL).[94] The use of a more permissive glycemic range (90-140 mg/dL) has been postulated as an optimal target that would be associated with a lower incidence of hypoglycemia compared with an euglycemic range, without incurring the negative effects of hyperglycemia (Figure 31-3).[95] A randomized controlled trial of glycemic control using this more permissive target is yet to be performed.

Critical Care Management of Specific Lesions

Single-Ventricle Anatomy and Physiology

For a variety of anatomic lesions, the systemic and pulmonary circulations are parallel, with a single ventricle effectively supplying both systemic and pulmonary blood flow (Table 31-7). The relative proportion of ventricular output to either the pulmonary or systemic vascular bed is determined by the relative resistance to flow in the two circuits. The pulmonary arterial and aortic oxygen saturations are equal, with mixing of the systemic and pulmonary venous

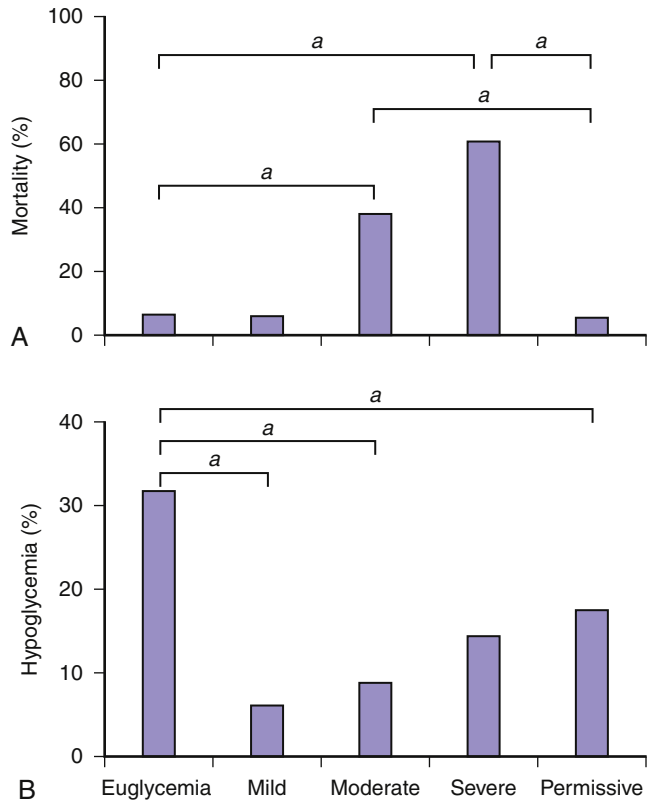

Figure 31–3. **A,** Mortality rates for the various groups, based on median blood glucose levels during postoperative days 2 to 5. **B,** Incidence of hypoglycemia during the postoperative period for the various groups, based on median blood glucose levels. Euglycemia (60-125 mg/dL), mild hyperglycemia (126-139 mg/dL), moderate hyperglycemia (140-179 mg/dL), severe hyperglycemia (>180 mg/dL), or permissive glycemic target (90-140 mg/dL). *a, P* <.0125 by chi-square test with Bonferroni correction. *(Data from Ulate KP, Lima Falcao GC, Bielefeld MR,* et al: *Strict glycemic targets need not be so strict: a more permissive glycemic range for critically ill children.* Pediatrics *122[4]:e898-e904, 2008.)*

Table 31–7 Factors Contributing to a Lower than Anticipated Oxygen Saturation in Patients with Common Mixing Lesions

Etiology	Considerations
Low F_{IO_2}	Low delivered oxygen concentration
	Failure of oxygen delivery device
Pulmonary vein desaturation	**1. Ventilation perfusion defects**
	Alveolar process (e.g., edema/infection/atelectasis)
	Restrictive process (e.g., effusion/bronchospasm)
	2. Intrapulmonary shunt
	Severe RDS
	Pulmonary AVM
	PA-to-PV collateral vessel(s)
↓ Pulmonary blood flow	Anatomic RV outflow obstruction
	Anatomic pulmonary artery stenosis
	Increased PVR
	Atrial level right-to-left shunt
	Ventricular level right-to-left shunt
↓ Oxygen content	**1. Low mixed venous oxygen level**
	Increased O_2 extraction: Hypermetabolic state
	Decreased O_2 delivery: Low cardiac output state
	2. Anemia

AVM, Arteriovenous malforamtion; *F_{IO_2},* fractional inspired concentration of oxygen; *PA,* pulmonary artery; *PV,* pulmonary vein; *PVR,* pulmonary vascular resistence; *RDS,* respiratory distress syndrome; *RV,* right ventricle.

return within a "common" atrium. Assuming equal mixing, normal cardiac output, and full pulmonary venous saturation, Sao_2 of 80% to 85%, with mixed venous oxygen saturation of 60% to 65%, indicates Q_p/Q_s is approximately 1 and hence a balance between systemic and pulmonary flow. Although "balanced," the single ventricle still must receive and eject twice the normal amount of blood: one part to the pulmonary circulation and one part to the systemic circulation. A Q_p/Q_s greater than 1 implies an intolerable volume burden on the heart. Although there may be specific management issues for certain defects with single-ventricle physiology, nevertheless there are common management considerations to balance flow and augment systemic perfusion.

Preoperative Management

Changes in PVR have a significant impact on systemic perfusion and circulatory stability, especially preoperatively when the ductus arteriosus is widely patent. In preparation for surgery, it is important that systemic and pulmonary blood flow be as well balanced as possible to prevent excessive volume overload and ventricular dysfunction that reduces systemic and end-organ perfusion. For example, a newborn with HLHS who has an arterial oxygen saturation greater than 90%, a wide pulse width, oliguria, cool extremities, hepatomegaly, and metabolic acidosis has severely limited systemic blood flow. Even though ventricular output is increased, the blood flow that is inefficiently partitioned back to the lungs is unavailable to the other vital organs. Immediate interventions are necessary to prevent imminent circulatory collapse and end-organ injury. In this "overcirculated" state, PVR is falling as it should in the normal postnatal state, and the ductus arteriosus is maintained widely patent with prostaglandin infusion to permit unrestricted blood flow from the single right ventricle across the ductus to the systemic bed. Blood flow manipulation of mechanical ventilation and inotropic support may temporarily stabilize the patient (see the following section), but surgery should not be delayed. Similarly, in a patient with pulmonary atresia and an intact ventricular septum, LV-dependent pulmonary circulation occurs. Ductal patency is necessary for pulmonary blood flow. As PVR falls, pulmonary blood flow will be excessive and eventually will steal from the systemic circulation. Preoperative management should focus on an assessment of the balance between pulmonary (Q_p) and systemic flow (Q_s). This is best achieved by thorough and continuous reevaluation of the clinical examination for cardiac output state and perfusion, an evaluation of chest radiograph for cardiac size and pulmonary congestion, a review of laboratory data for alterations in gas exchange, acid-base status,

and end-organ function, and echocardiographic imaging to assess ventricular function and AV valve competence. A central venous line positioned in the proximal SVC may be useful to monitor volume status and sample for mixed venous oxygen saturation as a surrogate of cardiac output and oxygen delivery. Central venous lines are not necessary in all circumstances; they may have significant complications in small newborns and do not substitute for clinical examination.

Initial resuscitation involves maintaining patency of the ductus arteriosus with a PGE_1 infusion at a rate of 0.02 to 0.05 μg/kg/min. Intubation and mechanical ventilation are not necessary in all patients. Patients usually are tachypneic, but provided the work of breathing is not excessive and systemic perfusion is maintained without a metabolic acidosis, spontaneous ventilation often is preferable to achieve an adequate systemic perfusion and balance of Q_p and Q_s. A mild metabolic acidosis and low bicarbonate level may be present but may not indicate poor perfusion and a lactic acidosis specifically. If the presentation involved circulatory collapse and end-organ dysfunction, then a period of days may be required to establish stability and allow return of vital organ function before surgery.

Patients require intubation and mechanical ventilation because of apnea secondary to PGE_1, presence of a low cardiac output state, or for manipulation of gas exchange to assist balancing pulmonary and systemic flow. Sao_2 greater than 90% indicates pulmonary overcirculation, that is, Q_p/Q_s greater than 1. PVR can be increased with controlled mechanical hypoventilation to induce a respiratory acidosis, often necessitating sedation and neuromuscular blockade, and with a low FIo_2 to induce alveolar hypoxia. Ventilation in room air may suffice, but occasionally a hypoxic gas mixture is necessary. This is achieved by adding nitrogen to the inspired gas mixture, reducing the FIo_2 from 0.17 to 0.19. Although these maneuvers often are successful in increasing PVR and reducing pulmonary blood flow, remember that these patients have a limited oxygen reserve and may desaturate suddenly and precipitously. Controlled hypoventilation in effect reduces FRC and therefore the oxygen reserve, which is further reduced by use of an hypoxic inspired gas mixture. An alternate strategy is to add carbon dioxide to the inspiratory limb of the breathing circuit, which also increases PVR, but because a hypoxic gas mixture is not used, systemic oxygen delivery is maintained.[96,97] Patients who have continued pulmonary overcirculation with high Sao_2 and reduced systemic perfusion despite these maneuvers require early surgical intervention to control pulmonary blood flow. At the time of surgery, a snare can be placed around either branch of the pulmonary artery to effectively limit pulmonary blood flow.

Decreased pulmonary blood flow in preoperative patients with a parallel circulation is reflected by hypoxemia with Sao_2 less than 75%. Preoperatively this may result from restricted flow across a small ductus arteriosus, increased PVR secondary to parenchymal lung disease, or increased pulmonary venous pressure secondary to obstructed pulmonary venous drainage or a restrictive ASD. Sedation, paralysis, and manipulation of mechanical ventilation to maintain an alkalosis may be effective if PVR is elevated. NO as a specific pulmonary vasodilator also may be useful in this situation. Systemic oxygen delivery is maintained by improving cardiac output and maintaining hematocrit greater than 40%. Among some newborns with HLHS, pulmonary blood flow may be insufficient because mitral valve hypoplasia in combination with the occasional finding of a restrictive or nearly intact atrial septum severely restricts pulmonary venous return to the heart. The newborn is intensely cyanotic and has a pulmonary venous congestion pattern on chest radiograph. Urgent interventional cardiac catheterization with balloon septostomy or dilation (or stent placement) of a restrictive ASD may be necessary.[98,99] Immediate surgical intervention and palliation is preferred in some centers.

Systemic perfusion is maintained with the use of volume and vasopressor agents. Inotropic support often is necessary because of ventricular dysfunction secondary to the increased volume load. Systemic afterload reduction with agents such as phosphodiesterase inhibitors may improve systemic perfusion, although they also may decrease PVR and thus not correct the imbalance of pulmonary and systemic flow. Oliguria and a rising serum creatinine level may reflect renal insufficiency from a low cardiac output. Necrotizing enterocolitis is a risk secondary to splanchnic hypoperfusion, and we prefer not to enterally feed newborns with a wide pulse width and low diastolic pressure (usually <30 mm Hg) before surgery. It is important to evaluate end-organ perfusion and function.

Bidirectional Cavopulmonary Anastomosis

In this procedure, also known as a *bidirectional Glenn shunt,* the SVC is transected and connected end-to-side to the right pulmonary artery, but the pulmonary arteries are left in continuity. Therefore flow from the SVC is bidirectional into both left and right pulmonary arteries. The SVC becomes the only source of pulmonary blood flow, and IVC blood returns to the common atrium. Performed between age 3 to 6 months, the BDG has proved to be an important early staging procedure for patients with single-ventricle physiology because the volume and pressure load is relieved from the systemic ventricle yet effective pulmonary blood flow is maintained. Q_p/Q_s is always less than 1, and the volume load to the single right ventricle is relieved compared with a systemic-to-pulmonary artery shunt. However, it is impractical in the newborn whose pulmonary cross sectional area is inadequate to accommodate sufficient passive pulmonary blood flow for tolerable oxygenation.

The BDG usually is performed on CPB using mild hypothermia with a beating heart. Therefore the complications related to CPB and aortic cross-clamping are minimal, and patients can be weaned and extubated in the early postoperative period.[100] Systemic hypertension is common after a BDG. The etiology remains to be determined, but possible factors include improved contractility and stroke volume after the volume load on the ventricle is removed and brainstem-mediated mechanisms secondary to the increased systemic and cerebral venous pressure. Treatment with vasodilators may be necessary during the immediate postoperative period and during the weaning process.

After the BDG anastomosis, arterial oxygen saturation should be in the 80% to 85% range. Persistent hypoxemia often is secondary to a low cardiac output state and low Svo_2. Treatment is directed at improving contractility, reducing afterload, and ensuring the patient has a normal rhythm and hematocrit. Hyperventilation is not an effective strategy to increase pulmonary blood flow and oxygen saturation in patients after a BDG anastomosis, as hypocapnia causes

cerebral vasoconstriction and effectively decreases the venous return from the SVC (the source of pulmonary blood flow). Instead, arterial oxygen saturation in these patients often benefits from normocapnia or a mild to moderate degree of hypercapnia. Increased PVR is an uncommon cause, and inhaled NO is rarely beneficial in these patients. This finding is not surprising because PA pressure and resistance and vascular tone are not high enough after this surgery to see a demonstrable benefit from NO.[76] Persistent profound hypoxemia should be investigated in the catheterization laboratory to evaluate hemodynamics, look for residual anatomic defects limiting pulmonary flow, such as PA stenosis or a restrictive ASD, and coil any significant venous decompressing collaterals, if present.

Fontan Procedure

Since the original description in 1971,[101] the Fontan procedure and subsequent modifications have been successfully used to treat a wide range of simple and complex single-ventricle congenital heart defects.[102] The repair is "physiologic" in that the systemic and pulmonary circulations are in series and cyanosis is corrected. However, given the current long-term outcome data, perhaps the repair should be viewed as palliative rather than curative.[103,104] The mortality and morbidity associated with this surgery have declined substantially over the years, and many patients with stable single-ventricle physiology can lead normal lives.[105] Considerations in managing a cavopulmonary connection are given in Table 31-8. Systemic venous pressure of 10 to 15 mm Hg and LA pressure of 5 to 10 mm Hg, that is, a transpulmonary gradient of 5 to 10 mm Hg, is ideal.

Intravascular volume must be maintained and hypovolemia must be treated promptly. Venous capacitance is increased, and as patients rewarm and vasodilate after surgery, a significant volume requirement of approximately 30 to 40 mL/kg on the first postoperative night is not unusual. Changes in mean intrathoracic pressure and PVR have a significant effect on pulmonary blood flow. Pulmonary blood flow has been shown to be biphasic after the Fontan procedure, and earlier resumption of spontaneous ventilation is recommended to offset the detrimental effects of positive pressure ventilation.[106,107] Using Doppler analysis, it has been demonstrated that pulmonary blood flow predominantly occurs during inspiration in a spontaneously breathing patient, that is, when the mean intrathoracic pressure is subatmospheric. Therefore the method of mechanical ventilation after a Fontan procedure requires close observation. A tidal volume of 8 to 10 mL/kg with the lowest possible mean airway pressure is appropriate. Although it is preferable to wean from positive pressure ventilation in the early postoperative period, hemodynamic responses must be closely monitored.

If appropriate selection criteria are followed, patients undergoing a modified Fontan procedure will have a low PVR without labile pulmonary hypertension. Therefore vigorous hyperventilation and induction of a respiratory and/or metabolic alkalosis often are of little benefit in this group of patients, and the related increase in mechanical ventilation requirements may be detrimental. A normal pH and $Paco_2$ of 40 mm Hg should be the goal and, depending on the amount of right-to-left shunt across the fenestration, the arterial oxygen saturation usually is in the 80% to 90% range.

Table 31–8 Management Considerations Following a Modified Fontan Procedure

	Aim	Management
Baffle (right side)		→ or ↑ Preload
Pressure 10–15 mm Hg	Unobstructed venous return	Low intrathoracic pressure
	PVR <2 Wood units • m^2	Avoid increases in PVR, such as from acidosis, hypoinflation and hyperinflation of the lung, hypothermia, and excess sympathetic stimulation
Pulmonary circulation	Mean Pap <15 mm Hg	Early resumption of spontaneous respiration
	Unobstructed pulmonary vessels	
Left atrial	Sinus rhythm	Maintain sinus rhythm
Pressure 5–10 mm Hg	Competent AV valve	→ or ↑ Rate to increase CO
	Ventricle	→ or ↓ Afterload
	Normal diastolic function	→ or ↑ Contractility
	Normal systolic function	PDE inhibitors useful because of vasodilatory, inotropic, and lusitropic properties
	No outflow obstruction	

AV, Atrioventricular; *CO,* cardiac output; *Pap,* pulmonary arterial pressure; *PDE,* phosphodiesterase; *PVR,* pulmonary vascular resistance.

However, PVR may increase after surgery, particularly secondary to an acidosis, hypothermia, atelectasis and hypoventilation, vasoactive drug infusions, and stress response. Any acidosis must be treated promptly. If the cause is respiratory, ventilation must be adjusted. A metabolic acidosis reflects poor cardiac output and treatment directed at the potential causes, including reduced preload to the systemic ventricle, poor contractility, increased afterload, and loss of sinus rhythm.

The use of PEEP continues to be debated. The beneficial effects of an increase in FRC, maintenance of lung volume, and redistribution of lung water need to be balanced against the possible detrimental effect of an increase in mean intrathoracic pressure. A PEEP of 3 to 5 cmH_2O, however, rarely has either hemodynamic consequence or substantial effect on effective pulmonary blood flow.

Alternative methods of mechanical ventilation have been used in these patients. High-frequency ventilation has been used successfully, although the hemodynamic consequences of the raised mean intrathoracic pressure must be continually evaluated.[108] Negative-pressure ventilation can be beneficial by augmenting pulmonary blood flow.[109] The development of new negative-pressure ventilators and cuirasses and jackets has increased the interest in this mode of ventilation for this group of patients, but the experience is relatively small and indications are not defined. Application is cumbersome.

Nonspecific pulmonary vasodilators, such as sodium nitroprusside, glycerol trinitrate, PGE_1, and prostacyclin have been used to dilate the pulmonary vasculature in an effort to improve pulmonary blood flow after a Fontan procedure, but the results are variable. Although PVR may fall, pulmonary blood flow also could increase as a result of reduced ventricular end-diastolic pressure after improved ventricular function secondary to the fall in systemic afterload. The response to inhaled NO also is variable, and the improvement may be related to changes in ventilation/perfusion matching rather than a direct fall in PVR.

Afterload stress is poorly tolerated after a modified Fontan procedure because of the increase in myocardial wall tension and end-diastolic pressure. The phosphodiesterase inhibitors milrinone and amrinone are particularly beneficial. Besides being weak inotropes with pulmonary and systemic vasodilating properties, their lusitropic action assists by improving diastolic relaxation and lowering ventricular end-diastolic pressure, thereby improving effective pulmonary blood flow and cardiac output.

Specific Complications After the Fontan Procedure

Pleuropericardial Effusions. The incidence of recurrent pleural effusions and ascites has decreased since the introduction of the fenestrated baffle technique. Nevertheless, for some patients they remain a major problem with associated respiratory compromise, hypovolemia, and possible hypoproteinemia. They usually occur secondary to persistent elevation of systemic venous pressure, and reevaluation with cardiac catheterization may be indicated.

Rhythm Disturbances. Atrial flutter and/or fibrillation; heart block; and, less commonly, ventricular dysrhythmia may have a significant impact on immediate recovery and on long-term outcome.[110] Sudden loss of sinus rhythm initially causes an increase in LA and ventricular end-diastolic pressure and a fall in cardiac output. The SVC or PA pressure must be increased, usually with volume replacement, to maintain the transpulmonary gradient. Prompt treatment with antiarrhythmic drugs, pacing, or cardioversion is necessary.

Premature Closure of the Fenestration. Not all patients require a fenestration for a successful, uncomplicated Fontan operation. Those with ideal preoperative hemodynamics often maintain adequate pulmonary blood flow and cardiac output without requiring a right-to-left shunt across the baffle. Similarly, not all Fontan patients who received a fenestration use it for a right-to-left shunt in the immediate postoperative period. These patients are fully saturated after surgery and may have an elevated right-sided filling pressure but nevertheless maintain an adequate cardiac output. The problem is predicting which patients are at risk for low cardiac output after a Fontan procedure, and who will benefit from placement of a fenestration. Even patients with ideal preoperative hemodynamics may manifest a significant low output state after surgery. Because of this possibility, the vast majority of patients having a Fontan procedure at Riley Hospital for Children, Indiana University, are fenestrated.

Premature closure of the fenestration may occur in the immediate postoperative period, leading to a low cardiac output state with progressive metabolic acidosis and large chest drain losses from high right-sided venous pressures. Patients may respond to volume replacement, inotrope support, and vasodilation; however, if hypotension and acidosis persist, cardiac catheterization and removal of thrombus or dilation of the fenestration may be urgently needed.

Persistent Hypoxemia. Arterial O_2 saturation levels may vary substantially after a modified Fontan procedure. Common causes of persistent arterial O_2 desaturation less than 75% include a poor cardiac output with a low Svo_2, a large right-to-left shunt across the fenestration, or additional "leak" in the baffle pathway producing more shunting. An intrapulmonary shunt and venous admixture from decompressing vessels draining either from the pulmonary artery to the systemic venous circulation or from the systemic vein to the pulmonary venous system are additional causes. Reevaluation with echocardiography and cardiac catheterization may be necessary.

Low Cardiac Output State. An elevated LA pressure after a modified Fontan procedure may reflect poor ventricular function from decreased contractility or increased afterload stress, atrioventricular valve regurgitation, and loss of sinus rhythm (Table 31-9). The right-sided filling pressure must be increased to maintain the transpulmonary gradient and treatment with inotropes and vasodilators initiated. If a severe low output state with acidosis persists, takedown of the Fontan operation and conversion to a BDG anastomosis or other palliative procedure might be lifesaving.

Tetralogy of Fallot

Pathophysiology

The four anatomic features of TOF are VSD, RV outflow tract obstruction, overriding of the aorta, and RV hypertrophy. In addition, there may be VSDs of the muscular region of the septum and right-sided obstruction of the pulmonary valve and the main and branch pulmonary arteries.

Resistance to RV outflow forces systemic venous return from right to left across the VSD (complex shunt) and into the aorta, producing arterial desaturation. Pulmonary blood flow is less than systemic flow. The amount of blood that shunts right to left through the VSD varies with the magnitude of the RV outflow tract obstruction and with SVR. Distal PVR is low and has minimal influence on shunting. Systemic vasodilation, in conjunction with increasing dynamic infundibular stenosis, intensifies right-to-left shunting and therefore hypoxemia, producing hypercyanotic "spells." Such spells can occur at any time before surgical correction of the anomalies and can be life-threatening. Their treatment is outlined in the after section. Because the morbidity associated with recurrent hypercyanotic spells is significant, many physicians consider recurrent episodes of hypercyanosis an indication for corrective surgery at any age.

Critical Care Management for the Early Postoperative Course

The surgical approach to TOF may involve either an early or delayed repair. Delayed repair requires early palliation with a systemic-to-pulmonary artery shunt to prevent

Table 31–9 Etiology and Treatment Strategies for Patients with Low Cardiac Output Immediately Following the Fontan Procedure

Low Cardiac Output	Etiology	Treatment
INCREASED TPG		
Baffle >20 mm Hg LAp <10 mm Hg ↑ TPG >> 10 mm Hg	Inadequate pulmonary blood flow and preload to left atrium Increased PVR Pulmonary artery stenosis	Volume replacement Reduce PVR Correct acidosis Inotropic support
Clinical state High Sao_2/low Svo_2 Hypotension/ tachycardia Core temperature high Poor peripheral perfusion SVC syndrome with pleural effusions and increased chest tube drainage Ascites/hepato-megaly Metabolic acidosis	Pulmonary vein stenosis Premature fenestration closure	Systemic vasodilation Catheter or surgical intervention
NORMAL TPG		
Baffle >20 mm Hg LAp >15 mm Hg TPG normal 5–10 mm Hg	Ventricular failure Systolic dysfunction Diastolic dysfunction AVV regurgitation and/or stenosis	Maintain preload Inotrope support Systemic vasodilation Establish sinus rhythm or atrioventricular synchrony
Clinical state Low Sao_2/low Svo_2 Hypotension/ tachycardia Poor peripheral perfusion Metabolic acidosis	Loss of sinus rhythm ↑ Afterload stress	Correct acidosis Mechanical support Surgical intervention, including takedown to BDG and transplantation

AVV, Atrioventricular valve; *BDG,* bidirectional Glenn anastomosis; *LAp,* left atrial pressure; *PVR,* pulmonary vascular resistance; Sao_2, systemic arterial oxygen saturation; *SVC,* superior vena cava; Svo_2, SVC oxygen saturation; *TPG,* transpulmonary gradient.

hypercyanotic episodes, followed by a transatrial and transpulmonary artery repair between ages 12 and 18 months. Excellent outcome has been achieved with this approach, and the need for a transpulmonary valve annulus outflow patch (transannular patch) at the time of surgery is reduced.[111] The risks of cyanosis and complications related to a systemic-to-pulmonary artery shunt argue for early complete repair of TOF. This can be performed in the neonate or young infant depending on the degree of obstruction and arterial oxygen saturation level.[112] Complete repair in neonates and young infants may more often require a transventricular approach to close the VSD, with pericardial augmentation of the RV outflow tract. A ventriculotomy is performed in the RV outflow tract and frequently is extended distally through the pulmonary valve annulus and beyond any associated pulmonary artery stenosis. The outflow tract is enlarged with pericardium or synthetic material, and obstructing muscle bundles are resected to relieve the outflow tract obstruction.[113] Being smaller and younger, these patients may be at increased risk for complications associated with CPB. Pulmonary regurgitation results after a transannular incision that may compromise ventricular function in the postoperative period. At Riley Hospital for Children, Indiana University, the routne use of a PTFE monocusp valve for reconstruction of the right ventricular outflow tract results in significantly less pulmonary regurgitation compared to traditional nonvalved transannular patch repairs.[114] In approximately 8% of patients, abnormalities in the origin and distribution of the coronary arteries preclude placement of the RV outflow patch,[115] making it necessary to bypass the stenosis by placing an external conduit from the body of the right ventricle to the pulmonary artery.[116]

Preoperative management of these patients should maintain systemic vascular resistance, minimize PVR, and avoid myocardial depression. Hypercyanotic spells in nonanesthetized children are traditionally treated initially with 100% oxygen by face mask, a knee-chest position (to increase SVR), and morphine sulfate. This regimen usually causes the dynamic infundibular stenosis to relax while maintaining systemic resistance. Deeply cyanotic and lethargic patients are given rapid IV crystalloid infusions to augment circulating blood volume. Continued severe hypoxemia is treated with a vasopressor (e.g., phenylephrine 1-2 μg/kg) to increase SVR and sometimes with judicious use of IV propranolol or esmolol to slow the heart rate. The latter allows more filling time and relaxes the infundibulum.[117] If a hypercyanotic spell persists despite treatment, immediate surgical correction of the anomaly is indicated. The child can be anesthetized with IV narcotics, and an inhalation agent such as halothane may be beneficial to reduce hyperdynamic outflow tract obstruction. Anesthetic agents that predominantly decrease SVR, such as isoflurane, should be used with caution. The pattern of mechanical ventilation is critical, as excessive inspiratory pressure or short expiratory times increases the mean intrathoracic pressure and further reduces antegrade flow across the RV outflow.

When weaning patients from CPB after tetralogy repair, the aim of therapy is to support RV function and minimize afterload on the right ventricle. This is particularly important after repair in neonates or small infants. Although systolic dysfunction of the right ventricle may occur after neonatal ventriculotomy, more commonly the clinical picture is one of a "restrictive physiology" reflecting reduced RV compliance or diastolic function.[28,29] Factors contributing to diastolic dysfunction include ventriculotomy, lung and myocardial edema after CPB, inadequate myocardial protection of the hypertrophied ventricle during aortic cross-clamp, coronary artery injury, residual outflow tract obstruction, volume load on the ventricle from a residual VSD or pulmonary regurgitation, and arrhythmias.

Patients usually separate from CPB with a satisfactory blood pressure and atrial filling pressures less than 10 mm Hg on inotropic support, such as dopamine 5 to 10 μg/kg/min.

However, in neonates during the first 6 to 12 hours after surgery, a low cardiac output state with increased right-sided filling pressures from diastolic dysfunction is common after a right ventriculotomy, and continued sedation and paralysis usually are necessary for the first 24 to 48 hours to minimize the stress response and associated myocardial work. Preload must be maintained, despite elevation of RA pressure.

In addition to high right-sided filling pressures, pleural effusions and/or ascites may develop. Significant inotropic support is often required, and a phosphodiesterase inhibitor, such as milrinone, is beneficial because of the lusitropic properties. Because of the restrictive physiology, even a relatively small volume load from a residual VSD or pulmonary regurgitation is often poorly tolerated in the early postoperative period, and 2 to 3 days may be required before RV compliance improves after surgery and cardiac output increases. Although the patent foramen ovale or any ASD usually is closed at the time of surgery in older patients, it is beneficial to leave a small atrial communication after neonatal repair. In the face of diastolic dysfunction and increased RV end-diastolic pressure, a right-to-left atrial shunt maintains preload to the left ventricle and therefore cardiac output. Patients may be desaturated initially after surgery because of this shunting. As RV compliance and function improve, the amount of shunt decreases and both antegrade pulmonary blood flow and arterial oxygen saturation increase.

Arrhythmias after repair include heart block, ventricular ectopy, and junctional ectopic tachycardia. It is important to maintain sinus rhythm to prevent additional diastolic dysfunction and an increase in end-diastolic pressure. Atrioventricular pacing may be necessary for heart block. Complete right bundle branch block is typical on the postoperative ECG.

Most patients recover systolic ventricular function postoperatively. However, there is a small group of patients, especially those repaired at older ages, in whom significant ventricular dysfunction remains.[118,119] Pulmonary valve insufficiency may contribute to residual ventricular systolic dysfunction.[120] The most common cause of systolic dysfunction immediately after repair of CHD is a residual or unrecognized additional VSD,[121] which causes a volume load on the left ventricle and pressure load on an already stressed right ventricle, leading to RV failure and poor cardiac output. A residual VSD combined with a residual RV outflow obstruction is particularly deleterious.

In some patients, the distal pulmonary arteries may be so hypoplastic and stenotic that they cannot be satisfactorily corrected. Suprasystemic pressure develops in the right ventricle, which in some cases can be ameliorated by partially opening the VSD to allow an intracardiac right-to-left ventricular shunt. This shunt unloads the compromised right ventricle at the expense of decreased arterial oxygen saturation.

Critical Care Management for Late Postoperative Care

Reconstruction of the RV outflow tract may lead to significant problems that affect RV function and risk for arrhythmias over time. Although most of the long-term outcome data pertain to patients after TOF repair, similar complications and risks are likely for those who have undergone an extensive RV outflow reconstruction, such as placement of a conduit from the right ventricle to the pulmonary artery for correction of pulmonary atresia, truncus arteriosus, and the Rastelli procedure for transposition of the great arteries with pulmonary stenosis.

Complete surgical repair of TOF has been successfully performed for more than 40 years, with studies reporting a 30- to 35-year actuarial survival of approximately 85%.[122] Many patients report leading relatively normal lives, but RV dysfunction may progress after repair and may be evident only on exercise stress testing or echocardiography. A spectrum of problems may develop, ranging from a dilated right ventricle with systolic dysfunction to diastolic dysfunction from a poorly compliant right ventricle, and these problems must be thoroughly evaluated preoperatively. In addition, continued evaluation is necessary because of the increased risk for ventricular arrhythmias and late sudden death. Factors that may adversely affect long-term survival include older age at initial repair, initial palliative procedures, and residual chronic pressure and/or volume load as occurs from pulmonary insufficiency or stenosis.

Systolic dysfunction secondary to a residual volume load from pulmonary regurgitation after tetralogy repair is a predictor of late morbidity. It is reflected as cardiomegaly on chest x-ray film, an increase in RV end-diastolic volume by echocardiography,[120] and a reduction in anaerobic threshold, maximal exercise performance, and endurance on exercise testing.[123] Patients who have significant pulmonary regurgitation and reduced RV function are at potential risk for a fall in cardiac output during anesthesia, particularly as positive pressure ventilation may increase the amount of regurgitation. Once again, it is difficult to predict those patients who are more likely to have instability during anesthesia for noncardiac surgery, nor is it possible to formulate a "recipe" for anesthesia that will be suited to all patients. Nevertheless, preoperative exercise testing may provide some insight into hemodynamic reserve.

An important group to distinguish consists of those who have continued restrictive physiology or diastolic dysfunction secondary to reduced ventricular compliance. They usually do not have cardiomegaly, they demonstrate better exercise tolerance, and the risk for ventricular dysrhythmias is possibly decreased. Although the right ventricle is hypertrophied, function is generally well preserved on echocardiography, with minimal pulmonary regurgitation.

The incidence of significant RV outflow obstruction developing over time is low. Residual obstruction contributes to early mortality within the first year after surgery but is well tolerated in the long term. A gradient more than 40 mm Hg across the RV outflow is uncommon, and the pressure ratio between the right ventricle and left ventricle usually is less than 0.5. The gradient may become more significant with time, but as the progression usually is slow, RV dysfunction occurs late.

A wide variation in the incidence of ventricular ectopy has been reported in numerous follow-up studies, including up to 15% of patients on routine ECG and up to 75% of patients on Holter monitor. Multiple risk factors, including an older age at repair, residual hemodynamic abnormalities, and duration of follow-up, have all been considered important.[124] In common with these factors are probable myocardial injury and fibrosis from chronic pressure and volume overload, as well as cyanosis. Although ventricular ectopy is common in asymptomatic patients during ambulatory ECG Holter monitoring and exercise stress testing, it often is low grade and has

not identified those patients at risk for sudden death. Electrophysiologic induction of sustained ventricular tachycardia (VT), especially when monomorphic, is suggestive of the presence of a reentrant arrhythmic pathway. Although dependent on the stimulation protocol used to induce VT, the presence of monomorphic VT in a symptomatic patient with syncope and palpitations is significant and indicates treatment with radiofrequency ablation, surgical cryoablation, antiarrhythmic drugs, or placement of an implantable cardioverter-defibrillator.[125] The risk for ventricular dysrhythmias during anesthesia and ICU care for subsequent hospitalizations is unknown. Although preoperative prophylaxis with antiarrhythmic drugs is not recommended, a means for external defibrillation and pacing must be readily available.

Pulmonary Atresia

Pathophysiology

Atresia of the pulmonary valve or main pulmonary artery forms a spectrum of cardiac defects, the management of which depends on the extent of atresia, size of the right ventricle and tricuspid valve (TV), presence of a VSD and collateral vessels, surface area of the pulmonary vascular bed, and coronary artery anatomy. At birth, pulmonary blood flow is derived from either a PDA or other aortopulmonary collateral blood vessels. These collaterals, which arise from the descending aorta and supply both lungs, may be extensive. The right ventricle usually is hypertrophied, and a restrictive physiology is common during initial postoperative recovery.[126]

At one end of the spectrum, critical pulmonary stenosis may exist with a variable degree of hypoplasia of the right ventricle, TV, and pulmonary artery. There is no VSD. With critical pulmonic stenosis, only a pinhole orifice is present in the pulmonic valve, but the right ventricle is generally less hypoplastic than with pulmonary atresia. A fixed obligatory shunt of all systemic venous return occurs from the right to the left atrium, where blood mixes completely with pulmonary venous blood. Some blood may flow into the right ventricle, but because there is no outlet, blood regurgitates back across the TV and eventually reaches the left atrium and left ventricle. Pulmonary blood flow is derived exclusively or predominantly from a PDA. These patients usually do not have extensive aortopulmonary collateral blood flow; consequently, they often become cyanotic when the PDA closes after birth. Critical pulmonary valve stenosis can be effectively treated by balloon dilation in the catheterization laboratory. Antegrade flow across the RV outflow may not improve immediately but may gradually increase over days as RV compliance improves.

Pulmonary valve atresia or short-segment main pulmonary artery atresia, with a VSD and normal size TV, right ventricle, and branch pulmonary arteries, is completely repaired in the neonate. The procedure usually involves placement of a pericardial patch to reconstruct the outflow tract. If there is long-segment pulmonary artery atresia, a homograft "conduit" is necessary to reconstruct the RV outflow. Conduits may be extrinsically compressed or kinked at the time of sternal closure, causing partial RV outflow obstruction or direct compression of a coronary artery leading to ischemia.

The intracardiac anatomy of TOF with pulmonary atresia is similar to that of simple TOF, but the RV outflow tract is atretic. Because of the atretic RV outflow tract, all systemic venous return courses right to left through the VSD. Therefore complete mixing of pulmonary and systemic venous return occurs in the left ventricle and aorta, producing arterial hypoxemia. Infants with TOF and associated pulmonary atresia regularly exhibit significant systemic-to-pulmonary collateral flow. If antegrade flow is established from the right ventricle into the main pulmonary artery by a reparative procedure, the left-to-right shunt via collateral flow will impose a diastolic load on the left ventricle. Preoperative occlusion of these collateral vessels can be accomplished by interventional techniques in the cardiac catheterization laboratory but may leave the child precariously cyanotic in the hours before operation. The most effective temporizing therapy is to reduce oxygen consumption (e.g., anesthesia, mechanical ventilation) and to increase the systemic perfusion pressure across other systemic-to-pulmonary communications.

Patients with pulmonary atresia, a VSD, but small right ventricle and TV may not tolerate a complete initial repair. The right ventricle may be unable to cope with the entire cardiac output, resulting in a low output state and RV failure (see the following section). Alternative management strategies therefore include initial palliation with a shunt and/or RV outflow patch to improve pulmonary blood flow, or a repair of the outflow tract with fenestration of the VSD patch to enable a right-to-left shunt at that level. Two-ventricle repair ultimately may be limited by growth of the TV.[126] If the right ventricle subsequently grows, the shunt and the patent foramen ovale ASD and VSD can be closed surgically.

Patients with pulmonary atresia and an intact ventricular septum usually have a small right ventricle and TV, a condition that often makes them unsuitable for a two-ventricle repair in the long term. Initial palliation with an aortopulmonary shunt is necessary. Reconstruction of the RV outflow with a pericardial patch or interventional catheter techniques also may be considered if the right ventricle is a sufficient size such that a two ventricle could be considered. Before intervention, the coronary anatomy should be determined, usually by cardiac catheterization. A large conal branch or aberrant left coronary artery across the RV outflow tract may restrict the size of a ventriculotomy and placement of a patch or conduit. Patients with pulmonary atresia, a hypoplastic right ventricle, and intact ventricular septum may have numerous fistulous connections (sinusoids) between the small hypertensive RV cavity and the coronary circulation.[127] Therefore a significant proportion of the myocardium may depend on coronary perfusion directly from the right ventricle. If, in addition, proximal coronary artery stenoses are restricting coronary perfusion from the aortic root, then decompression of the right ventricle after reconstruction of the RV outflow tract can lead to myocardial infarction.

At the worst end of the spectrum, severe pulmonary atresia may be associated with a hypoplastic right ventricle and diminutive pulmonary arteries that are not suitable for primary repair. A palliative procedure with a Blalock-Taussig or central shunt is usually necessary at first to improve pulmonary blood flow, followed by staged single-ventricle repair (see section on managing Fontan physiology).

Multiple aortopulmonary collateral arteries may be present, supplying some or all segments of the lung. They can be associated with a large left-to-right shunt, contributing to volume overload and pulmonary hypertension. Larger collateral vessels supplying significant portions of the lung can

be anastomosed or "unifocalized" to the native pulmonary arteries, with the ultimate aim being to establish full antegrade pulmonary blood flow. Smaller vessels to some segments of lung can be coiled in the cardiac catheterization laboratory, provided there is antegrade flow from the native pulmonary arteries to those lung segments.

When the pulmonary arteries are very diminutive, it is important to establish early antegrade flow from the right ventricle to the pulmonary artery, in an effort to promote growth and establish a pathway to the pulmonary arteries for subsequent balloon dilation. A Blalock-Taussig shunt may be necessary to provide sufficient pulmonary blood flow if the pulmonary arteries and right ventricle are small. Initially, the VSD can be left open, and postoperative management of cyanosis or CHF will be determined by the size of and the resistance offered by the pulmonary circuit. The course in these patients can be dynamic and demanding for even the most experienced practitioners. When collaterals are occluded in the operating room and right ventricle to diminutive pulmonary artery continuity is established, cyanosis may ensue and therapy is aimed at lowering PVR and/or (re)establishing adequate pulmonary blood flow. On the other hand, if the child is fully saturated in the aorta with elevated pulmonary artery oxygen saturation and LA pressure, then a left-to-right shunt through the VSD may be developing, which will produce a volume load on the left ventricle and an unstable postoperative course, dictating VSD closure. When the patient is not fully saturated in the aorta but is suffering from a volume-loaded left ventricle with low cardiac output and high LA pressure postoperatively, excessive systemic-to-pulmonary collaterals may be the culprits, requiring catheterization laboratory investigation and occlusion or immediate reoperation.

Critical Care Management

Critical care management of patients with pulmonary atresia is similar to that for TOF, except that hypercyanotic spells do not occur in the same fashion. Maintaining the patency of the ductus for the perioperative treatment of neonates with pulmonary atresia and critical pulmonary stenosis is essential. If the right ventricle is sufficiently well developed and the main pulmonary artery is present, it may be possible to perform a pulmonary valvotomy and provide adequate pulmonary blood flow without a supplemental systemic-to-pulmonary artery shunt. The goal of therapy is to improve oxygenation and decrease RV afterload. Because the underdeveloped noncompliant right ventricle requires high filling pressures, consequently there may be substantial right-to-left shunting through the foramen ovale, making these infants hypoxemic during the immediate postoperative period. With growth and improved compliance of the right ventricle, the right-to-left shunting diminishes and the infant's oxygenation improves substantially. If hypoxemia persists, a PGE_1 infusion should be started to increase pulmonary blood flow through the ductus arteriosus while arrangements are made to surgically create a pulmonary artery to systemic artery shunt.

In patients with long-segment pulmonary atresia, the need for a conduit to bridge the gap between the right ventricle and the pulmonary artery complicates the repair. Again, RV failure may occur postoperatively, especially when there is a residual VSD or an outflow obstruction. The conduit may obstruct acutely during chest closure, further elevating pressure in the right ventricle.

After the VSD is closed and blood flow is from the right ventricle to the pulmonary arteries, there may be excessive pulmonary blood flow ($Q_p/Q_s > 1$) as a result of the combined flow into the pulmonary arteries from the right ventricle and from aortopulmonary collaterals just described. If this occurs, the patient develops CHF and requires intraoperative inotropic support of the heart and an extended period of postoperative mechanical ventilation. With large collateral flows, the pulse pressure is large and diastolic pressure low. The patient may require surgery to ligate the collateral vessels or may require embolization.

Critical Care Management for Late Postoperative Care

Patients with TOF and pulmonary atresia are subject to the same late problems and complications as patients with TOF alone. In addition, they may develop progressive conduit obstruction after surgery. Conduit obstruction is accelerated by the presence of a porcine valve in the conduit.[128,129] Consequently, unless the patient has severe pulmonary hypertension, valveless conduits or homografts now are preferred by many.[116] At Riley Hospital for Children, Indiana University, the preferred repair involves the implantation of a heterologous bovine jugular vein bioprosthesis (Medtronics Contegra) with a trileaflet venous valve.[130] This has been the valved conduit of choice in patients younger than 18 years of age, whenever pulmonary regurgitant volume load to the RV is undesirable.[130] Recent data from our institution suggest that small caliber bovine jugular vein conduits may have significantly improved freedom from dysfunction at 5 and 10 years' follow-up compared to pulmonary homografts in patients operated during the first 2 years of life.[131]

Tricuspid Atresia

Pathophysiology

In this condition, an imperforate TV and hypoplasia of the right ventricle are present, often accompanied by a VSD of variable size and by pulmonic stenosis. A fixed obligatory shunt of all systemic venous return occurs from the right atrium through the patent foramen ovale or ASD into the left atrium, where complete mixing takes place. The degree of hypoxemia depends on the amount of pulmonary blood flow, which is regulated by the severity of the pulmonic stenosis. The common presentation is characterized by significant hypoxemia caused by the decreased pulmonary blood flow induced by either a restrictive VSD or a severe pulmonic stenosis.

Critical Care Management

The reparative operation of choice for tricuspid atresia is a modified Fontan procedure, but a palliative procedure may initially be required to improve pulmonary blood flow. A pulmonary artery band may be needed if the pulmonary blood flow is increased, or a shunt may have to be created for the severely hypoxemic child with decreased pulmonary blood flow upon ductal closure. The critical care management and complications are those discussed in the sections

on shunts, banding, and modified Fontan procedures. Complications of chronic hypoxemia and cyanosis are also present.

Transposition of the Great Arteries

Pathophysiology

With transposition of the great arteries, the right ventricle gives rise to the aorta. Almost 50% of patients with this anomaly have a VSD, and some of them have a variable degree of subpulmonic stenosis. Oxygenated pulmonary venous blood returns to the left atrium and is recirculated to the pulmonary artery without reaching the systemic circulation. Similarly, systemic venous blood returns to the right atrium and ventricle and is ejected into the aorta again. Obviously, this arrangement is compatible with life only for a few circulation times unless there is some mixing of pulmonary and systemic venous blood via a PDA or an opening in the atrial or ventricular septum at birth. The physiologic disturbance in these patients is one of inadequate mixing of pulmonary and systemic blood rather than one of inadequate pulmonary blood flow.

Mixing of blood at the atrial level can be improved by balloon atrial septostomy. If dangerous levels of hypoxemia persist after the septostomy and metabolic acidosis ensues, an infusion of PGE_1 can maintain the patency of ductus arteriosus, increase pulmonary blood flow (by increasing left-to-right shunting across the PDA), and thereby increase the volume of oxygenated blood entering the left atrium. The volume-overloaded left atrium is likely to shunt part of its contents into the right atrium and thereby improve the oxygen saturation of aortic blood. Unlike the kinetics with other lesions, increased shunting of blood during anesthesia improves arterial oxygen saturation before correction of the transposition.

Critical Care Management

Depending on the particular anatomy and the presence of a VSD or pulmonary stenosis, one of three corrective procedures is used. The intraoperative and postoperative problems encountered differ with each type of procedure.

Atrial Baffle Procedure (Mustard and Senning). An atrial level partition is created with baffling to redirect pulmonary venous blood across the TV to the right ventricle and thus to the aorta.[132,133] Systemic venous return is directed across the atrial septum to the mitral valve, into the left ventricle, and out the pulmonary artery. Although the pulmonary and systemic circuits are then connected serially instead of in parallel, this arrangement leaves the patient with a morphologic right ventricle and TV in continuity with the aorta. Therefore this ventricle must work against systemic arterial pressure and resistance.

One problem with atrial baffles is that they can obstruct systemic and pulmonary venous return.[134] When this occurs, the patient manifests signs and symptoms of systemic venous obstruction, as evidenced by SVC syndrome or other signs of systemic venous hypertension. When the pulmonary venous pathway is obstructed, pulmonary venous hypertension may be manifested by respiratory failure, poor gas exchange, and pulmonary edema. Severe pulmonary venous obstruction is manifested in the operating room by the presence of copious amounts of bloody fluid in the endotracheal tube, low cardiac output, and frequently poor oxygenation. Residual interatrial shunts also may cause intraoperative or postoperative hypoxemia. Long-term rhythm disturbances and the limitations of ventricular and AV valve function have made this operation nearly obsolete.

Arterial Switch Operation (Jatene Procedure). Because of the complications associated with atrial baffle procedures, Jatene and others explored whether anatomic correction of this lesion, by dividing both great arteries and reattaching them to the opposite anatomically correct ventricle, would improve survival.[135,136] This procedure requires excision and reimplantation of the coronary arteries to the neoaorta (formerly the proximal main pulmonary artery). The success of the arterial switch procedure depends on adequate preparation of the left ventricle and technical proficiency with the coronary transfer. Anatomic correction of transposition of the great vessels is done during the neonatal period when PVR (LV afterload) and LV pressure are high. Left ventricular mass decreases progressively after birth in this lesion, and if the ability of the left ventricle to tolerate the work required is misjudged, the child may develop severe LV failure postoperatively and require inotropic support and afterload reduction to provide normal cardiac output. Infants with transposition of the great arteries who are older than a few weeks of age and have an intact ventricular septum may have decreased LV pressure and mass. In such cases, the left ventricle may not tolerate the work required to perfuse the systemic vessels. However, if the neonate has a nonrestrictive VSD, the left ventricle is accustomed to high pressure and may tolerate the increased workload at any age. In older patients with an intact ventricular septum, banding the pulmonary artery can prepare the left ventricle to function as a systemic ventricle by increasing its afterload and muscle mass. If the left ventricle is "prepared" by banding the pulmonary artery and augmenting pulmonary blood flow with a modified Blalock-Taussig shunt, then an arterial switch procedure usually can be accomplished 1 week later, after hypertrophy and hyperplasia have occurred.[137] However, during this interval these patients are cyanotic, with a volume-loaded right ventricle and a pressure-loaded left ventricle, and they may require considerable pharmacologic support.[138]

In experienced centers, the incidence of mortality after neonatal repair of transposition of the great arteries now is less than 3% and may be less than 2% for most anatomic arrangements of coronary arteries if the aortic arch is normal.[139] Midterm follow-up of these patients shows excellent outcome. Alternative operations are reserved almost exclusively for patients with particularly difficult coronary anatomy [140,141] or pulmonic (neo-aortic) stenosis.

Myocardial ischemia or infarction may occur after mobilization and reimplantation of the coronary arteries, especially if they are stretched or twisted. Inotropic support, maintenance of coronary perfusion pressures, control of heart rate, and treatment with vasodilators may be particularly useful, as in adult patients with myocardial ischemia. Postoperative bleeding and tamponade occur more commonly with this operation because of the presence of multiple arterial anastomoses.

Ventricular Switch (Rastelli Procedure). In patients with a large VSD and severe subpulmonic stenosis, the VSD can be closed obliquely to direct LV flow to the aorta. The pulmonary valve is oversewn and the right ventricle is connected to the pulmonary artery with a conduit.[142]

Complications of the Rastelli procedure include obstruction of LV outflow as a result of narrowing of the subaortic region by the VSD patch. The conduit also may obstruct during or after the immediate postoperative period. A small but significant incidence of heart block in these patients can be a difficult postoperative problem.

Late Postoperative Care

Patients who have both a pulmonary ventricle and a morphologic right ventricle remaining as the systemic ventricle can be regarded as having a physiologic or functional two-ventricle repair. Actuarial survival rates at 15 years have been quoted up to 85%; however, significant long-term functional deterioration is likely with increasing risk for right heart failure, sudden death, and dysrhythmias.[143,144] This situation is evidenced by systemic (right) ventricular dysfunction and TV regurgitation long after the repair.[145] These patients also are prone to develop significant atrial dysrhythmias, including supraventricular tachyarrhythmias and sick sinus syndrome later in life.[146] The arrhythmias may be preceded by RV dysfunction but also may be an isolated finding and is potentially the major cause of sudden death in these patients. A number of large follow-up series have reported the probability of a patient remaining in sinus rhythm after an atrial level repair is 50% at 10 years and 40% at 20 years. Function of the sinus node may be seriously impaired by the atrial manipulations during surgery, and sick sinus syndrome (requiring pacemaker insertion) may occur late in the postoperative period. The atrial baffle provides a functional repair, although despite this, many patients continue to maintain relatively active lives with few subjective symptoms. Objective exercise testing on intermediate and late follow-up may demonstrate limited RV reserve in as many as 50% of patients. Exercise duration, peak heart rate response, and peak minute oxygen consumption have all been reported to be reduced compared with age-matched controls.[147]

One of the major advances in congenital heart surgery over the past 10 to 15 years has been the development of the ASO to correct transposition of the great arteries. In experienced centers, the early hospital mortality is less than 3%, and actuarial analyses indicate a 98% survival rate at 5 to 10 years.[139] Long-term survival data are not available given that the oldest survivors are only in their 20s, but based on intermediate-term follow-up data the risk for reoperation and complications after ASO remains small.

Virtually all coronary artery patterns are amenable to ASO. No particular pattern has been associated with late death. A report of coronary artery angiography in 366 patients after ASO (median age at follow-up, 7.9 years) revealed coronary artery stenosis or occlusion in 3% of patients.[148] The long-term significance of these coronary artery abnormalities has not been determined. Despite the angiographic findings, evaluation with serial ECG, exercise testing, and wall-motion abnormalities on echocardiography rarely demonstrate evidence of ischemia.[149]

After repair, the "native" pulmonary valve becomes the "neo-aortic" valve. A 30% incidence of trivial-to-mild aortic regurgitation has been reported on intermediate-term follow-up, without significant hemodynamic changes.[150] Severe regurgitation is unusual.

There appears to be a very low incidence of significant rhythm disturbances after ASO.[151] Supravalvar pulmonary artery stenosis was an early complication but now is less common with surgical techniques that extensively mobilize, augment, and reconstruct the pulmonary arteries. Supravalvar AS may develop but is rare.

Assessment of myocardial performance using echocardiography, cardiac catheterization, and exercise testing after ASO have demonstrated function identical to that in age-matched controls.[152] Based on the currently available clinical, functional, and hemodynamic data, a patient who has undergone ASO with no evidence of subsequent problems should be treated as any patient with a structurally normal heart when presenting for noncardiac surgery.

Late complications of the Rastelli procedure include progressive conduit obstruction and RV hypertension, residual VSDs, and occasionally subaortic obstruction from diversion of LV outflow across the VSD to the aorta.

Total Anomalous Pulmonary Venous Connection

Pathophysiology

Patients with TAPVC are cyanotic because their pulmonary veins connect to a systemic vein and they have various degrees of pulmonary venous obstruction. The venous connection may be above the level of the heart (e.g., to the SVC, innominate, or azygos vein), directly to the right atrium, or below the level of the heart and the diaphragm (e.g., to the hepatic veins). Patients with this anomaly must have a patent foramen ovale or an ASD that allows blood flow to the left side of the heart.

This anatomic arrangement provides complete mixing of all systemic and pulmonary venous blood in the right atrium. Unless there is significant stenosis of the pulmonary venous connection, most of this right atrial blood passes through the right ventricle into the pulmonary artery, which increases pulmonary blood flow. If pulmonary venous return is significantly diminished from obstruction, there is increased pulmonary venous congestion and decreased pulmonary blood flow.

Critical Care Management

These patients may be very ill, with hypoxemia, severe pulmonary edema, and pulmonary artery hypertension. Resuscitation, including mechanical ventilation, PEEP, and inotropic support of the myocardium, is followed by early surgical intervention to relieve the pulmonary venous obstruction. Although patients are hypoxemic, their primary pathology is caused by obstructed venous return from the lungs. Therapy that increases pulmonary blood flow (e.g., PGE_1) must be avoided. Surgical repair of TAPVC requires attachment or redirection of the pulmonary venous confluence to the left atrium.

Intraoperative and postoperative problems often are related to residual or recurrent stenosis of the pulmonary veins. In patients who had severe stenosis and pulmonary venous hypertension preoperatively, the pulmonary vascular bed is highly reactive. This reactivity may produce high pulmonary artery pressures and poor RV function after bypass and during

the early postoperative period. Critical care management of these patients after completion of the repair should emphasize inotropic support of the right ventricle, avoidance of myocardial depressant drugs, and minimization of PVR. Early extubation of the trachea usually is not feasible. Mechanical ventilation with gentle hyperventilation and other postoperative therapy to decrease PVR are required. Inhaled NO has been particularly useful in this population.[153]

Critical Care Management for Late Postoperative Care

Other than the potential for late development of recurrent pulmonary venous obstruction, these patients generally do well and have good cardiovascular reserve once recovery from the surgery is complete.[154] The size of the pulmonary veins at birth may be a predictor of late complications with recurrent pulmonary vein stenosis.[155]

Atrial Septal Defect

Pathophysiology

There are three anatomic varieties of ASD. The most common, ASD secundum, is a deficit in the septum primum, which ordinarily covers the region of the foramen ovale. ASD primum is a deficit of the inferior portion of the atrial septum (endocardial cushion) usually accompanied by a cleft in the anterior leaflet of the mitral valve. Sinus venous defects are located near the junction of the right atrium and the SVC or IVC. They frequently are associated with a partial anomalous pulmonary venous connection.

Left-to-right shunting (simple) occurs at the atrial level, causing a low-pressure volume load to the right ventricle. Pulmonary blood flow is increased, but generally not enough to make these patients symptomatic during early childhood. However, later in life, as the left ventricle becomes less compliant and the LA pressures increase, the left-to-right shunt and volume load increase and symptoms of CHF may occur. In rare patients the long-standing increase in pulmonary blood flow causes pulmonary vascular obstructive disease.[156]

Critical Care Management

The defect can be closed directly with sutures or, if it is sufficiently large, with a synthetic patch. Sinus venosus defects associated with partial anomalous pulmonary venous connection require a more extensive patch that also directs the partial anomalous pulmonary venous return into the left atrium.

These patients are among the healthiest encountered in the cardiac intensive care unit. Early tracheal extubation is usual. Atrial arrhythmias, including atrial flutter and atrial fibrillation, are rarely seen during the postoperative period. Mitral regurgitation may occur in patients who have undergone repair of an ASD primum. Although transient LV failure has been reported, these patients rarely require inotropic support. Residual ASDs are uncommon, but occasionally failure to recognize partial anomalous pulmonary venous return results in a residual left-to-right shunt. Most patients can be extubated during the immediate postoperative period or in the operating room. With the exceptions mentioned, these patients usually have nearly normal cardiovascular function and reserve after repair.

Ventricular Septal Defect

Pathophysiology

Defects in the ventricular septum occur at several locations in the muscular partition dividing the ventricles. Simple shunting occurs across the ventricular septum. The magnitude of pulmonary blood flow is determined by the size of the VSD and the PVR.[157] With a nonrestrictive defect, high LV flows and pressures are transmitted to the pulmonary artery. Therefore surgical repair is indicated within the first 2 years of life to prevent the progression of pulmonary vascular obstructive disease.[49] In patients with established pulmonary vascular disease, the pulmonary arteriolar changes may not recede when the defect is closed. In such cases, there may be progressive PVR elevation.[158,159] The growth and development of the pulmonary vascular bed are significant factors in the patient's ability to normalize pulmonary vascular hemodynamics after surgery.[160] When PVR approaches or exceeds systemic vascular resistance, right-to-left shunting occurs through the VSD and the patients develop progressive hypoxemia (Eisenmenger syndrome). Closing the VSD in this circumstance adds the risk for acute right heart failure to that of progressive increases in PVR.

Critical Care Management

The defects are closed during CPB. The most common septal defect, the membranous defect, is often repaired through a right atriotomy and the TV. However, lesions in the inferior apical muscular septum or those high in the ventricular outflow tract may require a left or right ventriculotomy. If so, postoperative ventricular function may be impaired.

Before repair, measures that decrease PVR may appreciably increase left-to-right shunting in patients with a nonrestrictive defect and may increase the degree of CHF. Postoperative RV or LV failure may be a manifestation of the preoperative status of the myocardium, a result of the ventriculotomy and CPB, or both. Small infants who fail to thrive, who are malnourished, and who have significant CHF preoperatively may have excessive lung water and may require prolonged mechanical ventilation postoperatively.[161] Such infants may have limited intraoperative tolerance for anesthetics that depress the myocardium or for maneuvers that increase pulmonary blood flow.

Persistent CHF and an audible murmur postoperatively, evidence of low cardiac output, or the need for extensive inotropic support intraoperatively suggests that a residual or previously unrecognized additional VSD is continuing to place a volume and pressure load on the ventricles. When PVR is increased preoperatively, the increase in RV afterload caused by closure of the VSD may be poorly tolerated, leading to the need for inotropic support of the heart and measures to decrease PVR. Occasionally ventricular outflow tract obstruction is caused by placement of the septal patch. Transesophageal echocardiography performed in the operating room is an important tool in diagnosing this problem so it can be addressed before complete separation from CPB. Aortic regurgitation caused by prolapse of one of the aortic valve cusps can develop in subaortic or subpulmonic VSDs. In addition, heart block may occur after closure of VSDs with a patch. A pacemaker may be needed to maintain an adequate heart rate and cardiac output.

Critical Care Management for Late Postoperative Care

In the absence of residual VSDs, outflow obstruction, and heart block, most of these patients regain relatively normal myocardial function, especially if the VSD is repaired early.[162] However, a small percentage of patients, especially those in whom a large defect was repaired late in childhood, continue to have some degree of ventricular dysfunction and some pulmonary hypertension.[163]

Atrioventricular Canal Defects

Pathophysiology

The endocardial cushion defect, or complete common AV canal, consists of defects in the atrial and ventricular septa and the AV valvular tissue. All four chambers communicate and share a single common AV valve. The atrial and ventricular shunts communicate volume and systemic pressures to the right ventricle and pulmonary artery. The ventricular shunt orifice usually is nonrestrictive (simple shunt); therefore PVR governs the degree of excess pulmonary blood flow. Mitral regurgitation and direct left-ventricular-to-right-atrial shunting may further contribute to atrial hypertension and total left-to-right shunting.

Critical Care Management

Surgical repair of this lesion consists of division of the common AV valve and closure of the ASD and VSD with a single patch. In addition, the mitral valve (and sometimes the TV) requires suture approximation and resuspension of the separated portions.

Before surgical repair, these patients have large left-to-right shunts. As a result of their high pulmonary blood flows, they have CHF and pulmonary hypertension. Myocardial depressants and therapies that decrease PVR while increasing shunt flow may be poorly tolerated before repair. Some patients, especially older children, may have obstructive pulmonary vascular disease. All of the potential complications of ASD and VSD closures are seen in these patients. In addition, the mitral valve may be severely regurgitant.[164] Inotropic support for the failing heart, afterload reduction for mitral regurgitation, and measures to decrease PVR may be required intraoperatively and postoperatively after repair.

Patients with Down syndrome frequently have an associated complete AV canal. Measures to decrease PVR and the use of prolonged ventilatory support are often necessary because their airways and pulmonary vascular beds tend to be hyperreactive. The large tongues, hypotonia, upper airway obstruction, and difficult vascular access of these patients pose additional problems. The most frequent postoperative problems in patients with Down syndrome are residual VSDs, mitral insufficiency,[165] and pulmonary hypertension.[10]

Patent Ductus Arteriosus

Pathophysiology

The ductus arteriosus is a fetal vascular communication between the main pulmonary artery at its bifurcation and the descending aorta below the origin of the left subclavian artery. When patent, it provides a simple shunt between the systemic and pulmonary arteries. The magnitude and direction of flow between the systemic and pulmonary vessels are determined by the relative resistances to flow in the two vascular beds and the diameter (resistance) of the ductus itself. With a large, nonrestrictive ductus and low PVR, the pulmonary blood flow is excessive and the volume load of the left heart is large. Systolic and diastolic flow away from the aorta may steal blood from vital organs (e.g., pulmonary steal) and compromise end-organ function at many sites.[166] In addition, overcirculated lungs and elevated LA pressure increase the work of breathing.[167,168]

Critical Care Management

Although the PDA of premature infants can often be closed medically with indomethacin, contraindications to use of this agent (e.g., intracranial hemorrhage, renal dysfunction, and hyperbilirubinemia) may require surgical closure of the defect.[169] Whereas thoracotomy and surgical ligation of the ductus arteriosus are standard in older infants and children, some centers now occlude the ductus with a percutaneously inserted vascular umbrella[170] or by using video-assisted thoracoscopic surgery.[171] Advantages of video-assisted thoracoscopic surgery compared with open thoracotomy include decreased postoperative pain, shorter hospital stay, and decreased incidence of chest wall deformity.[172]

Healthy asymptomatic patients undergoing surgery can be extubated in the operating room, allowing many options for anesthetic management. However, the fragile premature infant with severe lung disease may require mechanical ventilation for protracted periods after ligation of the ductus arteriosus. Fentanyl, pancuronium, oxygen, and air constitute a common anesthetic regimen for this procedure.[173] Management of the premature infant in the operating room requires special considerations of gas exchange, hemodynamic performance, temperature regulation, metabolism, and drug and oxygen toxicity. Thoracotomy and lung retraction usually decrease lung compliance and increase oxygen and ventilatory requirements. A transient rise in systemic blood pressure with ligation of the ductus arteriosus may increase LV afterload or elevate cerebral perfusion pressure to the detriment of a premature patient. Inadvertent ligation of the left pulmonary artery or descending aorta has occurred because the ductus arteriosus is often the same size as the descending aorta.

The ductus is located near the recurrent laryngeal nerve (RLN), which may be damaged during the procedure. In addition to the close relationship of the RLN to the PDA and descending aorta, the RLN has a variable course that may be difficult to identify during dissection. Prior reports of PDA ligation performed by open thoracotomy indicate that the incidence of RLN injury is 1.2% to 8.8%.[174,175] RLN paralysis causes hoarseness and is not detected until the endotracheal tube is removed. The incidence may be reduced by location of the RLN within the thorax before ligation or clip placement using direct intraoperative stimulation of the RLN and evoked electromyogram monitoring.[176]

Ligation of an isolated ductus arteriosus generally results in normal cardiovascular function and reserve several months postoperatively.[177]

Truncus Arteriosus

Pathophysiology

With truncus arteriosus the embryonic truncus fails to separate normally into the two great arteries. A single great artery leaves the heart and gives rise to the coronary, pulmonary, and systemic circulations. The truncus straddles a large VSD and receives blood from both ventricles.

Complete mixing of systemic and pulmonary venous blood in the single great artery causes mild hypoxemia. One or two pulmonary arteries may originate from the ascending truncus; the pulmonary artery orifice is seldom restrictive. The resulting shunt (simple) produces excessive pulmonary blood flow early in life as the PVR decreases. This "pulmonary steal" may elevate the arterial oxygen saturation and decrease the systemic blood flow. In such a case, net systemic oxygen transport decreases and lactic acidosis develops. Children with truncus arteriosus are at risk for developing early pulmonary vascular obstructive disease.[178] Regurgitation of blood through the truncal valve may place an additional volume load on the ventricles.

Critical Care Management

Complete repair of this lesion should be performed early, even in the neonate, before the development of irreversible pulmonary vascular changes.[5,179] The VSD is closed with a synthetic patch, and the pulmonary arteries are detached from the truncus. Continuity is established between the right ventricle and the pulmonary arteries with a valved conduit.[180] The truncal valve may require valvuloplasty if a significant amount of blood regurgitates through it.

Critical care management preoperatively centers around control of pulmonary blood flow and ventricular support. Pulmonary blood flow may increase further with anesthetic agents, hyperventilation, alkalosis, and oxygen administration, resulting in hypotension and acute ventricular failure. If measures for *increasing* PVR do not decrease pulmonary flow, temporary occlusion of one branch of the pulmonary artery with a tourniquet limits pulmonary flow and restores systemic perfusion pressure until CPB can be instituted. Because these patients are often in high-output CHF, myocardial depressants should be used with caution.

Immediately after repair, the combination of persistent pulmonary artery hypertension and RV failure can be fatal. Hence, aggressive measures should be taken to provide adequate myocardial function and lower PVR. A residual VSD adds volume and pressure load on the ventricles and may have a devastating impact on the patient's hemodynamics and oxygenation. A VSD should be suspected in patients who are not doing well postoperatively. Any residual VSD should be repaired if feasible. Truncal valve regurgitation or stenosis may induce LV failure early during the postoperative period.

Critical Care Management for Late Postoperative Care

Obstruction of the pulmonary conduit and the accompanying RV hypertension may occur early or late during the postoperative course. Usually the conduit is unable to support flow in the growing child after several postoperative years. Late development of truncal (aortic) valve regurgitation is possible. For patients who underwent repair later in childhood, residual persistent pulmonary hypertension may be a problem.

Left-Sided Obstructive Lesions

Pathophysiology

This category includes valvar, subvalvar, and supravalvar mitral and aortic stenosis (AS), aortic coarctation, and IAA. Although these lesions can occur as isolated defects, they often are accompanied by other congenital cardiac defects. Identification of additional structural defects is necessary for optimal preoperative, surgical, and postoperative treatment.

Patients with LV outflow tract obstruction tend to present as either neonates or young infants with significant LV dysfunction and CHF or later in childhood with LV hypertrophy but few symptoms. The dramatic presentation of a neonate with circulatory collapse typically occurs with lesions that obstruct systemic blood flow so severely that right-to-left shunting at the ductus arteriosus is required to perfuse the body. As the ductus significantly narrows or closes, the left ventricle becomes acutely pressure overloaded and begins to fail, leading to pulmonary edema and respiratory distress. When systemic perfusion becomes inadequate, the patient develops hypotension, weak pulses, metabolic acidosis, and oliguria. Classic examples include severe (or "critical") valvar AS, coarctation of the aorta, and HLHS (see earlier single ventricle discussion).

If the obstruction is less severe, the child can make the transition through ductal closure without notable LV dysfunction and maintain an adequate cardiac output. Over time, however, the pressure overload on the LV stimulates generalized hypertrophy. If untreated and significant, long-term pressure overload can cause LV diastolic dysfunction (compliance falls and end-diastolic pressure rises, causing pulmonary venous hypertension), LV systolic dysfunction, and episodic myocardial ischemia. Clinical manifestations of these changes can include reduced exercise tolerance, exertional chest pain, ventricular dysrhythmias, syncope, and sudden death. Significant LV dilation and/or clinical signs of CHF are ominous findings associated with a poor prognosis and an increased surgical mortality rate.

Aortic Stenosis

Of the three anatomic subtypes of AS, valvar AS occurs more frequently than subvalvar or supravalvar AS. The newborn with critical valvar AS who develops hypotension and acidosis as the ductus arteriosus closes requires resuscitation with PGE_1 to restore aortic flow plus mechanical ventilation and inotropic support to achieve stabilization before an intervention is performed. Currently, balloon dilation of the stenotic aortic valve during cardiac catheterization is the preferred intervention at many centers.[181] A surgical valvotomy under direct vision using CPB is the surgical alternative. Despite successful relief of obstruction, significant LV dysfunction and low cardiac output often persist for days after the procedure and require continued treatment with mechanical ventilation and vasoactive drugs. Until LV function recovers and can support the entire cardiac output, continuation of prostaglandin infusion may be necessary to maintain patency of the ductus arteriosus. Patients should be carefully evaluated after balloon aortic valvuloplasty for residual AS and aortic regurgitation, the chief potential complication of valve dilation, especially if cardiac output does not improve over several days.

Older infants, children, and adolescents with moderate (pressure gradient 50-70 mm Hg at catheterization) or severe

(pressure gradient >70 mm Hg at catheterization) valvar AS also are generally good candidates for balloon aortic valvuloplasty. If more than mild aortic regurgitation coexists with AS, however, a surgical intervention is preferred to balloon valvuloplasty.

The pathophysiology produced by all types of aortic outflow obstruction is similar, that is, the pressure-overloaded LV becomes progressively hypertrophied and develops reduced compliance and an abnormally elevated end-diastolic pressure.

Initial assessment of obstruction relief can occur when the patient is still in the catheterization laboratory or operating room by either direct pressure measurements or echocardiography. Nevertheless, reevaluation for residual obstruction by physical examination and/or echocardiography in the ICU as patients recover from anesthesia and baseline physiology returns is important because outflow gradients can change. A significant residual obstruction should be suspected in any patient with persistent low cardiac output after the intervention. Poor recovery of LV function after surgery can occur secondary to inadequate myocardial protection with cardioplegia in hearts with significant ventricular hypertrophy. Patients with marked hypertrophy are also at greater risk for developing VT and ventricular fibrillation early after surgery.

In patients with preserved LV systolic function who undergo an uncomplicated procedure, such as aortic valvuloplasty or subvalvar membrane resection, myocardial recovery after CPB is typically rapid and inotropic support is usually not required. Systemic hypertension is more common after relief of LV outflow obstruction, especially during emergence from anesthesia and sedation. Antihypertensive therapy in the initial 24 to 48 hours may be necessary to prevent aortic suture line and reconstructed valve leaflet disruption from excessive stress and to allow adequate hemostasis. Both beta-blockers (e.g., labetalol, propranolol, and esmolol) and vasodilators (e.g., nitroprusside), alone or usually in combination, are effective for lowering blood pressure in these patients.

In addition to assessing aortic valve and LV function, an evaluation for complications specific to each procedure is required. For example, if a myectomy is required as part of the resection of fibromuscular subvalvar AS, the possibility of a new VSD, mitral valve injury, and left bundle branch block should all be assessed. After the Ross procedure, it is important to assess patients for RV outflow tract and LV outflow tract obstruction, because the RV outflow tract is also reconstructed with a valved conduit.

Coarctation of the Aorta

Coarctation of the aorta is a constriction in the descending aorta located at the level of insertion of the ductus arteriosus. Narrowing of the aortic lumen is asymmetric, with the majority of the obstruction occurring because of posterior tissue infolding, leading to the common description of a posterior aortic "shelf." Depending on the severity of constriction, patients can present as neonates with severe obstruction (a "critical" coarctation of the aorta) upon ductal closure, as infants with CHF, or as children/adolescents with no symptoms except for upper body hypertension (especially with exercise).

Neonates presenting with critical coarctation of the aorta can often be distinguished clinically from patients with critical AS by their clearly discrepant upper versus lower body pulses, perfusion, and blood pressures. Other features at presentation, including evidence of CHF and inadequate blood flow to tissues, are similar. Because ductal narrowing or closure is common after hospital discharge, these patients often become critically ill and suffer end-organ damage before the ductus arteriosus can be reopened and resuscitation accomplished. Intestinal and renal ischemia leading to necrotizing enterocolitis and renal failure, respectively, are well-known complications of critical coarctation of the aorta. Echocardiography often reveals additional left-sided defects such as bicuspid aortic valve, valvar AS, aortic arch hypoplasia, and VSD. Preoperative management includes treatment with PGE_1 plus mechanical ventilation, inotropic agents, and diuretic agents, as needed, and adequate time for end-organ recovery before performing an intervention.

Coarctation of the aorta also occurs in association with complex defects such as D-transposition of the great arteries, single ventricle, and complete AV canal defect. If the ductus arteriosus is patent during echocardiographic evaluation of a neonate with suspected CHD, it often is not possible to predict the severity of coarctation of the aorta with confidence. A patient can have an abnormally narrowed aorta just proximal to the site of ductal insertion (i.e., the aortic isthmus) and a posterior shelf but still not develop a severe coarctation of the aorta after ductal closure. Therefore evaluation of the potential severity of coarctation of the aorta in the ICU often involves a strategy of close monitoring for aortic obstruction without PGE_1 to allow the PDA to close, followed by clinical and echocardiographic reassessment. An intervention to reduce aortic obstruction is indicated in any neonate with clinical or echocardiographic evidence of reduced ventricular function or impaired cardiac output. These indications are more important than the systolic blood pressure difference between upper and lower body per se, although differences greater than 30 mm Hg often are accompanied by diminished ventricular function.

The postoperative management of patients after surgical repair of coarctation of the aorta can vary depending on age at intervention. However, the key issues for assessment in all patients are adequate relief of obstruction and preservation of spinal cord function. Upper and lower body blood pressures and pulses should be compared serially and the lower extremities monitored closely for the return of sensation and voluntary movement in the early postoperative period. Equal pulses and a reproducible systolic blood pressure difference less than 10 to 12 mm Hg between upper and lower extremities indicate an excellent repair. Neonates and young infants typically require 1 to 2 days of mechanical ventilation after repair, and they are more likely to receive inotropic agents, especially if ventricular function was diminished before surgery. Older children and adolescents can frequently be extubated in the operating room and rarely require inotropic support. In fact, these patients are increasingly likely with older age at repair to have significant hypertension,[182] which should be treated aggressively early after surgery to reduce the risk of aortic suture disruption and bleeding. Beta-blockers and vasodilators, along with adequate analgesia and sedation, are effective. Patients with long-standing coarctation of the aorta frequently have persistent systemic hypertension despite an adequate repair; continued treatment with angiotensin-converting enzyme inhibitors is advocated to achieve normal blood pressures.

Four uncommon complications are associated with surgical repair of coarctation of the aorta. Postcoarctectomy syndrome

manifests as abdominal pain and/or distension in older patients and is presumed to be caused by mesenteric ischemia from reflex vasoconstriction after restoration of pulsatile aortic flow. Recurrent laryngeal nerve and phrenic nerve trauma can cause vocal cord paralysis and hemidiaphragm paresis or paralysis, respectively, with neonates and infants at highest risk. Disruption of lymphatic vessels or thoracic duct trauma can produce a chylous effusion that may require treatment by drainage and/or dietary modification.

Catheter-directed balloon angioplasty is used to treat both native and residual coarctation of the aorta.[183] The results of native coarctation of the aorta dilation after early follow-up appear similar to published surgical results, but aortic aneurysm formation has been reported.[184] Balloon angioplasty of recurrent coarctation of the aorta after surgery is effective and is generally preferred to reoperation.

Interrupted Aortic Arch

Patients with IAA typically present as neonates with either a loud systolic murmur or circulatory compromise as the ductus arteriosus closes. Therefore patient presentation can be similar to other severe left-sided obstructive lesions such as critical AS, critical coarctation of the aorta, and HLHS. Unlike either critical AS or coarctation of the aorta, however, severe pressure overload on the LV does not occur in the presence of an unrestrictive VSD, which functions as a "pop off" for LV outflow. The approach to resuscitation is similar to that described for the other ductal-dependent left-sided obstructive lesions, with attention to the possibility of pulmonary overcirculation as for HLHS.

Postoperative management issues specific to patients with IAA include assessment of possible residual left-sided obstruction, both in the aortic arch and in the subaortic region, shunting across a residual VSD, hypocalcemia (related to DiGeorge syndrome), dysrhythmias, and LV dysfunction with low cardiac output secondary to global effects of CPB and DHCA. Left-lung hyperinflation on postoperative chest radiographs suggests compression of the left mainstem bronchus. This complication tends to occur after difficult arch reconstructions when tension on the aorta causes it to press on the anterior surface of the bronchus, thus producing distal air trapping.

Hypoplastic Left Heart Syndrome

Pathophysiology. Among the congenital heart lesions, perhaps the most controversial has been management of HLHS. HLHS is a uniformly fatal disease if left untreated, and debates continue over a staged palliation, versus neonatal transplantation, versus comfort care alone. The results of surgical management vary among institutions and are clearly dependent upon expertise and experience,[184] the clinical condition of the neonate at presentation,[185] prematurity, multiple congenital anomalies, presence of an intact atrial septum, later age of presentation,[186] and degree of hypoplasia of left heart structures.[187,188]

This common example of single-ventricle physiology also represents the most severe form of obstructive left heart lesion. An anatomic spectrum of disease is implied for the lesion, but in its most severe and common presentation there is atresia or marked hypoplasia of the aortic and mitral valves with critical underdevelopment of the left atrium, left ventricle, and ascending aorta. A 1- or 2-mm ascending aorta gives rise to the coronary circulation and the head vessels before converging with the ductus arteriosus, where the aorta becomes larger and supplies the circulation to the lower body. Pulmonary venous return arrives in the diminutive LA and cannot cross the atretic mitral valve; therefore it is directed to the RA and RV, where common mixing occurs with the systemic venous return and all blood is ejected into the pulmonary artery. Systemic blood flow is then supplied from the pulmonary artery, right-to-left, across the PDA. As the PDA constricts in the neonatal period, systemic blood flow decreases and all ventricular output is directed to the lungs. The Q_p/Q_s ratio approaches infinity as Q_s nears zero. Therefore the paradoxical presentation of high Po_2 (70-150 mm Hg) in the face of shock and profound metabolic acidosis is seen. When the ductus arteriosus is reopened with PGE_1, systemic perfusion is reestablished, the acidosis resolves, and the Po_2 returns to the range of 40 to 60 mm Hg, representative of a Q_p/Q_s ratio between 1 and 2.

Critical Care Management. Adequate preoperative resuscitation with PGE_1 and correction of metabolic acidosis and end-organ dysfunction are crucial to the preparation and management of patients with this lesion. Further facilitation of resuscitation can be enhanced by judicious use of inotropic agents, which can optimize cardiac output and blood flow to organs such as the kidneys. However, excessive delay in the timing of surgical intervention results in gradual reduction in PVR over days, with excessive pulmonary blood flow and inadequate systemic perfusion. The surgical reconstructive approach to this lesion now commonly entails three operations that ultimately aim to provide a 2- to 5-year-old child with a reconstructed aortic arch and a Fontan-type circulation for single-ventricle physiology.[188,189] In the first stage of the reconstruction (Norwood operation),[190] the pulmonary artery is transected at the bifurcation and an anastomosis is performed to the ascending aorta, which has been surgically incised so that the aortic and pulmonary arterial confluence arises together from the single right ventricle as the neoaorta, which is extended into the remaining native aorta using homograft material. Pulmonary blood flow is established with a modified Blalock-Taussig shunt, usually 3.5 mm in diameter. The atrial septum is excised to ensure free flow of pulmonary venous return over to the TV. In addition to HLHS, the Norwood operation is used to repair other complex single-ventricle defects with systemic outflow obstruction or hypoplasia.[191]

The critical care considerations are the same as those outlined for patients with single-ventricle physiology. Perioperative management requires careful manipulation of PVR and SVR and support of ventricular function to provide adequate, but not excessive, pulmonary blood flow and systemic oxygen delivery while maintaining sufficient systemic and coronary artery perfusion.

Postoperative Management

Evolution of treatment strategies. Common teaching has held that postoperative mortality and hemodynamic lability are attributable to myocardial dysfunction and the physiologic burden imposed by a shunt-dependent pulmonary circulation in parallel with systemic blood flow. Treatment strategies have emphasized factors that may affect the balance between pulmonary and systemic blood flow. Immediately after a Norwood operation, PVR may be transiently elevated but

soon decreases. Once PVR falls, treatment is aimed at raising resistance to blood flow through the lungs and redirecting cardiac output to the systemic circulation. High inspired concentration of oxygen, hyperventilation, alkalosis, systemic vasoconstriction, and anemia will cause further increase in pulmonary blood flow and should be avoided. Therapies designed to raise PVR and thereby direct aortic blood flow to the systemic circulation have focused on lowering the FIo_2 or allowing the $Paco_2$ to rise with the pH falling toward 7.3. Further measures, such as ventilation with hypoxic gas mixtures or added carbon dioxide, have been advocated by some centers and have been intermittently embraced and abandoned by others. Validation of the effectiveness of these techniques to balance the pulmonary and systemic circulations has been difficult.

The clinical focus on caring for the newborn who has undergone Norwood palliation for HLHS has evolved in stages over the past 20 years. The early emphasis was on manipulating the PVR by optimizing mechanical ventilation (i.e., mean airway pressure, tidal volume, rate and inspiratory time, FIo_2, and Pco_2). It soon became apparent that the majority of this effort was aimed in the postoperative period to raise PVR and lower pulmonary blood flow while increasing systemic blood flow. Like any therapeutic strategy, manipulating gas exchange and inspired gases had its own set of adverse effects. High FIo_2 has well-defined pulmonary toxicity that may appear in a matter of days or even hours after exposure. Use of low FIo_2 (below room air concentrations) to raise PVR transiently and stabilize patients is both counterintuitive and a relatively uncommon therapy in clinical medicine. Whether iatrogenically induced or as part of a pathologic process, alveolar hypoxia can be life threatening when aggravated by unexpected hypoventilation. A mechanically ventilated and sedated patient on an FIo_2 less than 0.21 has little safety margin for dangerous hypoxemia even in the most intensively monitored environments. Excellent animal models of chronic pulmonary hypertension are produced by relatively brief exposure to hypoxic gas. A newborn breathing hypoxic gas mixtures in the preoperative period of stabilization may have a favorable response by raising PVR and diminishing pulmonary blood flow. However, if this treatment is prolonged during preparation for reconstructive or transplantation surgery, the caretakers may be frustrated by subsequent elevation in PVR that persists during and after weaning from CPB.

In centers where neonates are allowed to awaken and breathe spontaneously during the immediate postoperative period, pulmonary blood flow may become excessive and further stimulate hyperventilation and respiratory alkalosis. Adding carbon dioxide to the inspired gas may reverse this trend toward respiratory alkalosis and stabilize the relative balance of the pulmonary and systemic circulations if the forces that drive minute ventilation are suppressed with agents for sedation or analgesia. However, the metabolic cost of carbon dioxide breathing in an awakening child given little analgesia may discourage widespread application of this technique until the physiologic advantage over conventional means of controlling alveolar ventilation and $Paco_2$ has been demonstrated. This is especially true in unsedated, preoperative patients where factors controlling respiration during carbon dioxide breathing may permit minimal change of $Paco_2$ but substantially increase the respiratory rate and work of breathing.

The introduction of a 3.5-mm systemic-to-pulmonary shunt (rather than a 4-mm shunt) and the appreciation of the surgical complexity of an appropriately placed shunt did as much to reduce excessive pulmonary blood flow in the infants as did manipulation of the ventilator. Although the smaller shunts were associated with a rare but real incidence of shunt thrombosis, those involved in postoperative care found patient management with a small shunt substantially easier than struggling with a 4-mm shunt off of an innominate artery. By the late 1980s, it was apparent that this palliated circulation was required for only 10 to 12 weeks to reach an adequate patient size for the newly applied second stage of the procedure (bidirectional Glenn) to be performed. Therefore a relative increase in cyanosis (from a smaller shunt) was believed to be a justifiable price for more stable early postoperative hemodynamics. However, mortality rates did not plummet with the recognition of the advantage of smaller shunts and manipulating PVR, although by then many more centers were undertaking a staged reconstructive approach to HLHS. In the early 1990s, attention was redirected to the observation, that arterial oxygen saturation was only one variable in the assessment of Q_p/Q_s and that a perfectly "acceptable" arterial oxygen saturation of 80% in this disease may represent severe pulmonary overcirculation if the mixed venous oxygen saturation was only 20%. Hence a renewed interest in measuring and monitoring arterial and mixed venous oxygen saturations emerged. Thus in overcirculated patients with a small (3.5 mm) fixed-diameter shunt off of the subclavian artery, there was less emphasis on micromanagement of PVR and more interest in pharmacologically supporting cardiac output while reducing the *systemic* afterload to diminish the driving pressure across the shunt. Use of the alpha-blocker phenoxybenzamine has been advocated by some for blunting systemic vascular reactivity and dilating the peripheral circulation,[192] but its potent, long-lasting effects and associated hypotension that is not ameliorated by the usual alpha-agonist vasoactive agents can be challenging. The phosphodiesterase inhibitors then enjoyed a new and extensive application in pediatric critical care: lowering SVR, increasing cardiac output, and lowering filling pressures. The new strategy was to monitor (arteriovenous) Do_2, support cardiac output, and reduce SVR.

Later in the decade, the observation of limited coronary reserve, low mixed venous oxygen saturation, rising lactate, and hemodynamic collapse in the first 48 hours helped emphasize the fundamental limitation of myocardial function and cardiac output in the early postoperative period. The morphologic right ventricle and TV seem ill suited to support adequate systemic plus pulmonary blood flow. Several centers then embraced mechanical support of the circulation temporarily for the failing Norwood patient in the early postoperative period.

Specific considerations for the Norwood operation. Management of patients after a Norwood-type operation is complex. Intensive monitoring is essential because the patient's clinical status can change abruptly with rapid deterioration. Persistent or progressive metabolic acidosis is a bad prognostic sign and must be aggressively managed. Considerations in the assessment of the circulation after the Norwood operation are given in Table 31-10.

Ideally the pH should be 7.40, $Paco_2$ 40 mm Hg, and Pao_2 40 mm Hg in room air, with a mixed venous O_2 saturation

Table 31–10 Management Considerations for Patients Following a Norwood Procedure

Scenario	Etiology	Management
Sao_2 ~80%		No intervention
Svo_2 ~60%	Balanced flow	
Normotensive	$Q_p = Q_s$	
Sao_2 >90%		Raise PVR
Hypotension	OVERCIRCULATED $Q_p = Q_s$ Low PVR Large BT shunt Residual arch obstruction	Controlled hypoventilation Low Fio_2 (0.17–0.19) Add CO_2 (3%–5%) Increase systemic perfusion Afterload reduction, vasodilation Inotropic support Surgical shunt revision
Sao_2 <75%		Lower PVR
Hypertension	UNDERCIRCULATED $Q_p < Q_s$ High PVR Small, kinked, thrombosed BT shunt	Controlled hyperventilation Alkalosis Sedation/paralysis Increase cardiac output Inotropic support Hematocrit >40% Surgical interventon
Sao_2 <75% Hypotension Low Svo_2	Low cardiac output Ventricular failure Myocardial ischemia Residual arch obstruction Atrioventricular valve regurgitation	Minimize stress response Inotropic support Surgical revision Consider mechanical support Consider transplantation

BT, Blalock-Taussing; *Fio_2,* inspired oxygen concentration; *PVR,* pulmonary vascular resistance; *Q_p,* pulmonary blood flow; *Q_s,* systemic blood flow; *Sao_2,* arterial oxygen saturation; *Svo_2,* mixed venous oxygen saturation.

of 60% reflecting a well-balanced circulation. Higher saturations can be achieved if the systemic circulation is well dilated without compromising perfusion pressure. Frequent changes in mechanical ventilation settings and FIo_2 may be necessary in the first few hours after surgery. However, manipulations of FIo_2 in the face of a restrictive 3.5-mm shunt may have less impact on pulmonary blood flow than would systemic vasodilation.[193] Leaving the sternum open after surgery may facilitate lower filling pressures, a balanced circulation, and stable ventilation pattern.

Deep sedation or even muscle paralysis and anesthesia often are continued after surgery to minimize the stress response until the patient has a stable circulation and gas exchange. Inotropic support with dopamine and occasionally low doses of epinephrine usually are required, titrated to systemic pressure and perfusion. Afterload reduction with milrinone as second-line agents is beneficial to reduce myocardial work and improve systemic perfusion. Monitoring SVC O_2 saturations, as a measure of mixed venous O_2 saturation (Svo_2) and cardiac output, is useful in this assessment.[194] Volume replacement to maintain preload is essential, aiming for a common atrial pressure approximating 10 mm Hg.

The type, diameter, length, and position of the shunt affects the balance of pulmonary and systemic flow. Generally, a 3.5-mm modified Blalock-Taussig shunt from the distal innominate artery provides adequate pulmonary blood flow without excessive steal from the systemic circulation for most full-term neonates. Nevertheless, a shunt resulting in a low diastolic pressure (<30 mm Hg) in turn affects perfusion to other vascular beds, particularly the coronary, cerebral, renal, and splanchnic perfusion. This may contribute to a prolonged and difficult postoperative course.

Overcirculation in the immediate postoperative period with an Sao_2 greater than 90% may reflect a low PVR or increased flow across the shunt if the shunt size is too large or the perfusion pressure increased from residual aortic arch obstruction distal to the shunt insertion site. The increased volume load on the systemic ventricle results in congestive cardiac failure and progressive systemic hypoperfusion with cool extremities, oliguria, and possibly metabolic acidosis. Although manipulation of mechanical ventilation and inspired oxygen concentration may help limit pulmonary blood flow, surgical revision to reduce the shunt size may be necessary.

If there is significant diastolic runoff through a large shunt, coronary perfusion may be reduced and lead to ischemia, low output, arrhythmias, and cardiac arrest. Rhythm disturbances are uncommon in the immediate postoperative period after a Norwood operation, and a sudden loss of sinus rhythm, and particularly heart block or ventricular fibrillation, should increase the suspicion of myocardial ischemia.

In the immediate postoperative period, mild hypoxemia with a Sao_2 of 70% to 75% and Pao_2 of 30 to 35mm Hg is preferable to an overcirculated state with high systemic oxygen saturations and falling mixed venous oxygen saturation. Pulmonary blood flow often increases on the first postoperative day as ventricular function improves and PVR falls during recovery from CPB. Pulmonary venous desaturation from parenchymal lung disease such as atelectasis, pleural effusions, and pneumothorax requires aggressive management.

Persistent desaturation and hypotension reflects a low cardiac output from poor ventricular function, thereby decreasing the perfusion pressure across the shunt. Svo_2 is low (often <40%), and treatment directed first at augmenting contractility with inotropic agents and subsequently reducing afterload with a vasodilator. This is a serious clinical problem with a high mortality after a Norwood operation. The related myocardial ischemia and acidosis further impair myocardial function and systemic perfusion, leading to circulatory collapse.

Atrioventricular valve regurgitation and residual aortic arch obstruction are important causes of persistent low cardiac output and inability to wean from mechanical ventilation. Echocardiography is useful for assessing valve and ventricular function but is less accurate for assessing the degree of residual arch obstruction. Cardiac catheterization is sometimes necessary and will enable fine-tuning of hemodynamic support or balloon dilation of a hypoplastic segment of narrowed aorta. Occasionally, surgical revision of the aortic arch or atrioventricular valve is necessary, although this is seen more commonly in the interval before the bidirectional cavopulmonary shunt.

A more recent modification of the Norwood procedure involves placement of conduit from the right ventricle to the

PA confluence (RVPA shunt).[195-197] The primary advantage of this procedure in the immediate postoperative period is improved diastolic perfusion without runoff across an aortopulmonary shunt. Ventricular function is less likely to be compromised after surgery because the volume load to the ventricle is reduced from a lower Q_p/Q_s, along with a reduced risk for myocardial ischemia because of improved coronary perfusion. Perfusion to cerebral, renal, and splanchnic circulations also is likely to be improved with the lack of diastolic runoff to the pulmonary circulation, which may enhance postoperative recovery. Because pulmonary blood flow occurs only during ventricular systole across the right ventricle to pulmonary artery conduit, there may be a critical reduction in pulmonary blood flow and excessive hypoxemia, especially during periods of low cardiac output or if there is dynamic obstruction to flow at the ventricular insertion site. Efforts to overcome this limitation by creating a larger RV incision run the longer-term risk of ventricular dysfunction, arrhythmias or aneurysm formation.

A recent multicentric, randomized, controlled trial involving 549 neonates with HLHS demonstrated a significantly improved transplantation free survival for patients randomized to receive a RVPA shunt compared to those palliated with a modified Blalock-Taussig shunt (74% vs. 64%, $P = .01$).[198] Moreover, major concerns about the potential for harmful effects of the right ventriculotomy proved to be unwarranted, at least at early follow up, although additional, unplanned interventions were more frequent in the RVPA shunt group to maintain shunt patency. The major benefit of the RVPA shunt seems to be an increased survival rate in the early period after the procedure, but longerterm follow-up will be required to assess effects beyond the 12-month period assessed in this trial.[198] The short-term survival advantage of the Sano modification of the Norwood operation for centers where mortality rate after the Norwood operation already was below 15% will be hard to demonstrate.

Orthotopic heart transplantation has gained acceptance as an alternative treatment for HLHS.[199] Neonatal transplants appear to be well tolerated, and some centers have avoided maintenance steroid therapy while achieving excellent midterm results using transplantation as the sole therapeutic option for this disease.[199,200] Others have successfully advocated a combined approach using either transplantation or staged reconstruction, depending on the pathophysiologic state of the child and the availability of a donor heart.[201] However, the critical shortage of donor organs places a marked limitation on correction of this common congenital heart lesion.

It is apparent that many children have derived benefit from a completed, staged reconstruction or heart transplantation for this previously fatal illness. They are often able to lead active, productive lives and to develop normally.[202,203] Both survival and developmental outcomes for this disease are improving worldwide. However, the long-term prognosis for this evolving therapy will not be known for several years.

Recently, an innovative alternative to the stage I Norwood palliation that eliminates the insult associated with CPB in the fragile neonate with HLHS has been developed. This approach combines interventional cardiac catheterization techniques with less involved surgery: the *hybrid procedure*.[204] The goal is to replicate the physiologic state of the Norwood procedure by the combination of three interventions: 1) placement of bilateral pulmonary artery bands to limit blood flow to the lungs, 2) placement of an endovascular stent to maintain the long term patency of the ductus arteriosus, and 3) balloon atrial septostomy with or without stenting of the atrial communication to ensure adequate mixing and unrestricted left to right atrial flow.[204,205] The procedure is accomplished through a standard medial sternotomy and does not require CPB.

The procedure requires superb coordination between the surgical and cardiac catheterization teams. It is generally performed in a hybrid suite consisting of a large modern cardiac catheterization laboratory with enough room to accommodate the surgeons and supporting operating room staff, in addition to the interventional cardiology team and anesthesiologists. Preliminary results have been encouraging with early mortality comparable with that of standard protocols (about 15%-20%).[206,207] Direct comparison of the two methods is complicated, as the hybrid procedure generally has been reserved for patients regarded as high risk for bypass surgery (low birth weight, unstable haemodynamics, and poor ventricular function).[205] Interstage mortality rates are high (15%-20%),[208] and case-matched studies have shown no benefit over conventional surgery.[207] One barrier to the widespread impementation of the hybrid procedure is that results of conventional surgery in the low-risk groups are now so good that many centers of excellence have been reluctant to undertake a new procedure with its attendant learning curve.

The hybrid procedure poses some unique technical challenges. The ductal stent position is crucial and, if patients have a diminutive ascending and transverse aorta, then the procedure does not address this impediment to coronary flow. If the transverse aorta is small, the stent itself might distort or interfere with retrograde flow into the arch, and for this reason most centres do not recommend the hybrid approach in the setting of a small transverse arch.[205] Nevertheless, the procedure has a role in the management of patients with HLHS and, with continued encouraging results,[209] it will most likely find a niche among high-risk patients or as a bridge to transplantation.[210]

Up to 50% of patients that survive the stage I hybrid procedure require catheter re-intervention due to stent migration or restrictive flow across the atrial communication.[208] The stage II procedure becomes much more extensive than the conventional stage II because the aortic arch needs to be reconstructed (excising the ductal stent), the bands removed, and the pulmonary arteries repaired with a patch in addition to creating the the cavopulmonary connection.[205] Consequently, the stage II after the hybrid procedure carries substantial operative mortality (10%-15%) and this needs to be taken into account when comparing it with conventional techniques.[208,209] No consensus exists on the future of the hybrid procedure. This innovative approach offers potential benefits that still need to be proven by careful study and long-term follow-up.

Summary

The cardiac ICU has become the epicenter of activity in large cardiovascular programs. Nowhere are collaborative practices and multidisciplinary skills more valued or necessary. A curriculum in cardiac intensive care is now formally incorporated into cardiology training. Pediatric intensive care training programs have a mandate to include curricula and experience

in management of postoperative cardiac patients. Additional cardiac intensive care training is offered in selected centers to pediatric intensive care specialists wishing to pursue a career in the cardiac ICU. Specialists in this field must have in-depth training in pediatric intensive care and cardiology as the scope of practice goes well beyond the cardiovascular system and requires expertise in complex respiratory physiology, diagnosis and management of multiorgan system dysfunction, and the various supportive techniques vital to the discipline of intensive care, to name a few. Increased complexity of disease, advances in technology and applied research, shortened lengths of stay, and improved survival all describe the fast-paced specialized environment that has accompanied the development of this new specialty of pediatric cardiac intensive care. Although the dramatic reduction in mortality has been gratifying in cardiac intensive care and is attributable to many factors, achieving 100% survival with minimal morbidity remains our elusive goal. It will challenge the next generation of practitioners.

References are available online at http://www.expertconsult.com.

Cardiac Transplantation

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PEARLS

- Indications for transplantation are cardiomyopathy and complex palliated congenital heart disease with severe myopathic ventricular dysfunction.
- Pediatric patients on inotropic support or circulatory support and who have life-threatening arrhythmia receive priority for available pediatric donors.
- Selection of the agent to initiate inotropic support has evolved from sympathomimetic agents (dobutamine/dopamine) to the phosphodiesterase inhibitor milrinone.
- Virtual crossmatch is now utilized in sensitized patients to improve organ allocation.
- It is imperative that immune suppression be initiated immediately after heart transplantation.
- The high-risk period for acute allograft rejection is in the first month after transplantation.
- Complications of immune supression are infection, acute renal failure, malignancy, and hyperglycemia.

It has now been a quarter of a century since the first successful pediatric heart transplant was performed at Stanford University.[1] The introduction of cyclosporine as the primary immune suppressant agent used in solid organ transplantation was a key discovery because it was the first selective immunosuppressive agent used in solid organ transplant recipients. It has spared corticosteroid use and has made heart transplantation a cost-effective procedure.[2] In the past 25 years, perioperative mortality has become negligible even in patients with the most complex congenital heart defects. Advances have occurred in our understanding of the immune system, and improvement in critical care management of both donor and recipient patients has resulted in an increased survival benefit. This chapter reviews critical care management of the pediatric patient with cardiopulmonary failure who is evaluated for orthotopic heart transplantation. Donor management, physiology of the transplanted heart, and preoperative and perioperative critical care all play important roles in the successful outcome of critically ill children with no option other than heart replacement surgery.

Indications for transplantation are cardiomyopathy and complex palliated congenital heart disease with severe myopathic ventricular dysfunction.[3] The Pediatric Heart Transplant Study Group reviewed the causes of death after heart transplantation from a prospective database initiated in 1993. Patients were entered into the database on an intention-to-treat basis.[4-6] Using parametric data analysis with competing outcomes, death while waiting for transplant has been analyzed for all age groups, pretransplant diagnosis, blood type, and urgency status. Early death after heart transplant has been categorized as primary heart allograft failure. This includes inadequate preservation from long ischemic time and primary right ventricular failure from high pulmonary vascular resistance (PVR). Acute allograft rejection is an exceedingly rare event immediately after implantation. Late death after transplant is the result of posttransplant coronary vasculopathy, malignancy, or nonadherence to immune suppression regimens.[7,8]

The technical complexities of heart transplantation in children with palliated congenital heart disease contributed to the early perioperative mortality, which exceeded 30%. In addition, difficulties in estimating PVR, variable pulmonary artery anatomy, and complications from multiple repeat thoracotomy and sternotomy all contributed to early morbidity and mortality.[9] Solid organ preservation, surgical experience, and recipient selection have all improved with experience, resulting in reduced perioperative mortality that is equivalent to transplantation of the primary cardiomyopathic patient who has not had a previous sternotomy.[9,10] Primary transplantation in the neonate with hypoplastic left heart syndrome (HLHS) has caused controversy, because an acceptable surgical alternative is available and infant donor heart resources are limited.[11] In reviews from the Pediatric Heart Transplant Study Group Database, the mortality of infants waiting for donor heart availability exceeds 25%.[4] In recent years, deaths while waiting for transplantation have decreased, but this decrease reflects the smaller number of infants listed and those who have opted for the Norwood procedure and single-ventricle palliation. The Norwood procedure does not preclude the possibility of future transplantation.

Late death after heart transplantation is related to either accelerated allograft coronary artery disease or primary malignancy.[12,13] The major cause of death in the adolescent heart transplant recipient is now noncompliance with the medical regimen.[7] With the decrease in perioperative mortality, we now expect 5-year survival after heart transplantation to exceed 80%. From the newest survival data (International Society for Heart and Lung Transplantation 2009 Report), the transplant half-life (the time at which 50% of the recipients remain alive) is 11.3 years for teens and 15.8 years for infants.[14] Rehospitalization after the first year is rare, and quality of life has been excellent.[15]

Critical Care of the Pediatric Patient Waiting for Heart Transplantation

An inadequate number of good donor hearts is available to satisfy the number of potential adult recipients. Statistics from the United Network for Organ Sharing (UNOS) demonstrate this discrepancy between the number of potential recipients for heart and lung transplants and the availability of potential donors.[16] Donor availability for the pediatric patient is not as critical. Pediatric patients usually receive an appropriate donor offer unless they are infants or are adolescents of a size such that they are competing with critically ill adult patients. Guidelines from UNOS regarding organ distribution have changed to ensure that pediatric adolescent donors are available first to potential adolescent and young adult pediatric recipients for both heart and lungs.

For potential heart transplant recipients, urgency criteria have been established for the most critically ill patients. Pediatric patients on inotropic support or circulatory support or who have life-threatening arrhythmia receive priority for available donors (Box 32-1).

Management of the Potential Heart Transplant Recipient

The pretransplant management of the critically ill patient with end-stage myocardial dysfunction can determine the outcome of that patient after thoracic transplant. The principles of inotropic support, preservation of end-organ function, and attention to issues of nutrition and infection are the same for all critically ill patients in the pediatric intensive care unit.

Evaluation of the potential heart transplant recipient requires a careful pretransplant hemodynamic assessment. This information can guide the fluid and inotropic therapy by optimizing preload and afterload while waiting for organ availability. The critical hemodynamic information influencing the function of the donor heart is an assessment of pulmonary artery pressure and PVR in the recipient before implantation. High PVR is associated with an increased perioperative transplant mortality rate and adverse long-term outcome.[17,18] A transpulmonary gradient greater than 15 mm Hg (mean pulmonary arterial pressure minus mean left atrial pressure) is associated with a higher incidence of heart graft dysfunction.[18] Preoperative hemodynamic assessment should include measurement of both left and right heart pressures with interventions to manipulate the PVR if elevated. Remeasuring hemodynamics with Fio_2 of 1, nitric oxide, prostacyclin, and aggressive vasodilator therapy to decrease systemic vascular resistance (SVR) can help determine whether the patient is a heart transplant candidate or if he or she should be considered for lung or heart and lung transplantation.[19,20]

Box 32–1 Heart Transplantation Justification: Pediatric Cardiology Status IA

- Requires assistance with a ventilator
- Requires assistance with a mechanical assist device (e.g., extracorporeal membrane oxygenation, left ventricular assist device)
- Requires assistance with an intra-aortic balloon pump
- Patient younger than 6 months with congenital or acquired heart disease exhibiting reactive pulmonary hypertension >50% of systemic blood pressure levels
- Requires infusion of a single high-dose inotrope (e.g., dobutamine ≥7.5 μg/kg/min or milrinone ≥0.5 μg/kg/min)
- Patient does not meet any of the criteria specified above but has a life expectancy without a heart transplant of less than 14 days (i.e., refractory arrhythmia)

Inotropic Support

Critically ill children with myopathic ventricular dysfunction severe enough for them to be in the intensive care unit are on inotropic support. These agents increase contractility through a common pathway of increasing intracellular levels of cyclic adenylate monophosphate (cAMP). Increased cytoplasmic levels of cAMP cause increased release of calcium from the sarcoplasmic reticulum and increase contractile force generation. Increases in cAMP occur either by β-adrenergic–mediated stimulation (increase in production) or phosphodiesterase III (PDE III) inhibition (decreased degradation). Milrinone has proven to be a well-tolerated agent. Intravenous administration of milrinone increases cardiac output and reduces cardiac filling pressures, PVR, and SVR, with minimal effect on heart rate. Milrinone has been well studied in the pediatric population, and the benefit is primarily related to effect on SVR and PVR rather than inotropy.[21,22] Milrinone is initiated at doses of 0.25 μg/kg/min and increased to 1 μg/kg/min without adverse effects. Although atrial and ventricular ectopy are less common with milrinone than dobutamine, ventricular ectopy/ventricular tachycardia can occur with the initiation of milrinone therapy. Tachyphylaxis is unusual with this agent. Milrinone has a long half-life and should be used cautiously in patients with hypotension. This drug is primarily excreted in the urine, so concentrations can increase in the presence of renal failure. We have observed severe hypotension and renal dysfunction precipitated by use of an angiotensin-converting enzyme inhibitor in a patient already on milrinone infusion. The addition of low-dose dobutamine (5-10 μg/kg/min) or epinephrine (dose 0.01-0.05 μg/kg/min) can help stabilize the critically ill child who is not responding adequately to milrinone therapy alone.

Nesiritide, a recombinant B-type natriuretic peptide, is now approved for treatment of acutely decompensated heart failure. Endogenous B-type natriuretic peptide is a cardiac hormone produced by the failing heart, and nesiritide is identical to the naturally occurring peptide. Nesiritide reduces preload and afterload, leading to increases in cardiac output/index without reflex tachycardia or direct inotropic effect. In addition, this drug promotes natriuresis and diuresis, and suppresses the renin-angiotensin axis and endogenous catecholamines. Although this drug has not been studied extensively in the pediatric age group, in our and others' experiences, it has been found to be a safe and effective adjunctive therapy.[23,24]

Mechanical Support

Most patients waiting for transplantation who are on inotropic support do not remain hemodynamically stable indefinitely. Progressive end-organ dysfunction ensues, requiring escalation of support that includes multiple inotropic agents, in addition to respiratory and circulatory support. Mechanical

circulatory support has become an important addition to the treatment armamentarium for the infant or child with decompensated heart failure and low cardiac output unresponsive to pharmacologic maneuvers.[25] Options include extracorporeal membrane oxygenation (ECMO), intra-aortic balloon, and left and right ventricular assist devices. Experience with ECMO as a bridge to heart transplantation has been reported by several pediatric transplant centers.[26,27] ECMO support can be used for 2 to 3 weeks without major complications from bleeding or infection, extending the window for donor organ availability. Isolated ventricular support devices, such as the Thoratec, Berlin Heart,[28] and DeBakey centrifugal pump, are now available for children.[29,30] The Berlin Heart EXCOR has become the primary extrcorporeal circulatory device in infants and children. The current data from Berlin Heart show there have been a total of 698 patients supported for more than 47,000 days with this pneumatic-driven device (personal communication, Berlin Heart). The longest time of support in an individual patient was 902 days, with an average of 68 days of support before transplantation, explant, or death. The pediatric demography is that this device is used for all pediatric age ranges, but the mean age of 5 years and the median age of 2 years reflect the benefit in small children because of the availability of a pump size that can deliver 10-mL stroke volume. Actuarial survival of patients at 1 year who have been bridged to heart transplant or explanted now exceeds 80% (personal communication, Berlin Heart). In the past, use of these devices had always been considered extraordinary and usually proposed in patients with severe end-organ dysfunction. Placement of a device in a patient with multisystem organ failure usually results in a poor outcome. We propose that these devices be placed early, before end-organ dysfunction; doing so will enable rehabilitation of the patient, who then becomes a more optimal candidate for organ transplantation.

Anticoagulation

All patients with severe myocardial dysfunction are at risk for complications of systemic and pulmonary embolus. In our experience, nearly all explanted hearts have mural thrombi in both the left and right ventricles. Pulmonary emboli lead to increased PVR and the potential for lung abscess. The most devastating result of systemic embolus is stroke. All patients waiting for transplantation should be managed with systemic anticoagulation. Heparin is preferred, but warfarin is acceptable in a stable patient on inotropic support. We add a word of caution regarding the use of low-molecular-weight heparin for prophylaxis. Enoxaparin cannot be easily reversed in a patient who must go to the operating room emergently because a donor heart has been identified. Cardiovascular surgeons prefer using heparin for prophylactic anticoagulation.

Management of the Potential Heart Donor

Many potential heart donors are lost because of suboptimal management after brain death has occurred. Associated with brain death is a catecholamine surge causing unnatural circulatory physiology that rapidly evolves, making management of the donor difficult. This intense sympathomimetic outflow initially causes vasoconstriction resulting in tachycardia, hypertension, and increased myocardial oxygen demand. The result can be a direct injury to the myocardium in the potentially transplantable heart. Myocardial structural damage is seen and includes myocytolysis, contraction band necrosis, subendocardial hemorrhage, edema formation, and interstitial mononuclear infiltration.[31] This initial sympathetic outflow is followed by a loss of sympathetic tone resulting in marked vasodilatation and hypotension. The hypotension and cardiovascular collapse are related to decreased SVR rather than primary myocardial dysfunction. Large fluid volumes and high-dose inotropic agents at α-adrenergic dosing range are administered, causing volume overload and vasoconstriction that can injure all donor organs. Hearts that are supported on high-dose inotropic agents will likely exhibit myocardial injury. A risk factor that predicts donor heart failure is a history of use of high-dose dopamine, dobutamine greater than 20 μg/kg/min, and epinephrine greater than 0.1 μg/kg/min.

Hormonal changes occur with brainstem injury and death. Early depletion of antidiuretic hormone causes inappropriate diuresis. Depletion of free triiodothyronine (T_3) has been implicated in myocardial dysfunction. Falling insulin levels lead to decreased intracellular glucose levels. A significant decrease in cortisol levels contributes to cardiovascular instability.[32,33]

Our present understanding of the physiology of brain death has resulted in "protocol" development for management of the potential donor. The principles of support include the following:

- Invasive cardiovascular monitoring maintaining a mean arterial blood pressure greater than 60 mm Hg and central venous pressure of 6 to 10 mm Hg.
- Vasopressin is now the first-line blood pressure support medication because it treats diabetes insipidus in addition to supporting blood pressure. Infusion of less than 2.5 U/hour usually is sufficient to increase mean arterial blood pressure and not cause end-organ injury.
- Respiratory support to maximize oxygen delivery to transplantable organs. Recommended ventilatory strategies are aimed at optimizing oxygenation and preventing lung injury.
- Hormonal support including high-dose corticosteroids in the form of Solu-Medrol, insulin, and, possibly, infusions of the thyroid hormone T_3 or T_4. The benefits of thyroid hormone replacement in the brain-dead donor are debated, but there are studies supporting their use.[32] Resuscitation of the "marginal donor heart" is worth the effort, given the shortage of available donor organs. Administration of T_3 has been advocated for reversal of myocardial dysfunction induced by the catecholamine surge of brain death.[32]

Pediatric heart transplantation after declaration of cardiocirculatory death has received significant interest in the transplant community because of the shortage of donor organs. Protocols are controversial because donor care is provided under the direction of the pediatric intensivists. The donor is moved to the operating room and femoral arterial and venous lines are inserted for access to perform organ resuscitation. The donor is given comfort care, extubation is accomplished, and the donor is monitored for circulatory death by auscultation of the heart and palpation of pulses. When circulatory death has occurred, the donor is observed for a period of 1.25 to 3 minutes before death is declared. If cardiocirculatory death occurs within 30 minutes after extubation, the donor is declared a candidate for organ donation. Cold cardioplegia

is infused into the catheter that was positioned in the ascending aorta, sternotomy is performed and topical cooling of the heart is initiated, and the inferior vena cava is opened to prevent distension of the heart. The routine technique for cardiectomy is then performed.[34] Organ donation after circulatory death for kidney and liver transplantation is becoming more common but since the heart is more vulnerable to ischemia, this practice has not become common. The practice of transplantation after cardiocirculatory death for any organ remains an ethically controversial practice for many pediatric critical care intensivists.[35]

Critical Care Management of the Orthotopic Heart Transplant Recipient

Intraoperative Considerations

Heart replacement can be accomplished in virtually any congenital heart anomaly, because the aorta, pulmonary arteries, and left atrium are in a relatively constant position near the midline. Regardless of malposition or positional relationships of the great arteries, the aorta of the recipient can be mobilized to make anastomosis with the donor aorta possible. The left atrium is a midline structure, and even when anomalies of the pulmonary venous return exist, pulmonary veins usually approach the midline and can be incorporated into the repair.[36]

Techniques of implantation have not changed significantly since the original description.[1,37] The newest innovation is the bicaval anastomosis.[38,39] This technique has the advantage of preserving sinus node function.[40] Implantation techniques require that the pulmonary veins come to the midline. The pulmonary artery and aorta can be malpositioned but this adds little to the technical difficulty of the procedure. Aortic root size mismatch can, however, cause technical difficulty. Implantation of recipients with complex congenital heart disease usually can be accomplished by harvesting additional donor pulmonary artery, aorta, and caval tissue to replace deficient recipient tissue or to correct malposition of the vena cava or great arteries.[36,41]

Donor heart function is related to proper management of the donor and the total ischemic time of the donor heart. The amount of time the aorta is cross-clamped on the donor until the aortic anastomosis is completed on the recipient (total ischemic time) is a major factor determining early postoperative donor heart function. Nevertheless, donor hearts have been exposed to more than 8 hours of ischemia and recovered function after transplantation.

Early Perioperative Management

The early perioperative management of the recipient is not significantly different from the management of any postcardiac surgical patient. The physiologic responses of the newly transplanted heart are altered because of denervation. The major changes related to autonomic denervation include diastolic dysfunction and exaggerated response to exogenously administered catecholamines. The transplanted heart also must adapt to a new environment related to recipient lung function and elevated PVR.

Autonomic system denervation results in a relatively fixed heart rate without respiratory variation. Heart rates are between 90 and 110 bpm, but can be faster because of exogenous catecholamine administration. (The sinus node is transplanted with the donor heart.) Heart rates can be slower if the recipient has been exposed to amiodarone pretransplant or if there was injury to the blood supply of the donor sinus node at the time of donor heart removal.

Early blood pressure instability is common because of loss of baroreceptor regulation and dependence of the transplanted heart on endogenous or exogenous catecholamines. Hypertension occurs because of a fixed stroke volume into a systemic vascular bed that is abnormal because of longstanding increase is systemic vascular resistance from compensatory heart failure. Size mismatch between donor and recipient can also contribute to the hypertension because of a large stroke volume from the transplanted heart. The other concern about donor heart/recipient mismatch is "big heart," or hyperperfusion syndrome. A well-functioning large allograft generates a large stroke volume causing systemic hypertension and high cardiac output in a patient who previously had a low cardiac output state. This increase in cerebral blood flow has the potential to cause cerebral vasoconstriction and symptomatic seizures, headache, or changes in mental status.[42] These symptoms are limited to the first few days after transplantation. There is a gradual adaptation in allograft stroke volume to the needs of the recipient. This adaptation of oversized cardiac allografts in children is part of the "shrink and grow" phenomenon previously described.[42] The oversized donor heart eventually undergoes remodeling with regression of hypertrophy. Although this is a rare problem in children, symptomatic hypertension must be treated aggressively early in the perioperative period.

Early myocardial function of the transplanted heart is dependent on catecholamine support. Small infusions of β-adrenergic agents such as isoproterenol for several days are often necessary to maintain optimal heart allograft function.[43]

The hemodynamics of the transplanted heart reflect a significant shift to the left of the pressure/volume curve. Diastolic dysfunction can be demonstrated from the early transplant period. Why this hemodynamic abnormality is present early because of preservation injury is understandable, but diastolic dysfunction persists well into the recovery phase and beyond. Fluid administration of 10 mL/kg to a heart transplant recipient months remote from transplant will uncover an occult restrictive hemodynamic pattern. Pulmonary artery wedge pressure will increase by twofold, and right atrial pressure will increase more than expected.[44] In the normal heart, right atrial pressure will not change and left atrial pressure will increase by 1 to 2 mm Hg in response to a fluid challenge.

Diastolic dysfunction is a significant impairment to early allograft function, limiting cardiac output. Diastolic dysfunction emphasizes the importance of heart rate and early sinus node function. The capability for temporary pacing in the early perioperative period is mandatory.

Management of Early Heart Allograft Dysfunction

Early heart allograft dysfunction is related to primary failure of the heart allograft because of unsuspected injury to the heart prior to procurement or because of preservation injury. The other major cause of primary allograft failure is elevated PVR in the recipient. Allograft failure is rarely caused by acute

antibody-mediated injury. Risk factors associated with donor heart dysfunction, if present, should be factored into the decision of accepting that particular heart for your patient. Obviously the condition of the recipient and the expected length of survival would mandate, at least, consideration for acceptance of a "marginal heart."

Risk factors for donor heart dysfunction include "down time of the donor" (length of initial resuscitation), evidence of myocardial injury with elevation of troponin I, and a history of high-dose inotropic support (dopamine/dobutamine >20 μg/kg/min or epinephrine/norepinephrine >0.1 μg/kg/min) in the donor. Objective assessment of donor heart function can be made by obtaining an echocardiogram and electrocardiogram. The echocardiogram assesses donor heart systolic function (shortening fraction or left ventricular ejection fraction), and will detect the presence of mitral valve regurgitation or wall-motion abnormalities. The presence of any of these abnormalities makes the donor heart "marginal" for transplantation. In assessing the donor heart function, serial echocardiograms are imperative before determining that the heart is not usable for transplantation. Abnormal heart function seen in the midst of the catecholamine storm of brain death can recover. Repeating the echocardiogram remote from the initial resuscitation period or after the reduction or discontinuation of inotropic support can increase one's confidence in accepting the donor heart.

The other major reason for primary donor heart dysfunction is right heart failure from high pulmonary vascular resistance (PVR). We have known since the early days of heart transplantation that the donor right ventricle will not function when exposed to an abnormal pulmonary circulation. High PVR in the recipient increases perioperative morbidity and mortality and can affect late survival. All potential heart recipients undergo cardiac catheterization prior to heart transplantation to document the anatomy of systemic and pulmonary venous connections, determine pulmonary artery size and distribution, and calculate PVR. The upper limit of PVR associated with successful orthotopic heart transplantation is not known. Criteria developed from the adult heart transplant experience indicate that a PVR greater than 6 Wood units or a transpulmonary gradient (pulmonary artery mean pressure minus left atrial mean pressure) greater than 15 mm Hg is associated with increased perioperative mortality. The transpulmonary gradient is the most useful number for estimating PVR, because measurement of cardiac output in the catheterization laboratory can be flawed. In children, PVR index (PVRI), determined by dividing transpulmonary gradient by cardiac index, is more useful, because children come in all sizes. PVRI less than 6 index units is associated with low perioperative mortality. Orthotopic heart transplants have been successful with PVRI greater than 6 and as high as 10 index units, but with increased morbidity and mortality rates. The diagnosis of high PVR is evident as the patient is weaned from cardiopulmonary bypass. Intraoperative transesophageal echocardiography demonstrates dilatation of the right ventricle and a small, underfilled left heart. Acute management of high PVR and right heart dysfunction includes high Fio_2 and administration of nitric oxide at 20 to 40 ppm. The need for continuous pulmonary vasodilator medications in the immediate perioperative period is unusual, but prostacyclin and sildenafil have both proved effective in this situation.[45]

The sinus node artery from the donor heart is at risk at the time of procurement, and the incidence of sinus node dysfunction causing junctional rhythm or atrial flutter/fibrillation is 10% to 20%. Nearly 5% of children require pacemaker therapy after transplantation because of sinus node dysfunction.[46] All transplant recipients have temporary pacing wires, so bradyarrhythmias are not an issue. If the patient is in atrial flutter/fibrillation, then cardioversion should be performed. Persistent sinus node dysfunction with bradycardia can be problematic because of early diastolic dysfunction of the heart allograft. In the usual scenario, the patient returns from the operating room in an atrial paced rhythm. When the pacemaker is turned off, the underlying rhythm is a junctional rate between 100 and 120 beats/min. As inotropic support is discontinued, the junctional rate slows to an unacceptable rate in the 50 to 80 beats/min range. Usually an occasional atrial contraction is conducted, but the sinus node has been injured. Initiating theophylline at a dose of 10 mg/kg/day is helpful. Permanent pacing is recommended if sinus or atrial conducted rhythm has not returned within 2 weeks.

Heart Allograft Rejection and Immune Suppression

It is imperative that immune suppression be initiated early after heart transplantation. Solid organ transplants transfer antigen-presenting cells (APCs) that are recognized by the recipient's human leukocyte antigen (HLA) immune system as foreign, which sets up a cascade of lymphocyte stimulation and proliferation. These lymphocytes then migrate to the heart allograft, where they can adhere to myocytes and endothelial receptors and cause tissue destruction. T-cell activation is the prime mover of allograft rejection. The initial signal is T-cell receptor binding of antigen on the surface of an APC. The APC is derived from the donor in the form of a monocyte, or a tissue macrophage. Interaction of the APC and T-cell receptor causes release of interleukin (IL)-1 from the APC, which causes activation of the T cell. Activated T cells secrete IL-2 and other lymphokines that induce proliferation of activated T cells, which migrate to the allograft causing tissue damage.

Initial immune suppression protocols include high-dose corticosteroids, induction with IL-2 receptor blockade, or antithymocyte globulin, followed by introduction of the calcineurin inhibitors cyclosporine or tacrolimus (Table 32-1).

Induction protocols with lympholytic agents OKT3 or antithymocyte globulin are effective in delaying the time until the first allograft rejection episode but do not have a long-term survival benefit.[47] The benefit of induction with IL-2 receptor blockade in preventing early heart allograft rejection is supported by recent studies.[48]

Corticosteroids have been part of standard protocols since the early days of solid organ transplantation. High-dose methylprednisolone (5 to 10 mg/kg) is administered at the time of aortic cross-clamp removal and continued in tapering doses over the first several days after surgery. Corticosteroids have immunosuppressive properties and benefit the allograft because of membrane-stabilizing and antioxidant effects on the graft.

More controversial is the timing of the introduction of calcineurin inhibitors cyclosporine and tacrolimus. A major complication in the early perioperative course after heart transplantation is renal dysfunction. In the past, calcineurin

Table 32–1 Immune Suppression in the Intensive Care Unit

Agent	Mechanism of Action	Dose	Monitoring	Major Side Effect(s)
INDUCTION IMMUNE SUPPRESSION				
Corticosteroids	Redistribution of peripheral lymphocytes, inhibition of lymphokine IL-2 production, impairment of macrophage response to lymphocyte signals	2 mg/kg days 1-3 1 mg/kg days 4-7	Glucose	Infection, cushingoid appearance, hypertension, hyperlipidemia, glucose intolerance
Basiliximab	Monoclonal antibody binds to IL-2 receptor	20 mg >35 kg 10 mg <35 kg, administer days 1 and 4	CBC	Anaphylaxis
Antithymocyte globulin	Nonspecific T-cell lysis	1.5 mg/kg/day for 5–7 days	T-lymphocyte subsets	Thrombocytopenia, anaphylaxis, infection, PTLD, localized pain with RATG administration, serum sickness
Cyclosporine	Calcineurin inhibitor, inhibition of T-cell receptor lymphokine production and T-cell proliferation	2.5 mg/kg/24 hours IV	Monoclonal whole blood assay 100–400 ng/mL, depending on time since transplantation	Nephrotoxicity, central nervous system seizures, decreased magnesium, hypertension, hirsutism, gingival hyperplasia
Tacrolimus	Calcineurin inhibitor, inhibition of T-cell receptor lymphokine production and T-cell proliferation	IV: 0.03–0.05 mg/kg/24 hr Oral: 1.0 mg bid; increase dose based on daily level	5–15 ng/mL, whole blood	Nephrotoxicity, anemia/neutropenia, headache, tremors, insomnia, glucose intolerance
MAINTENANCE IMMUNE SUPPRESSION				
Cyclosporine		5–20 mg/kg bid or tid		
Tacrolimus		0.3 mg/kg/day divided bid		
Sirolimus	Inhibition of T-cell activation and proliferation by preventing translation of mRNA	Loading dose of 3 mg/m^2 PO, then 1 mg/m^2/day given 4 hours after cyclosporine or tacrolimus	Triglycerides, platelets 5–10 mg/mL	Nephrotoxicity, hyperlipidemia, thrombocytopenia, leukopenia, gastrointestinal intolerance
Azathioprine	Antimetabolite inhibits purine and DNA synthesis	1–2 mg/kg/day	WBC <4000 ANC >1500	Bone marrow suppression
Mycophenolate mofetil		30–60 mg/kg/day in divided doses	WBC <4000 ANC >1500	Bone marrow suppression, gastrointestinal intolerance
Prednisone		1–3 mg/kg/day		
ACUTE CELLULAR REJECTION				
Methylprednisolone		10–25 mg/day for 3–4 days		
Antithymocyte globulin		1.5 mg/kg/day for 7–14 days		Peripheral lymphocyte count, platelet count

ANC, Absolute neutrophil count <1000; *PTLD,* posttransplant lymphoproliferative disease; *RATG,* rabbit antithymocyte globulin.

inhibitors cyclosporine and tacrolimus were major contributors. The APC and lymphocyte receptor interaction occurs within hours of the transplant; therefore, early introduction of calcineurin inhibitors is important. Because bioavailability of these drugs is so variable, early, continuous IV administration of these drugs have been a standard protocol.[49] We continue to experience a group of recipients who develop acute renal failure with intravenous administration of these drugs and therefore avoid IV use of cyclosporine and tacrolimus. Current protocols are based on oral/nasogastric administration of a standard dose of tacrolimus beginning on the day of transplant. Target levels of this drug are reached 3 to 5 days after transplant if subsequent doses are based on the trough level obtained each morning (see Table 32-1).[50]

The high-risk period for acute cellular rejection (ACR) is the first month after transplantation. ACR is a phenomenon that rarely occurs in the first week after transplant. Hyperacute rejection is uncommon, but can occur when a heart transplant recipient has preformed HLA antibody that reacts with a donor who has those specific HLA antigens. A positive crossmatch will be reported, which means the recipient's serum causes lysis of donor T cells obtained from lymph nodes from the donor at the time of organ procurement. Heart transplant recipients at risk for hyperacute rejection are identified by

measuring the presence of HLA antibody in their serum. Specificity and quantification of these HLA antibodies can be measured by Luminex beads, which enable a virtual crossmatch to be done between potential donors and recipients. Children with palliated congenital heart disease are at particular risk for HLA sensitization because of exposure to blood products at the time of their previous surgical procedures. Rapid institution of plasmapheresis immediately after implantation and continuing through the first several days after the operation is the optimal way to clear the offending antibody causing heart allograft dysfunction.

The diagnosis of ACR is made by endomyocardial biopsy. Histopathology in cardiac tissue obtained by endomyocardial biopsy remains the gold standard for diagnosis of acute cardiac allograft rejection. The numbers of infiltrating lymphocytes and the presence of myocyte injury are used to grade rejection and to guide allograft rejection therapy. Surveillance endomyocardial biopsies are performed within the first 2 weeks after transplant and then at strategic times depending on the size of the child, available access, and the technical difficulty of obtaining tissue.

Clinical recognition of acute allograft rejection can be subtle, but is obviously important because tissue diagnosis is not always possible, and surveillance techniques using peripheral blood, electrocardiography, and echocardiography have limitations. Acute cellular rejection can be present in the allograft without any symptoms or clinical findings. When ACR has progressed to hemodynamically significant allograft dysfunction, then symptoms of abdominal pain and vomiting are prevalent, and findings of systemic venous congestion, liver enlargement, and low cardiac output dominate. Symptoms of pulmonary venous congestion/pulmonary edema are rare findings. When ACR is suspected, histologic confirmation is always desirable if it can be safely performed. The principles of management are to acutely augment immune suppression with methylprednisolone or a lympholytic agent depending on the histologic and clinical severity of the heart allograft dysfunction. Following acute treatment, increases in maintenance of immune suppression agents are prescribed and follow-up endomyocardial biopsy is scheduled.

Complications of Immune Suppression in Heart Transplant Recipients Occurring in the Pediatric Intensive Care Unit

Infection

Infections are a major cause of mortality and morbidity in the early period after heart transplantation.[51,52] Factors that predispose to infection can be divided into preexisting factors related to the donor and recipient, and factors secondary to events in the intraoperative and postoperative periods. For example, the site of the organ transplanted provides a clue to the site of infection. Renal transplant recipients acquire urinary tract infections, whereas heart transplant recipients are exposed to chest cavity infections. The type and severity of the underlying illness leading to organ failure can increase the risk for rejection. Children with cardiomyopathy can be severely malnourished, require prolonged mechanical respiratory or circulatory support, and have chronic indwelling venous catheters, all of which predispose to infection. The presence of a pretransplant pulmonary infarction is associated with lung abscess in the posttransplant recovery period.[53] Neonates may experience severe sepsis from coagulase-positive staphylococci more often than older children.

The herpes virus family plays a significant role in infections occurring after transplantation. The clinical expression of cytomegalovirus and Epstein-Barr virus infection in the young patient is more severe because it is often a primary exposure.[54] Clinical infections related to these viruses rarely present before 1 month following organ transplantation and are most common in the first 6 months after heart transplantation.

Antibiotic management of the heart transplant recipient in the intensive care unit can be focused primarily on clinical suspicion, time of infection after transplant, and predisposing factors. Immune suppression is selective and targets T cells. Neutrophil function is normal except for the effect of high-dose corticosteroids. Neutropenia can occasionally be a problem because of bone marrow suppression caused by antimetabolites and tacrolimus. Prophylactic antibiotics, in the form of third-generation cephalosporins, are used for patients after sternotomy and continued until chest tubes and central lines are removed. The strategy against infection includes initial isolation, routine surveillance cultures, and regular replacement of indwelling catheters. In the early setting after transplantation, temperature elevation should indicate active infection and serious complication. If an infection is suspected, early and aggressive investigation is necessary and broad-spectrum antibiotics/antifungal agents should be initiated until the source of the fever is identified.

Renal Function

Acute renal failure is a major complication following orthotopic heart transplantation. Renal failure is multifactorial in etiology, and the premorbid risk factors of heart transplant recipients cannot necessarily be controlled. We can monitor and control use of calcineurin-inhibitor immune suppression agents. Therapeutic strategies include delayed initiation of cyclosporine and tacrolimus by using antithymocyte globulin or IL-2 receptor blockade for induction of immune suppression. The other option is to use a modified oral/nasogastric protocol for tacrolimus administration.[55] This protocol targets tacrolimus levels to below 6 ng/mL in the first 3 days after transplantation and then aggressively increases dosing and target level over the next 4 days. It is important to avoid early IV administration of these agents, because they invariably lead to renal afferent arteriolar vasoconstriction and oliguria. If renal dysfunction is complicating the posttransplant course, it is still difficult to withdraw calcineurin inhibitors completely, but lowering the target level to less than 6 ng/L and substituting higher doses of mycophenolate mofetil and adding sirolimus are reasonable options.[56] The other means for reversing renal toxicity is to target mechanisms of calcineurin inhibitor toxicity. Renal arteriolar vasoconstriction is an imbalance between vasodilator prostaglandins and vasoconstrictor thromboxane A_2. Thus prostaglandin E1 (PGE1) has been used for promoting renal vasodilatation, with some success. Oral PGE1 analogues have received mixed reviews. Calcium channel antagonists have also been used to prevent renal toxicity. Felodipine has been shown to cause a naturesis and to prevent the decline in renal hemodynamics produced

by angiotensin II. We have not had enough experience using this potentially useful drug in reversing cyclosporine/tacrolimus nephrotoxicity.[57]

Diabetes Mellitus

Hyperglycemia is common after heart transplantation with tacrolimus-based immune suppression. The combination of decreased insulin production from islet cells caused by tacrolimus and decreased peripheral utilization related to high-dose corticosteroids results in nonketotic hyperglycemia. Insulin is initially mandatory in management but often can be discontinued if the tacrolimus dose is reduced and the corticosteroid portion of maintenance immune suppression is discontinued.[58]

Future Management Strategies for Critical Care of Infants and Children with Cardiopulmonary Failure

Heart transplantation in children has gained wide acceptance as an important adjunct to treatment of children with end-stage cardiomyopathic function from cardiomyopathy and palliated congenital heart disease. Successful transplantation has produced longer and better-quality lives for many infants and children. Ten-year survival free of malignancy and coronary vasculopathy is the expected outcome.[59]

The future is moving toward fewer transplant procedures in children. Palliation techniques for complex congenital heart disease (i.e., single-ventricle Fontan procedure) are improving, and most of these patients will survive well into adulthood before requiring transplantation. Complications of adolescents with transposition of the great arteries who have undergone a Senning procedure and now present with systemic or right ventricular dysfunction will begin to disappear because of success with the arterial switch.

The natural history of cardiomyopathy is changing because of our understanding of the cellular mechanisms of myocardial function. New treatment strategies using angiotensin receptor and β-adrenergic blockade therapy are delaying or replacing the need for heart transplantation.

Circulatory support is being miniaturized by the development of the Berlin Heart and the DeBakey centrifugal pump. These devices can cause reversed ventricular modeling, allowing discontinuation of support without heart replacement therapy. The other major benefit of circulatory support is that, if initiated early, it can rehabilitate the child, recover end-organ function, and reduce the risks of heart transplantation surgery.

References are available online at http://www.expertconsult.com.

Physiologic Foundations of Cardiopulmonary Resuscitation

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PEARLS

- Both the cardiac and thoracic pump mechanisms play a role in infants and children during cardiopulmonary resuscitation, so attention to excellent chest compression technique with an emphasis on "push hard, push fast" is critical to attaining sufficient cardiac output to maintain coronary and cerebral blood flow.
- Use of any vasoconstrictor (including vasopressin) should be sufficient to raise aortic diastolic pressure during cardiopulmonary resuscitation above the critical level for resuscitation success (>15 to 20 mm Hg).
- Amiodarone may be the most effective pharmacologic treatment for shock-resistant ventricular tachycardia or fibrillation.
- Use of the biphasic defibrillator is an important advance in the treatment of tachyarrhythmias and has advantages in its safety profile compared with monophasic defibrillators.
- Post–cardiac arrest resuscitative care is critical to survival and includes appropriate uses of inodilators and neuroprotective strategies, including mild to moderate hypothermia.

With the development of basic cardiopulmonary resuscitation (CPR) in the early 1960s, skilled resuscitation teams both in and out of the hospital were formed. The development of CPR saved lives; previously every victim of cardiac arrest had died. Soon thereafter, successful resuscitation of patients by basic life support measures, defibrillation, and medications became common even as long as 5 hours after commencement of CPR. Data show that the success of CPR depends on many factors. Rapid institution of basic life support measures (i.e., bystander CPR for sudden out-of-hospital cardiac arrest and immediate electrical countershock for ventricular fibrillation (VF) improve the chances of survival for patients experiencing sudden out-of-hospital cardiac arrest.[1] These measures led to the growing deployment of automatic external defibrillators (AEDs) in public places. Although immediate defibrillation currently is the standard of care, accumulating evidence indicates that basic life support and other measures directed at restoring energy substrates to the myocardium before countershock in patients with prolonged VF may further improve outcome.[2-4]

Other preexisting factors that play a role in successful resuscitation include the patient's age, prior medical condition, presenting cardiac rhythm, and the etiology of cardiac arrest. In 2008, a multiinstitutional prospective study was published that examined these preexisting factors and further described in two additional studies the clinical characteristics, hospital course, and outcomes of a cohort of children after in-hospital or out-of-hospital arrest. Besides demonstrating differences in clinical characteristics, these studies offered future considerations for the care of children who had experienced cardiac arrest and postresuscitative care, including hypothermia.[5,6] The low resuscitation rate in children, even when the patient does not have preexisting disease, probably results from the high incidence of asystole as the presenting rhythm. Asystole is the most common presenting rhythm in both in-hospital and out-of-hospital arrests, and is noted in 55% to 70% of victims.[7-11] Bradycardia and pulseless electrical activity (PEA) are other common rhythms. The high incidence of asystole in children who experience cardiac arrest can be explained by systemic disturbances such as hypoxia, acidosis, sepsis, and hypovolemia that commonly precede the arrest. Although ventricular arrhythmias usually are reported to be infrequent (range, 1.3% to 3.8%),[12] out-of-hospital series report VF in 10% to 19% of victims younger than 20 years.[13] These series, along with the observation that the frequency of witnessed arrest is much lower than in adults,[14] suggests that ventricular rhythms may be more common than usually estimated and that delay in resuscitation results in progression of nonperfusing rhythms to asystole. Increasing availability of AEDs may be contributing to the increased recognition of ventricular arrhythmias in out-of-hospital pediatric cardiac arrest. In specialized cardiac intensive care units (ICUs), ventricular arrhythmias account for as many as 30% of the arrests.[15]

In their original work on CPR, Kouwenhoven et al.[16] proposed that blood flow during closed-chest compressions resulted from squeezing of the heart between the sternum and vertebral column, now termed the cardiac blood flow mechanism. In fact, the precise mechanism by which forward circulatory flow is generated during closed-chest cardiac massage has major implications for current approaches to CPR. Other methods, such as vest CPR, simultaneous compression ventilation CPR (SCV-CPR), active compression-decompression CPR (ACD-CPR) both without and with an impedance

threshold valve (ITV), and interposed abdominal compressions with CPR (IAC-CPR), take into account advances in our understanding of the mechanism of blood flow during resuscitation.

The pharmacology of resuscitation remains controversial, and these controversies have led to major changes in the guidelines for CPR. Use of sodium bicarbonate, calcium chloride, and glucose remains unresolved at this time. The role of epinephrine and especially high-dose epinephrine has been readdressed because of concerns over postresuscitation deleterious effects on myocardial performance and poor outcomes. Evidence favoring a role for vasopressin, with a relatively pure vasoconstrictor effect, is accumulating. The role of lidocaine as the antiarrhythmic of choice for ventricular ectopy has been questioned as new data on the efficacy of amiodarone in persons in cardiac arrest have been generated. Research is ongoing into alternative vasoconstrictors[17] and the use of "pharmacologic cocktails" that may include β-blockers, antiarrhythmic agents, antioxidants, nitroglycerin,[1,18,19] and a vasoconstrictor in attempts to improve the resuscitation outcome and postresuscitation cardiac function.

Developments in the use of direct current countershock have occurred. Biphasic defibrillators are now widely in use and appear to improve the success of defibrillation at lower delivered energies and, it is hoped, decrease myocardial injury. As noted, the role of "shock first" is being reassessed because the success of electrical countershock in restoring spontaneous circulation declines rapidly after 3 to 4 minutes have elapsed.

Postresuscitation cerebral preservation has become an important area of focus, and mild therapeutic hypothermia has been found to improve neurologic outcome after adult cardiac arrest.

This chapter discusses the physiologic foundations of CPR. In the first section, the possible mechanisms of blood flow by the thoracic and cardiac pump mechanisms are discussed, including how the specific chest geometry of children and infants helps decide which of these mechanisms applies. Then newer CPR techniques, which take into account the physiologic mechanisms discussed in the first section, are discussed. Controversies and advances in pharmacologic management during CPR and current guidelines for use of drugs for resuscitation are addressed. New developments in the use of countershock, including the timing of shocks, the energy used, and the type of current delivery system used (biphasic or monophasic), are discussed. Finally, the role of therapeutic hypothermia is reviewed.

Mechanisms of Blood Flow

Cardiac Versus Thoracic Pump Mechanism

The cardiac pump hypothesis holds that blood flow is generated during closed-chest compressions when the heart is squeezed between the sternum and the vertebral column. This mechanism of flow implies that ventricular compression causes closure of the atrioventricular valves and that ejection of blood reduces ventricular volume. During chest relaxation, ventricular pressure falls below atrial pressure, allowing the atrioventricular valves to open and the ventricles to fill. This sequence of events resembles the normal cardiac cycle and occurs during cardiac compression when open-chest CPR is used.

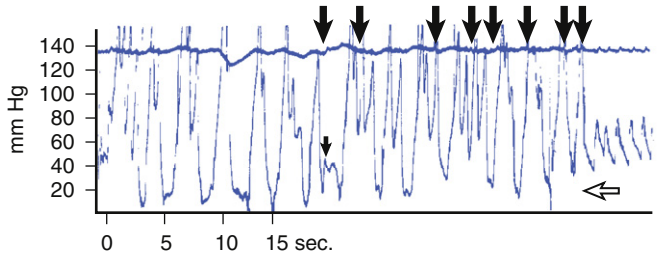

Figure 33–1. Cough-cardiopulmonary resuscitation during prolonged ventricular asystole after coronary arteriographic injection. An 18-second period of asystole after right coronary arteriographic injection is depicted. During this period, the patient coughed every 2 seconds, generating peak aortic pressures >140 mm Hg. *Large arrows* mark the intrinsic QRS complexes after the 18-second period of asystole. *Small arrow* marks the resultant aortic pressure from the first intrinsic beat. The patient continued to cough until the cardiac rhythm stabilized 40 seconds later. *(From Criley JM, Blaufuss AH, Kissel GL: Cough-induced cardiac compression. Self-administered form of cardiopulmonary resuscitation,* JAMA *263:1246, 1976.)*

Numerous clinical observations have conflicted with the cardiac pump hypothesis of blood flow. In 1964, Mackenzie et al.[20] found that closed-chest CPR produced similar elevations in arterial and venous intravascular pressures, the result of a generalized increase in intrathoracic pressure. In 1976, Criley et al.[21] made the dramatic observation that several patients in whom VF developed during cardiac catheterization produced enough blood flow to maintain consciousness by repetitive coughing (Figure 33-1). The production of blood flow by increasing thoracic pressure without direct cardiac compression describes the thoracic pump mechanism of blood flow during CPR.

During normal cardiac function, the lowest pressure in the vascular circuit occurs on the atrial side of the atrioventricular valves. This low pressure compartment is the downstream pressure for the systemic circulation, which allows venous return to the heart. Angiographic studies show that blood passes from the venae cavae through the right heart into the pulmonary artery and from the pulmonary veins through the left heart into the aorta during a single chest compression.

Echocardiographic studies show that, unlike normal cardiac activity or during open-chest CPR, during closed-chest CPR in both dogs[22] and humans,[23] the atrioventricular valves are open during blood ejection and aortic diameter decreases rather than increases during blood ejection. These findings during closed-chest CPR support the thoracic pump theory and argue that the heart is a passive conduit for blood flow (Figure 33-2).[24]

Initial measurements of hemodynamic data during chest compression for CPR found the generation of almost equal pressures in the left ventricle, aorta, right atrium, pulmonary artery, and esophagus (Figure 33-3).[25] The finding that all intrathoracic vascular pressures are equal implies that suprathoracic arterial pressures must be higher than suprathoracic venous pressures. The unequal transmission of intrathoracic pressure to the suprathoracic vasculature establishes the gradient necessary for blood flow. The transmission of intrathoracic pressure to the suprathoracic veins may be modulated by venous valves. The presence of these jugular venous valves has been demonstrated in animals[26] and humans[27,28] undergoing CPR. An ultrasonography study of healthy children confirmed the presence of these valves in 84% of 239 jugular

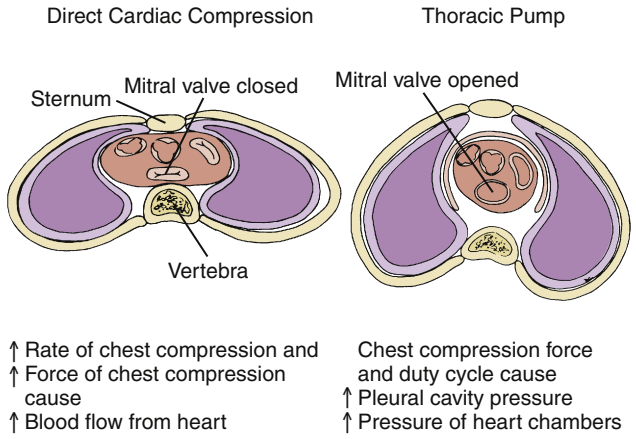

Figure 33–2. Possible mechanisms for blood flow during cardiopulmonary resuscitation include direct cardiac compression *(left)* and the thoracic pump *(right)*. With direct cardiac compression, an increase in chest compression rate causes an increase in blood flow by squeezing the heart between the vertebral column and sternum. With the thoracic pump mechanism, factors that increase pleural pressure cause an increase in pressure within the heart chambers and ultimately an increase in blood flow. *(From Schleien CL et al: Controversial issues in cardiopulmonary resuscitation,* Anesthesiology *71:135, 1989.)*

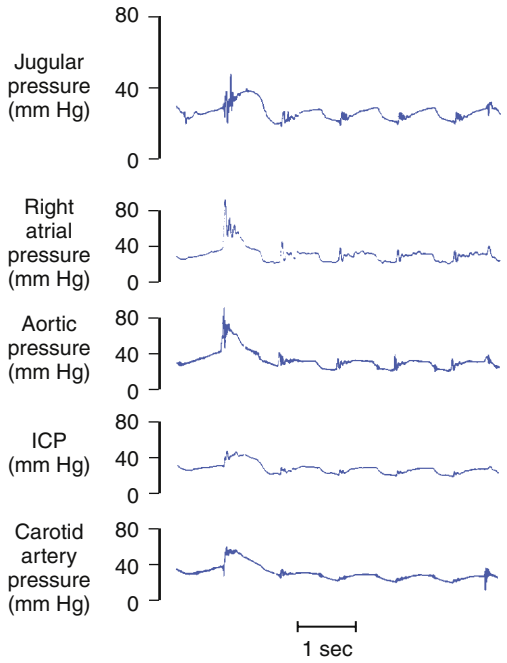

Figure 33–3. Original record during conventional cardiopulmonary resuscitation. The first compression for conventional cardiopulmonary resuscitation follows the lung inflation that occurred during the previous release phase. Note increase in pressure on this compression. *ICP,* Intracranial pressure. *(From Koehler RC, Chandra N, Guerci AD, et al: Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs,* Circulation *67:266, 1983.)*

veins studied. The valves were bilateral in 74% of children.[29] Transmission of intrathoracic pressure to the intracranial vault during CPR indicates that any such valve function is partial. Pathologic studies have also identified valves in the subclavian vein in the large majority of cadavers studied (87%). The absence of these valves in some patients is postulated to lead to failure of closed-chest CPR.[30]

Subsequent hemodynamic and echocardiographic studies found different results. Deshmukh et al.[31] demonstrated in a porcine model that mitral valve function persisted throughout resuscitation in 17 of 22 animals and that in successfully resuscitated animals, maximal aortic pressure exceeded that in the right atrium throughout the resuscitation. In another porcine model of resuscitation, Hackl et al.[32] manipulated the compressive force and depth of resuscitation by using a mechanical resuscitator. The frequency of mitral valve closure during compressive systole was directly proportional to the force and depth of chest compression. When the depth of compression reached 25% of the anteroposterior diameter, valve closure occurred in 95% of cycles. They concluded that the mechanism of blood flow was dependent on the force and depth of compression. In a study of CPR using transesophageal Doppler echocardiography in adults, Porter et al.[33] demonstrated mitral valve closure in compressive systole in the majority of patients (12 of 17) but not all patients. Peak mitral flow occurred in diastole and was significantly higher in the group with mitral valve closure. Peak mitral flow occurred during compressive systole in those without valve closure. Left ventricular fractional shortening correlated with change in anteroposterior chest wall diameter and not mitral valve flow. These authors concluded that nonuniform increased intrathoracic pressure plays a role in determining whether valve closure occurs during chest compressions. As noted, a decrease in aortic dimension during CPR has been demonstrated by echocardiography and taken as evidence for the thoracic pump mechanism of blood flow. Hwang et al.[34] readdressed this issue using transesophageal echocardiography. They studied the aortic dimension of the proximal and distal thoracic aorta and noted a decrease in the aortic dimension in the distal aorta directly inferior to the zone of direct compression and an increase in the dimension of the proximal aorta. They also noted mitral valve closure in all subjects and a decrease in left ventricular (LV) volume of almost 50% at end compression. These findings were believed to be most consistent with the cardiac pump mechanism of blood flow.[35] Kim et al.[36] also used transesophageal echocardiography to explore the role of the LV during nontraumatic arrests. They noted that during the compression phase of CPR, there was anterograde flow from the ventricle to the aorta, as well as retrograde flow toward the mitral valve. The mitral valve remained closed during compression and open during relaxation, while the aortic valve remained open during compression and closed during relaxation, which they concluded to be consistent with the cardiac pump mechanism.

The cardiac pump mechanism appears to predominate during closed-chest CPR in specific clinical situations. As noted, increasing the applied force during chest compressions increases the likelihood of direct cardiac compression.[32,36] A smaller chest size may allow for more direct cardiac compression. Adult dogs with small chests have better hemodynamics during closed-chest CPR than do dogs with large chests. Because the infant chest is smaller and more compliant than the adult chest, direct compression of the heart during CPR is more likely to occur. Blood flow during closed-chest CPR in a piglet model of cardiac arrest is higher than that achieved in adult models.[37] In contrast to adult animals, increasing intrathoracic pressure by SCV-CPR does not augment vascular pressure or regional organ blood flow during CPR in piglets.[38] The failure of SCV-CPR to increase blood

flow in the infant implies that direct compression occurs with conventional CPR and that additional intrathoracic pressure is of no benefit.

Rate and Duty Cycle

In 2010 the American Heart Association (AHA) recommended a rate of chest compressions of at least 100 per minute.[39] At faster rates, blood flow is enhanced whether the thoracic pump mechanism or the cardiac pump mechanism is invoked. Duty cycle is defined as the ratio of the duration of the compression phase to the entire compression-relaxation cycle expressed as a percent. For example, at a rate of 30 compressions/min, a 1.2-second compression time produces a 60% duty cycle. If blood flow is generated by direct cardiac compression, then the stroke volume is determined primarily by the force of compression. Prolonging the compression (increasing the duty cycle) beyond the time necessary for full ventricular ejection should have no additional effect on stroke volume. Increasing the rate of compressions should increase cardiac output because a fixed, relatively small volume of blood is ejected with each cardiac compression. In contrast, if blood flow is produced by the thoracic pump mechanism, the volume of blood to be ejected comes from a large reservoir of blood contained within the capacitance vessels in the chest. With the thoracic pump mechanism, flow is enhanced by increasing either the force of compression or the duty cycle but is not affected by changes in compression rate over a wide range of rates.[27] Additionally, the "push hard, push fast" recommendation is based on the maintenance of a higher compression rate with a higher force of compression. Allowing total recoil of the chest allows for full blood return during the relaxation phase of the cycle.[40]

Mathematical models of the cardiovascular system confirm that blood flow is determined by both the applied force and the compression duration with the thoracic pump mechanism.[41] A mathematical model equating CPR to a circuit, constructed by Babbs,[42] determined that while hemodynamics did not vary with compression rate, total flow and coronary flow were greatest when compression time equaled 30% of cycle time.

It appears from experimental animal data that both the thoracic pump and cardiac pump mechanisms can effectively generate blood flow during closed-chest CPR. Differences between various studies may be attributed to differences in animal models or compression techniques. Important differences in animal models include chest wall geometry, compliance and elastic recoil, compliance of the diaphragm, and intraabdominal pressure. Differences in technique include the magnitude of sternal displacement, compression force, momentum of chest compression, compression rate, and duty cycle. Experimental and clinical data support both mechanisms of blood flow during CPR in human infants.

Results of several studies in dogs demonstrated a benefit of a compression rate of 120 per minute compared with slower rates during conventional CPR.[43,44] In studies of piglets,[45] puppies,[46] and humans,[27,47] no differences were found comparing different rates of compression during conventional CPR. In a study of piglet CPR, duty cycle was the major determinant of cerebral perfusion pressure. The duty cycle at which venous return became limited varied with age. A longer duty cycle was more effective in younger piglets.[45]

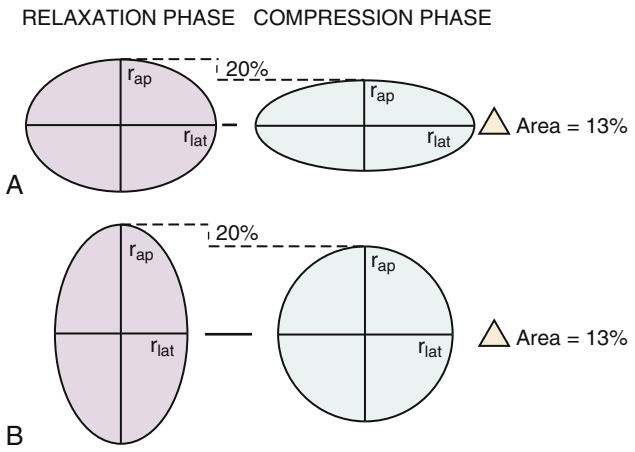

Figure 33–4. Changes in area of ellipses with constant circumference. Each ellipse is labeled with the anteroposterior *(ap)* and lateral *(lat)* radii, and a 20% anteroposterior compression is applied. Indicated change in area equals relaxed area – compressed area. **A,** Initial anteroposterior/lateral ratio = 0.7, and compression leads to positive ejection because relaxed area – compressed area is negative. **B,** Initial anteroposterior/lateral ratio = 1.4, and compression toward a circular shape results in an increase in area. *(From Dean JM, Koehler RC, Schleien CL, et al: Age-related changes in chest geometry during cardiopulmonary resuscitation,* J Appl Physiol *62:2212, 1987.)*

The discrepant importance of rate and duty cycle in various models (by different investigators) is confusing. However, increasing the rate of compressions during conventional CPR to 100 per minute satisfies both those who prefer the faster rates and those who support a longer duty cycle. This is true clinically because producing a longer duty cycle is easier when compressions are administered at a faster rate.

Chest Geometry

Chest geometry plays an important role in the ability of extrathoracic compressions to generate intrathoracic pressure. Shape, compliance, and deformability, which change greatly with age, are the chest characteristics that have the greatest impact during CPR.

The change in cross-sectional area of the chest during anterior to posterior delivered compressions is related to its shape (Figure 33-4).[48] The ratio of the chest anteroposterior diameter to the lateral diameter is referred to as the thoracic index. A keel-shaped chest, as seen in an adult dog, has a greater anteroposterior diameter and thus a thoracic index greater than 1. A flat chest, as in a thin human, has a greater lateral diameter and thus a thoracic index less than 1. A circular chest has a thoracic index equal to 1. A circle has a larger cross-sectional area than either of these elliptical chests. As an anteroposterior compression flattens a circle, the cross-sectional area decreases and compresses its contents. In contrast, as an anteroposterior compression is applied to the keel-shaped chest, the cross-sectional area increases as a circular shape is approached. The cross-sectional area of the keel-shaped chest does not decrease until the chest compression continues past the circular shape to flatten the chest. This implies a threshold past which the compression must proceed before intrathoracic contents are decreased and squeezed.[48] Thus the rounder, flatter chests of small dogs and pigs may require less chest displacement than the keel-shaped chests of adult dogs

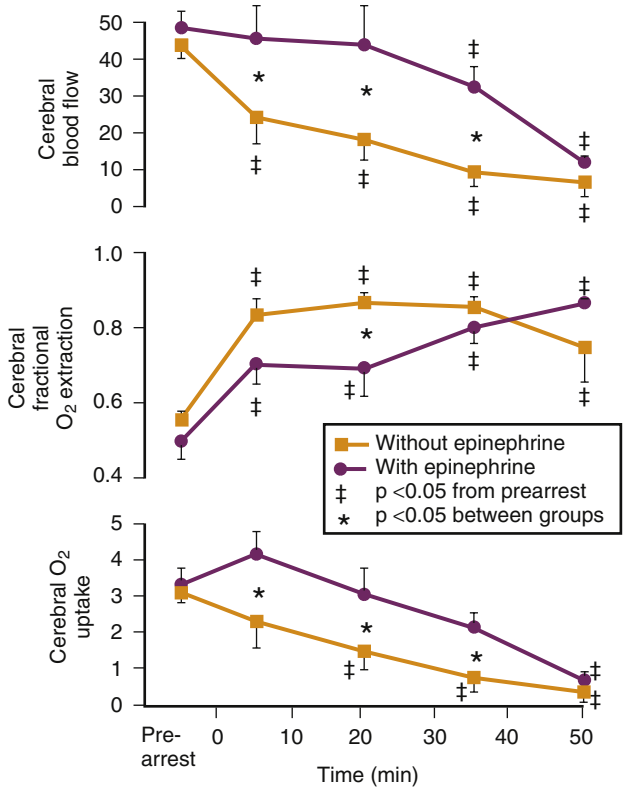

Figure 33–5. Total cerebral blood flow, cerebral fractional O_2 extraction, and cerebral O_2 uptake before cardiac arrest and during 50 minutes of cardiopulmonary resuscitation in the groups with and without epinephrine.

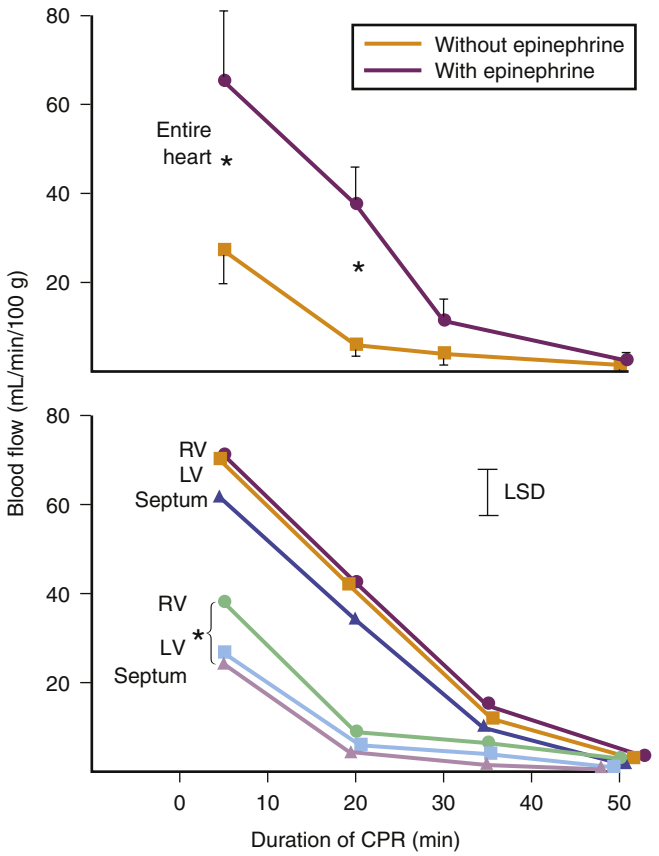

Figure 33–6. Top, Total myocardial blood flow during cardiopulmonary resuscitation (CPR) in piglets with and without epinephrine. *Asterisk* indicates significant difference between groups at 5 and 20 minutes. Bottom, Blood flow to right ventricular free wall *(RV, circle),* left ventricular free wall *(LV, squares),* and interventricular septum *(triangles)* in the groups with and without epinephrine. Standard error bars are omitted for clarity, but the least significant difference bar *(LSD,* derived from Duncan multiple-range test) is shown for comparisons among heart regions within an animal group. (Means must differ by height of bar for $P < .05$.) LSD for comparing means between groups is twice that shown for within-group LSD. *Asterisk* indicates that RV blood flow was greater than LV and septal blood flows at 5 minutes in the group without epinephrine. Flows in all three regions in the group with epinephrine were greater than those in the respective regions in the group without epinephrine at 5 and 20 minutes. *(From Schleien CL, Dean MJ, Koehler RC, et al: Effect of epinephrine on cerebral and myocardial perfusion in an infant animal preparation of cardiopulmonary resuscitation,* Circulation *73:809, 1986.)*

to generate thoracic ejection of blood. This dynamic has been demonstrated in small dogs having round chests compared with adult dogs having keel-shaped chests.[49]

As humans age, the cartilage of the rib cage calcifies and chest wall compliance decreases. Older patients may require greater compression force to generate the same sternal displacement. A 3-month-old piglet requires a much greater compression force for anteroposterior displacement than its 1-month-old counterpart.[48] Direct cardiac compression is more likely to occur in the more compliant chest of younger animals. Cerebral and myocardial blood flow during closed-chest CPR was much higher in infant piglets than in adults[50] (Figures 33-5 and 33-6). This finding supports the cardiac pump mechanism of blood flow in infants because the level of organ blood flow achieved during closed-chest CPR in piglets approaches the level achieved during open-chest cardiac massage in adults.

Marked deformation of the chest can occur during prolonged CPR and may alter the effectiveness of CPR (Figure 33-7).[50] Over time, the chest assumes a flatter shape, producing a larger percent decrease in cross-sectional area at the same absolute chest displacement. Progressive deformation may be beneficial if it leads to more direct cardiac compression. Unfortunately, too much deformation may decrease the recoil of the chest wall during the relaxation phase, leading to decreased cardiac filling. A progressive decrease in the effectiveness of chest compressions to produce blood flow is seen in piglets receiving conventional CPR.[50] Permanent deformation of the chest in this model approaches 30% of the original anteroposterior diameter. Attempting to limit deformation by increasing intrathoracic pressure from within during CPR with SCV-CPR was ineffective.[51] Using a thoracic vest to limit deformation when performing CPR greatly decreased the permanent chest deformation (3% vs. 30%) but did not attenuate the deterioration of vital organ blood flow with time.[52]

The characteristics of chest geometry of animals may relate to that in humans. Body weight, surface area, chest circumference, and diameter did not correlate with the magnitude of aortic pressure produced during CPR in a study of nine adults already declared dead.[52] A direct comparison of adult and pediatric human CPR has not been performed. The higher intravascular pressures and organ blood flow during CPR in infants compared with adults may result from more effective transmission of the force of chest compression because of the higher compliance and greater deformability of the infant chest.

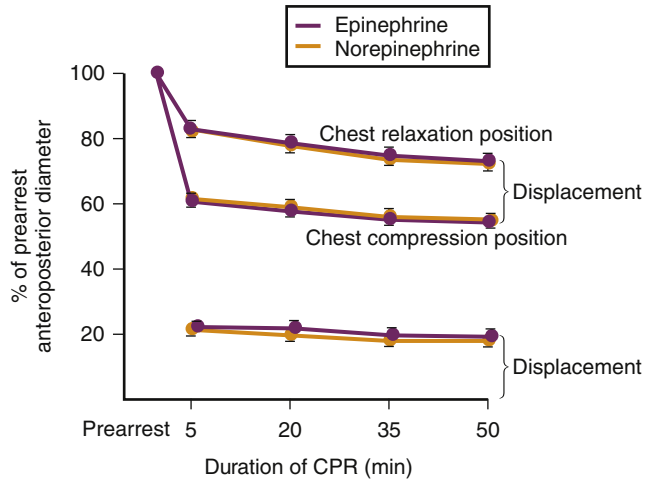

Figure 33–7. Piston position during chest compression and relaxation phases of the cycle, and net piston displacement expressed as a percent of prearrest anteroposterior chest diameter (12.0 ± 0.3 cm) in piglets. Note that displacement was essentially unchanged over the 50-minute duration, but marked deformation occurred during the relaxation phase by 5 minutes and continued to further deform over the 50-minute period in the groups with or without epinephrine. *CPR,* Cardiopulmonary resuscitation. *(From Schleien CL, Dean MJ, Koehler RC, et al: Effect of epinephrine on cerebral and myocardial perfusion in an infant animal preparation of cardiopulmonary resuscitation,* Circulation *73:809, 1986.)*

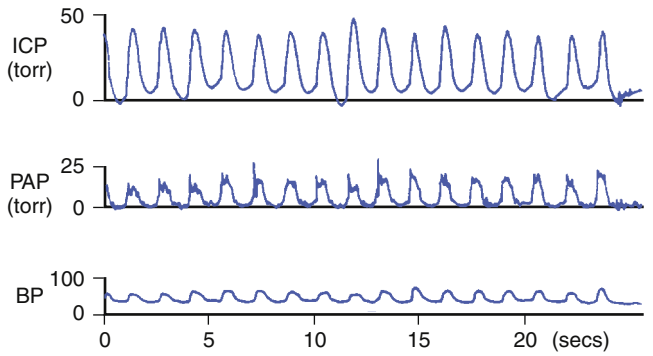

Figure 33–8. Relationship of intracranial pressure (ICP), pulmonary artery pressure (PAP), and arterial blood pressure (BP) during closed-chest cardiac massage. Note that each chest compression is accompanied not only by a rise in arterial and pulmonary artery pressure but also by a sharp rise in intracranial pressure. *(From Rogers MC, Nugent SK, Stidham GL: Effects of closed-chest cardiac massage on intracranial pressure,* Crit Care Med *7:454, 1979.)*

Effects of Cardiopulmonary Resuscitation on Intracranial Pressure

When chest compressions are applied, the increase in intrathoracic pressure is transmitted through the venous system of the head and neck to the intracranial vault, resulting in an increased intracranial pressure (ICP). Pressure is transmitted via the paravertebral veins and the cerebrospinal fluid during CPR in dogs.[53] Large swings in ICP corresponding to chest compressions occur in children undergoing CPR (Figure 33-8).[54] This transmission of intrathoracic pressure to the intracranial contents accounts for the low cerebral perfusion pressure by increasing the downstream pressure and cerebral blood flow during closed-chest CPR.

The relationship of ICP to intrathoracic pressure during CPR is linear. In dogs receiving conventional CPR, ICP increased by one third of the rise of intrathoracic pressure in a range from 10 to 90 mm Hg.[53] However, some modes of CPR change the intrathoracic to ICP relationship. In dogs, abdominal binding increases the transmission of pressure to the intracranial space to one half of the rise of intrathoracic pressure.[55] SCV-CPR, a mode of CPR designed to generate higher intrathoracic pressure, is similar to conventional CPR in its transmission of pressure to the cranium. Open-chest CPR decreases the transmission of pressure and improves cerebral perfusion pressure compared with conventional CPR. Thus increasing intrathoracic pressure may decrease cerebral blood flow because of the increase in downstream pressure, the ICP.

In this regard, ACD-CPR and ACD-ITV-CPR may have an advantage over conventional CPR. These techniques are designed to reduce intrathoracic pressure. Lindner et al.[56] showed in a porcine model that cerebral perfusion is increased with ACD-ITV-CPR compared with standard CPR. Using an adult porcine model of hypothermic VF arrest, the same group demonstrated by microdialysis techniques improved lactate/pyruvate ratios and reduced glucose accumulation in the ACD-ITV group compared with standard CPR.[57] In a pediatric porcine model of resuscitation, Voelckel et al.[58] found that ACD-CPR with ITV provided superior cerebral blood flow compared with standard CPR.

Newer Cardiopulmonary Resuscitation Techniques

Simultaneous Compression Ventilation Cardiopulmonary Resuscitation

SCV-CPR is a technique designed to increase blood flow during conventional CPR by increasing the thoracic pump mechanism contribution to blood flow. Delivering a breath simultaneously with every compression, instead of after every fifth compression, increases intrathoracic pressure and augments blood flow produced by closed-chest CPR.

Experimental studies have shown that SCV-CPR increases carotid blood flow compared with conventional CPR alone.[59] Subsequent studies confirmed physiologic advantages of SCV-CPR in canine models.[25] However, in infant piglets[51] and small dogs,[49] SCV-CPR offered no advantage over conventional CPR. In these small animals, the compliance and geometry of the chest may allow more direct cardiac compression. Thus higher intrathoracic pressure may be achieved with conventional CPR alone.[45,50] Coronary perfusion pressure (CPP) was either only minimally increased or even decreased in humans during SCV-CPR compared with conventional CPR. Survival was significantly worse in both animals[60] and humans[61] who received SCV-CPR compared with conventional CPR. No study has shown an increased survival rate with this technique of CPR.

Interposed Abdominal Compression Cardiopulmonary Resuscitation

IAC-CPR is the delivery of an abdominal compression during the relaxation phase of chest compression. An extensive review by Babbs[62] has been published. IAC-CPR may augment conventional CPR in several ways. First, IAC-CPR may return venous blood to the chest during chest relaxation.[63,64] Second, IAC-CPR increases intrathoracic pressure and augments the

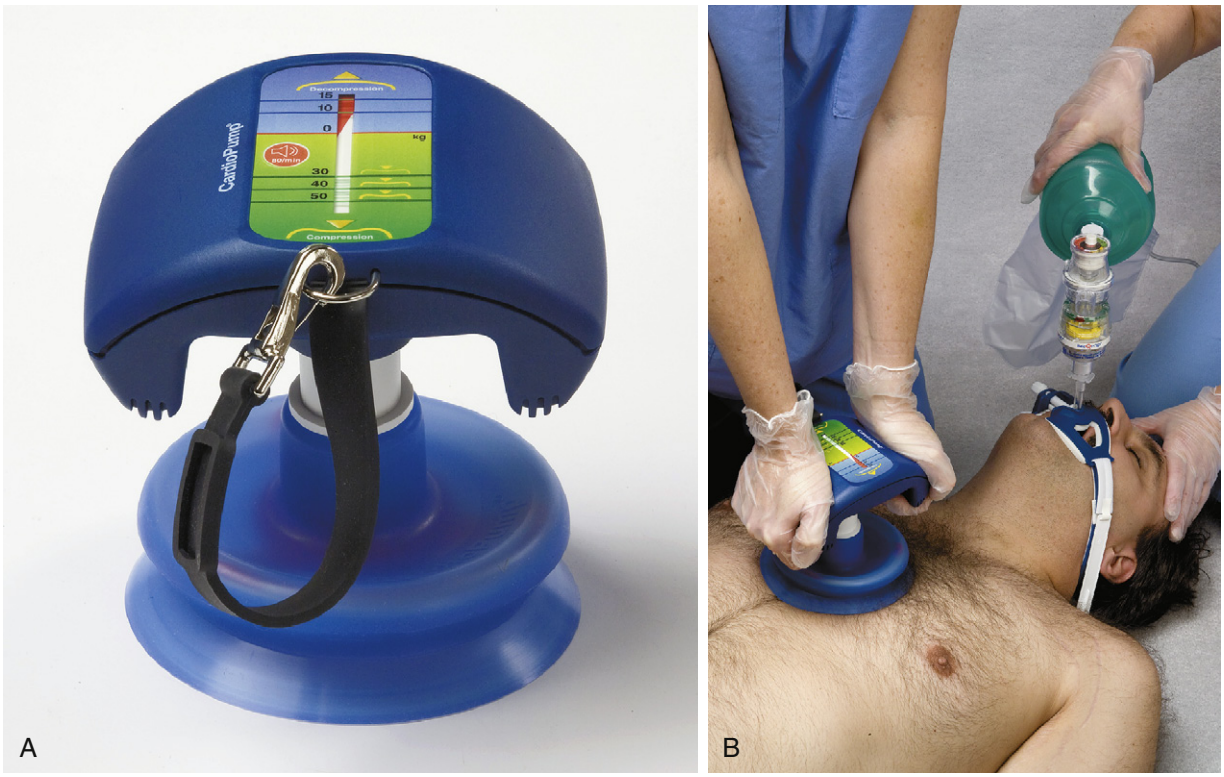

Figure 33–9. Device for performing active compression-decompression CPR. The upper part is a handle and the lower part is a suction cup. *(Courtesy AMBU Corporation. From Halperin H: New devices for generating blood flow during cardiopulmonary resuscitation,* Curr Opin Crit Care *10:188-192, 2004.)*

duty cycle of chest compression.[63,65] Third, IAC-CPR may compress the aorta and return blood retrograde to the carotid or coronary arteries.[64] IAC-CPR is an attractive alternative to some of the newer techniques of CPR because it requires no additional equipment for implementation; however, it does require training and manpower.

In animal experiments, cardiac output and cerebral and coronary blood flow were improved when comparing IAC-CPR with conventional CPR,[66] but not in an infant model.[67] Initial human studies also demonstrated an increase in aortic pressure and CPP during IAC-CPR compared with conventional CPR.[68] Four randomized controlled trials have compared IAC-CPR with standard CPR. The first trial reported in 1985 by Mateer et al.[69] was the largest and included 291 patients. IAC-CPR was applied in the field by paramedics until ambulance transport. No differences in mortality were found. The later trials involved a total of 279 hospitalized patients.[70,71,269] The results from these trials are more positive, and a meta-analysis of these studies found an increased likelihood of return of spontaneous circulation (ROSC) and intact survival to discharge with IAC-CPR versus standard CPR.[72] Although no intraabdominal trauma was detected in any of the 426 patients in these trials, one pediatric case report demonstrated direct pancreatic injury. Alternative techniques for abdominal hand position were studied in adult swine.[73,74] A stacked hand position similar to the usual position for chest compression over the abdominal aorta was compared with a diffuse hand position in which the hands were placed on the abdomen separately. This study demonstrated a significant increase in aortic diastolic pressure compared with standard CPR. However, CPP was not augmented because the right atrial diastolic pressure was also elevated. Stacked hand position was found to produce a CPP equivalent to standard CPR. Diffuse hand position, however, was associated with decreased CPP, so if the technique is applied, this hand position should be avoided. Application of IAC-CPR is limited by the need for training and for the additional manpower. Although it has not been studied in a pediatric group, with skilled personnel available, IAC-CPR should be considered for use with inpatient arrests.

Active Compression-Decompression Cardiopulmonary Resuscitation and Impedance Threshold Valve Interposition

ACD-CPR uses a negative pressure "pull" on the thorax during the release phase of chest compression using a hand-held suction device (Figure 33-9).[75] This technique improves vascular pressures and minute ventilation during CPR in animals[77,78] and humans.[75,79] The mechanism of benefit of this technique is attributed to enhancement of venous return by the negative intrathoracic pressure generated during the decompression phase; in addition, it reverses the chest wall deformation that accompanies standard CPR.[80] Preliminary results in adults were promising,[77,81,82] and a large multiinstitutional study of ACD-CPR completed in Europe found that ACD-CPR was superior to standard CPR. In this study, a total of 750 patients were randomly assigned to receive standard CPR or ACD-CPR. In the experimental group, 5% survived to 1 year (12 patients with intact neurologic status), versus 2% (three patients with intact neurologic status) in the standard group.[83] However, a number of other trials have not shown a difference between standard CPR and ACD-CPR. A Cochrane Database Systematic Review concluded there was no consistent benefit from use of this technique.[84] The effectiveness of

ACD-CPR appears to be relatively site specific. Explanations for this variability have focused on the effectiveness of training for providers and intersite variation of on-scene advanced life support techniques.[80] Use of ACD-CPR requires significantly more physical effort than conventional CPR, and this requirement may have influenced outcome.[85] No device is currently cleared for clinical use in the United States at this time.

Use of an inspiratory threshold valve has been evaluated in attempts to improve the outcome with ACD-CPR.[83,86] This technique involves the use of a valve placed between the ventilating bag and the airway, which is designed to close when the tracheal pressure falls below atmospheric pressure, enhancing the development of negative intrathoracic pressure during ACD-CPR (Figures 33-10 and 33-11). Animal studies,[87,88] including a young porcine model,[58] showed improved organ perfusion, and brain microdialysis studies demonstrated decreased lactate accumulation and improved glucose utilization.[57] In a small series of patients, diastolic pressure was raised along with CPP and end-tidal CO_2 ($EtCO_2$) release.[89] These studies led to an inclusion of the technique as an acceptable alternative to standard CPR in the 2000 AHA guidelines and subsequent revised guidelines.[90] Plaisance et al.[83] reported on a series of 400 patients randomly assigned to ACD-CPR with ITV or sham ITV. Survival at 24 hours was significantly improved. There was a nonsignificant trend toward improved neurologic survival, with 6 of 10 discharged patients having intact survival compared with 1 of 8 discharged survivors in the sham ITV group. In two randomized control studies by Wolcke et al. and Plaisance et al. of 610 adults in cardiac arrest in the out of hospital setting, use of ACD-CPR plus the ITD was associated with improved ROSC and 24-hour survival rates when compared with CPR alone.[91] The addition of the ITD was associated with improved hemodynamics during standard CPR in one clinical study.[90] The ultimate role of this technique, which requires specialized equipment and significant resuscitator training, remains to be determined.[83,92]

Vest Cardiopulmonary Resuscitation

Vest CPR uses an inflatable bladder resembling a blood pressure cuff that is wrapped circumferentially around the chest and inflated phasically to increase intrathoracic pressure. Because chest dimensions are changed minimally, direct cardiac compression is unlikely. In addition, the even distribution of the force of compression over the entire chest wall decreases the likelihood of trauma to the skeletal chest wall and its thoracic contents.

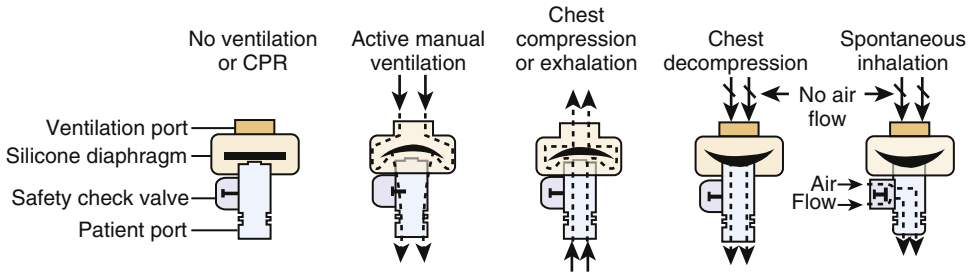

Figure 33–10. Schematic diagram of impedance threshold valve. During a positive pressure ventilation the valve is open and gas flows. During chest compression or exhalation air moves freely through the valve. During chest decompression airflow is impeded by the valve decreasing intrathoracic pressure. During spontaneous ventilation the check valve opens allowing gas flow. *CPR,* Cardiopulmonary resuscitation. *(From Lurie KG, Barnes TA, Zielinski TM, et al: Evaluation of a prototypic inspiratory impedance valve designed to enhance the efficiency of cardiopulmonary resuscitation,* Resp Care *48[1]:52-57, 2003.)*

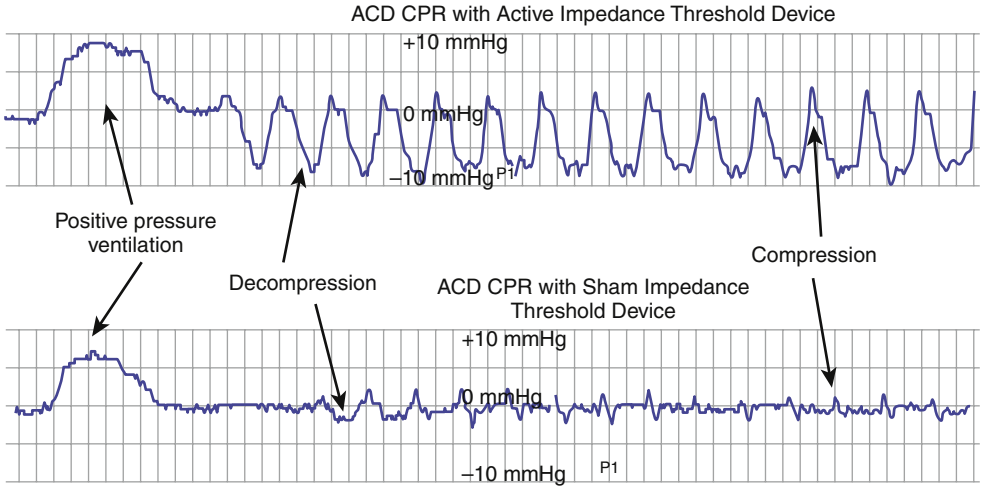

Figure 33–11. Example of intratracheal pressures, a surrogate for intrathoracic pressures, in a patient undergoing cardiopulmonary resuscitation (CPR) with an automated compression device (ACD) with and without an impedance threshold device attached to a face mask. CPR was delivered at 100 compression/decompression cycles/min with a synchronized compression/ventilation ratio of 15:2. Note the absence of significant decreases in intratracheal pressures with a sham device. With the active impedance threshold device, wide fluctuations in intratracheal pressure are seen with each compression and decompression. *(Courtesy M. Lurie, MD, and Advanced Circulatory Systems, Inc.)*

Improvement of cerebral and myocardial blood flows[93,94] and survival[95,96] with vest CPR compared with conventional CPR was seen in dogs. In piglets, a 3% permanent chest deformation was seen after 50 minutes of vest CPR,[52] compared with an almost 30% deformation produced during an equivalent period of conventional CPR.[50] In a human study, vest CPR increased aortic systolic pressure but had little effect on aortic diastolic pressure compared with conventional CPR.[97] Despite its late application, vest CPR improved the hemodynamics and the rate of ROSC in adult patients in another study.[98] Evidence from a case control study of 162 adults documented improvement in survival to the emergency department when vest CPR was administered by adequately trained personnel to patients in cardiac arrest in the out-of-hospital setting.[99] The lack of metallic parts has allowed vest CPR to be used experimentally during nuclear magnetic resonance spectroscopy to study brain intracellular pH.[100] The vest also has been used as an external cardiac assist device in nonarrested dogs with heart failure.[101] Clinically, the use of vest CPR depends on sophisticated equipment and remains experimental at this time.

Abdominal Binding

Abdominal binders and military antishock trousers have been used to augment closed-chest CPR. Both methods apply continuous compression circumferentially below the diaphragm. Three mechanisms have been proposed for augmentation of CPR by these binders. First, binding the abdomen decreases the compliance of the diaphragm and raises intrathoracic pressure. Second, blood may be moved out of the intrathoracic structures to increase circulating blood volume. Third, applying pressure to the subdiaphragmatic vasculature and increasing its resistance may increase suprathoracic blood flow. These effects increase aortic pressure and carotid blood flow in both animals[25] and humans.[102] Unfortunately, as aortic pressure increases, the downstream component of CPP, namely, right atrial pressure, increases to an even greater extent, resulting in decreased CPP and myocardial blood flow.[22] These techniques also lower the cerebral perfusion pressure by enhanced transmission of intrathoracic pressure to the intracranial vault, which raises ICP (the downstream component of cerebral perfusion pressure). Clinical studies have failed to show an increased survival when an abdominal binder or military antishock trouser suit was used to augment CPR.

Open-Chest Cardiopulmonary Resuscitation

Use of open-chest cardiac massage has generally been replaced by closed-chest CPR. Compared with closed-chest CPR, open-chest CPR generates higher cardiac output and vital organ blood flow. During open-chest CPR there is less elevation of intrathoracic, right atrial, and intracranial pressure, resulting in higher coronary and cerebral perfusion pressure and higher myocardial and cerebral blood flow.[103]

Open-chest CPR is not a technique that can be applied by most health care personnel. It can be used in the operating room, ICU, or emergency department equipped with the necessary surgical and technical equipment and personnel. It is easily used in the operating room or ICU after cardiac surgery when the open chest can be easily accessed. Open-chest CPR is indicated for cardiac arrest resulting from cardiac tamponade, hypothermia, critical aortic stenosis, and ruptured aortic aneurysm. Other indications include cardiac arrest resulting from penetrating or crushed chest wall abnormalities that make closed-chest CPR impossible or ineffective.[40] Open-chest CPR is indicated for select patients when closed-chest CPR has failed, although exactly which patients should receive this method of resuscitation under this condition is controversial. When initiated early after failure of closed-chest CPR, open-chest CPR may improve outcome.[104] When performed after 15 minutes of closed-chest CPR, open-chest CPR significantly improves CPP and the rate of successful resuscitation.[105]

Cardiopulmonary Bypass

Because of the low rate of survival after prolonged CPR, more aggressive methods have been suggested to improve its success: cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation CPR.[39]

CPB is one of the most effective ways to restore circulation after cardiac arrest. Animal studies show that CPB increases survival at 72 hours, increases recovery of consciousness, and preserves the myocardium better than does conventional CPR.[106] In dogs, CPB resulted in better neurologic outcome than conventional CPR after a 4-minute ischemic period; however, neurologic outcome was dismal in both groups when the ischemic period lasted 12 minutes.[106] Some 90% of dogs survived 24 hours after 15 to 20 minutes of cardiac arrest, but only 10% survived when the arrest time was prolonged to 30 minutes when CPB was used for stabilization during defibrillation.[108] CPB decreased myocardial infarct size in a model involving coronary artery occlusion compared with conventional CPR.[109] In all animal models, CPB improves the success of resuscitation compared with conventional CPR.

Human experience with CPB for cardiac arrest outside the operating room is growing. Morris et al.[110] reviewed these data. Accumulated experience now includes seven pediatric series reporting on 127 cases and 10 adult series reporting on 331 cases. Overall survival is excellent compared with conventional CPR despite long arrest times. In both groups, survival to decannulation is approximately 60% despite average precannulation CPR times, where reported, ranging from 16 to 60 minutes for children and from 20 to 80 minutes for adults. Long-term survival is remarkable, with 47% of children and 31% of adults achieving long-term survival. In the largest series of children reported by Morris et al.,[110] between 1995 and 2002, 64 children underwent 66 extracorporeal membrane oxygenation (ECMO) runs initiated during active resuscitation with chest compressions or internal cardiac massage. Of these patients, 33 (50%) were decannulated and survived for more than 24 hours, 21 (33%) survived to hospital discharge, and 16 (26%) reportedly had no major changes in neurologic outcome. The average duration of CPR before cannulation in the survivors was 50 minutes. Of the six surviving children who required more than 60 minutes of CPR before ECMO, three had no apparent change in neurologic status. During the same period, 73 children underwent standard CPR; 10 received CPR for more than 30 minutes, with no survivors. Duncan et al.[111] reported a series of 18 pediatric cardiac surgical patients at the Boston Children's Hospital who received ECMO during active chest compressions. Of the first seven patients, only 29% survived. This led to the development of a rapid ECMO deployment strategy in which an ECMO pump is

kept saline-primed in the ICU at all times, allowing initiation of extracorporeal support within 15 minutes. Precannulation support times dropped from an average of 90 minutes but still remained high at an average of 50 minutes. Of the remaining 11 patients, 10 were decannulated successfully, with 6 long-term survivors, 5 of whom were in New York Heart Association class I. This rapid deployment strategy likely will become more commonplace in large pediatric centers.

Under current 2010 AHA guidelines, centers should consider extracorporeal membrane oxygenation CPR for in-hospital cardiac arrest refractory to standard resuscitation attempts if the condition leading to cardiac arrest is reversible or amenable to heart transplantation, if excellent conventional CPR has been performed after no more than several minutes of no-flow cardiac arrest, and if the institution is able to rapidly perform ECMO. Long-term survival has been reported even after more than 150 minutes of CPR in selected patients.[112]

Data are emerging involving the role of ECMO in persons with refractory ventricular fibrillation.[113] These data have solely been in the form of case reports but may represent a future direction for the care of patients with VF. In 2006, Samson et al.[114] reported successful treatment of in-hospital VF in children with ECMO after cardiac arrest who had an initial rhythm of VF and immediate initiation of CPR.

CPB and ECMO require a great deal of technical support and sophistication. In units with preprimed circuits on standby, CPB can be implemented quickly and with moderate success in a population of children who would otherwise almost certainly die. The success with some patients undergoing very long CPR times followed by ECMO use is encouraging and suggests the possibility of reversible myocardial injury as a cause of resuscitation failure in a subset of patients. Overall, ECMO is unlikely to have a major impact on pediatric outcome because of its limited availability.

Transcutaneous Cardiac Pacing

Transcutaneous cardiac pacing (TCP) is used as a method for noninvasive pacing of the ventricles for a relatively short period. Emergency cardiac pacing is successful in resuscitation only if it is initiated soon after the onset of arrest. In the absence of in situ pacing wires or an indwelling transvenous or esophageal pacing catheter, TCP is the preferred method for temporary electrical cardiac pacing. Since 1992, the AHA advanced cardiovascular life support (ACLS) guidelines have recommended the early use of an external pacemaker in patients with symptomatic bradycardia or asystole.[115]

Since Zoll[116] established TCP in 1952 as a clinically useful method of pacing adult patients during ventricular standstill (Stokes-Adams attacks) and bradycardia-associated hypotension, numerous anecdotal reports have supported its use for bradycardic or asystolic arrests. Zoll et al.[117] reported successful in-hospital resuscitation of 12 of 16 patients with hypotensive bradycardia or asystole if TCP was initiated within 5 minutes of the arrest. In contrast, if TCP was started between 5 and 30 minutes after the arrest, only 8 of 44 patients with either of these rhythms could be resuscitated.[117] In two controlled clinical trials of prehospital TCP, no differences in the survival rate or success of resuscitation were observed in paced and nonpaced patients who had asystole or PEA.[118,119] In patients with symptomatic bradycardia, TCP improved resuscitation and the survival rate.[120]

To date the efficacy of TCP in resuscitation of children has not been studied. Beland et al.[121] showed that effective TCP could be achieved in hemodynamically stable children during induction of anesthesia for heart surgery. They were successful in 53 of 56 pacing trials, and the patients experienced no complications.[121]

TCP is indicated for patients whose primary problem is impulse formation or conduction and who have preserved myocardial function. TCP is most effective in patients with sinus bradycardia or high-grade atrioventricular block with slow ventricular response who also have a stroke volume sufficient to generate a pulse. TCP is not indicated for patients in prolonged arrest because in this situation TCP usually results in electrical but not mechanical cardiac capture, and its use may delay or interfere with other resuscitative efforts.

To set up pacing, one electrode is placed anteriorly at the left sternal border and the other posteriorly just below the left scapula. Smaller electrodes are available for infants and children; adult-sized electrodes can be used in children weighing more than 15 kg.[121] Electrocardiographic leads should be connected to the pacemaker, the demand or asynchronous mode selected, and an age-appropriate heart rate used. The stimulus output should be set at zero when the pacemaker is turned on and then increased gradually until electrical capture is seen on the monitor. The output required for a hemodynamically unstable rhythm is higher than that for a stable rhythm in children in whom the mean stimulus required for capture was between 52 and 65 mA. After electrical capture is achieved, one must ascertain whether an effective arterial pulse is generated. If pulses are not adequate, other resuscitative efforts should be used.

The most serious complication of TCP is induction of a ventricular arrhythmia.[122] Fortunately, this complication is rare and may be prevented by pacing only in the demand mode. Mild transient erythema beneath the electrodes is common. Skeletal muscle contraction can be minimized by using large electrodes, a 40-ms pulse duration, and the smallest stimulus required for capture. Sedatives or analgesics may be necessary in the patient who is awake. If defibrillation or cardioversion is necessary, one must allow a distance of 2 to 3 cm between the electrode and paddles to prevent arcing of the current.

Pharmacology

Adrenergic Agonists

In 1963, only 3 years after the original description of closed-chest CPR, Pearson and Redding[123] described the use of adrenergic agonists for resuscitation. They subsequently showed that early administration of epinephrine in a canine model of cardiac arrest improved the success rate of CPR. They also demonstrated that the increase in aortic diastolic pressure by administration of α-adrenergic agonists was responsible for the improved success of resuscitation. They theorized that vasopressors such as epinephrine were of value because the drug increased peripheral vascular tone, not because of a direct effect on the heart.[124]

Yakaitis et al.[125] investigated the relative importance of α- and β-adrenergic agonist actions during resuscitation. Only 27% dogs that received a pure β-adrenergic receptor agonist along with an α-adrenergic antagonist were resuscitated successfully, compared with all of the dogs that received a pure α-adrenergic agonist and a β-adrenergic antagonist

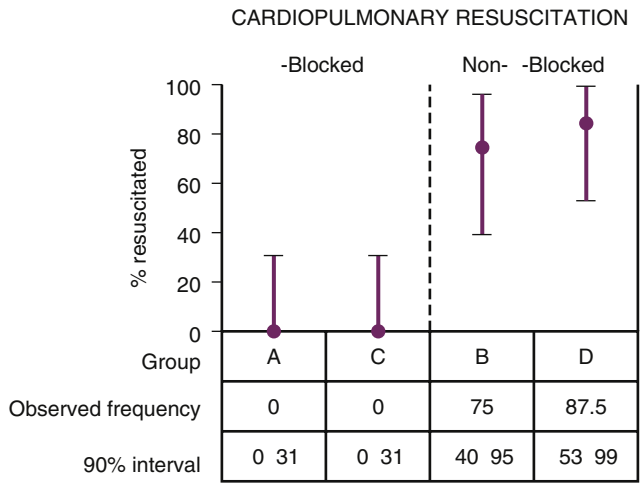

Figure 33–12. Beneficial effect of α-adrenergic activity on resuscitation. Animals in group A received phenoxybenzamine; group B received propranolol; group C received phenoxybenzamine and propranolol; and group D received no drug. The 90% confidence intervals are reported for the sample size and observed resuscitation success. The lack of overlap between the α- and non–α-blocked groups indicates a significant benefit ($P \leq .01$) during resuscitation when α-adrenergic activity is intact. *(From Yakaitis RW, Otto CW, Blitt CD: Relative importance of alpha and beta adrenergic receptors during resuscitation,* Crit Care Med *7:293, 1979.)*

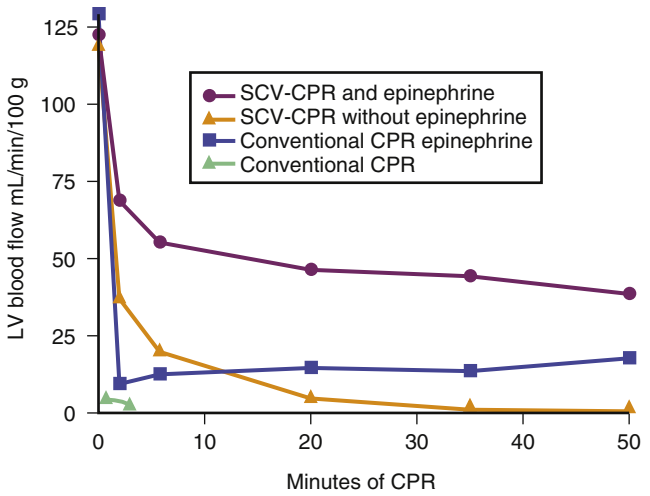

Figure 33–13. Left ventricular (LV) blood flow before arrest and during four types of cardiopulmonary resuscitation (CPR). Note the rapid falloff of LV blood flow when epinephrine is not used. *SCV-CPR,* Simultaneous compression ventilation CPR. *(From Michael JR, Guerci AD, Koehler RC, et al: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs,* Circulation *69:822, 1984.)*

(Figure 33-12). Later studies reconfirmed this finding. Michael et al.[37] demonstrated that the α-adrenergic effects of epinephrine result in intense vasoconstriction of the resistance vessels of all organs of the body, except those supplying the heart and brain. Because of the widespread vasoconstriction in nonvital organs, adequate perfusion pressure and thus blood flow to the heart and brain can be achieved despite the fact that cardiac output is very low during CPR (Figure 33-13).[50]

The increase in aortic diastolic pressure associated with epinephrine administration during CPR is critical for maintaining coronary blood flow and enhancing the success of resuscitation. Even though the contractile state of the myocardium is increased by use of β-adrenergic agonists in the spontaneously beating heart, during CPR, β-adrenergic agonists actually may decrease myocardial blood flow by increasing intramyocardial wall pressure and vascular resistance. This decrease in mycoardial blood flow could redistribute intramyocardial blood flow away from the subendocardium, increasing the likelihood of ischemic injury to this region.[126] Moreover, evidence indicates that left ventricular end-diastolic pressure (LVEDP) rises with epinephrine use, reducing the overall impact of the vasoconstrictor effects of epinephrine on CPP. Tang et al.[127] showed elevated LVEDP and decreased measures of diastolic performance in epinephrine-resuscitated rats after induced VF compared with phenylephrine-resuscitated animals or epinephrine-resuscitated animals who also received a β-blocker. Similar data were found by McNamara, who used a rat pup model of asphyxial arrest. LVEDP was increased and diastolic function indices decreased with epinephrine compared with either saline solution alone or epinephrine combined with verapamil. These data imply that excessive β-adrenergic effects prevent the intracellular calcium reuptake during diastole that is required for myocardial relaxation. By its inotropic and chronotropic effects, β-adrenergic stimulation increases myocardial oxygen demand, which, when superimposed on low coronary blood flow, increases the risk of ischemic injury. This combination of increased oxygen demand by β-adrenergic agonists[128] and decreased oxygen supply may damage an already ischemic heart, raising the question of whether a pure α-adrenergic agonist would be better than epinephrine, which has significant β-adrenergic effects (Box 33-1). The effects on energy utilization and oxygen supply not only have implications for the success of the initial resuscitation but also for the postresuscitation function of the myocardium.

A number of studies have attempted to settle this controversy and actually have shown that pure α-adrenergic agonists can be used in place of epinephrine during CPR. Phenylephrine[50,124,125] and methoxamine are two pure α-adrenergic agonists that have been used in animal models of CPR with success equal to that of epinephrine. More recently, vasopressin has been studied as a noncatecholamine vasoconstrictor in the management of patients who experience cardiac arrest.[12] This agent is discussed in the section on vasopressin. These agents cause peripheral vasoconstriction and increase aortic diastolic pressure, resulting in improved myocardial

Box 33–1 α-Adrenergic vs. β-Adrenergic Agonist Effects

α-Adrenergic Effects

- Vasoconstrict peripheral vessels
- Maintain aortic diastolic pressure
- Improve coronary blood flow
- *No* metabolic stimulatory effect

β-Adrenergic Effects

- Vasodilate peripheral vessels
- Decrease aortic diastolic pressure
- Increase cellular metabolic rate
- Positive inotrope
- Increase intensity of ventricular fibrillation
- Increase heart rate and/or dysrhythmias following resuscitation

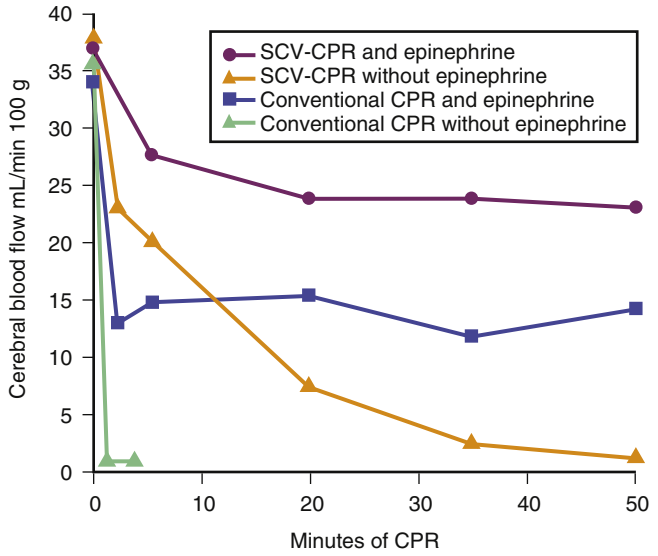

Figure 33–14. Cerebral blood flow before arrest and during four types of 50 minutes of cardiopulmonary resuscitation (CPR). *SCV-CPR,* Simultaneous compression ventilation CPR. *(From Michael JR, Guerci AD, Koehler RC, et al: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs,* Circulation *69:822, 1984.)*

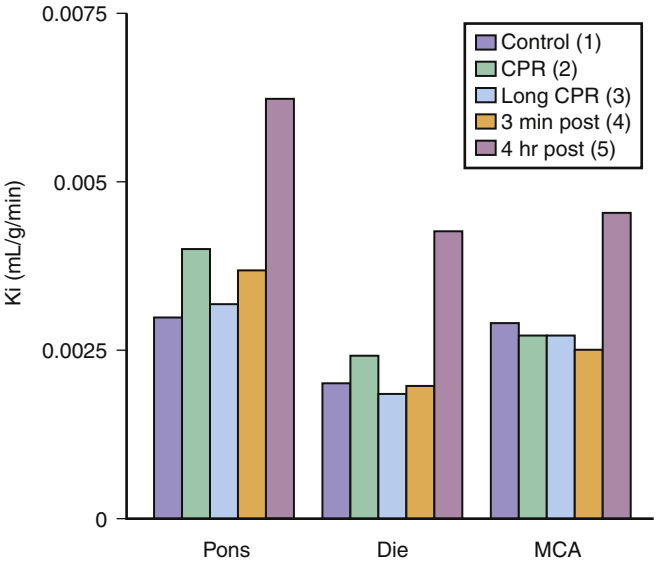

Figure 33–15. Transfer coefficient (K_i) of α-aminoisobutyric acid for pons, diencephalon (DIE), and middle cerebral (MCA) artery regions. Control group; 8 minutes ischemia and 10 minutes cardiopulmonary resuscitation (CPR); 8 minutes ischemia and 40 minutes cardiopulmonary resuscitation; 3 minutes after resuscitation; 4 hours after resuscitation. Group 5 in each region $*P < .05$, different from group 1 by one-way analysis of variance and Dunnett test for all three regions. *(From Schleien CL, Koehler RC, Schaffner DH, et al: Blood-brain barrier disruption after cardiopulmonary resuscitation in immature swine,* Stroke *22:477, 1991.)*

and cerebral blood flow. This effect results in a higher oxygen supply/demand ratio in the ischemic heart and, at least, a theoretical advantage over the combined α- and β-adrenergic agonist effects of epinephrine. These agonists,[124,130] as well as vasopressors such as vasopressin,[12] have been used successfully for resuscitation. These drugs maintain blood flow to the heart during CPR as well as epinephrine does. In an animal model of VF cardiac arrest, a resuscitation rate of 75% was reported for both epinephrine- and phenylephrine-treated groups. In this study, the ratio of endocardial to epicardial blood flow was lower in the group treated with epinephrine, suggesting the presence of subendocardial ischemia.[50] However, studies of this kind are difficult to interpret because of the inability to measure the degree of α-receptor activation by the different vasopressors. The higher subendocardial blood flow in the phenylephrine group may have been the result of less α-receptor activation.[131-133] Moreover, some investigators have questioned the merits of using a pure α-adrenergic agonist during CPR. Although the inotropic and chronotropic effects of β-adrenergic agonists may have deleterious hemodynamic effects during CPR administered for VF, increases in both heart rate and contractility increase cardiac output when spontaneous coordinated ventricular contractions are achieved.

Cerebral blood flow during CPR, like coronary blood flow, depends on peripheral vasoconstriction and is enhanced by use of α-adrenergic agonists. This action produces selective vasoconstriction of noncerebral peripheral vessels to areas of the head and scalp without causing cerebral vasoconstriction.[50] As with myocardial blood flow, pure α-agonist agents are as effective as epinephrine in generating and sustaining cerebral blood flow during CPR in adult animal models[130] and in infant models (Figure 33-14).[50] No difference in neurologic deficits 24 hours after cardiac arrest was found between animals receiving either epinephrine or phenylephrine during CPR.[134]

Analogous to the heart, β-adrenergic agonists could increase cerebral oxygen uptake if a sufficient amount of drug crosses the blood-brain barrier during or after resuscitation. In addition, adrenergic agonists may vasoconstrict or dilate cerebral vessels, depending on the balance between α- and β-adrenergic receptors. Epinephrine and phenylephrine had similar effects on cerebral blood flow and metabolism, maintaining normal cerebral oxygen uptake for 20 minutes of CPR in dogs. This finding implies that cerebral blood flow was high enough to maintain adequate cerebral metabolism and that β-receptor stimulation did not increase cerebral oxygen uptake, despite the fact that the combined effects of brain ischemia and CPR can increase the permeability of the blood-brain barrier to drugs used during CPR or when enzymatic barriers to vasopressors (e.g., by monoamine oxidase) are overwhelmed during tissue hypoxia. Mechanical disruption of the barrier could occur during chest compressions by large fluctuations in cerebral venous and arterial pressures or as a result of hyperemia, the large increase in cerebral blood flow that occurs during the early reperfusion period when the cerebral vascular bed is maximally dilated following resuscitation, particularly if systemic hypertension occurs.[135] No blood-brain barrier permeability changes during CPR immediately after resuscitation or 4 hours after resuscitation were found in adult dogs.[135] However, after 8 minutes of cardiac arrest and 6 minutes of CPR in piglets, the blood-brain barrier was permeable to the small neutral amino acid α-aminoisobutyric acid 4 hours after cardiac arrest (Figure 33-15).[136] The increase in permeability could be prevented by prearrest administration of conjugated superoxide dismutase and catalase,[137] indicating a role of oxygen free radicals in the pathogenesis of this injury to the blood-brain barrier (Figure 33-16). These endothelial membrane changes frequently were associated with the

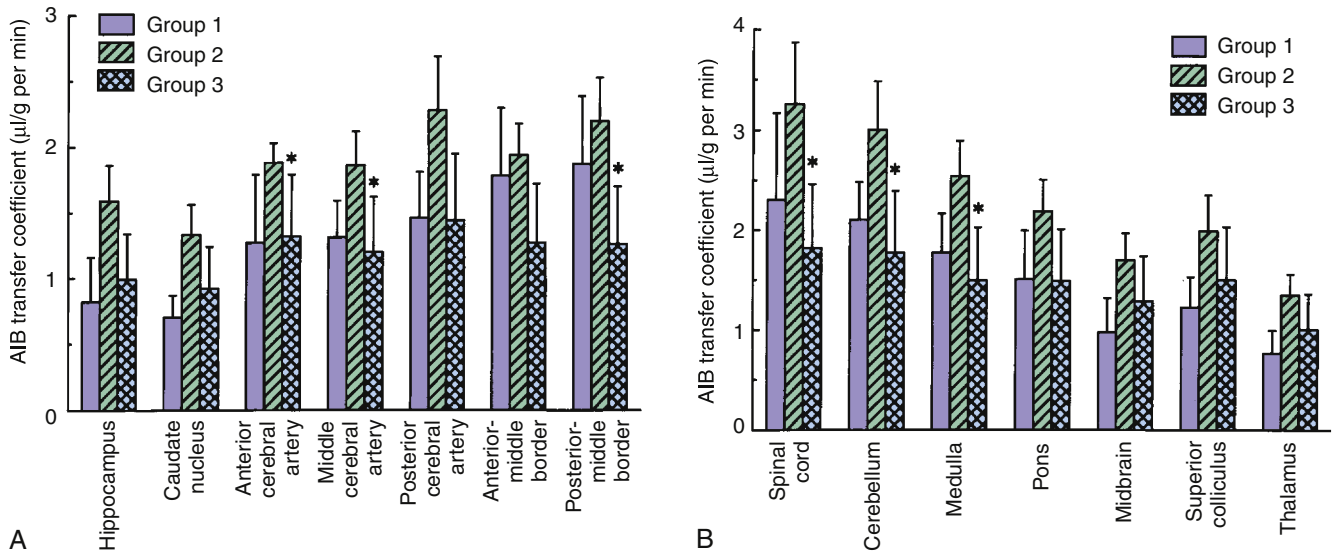

Figure 33–16. **A,** Bar graph showing transfer coefficient of α-aminoisobutyric acid (AIB) from plasma to brain in hippocampus, caudate nucleus, and primary supply and border regions of cerebral arteries in nonischemic time controls (group 1; n = 5), ischemia group treated with polyethylene glycol (PEG) (group 2; n = 8), and ischemia group treated with PEG-superoxide dismutase and PEG-catalase (group 3; n = 8). Error bars represent standard error of the mean (SEM). *$P < .05$ between groups 2 and 3 by Mann-Whitney U test. **B,** Transfer coefficient of AIB from plasma to brain in caudal brain regions in nonischemic time controls (group 1; n = 5), ischemia group treated with PEG (group 2; n = 8), and ischemia group treated with PEG-superoxide dismutase and PEG-catalase (group 3; n = 8). Error bars represent SEM. *$P < .05$ between groups 2 and 3 by Mann-Whitney U test. *(From Schleien CL, Eberle B, Schaffner DH, et al: Reduced blood-brain barrier permeability after cardiac arrest by conjugated superoxide dismutase and catalase in piglets,* Stroke *25:1830, 1994.)*

presence of intravascular polymorphonuclear and monocytic leukocytes.[138] Whether leukocytes disrupt the blood-brain barrier by release of toxic substances, such as oxygen free radicals or proteases, or appear in the postischemic microvessels as an epiphenomenon of a more important derangement is unknown (Figure 33-17).

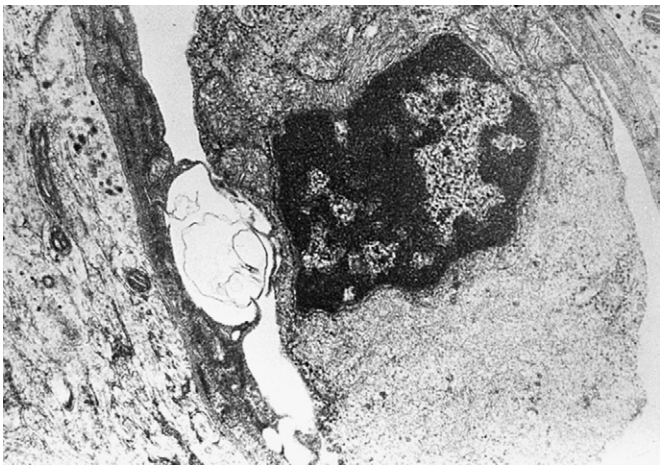

Figure 33–17. Transmission electron micrograph of an infant piglet brain 4 hours after 8 minutes of cardiac arrest and 6 minutes of cardiopulmonary resuscitation (magnification ×5000). An intravascular leukocyte, which has the morphologic features of a monocyte, is adherent to the endothelial surface of a venule and appears to be occluding the lumen. The luminal surface of the endothelial cell contains membrane blebs and discontinuities. *(From Caceres MJ, Schleien CL, Kuluz JW, et al: Early endothelial damage and leukocyte accumulation in piglet brains following cardiac arrest,* Acta Neuropathol *90:582, 1995.)*

Vasopressin

The role of vasopressin as a noncatecholamine vasoconstrictor in the management of patients who experience cardiac arrest has received a great deal of interest. Work by Lindner in Europe and Landry in the United States during the past 2 decades has established sufficient evidence of efficacy for its use to be included in the 2010 AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.[39,112] Vasopressin can be used as an alternative to the first or second dose of epinephrine for refractory VF in adults, and according to the 2010 AHA Guideline, its evidence class is indeterminate[39]; it is also an option of indeterminate merit for children.[112] Increasing evidence indicates that vasopressin is a useful agent in the management of shock of multiple etiologies and therefore may have a role in postresuscitation management of the arrest victim.

Arginine vasopressin is a short peptide hormone secreted by the posterior pituitary gland in response to changes in tonicity and changes in effective intravascular volume, signaled primarily via baroreceptor unloading in the aorta. Severe shock is the most potent stimulus to vasopressin secretion. Serum levels twentyfold to 200-fold higher than normal may be found immediately after cardiac arrest, as well as in other severe shock states. Despite these observations, lower than expected vasopressin levels have been found in some patients with profound shock,[139-141] and patients dying of cardiac arrest have been found to have significantly lower vasopressin levels than do survivors.[142] The cause of lower than expected vasopressin levels in some patients is unclear. Observations in dogs suggest depletion of vasopressin stores as a potential mechanism. Dogs subjected to profound hemorrhagic shock have an early massive elevation of vasopressin levels immediately after the event, followed by a depression of levels below that expected within 1 hour of the insult. Severe depletion of vasopressin

stores from the posterior hypophysis was noted in these animals.[141] These animals developed a catecholamine-refractory vasodilatory shock that responded dramatically to low doses of vasopressin.[143] These observations have led to an exploration of the use of vasopressin in both cardiac arrest and shock states.

Vasopressin is an extremely potent vasoconstrictor. Its effects on vascular tone are primarily mediated through interaction with a specific G protein–coupled receptor referred to as the $V1_a$ receptor, which is distributed widely throughout vascular beds.[139] Of note, the $V1_a$ receptor is linked to the same second messenger system as the α-adrenergic receptor that mediates vasoconstriction through an alteration of intracellular calcium levels. However, in the pulmonary circulation, vasopressin activation of V1 receptors mediates the release of nitric oxide and causes pulmonary vasodilation. Vasopressin also interacts with its V_2 receptor, which regulates aquaporin expression on the renal collecting duct epithelium. Stimulation of the V_2 receptor occurs at substantially lower levels than those required to activate the $V1_a$ receptor.

Vasopressin use during resuscitation has been studied in animals and humans. In an adult porcine model of VF, vasopressin at a dose of 0.8 μg/kg was found to be superior to the maximally effective dose of epinephrine 200 μg/kg in restoring left ventricular myocardial blood flow, increasing diastolic CPP and total cerebral blood flow, as well as rates of ROSC. Moreover, the duration of the effect was sustained for 4 minutes compared with 1.5 minutes for epinephrine.[56,129] Adverse effects noted in the postresuscitation phase included decreased renal and adrenal blood flow and reduced cardiac output.[144,145]

In a pediatric porcine model of cardiac arrest,[146] vasopressin at a dose of 0.8 μg/kg was not as effective as epinephrine, 200 μg/kg, in restoring LV myocardial blood flow or achieving ROSC. Only 1 of 6 animals achieved ROSC compared with 6 of 6 in the epinephrine group. A combination group that received both epinephrine, 45 μg/kg, and vasopressin, 0.8 μg/kg, fared better (ROSC in 4 of 6 animals). Possible explanations for the difference between adult and juvenile animals include different dose-response curves for the two drugs, failure of maturation of vasopressin receptors, a different distribution of vasopressin receptors than seen in adults, or the different experimental model.

In an initial small randomized clinical trial of vasopressin compared with epinephrine for refractory VF, the rate of achieving ROSC was higher in the vasopressin group.[147] These findings led to the inclusion of vasopressin in the adult guidelines. A large multicenter randomized trial of vasopressin for cardiac arrest in adults has been reported.[148] More than 1200 patients were randomly assigned in the field to receive two doses of either 40 International Units of vasopressin or 1 mg of epinephrine followed by additional treatment with epinephrine, if necessary. Vasopressin was equivalent to epinephrine in achieving survival to both hospital admission and discharge in patients with either PEA or VF. In patients with asystole, vasopressin was superior to epinephrine in achieving both survival to admission and discharge, although intact neurologic outcome was not improved. In patients in whom ROSC was not achieved after two doses of medication, a third dose of medication such as epinephrine could be added at the resuscitating physician's discretion. In the group receiving a third dose of medication such as epinephrine, survival was greater in the vasopressin group. Subsequently, a meta-analysis of five randomized trials showed no significant differences between vasopressin and epinephrine for ROSC, 24-hour survival, or survival to hospital discharge, while a subgroup analysis of the initial cardiac rhythm showed no significant difference in survival to hospital discharge.[149] In a study of 200 patients with in-hospital cardiac arrest, patients were randomly assigned to receive either 1 mg of epinephrine or 40 Units of vasopressin. Again, no statistical difference in survival to 1 hour or to hospital discharge was found between groups or subgroups.[150] The results of these studies led to the classification of evidence for vasopressin for use in adults as indeterminate in the 2010 AHA guidelines.[39]

The published experience with vasopressin in children who experience cardiac arrest is limited. The first case series of vasopressin use in CPR reported the outcome of four children with six prolonged refractory cardiac arrests that were unresponsive to standard resuscitation efforts.[151] Each child received one or more bolus doses of vasopressin (0.4 μg/kg) as rescue therapy. In all children, the initial rhythm was a form of PEA that deteriorated to asystole in four of six events. Three children had ROSC for more than 60 minutes, including one child with asystole. Two children survived for more than 24 hours and one survived to hospital discharge. A second retrospective case series of pediatric cardiac arrests unresponsive to epinephrine found that ROSC was achieved in 6 of 8 episodes that were treated with terlipressin, a long-acting synthetic analog of vasopressin, at a dose of 15 to 20 μg/kg. Four of those patients survived without neurologic sequelae.[152] A review of a national registry of in-hospital CPR showed that patients who received vasopressin had a lower incidence of ROSC greater than 20 minutes (22 [34%] of 64) than patients who did not receive the medication (675 [55%] of 1229).[153] The association of poor outcome with vasopressin persisted even with multivariate analysis with logistic regression to attempt to control for other factors that might effect ROSC. The current evidence only examines the use of vasopressin as a potential alternative when standard therapies, such as epinephrine, fail to cause ROSC. Unfortunately, variables such as dosing, timing of vasopressin infusion, or pediatric risk of mortality scores have not been controlled for in these studies. No double-blinded, randomized controlled studies have been performed, and thus no firm recommendations are available concerning the use of vasopressin for CPR in infants and children.

The current recommended dose of vasopressin for adults in cardiac arrest is 40 International Units. No data comparing this dose to other doses are available, and concern exists regarding postresuscitation complications related to this dose. We have selected 0.5 μg/kg as the standard for cardiac arrest. Further data are needed before more definitive dosing recommendations can be made.

Use of vasopressin in postresuscitation management may be considered. A relative vasopressin deficiency has been noted in a number of shock states, including hemorrhage, sepsis, and post-CPB, as well as in patients who have unsuccessful resuscitations. In these settings, shock may be refractory to catecholamines (norepinephrine doses of 2 to 4 μg/kg). These patients may respond to a vasopressin infusion, allowing the weaning of high-dose catecholamines. Although a role in the postresuscitation setting has not been demonstrated based on the data related to refractory shock, consideration of the use of vasopressin for refractory hypotension may be appropriate.

High-Dose Epinephrine

The physiologic responses of animals and humans to higher doses of epinephrine include higher cerebral blood flow,[154,155] increased myocardial and submyocardial blood flow, improved oxygen delivery relative to oxygen consumption,[132,156-158] and less depletion of myocardial adenosine triphosphate (ATP) stores with more rapid repletion of phosphocreatine.[159] Contrary results, with increased myocardial oxygen consumption and decreased myocardial blood flow, have been demonstrated during CPR following VF cardiac arrest.[35,38] In a piglet model, high-dose epinephrine (HDE) produced lower myocardial blood flow than achieved with standard-dose epinephrine (SDE).[154] In neonatal lambs following asphyxia-induced bradycardia, HDE resulted in higher heart rate but a lower stroke volume and cardiac output.[160]

Studies regarding survival of patients who were given HDE have been contradictory. In out-of-hospital patients who experienced cardiac arrest, HDE produced higher aortic diastolic pressure during CPR and increased the rate of ROSC compared with standard doses of epinephrine. Gonzalez et al.[161,162] demonstrated a dose-dependent increase in aortic blood pressure by epinephrine in patients who failed to respond to prolonged resuscitative efforts. Paradis et al.[163] showed that HDE increased aortic diastolic pressure and improved the rate of successful resuscitation in patients in whom ACLS protocols had failed. This group also reported on a series of 20 children treated with HDE and compared them with 20 historic control subjects consisting of children with cardiac arrest treated with SDE.[164] They reported that 14 of the children in the HDE group had ROSC, eight survived to hospital discharge, and three were neurologically intact. There were no survivors in the SDE comparison group. Other centers have claimed that higher-than-standard doses of epinephrine during CPR in children improve the hemodynamics and increase the success of CPR; however, no one has provided any valid data that suggest that HDE improves survival beyond the immediate postresuscitation period.[83,163,165,166] Based on these studies, the 1992 AHA guidelines for pediatric advance life support recommended HDE if an initial SDE failed to resuscitate the child.

Three large multicenter studies subsequently were published that dampened enthusiasm for the use of HDE. Stiell et al.[167] studied 650 adult patients after cardiac arrests who were randomly assigned to receive either an SDE or HDE (7 mg) epinephrine protocol. No differences were observed between the groups with regard to 1-hour survival (23% vs. 18%), rate of hospital discharge (5% vs. 3%), or neurologic outcome. Brown et al.[168] reported on 1280 adult patients who received either SDE (0.02 mg/kg) or HDE (0.2 mg/kg) after cardiac arrest. Again, no differences in ROSC, short-term survival, survival to hospital discharge, or neurologic outcome were observed between the two groups of patients. In a study of 816 adults, Callaham et al.[169] reported a higher ROSC in the HDE group. However, there were no differences in the rate of hospital discharge or ultimate survival of these patients. In addition to these studies, a specific pediatric animal study was published that failed to demonstrate a clear survival benefit for HDE, although the occurrence of ROSC appeared to be greater.[38] The 2000 AHA guidelines changed the recommendation for HDE to an option for second and subsequent doses of epinephrine.

Most recently, a prospective, randomized, double-blind clinical trial of HDE in 68 pediatric inpatients was reported by Perondi et al.[9] ROSC for more than 20 minutes was achieved in 15 of 34 patients who received HDE but in only 8 of 34 patients who received SDE ($P = .07$). However, survival to 24 hours occurred in only two of the HDE group versus seven of the SDE group ($P = .05$). In the group that experienced an asphyxial arrest, none of 12 treated with HDE was alive at 24 hours, whereas seven of 18 patients in the SDE group survived. Four survived to hospital discharge, and two patients were neurologically normal.[9] This trial reinforces concerns that HDE may account for some of the adverse effects that occur after resuscitation[136,172] and is the basis of the 2010 AHA guidelines' recommendation against the use of HDE during CPR.[39] As discussed previously, epinephrine can worsen myocardial ischemic injury secondary to increased oxygen demand and result in tachyarrhythmias, hypertension, pulmonary edema, hypoxemia, and cardiac arrest.[136,173] Use of a β-adrenergic antagonist during or after ROSC has been suggested to attenuate the adverse effects of epinephrine.[65,96,174] Epinephrine causes hypoxemia and an increase in alveolar dead space ventilation by redistributing pulmonary blood flow.[175,176] In one study, HDE (>15 mg) given to adults during CPR resulted in a lower cardiac index, systemic oxygen consumption, and oxygen delivery immediately after resuscitation.[160] Prolonged peripheral vasoconstriction by excessive doses of epinephrine may delay or impair reperfusion of systemic organs, particularly the kidneys and gastrointestinal tract.

Atropine

Atropine, a parasympatholytic agent, acts by blocking cholinergic stimulation of the muscarinic receptors of the heart, which usually results in an increase in the sinus rate and shortening of the atrioventricular node conduction time. Atropine may activate latent ectopic pacemakers. Atropine has little effect on systemic vascular resistance, myocardial perfusion pressure, or contractility.[177]

Atropine is indicated for treatment of asystole, PEA, bradycardia associated with hypotension, second- and third-degree heart block, and slow idioventricular rhythms. In children who present in cardiac arrest, sinus bradycardia and asystole are the most common initial rhythms, which makes atropine useful as a first-line drug. Atropine is particularly effective in clinical conditions associated with excessive parasympathetic tone.

The recommended dose of atropine is 0.02 mg/kg, with a minimum dose of 0.15 mg and a maximum dose of 2.0 mg. Smaller doses than 0.15 mg, even in small infants, may result paradoxically in bradycardia because of a central stimulatory effect on the medullary vagal nuclei by a dose that is too low to provide anticholinergic effects on the heart. Atropine may be given by any route, including intravenous, endotracheal, intraosseous, intramuscular, and subcutaneous. Its onset of action occurs within 30 seconds, and its peak effect occurs between 1 and 2 minutes after an intravenous dose. The recommended adult dose is 0.5 mg every 5 minutes until the desired heart rate is obtained up to a maximum of 2 mg. For asystole, 1 mg is given intravenously and repeated every 5 minutes if asystole persists. Full vagal blockade usually is obtained with a dose of 2 mg in adults.

Because of its parasympatholytic effects, atropine should not be used in patients in whom tachycardia is undesirable. In patients after myocardial infarction or ischemia with persistent bradycardia, atropine should be used in the lowest dose possible to increase heart rate. Using the lowest possible dose will limit tachycardia, a potent contributor to increased myocardial oxygen consumption, which could lead to VF. In addition, atropine should not be used in patients with pulmonary or systemic outflow tract obstruction or idiopathic hypertrophic subaortic stenosis because tachycardia decreases ventricular filling and lowers cardiac output in this setting.

Sodium Bicarbonate

The administration of sodium bicarbonate results in an acid-base reaction in which bicarbonate combines with hydrogen to form carbonic acid, which dissociates into water and carbon dioxide. Because of the generation of carbon dioxide, adequate alveolar ventilation must be present to achieve the normal buffering action of bicarbonate. Use of sodium bicarbonate during CPR remains controversial because of its potential adverse effects and the lack of evidence showing any benefit from its use during CPR.[178,179]

Sodium bicarbonate is indicated for correction of significant metabolic acidosis, especially when signs of cardiovascular compromise are present. Acidosis itself may have a number of negative effects on the circulation, including depression of myocardial function by prolonging diastolic depolarization, depressing spontaneous cardiac activity, decreasing the electrical threshold for VF, decreasing the inotropic state of the myocardium, and reducing the cardiac response to catecholamines. Acidosis also decreases systemic vascular resistance and attenuates the vasoconstrictive response of peripheral vessels to catecholamines. This effect is contrary to the desired effect during CPR. In addition, particularly in patients with a reactive pulmonary vascular bed, pulmonary vascular resistance is inversely related to pH. Rudolph and Yuan[180] observed a twofold increase in pulmonary vascular resistance in calves when pH was lowered from 7.4 to 7.2 under normoxic conditions. Therefore correction of even mild acidosis may be helpful in resuscitating patients who have the potential for increased right-to-left shunting through a cardiac septal defect, patent ductus arteriosus, or aortic-to-pulmonary shunt during periods of elevated pulmonary vascular resistance.

Multiple adverse effects of bicarbonate administration include metabolic alkalosis, hypercapnia, hypernatremia, and hyperosmolality. All of these adverse effects are associated with a high mortality rate. Alkalosis causes a leftward shift of the oxyhemoglobin dissociation curve, thus impairing release of oxygen from hemoglobin to tissues at a time when oxygen delivery already may be low. Alkalosis can result in hypokalemia, by enhancing potassium influx into cells, and ionic hypocalcemia, by increasing protein binding of ionized calcium. Hypernatremia and hyperosmolality may decrease tissue perfusion by increasing interstitial edema in microvascular beds. The marked hypercapnic acidosis that occurs during CPR on the venous side of the circulation, including the coronary sinus, may be worsened by administration of bicarbonate.[181,182] Myocardial acidosis during cardiac arrest is associated with decreased myocardial contractility. The mean venoarterial P_{CO_2} difference was 24 ± 15 mm Hg in five patients during CPR and actually increased from 16 to 69 mm Hg in one patient after administration of bicarbonate.[183] Another group showed a mean difference of 42 mm Hg between partial pressure of carbon dioxide in mixed venous blood (P_{vCO_2}) and P_{aCO_2} during CPR. Paradoxical intracellular acidosis after bicarbonate administration is possible because of rapid entry of carbon dioxide into cells with a slow egress of hydrogen ion out of cells. Paradoxical intracellular acidosis in the central nervous system after bicarbonate administration has been proposed but not definitively shown. In neonatal rabbits recovering from hypoxic acidosis, bicarbonate administration increased both arterial pH and intracellular brain pH as measured by nuclear magnetic resonance spectroscopy.[184] In another study, intracellular brain ATP concentration in rats did not change during severe intracellular acidosis in the brain produced by extreme hypercapnia.[185] The rats who maintained ATP concentration even in the face of severe brain acidosis had no functional or histologic differences from normal control subjects. Using nuclear magnetic resonance spectroscopy of the brain in dogs during cardiac arrest and CPR, intracellular brain pH decreased to 6.29 with total depletion of brain ATP after 6 minutes of cardiac arrest. However, following effective CPR, ATP levels rose to 86% of prearrest levels and to normal by 35 minutes of CPR despite ongoing peripheral arterial acidosis (Figure 33-18).[100] However, cerebral pH decreased in parallel with blood pH when CPR was started immediately after arrest. Bicarbonate administration ameliorated and did not worsen the cerebral acidosis, indicating that the blood-brain pH gradient is maintained during CPR.[186]

The 2010 AHA guidelines state that sodium bicarbonate has not been shown to improve outcome during CPR and

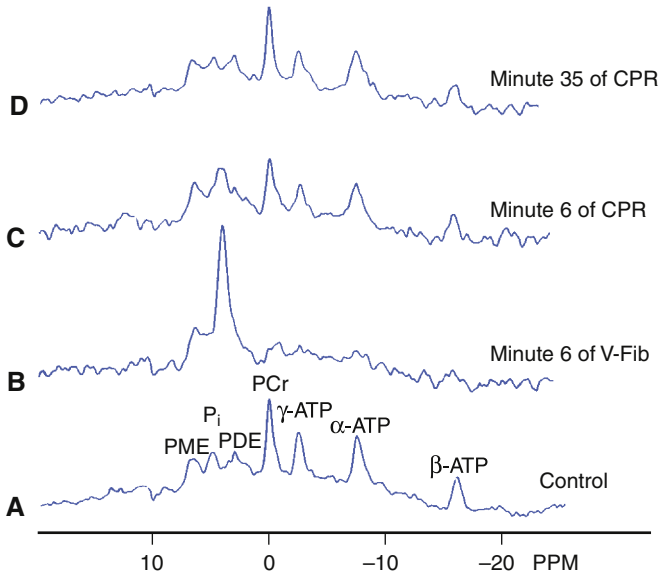

Figure 33–18. ^{31}P magnetic resonance spectroscopy spectra from in situ dog brain during vest cardiopulmonary resuscitation (CPR) after a 6-minute delay in the onset of CPR from time of arrest. Each spectrum was acquired in 1 minute. The frequency of the inorganic phosphate (P_i) peak is pH dependent. Note complete absence of adenosine triphosphate (ATP) and phosphocreatine (PCr), and pH_i = 6.28 in *trace B* after 6 minutes of ventricular fibrillation (v-fib) without CPR. After 6 minutes of CPR *(trace C),* ATP is more than 85% recovered, but pH is only 6.61. After 35 minutes of CPR *(trace D),* pH_i has returned to 7. *PDE,* phosphodiesters; *PME,* phosphomonoesters; *PPM,* parts per million. *(From Eleff SM, Schleien CL, Koehler RC et al: Brain bioenergetics during cardiopulmonary resuscitation in dogs,* Anesthesiology *76:77, 1992.)*

only recommends its use in special situations, such as intoxications.[39] A Cochrane study looking at the use of empirical sodium bicarbonate administration versus placebo in out-of-hospital cardiac arrests in 874 adults found no difference in survival to the hospital.[188] Levy[189] reviewed more than 30 animal studies evaluating the efficacy of sodium bicarbonate administration during CPR. Among studies with survival as the primary outcome, four showed benefit and seven did not. When assessing myocardial performance, 12 studies concluded that sodium bicarbonate worsened performance, two studies showed no difference, and no study showed benefit. When reviewing 19 retrospective human adult studies examining mortality rates, eight of these suggested a deleterious effect of sodium bicarbonate, 11 showed no difference in outcomes, and none showed benefit.[189] When $Paco_2$ and pH are known, the dose of bicarbonate to correct the pH to 7.4 is calculated using the following equation:

$$\text{Sodium bicarbonate (mEq)} = 0.3 \times \text{Weight} \times \text{Base deficit}$$

(Because of its possible adverse effects and the large venous to arterial carbon dioxide gradient that develops during CPR, we recommend giving half the dose that would be given based on a volume of distribution of 0.6.) If blood gases are not available, the initial dose is 1 mEq/kg, followed by 0.5 mEq/kg every 10 minutes of ongoing arrest. Alveolar ventilation must be maintained because of the generation of carbon dioxide and can be assessed only by serial measurements of arterial blood gases and pH. Because of the potential adverse effects of bicarbonate, the indications for its use at this time are limited to cardiac arrest associated with hyperkalemia, patients with preexisting metabolic acidosis, and after approximately 10 minutes of CPR.

$EtCO_2$ monitoring is useful during CPR because it provides important information regarding both pulmonary and cardiac function. $EtCO_2$ is measured instantaneously in the exhaled gas of every breath. In the absence of lung disease, $EtCO_2$ correlates closely with $Paco_2$, provided pulmonary blood flow is at least 20% to 25% of normal. As a respiratory monitor, $EtCO_2$ analyzers accurately distinguish a tracheal ($EtCO_2$ >10) from an esophageal ($EtCO_2$ <5) intubation in infants and children.[190-192] Because measurements are made with every breath, dislodgment of the endotracheal tube from the trachea can be identified immediately. When cardiac output is extremely low, as occurs during ineffective CPR, delivery of carbon dioxide to the lungs is so limited that the total amount exchanged across the alveolar-capillary membrane is markedly reduced. In this situation, the measured $EtCO_2$ is very low even when $Paco_2$ is elevated. As cardiac output increases, $EtCO_2$ increases and the difference between end-tidal and arterial CO_2 becomes smaller.[193] $EtCO_2$ has been correlated with CPP,[193] the critical parameter for resuscitation of the heart. However, a low $EtCO_2$ may occur in the presence of adequate cardiac output during CPR after the administration of epinephrine because of its ability to increase intrapulmonary shunting.[175,194,195] In this case, a low $EtCO_2$ underestimates cardiac output. Other causes of low $EtCO_2$ include airway obstruction, tension pneumothorax, pericardial tamponade, pulmonary embolism, hypothermia, severe hypocapnia (which occurs commonly with overaggressive hand ventilation), and esophageal intubation.

Levine et al.[196] monitored $EtCO_2$ in 150 adults with an out-of-hospital cardiac arrest who had electrical activity but no pulse. They found that after 20 minutes of ACLS, an $EtCO_2$ level of 10 mm Hg successfully predicted survival to hospital admission with a sensitivity, specificity, and positive- and negative-predictive value of 100%. Grmec and Klemen[197] prospectively studied the initial, average, maximal, minimal, and final $EtCO_2$ as a prognostic indicator for outcomes in adult resuscitation. They found that using an initial, average, and final $EtCO_2$ level of 10 mm Hg identified 100% of patients who were successfully resuscitated, with specificity of 74%, 90%, and 81%, respectively.[197] The 2010 AHA guidelines state that while use of $EtCO_2$ as an indicator of cardiac output may be useful in adults (evidence class IIb),[39] currently no studies have evaluated the use of $EtCO_2$ in pediatric arrests. However, given the noninvasive nature of $EtCO_2$ monitoring and also extrapolating from adult data, maintaining an $EtCO_2$ of >10 to 15 mm Hg through the use of $EtCO_2$ monitoring is recommended during pediatric arrests.[112]

Other Alkalinizing Agents

A number of other alkalinizing agents have been used experimentally in animals and humans. However, none has demonstrated any real advantages over sodium bicarbonate. Carbicarb, a solution of equimolar amounts of sodium bicarbonate and sodium carbonate, corrects metabolic acidosis without many of the adverse effects of sodium bicarbonate.[63] The buffering action of sodium carbonate occurs by consumption of carbon dioxide with generation of bicarbonate ion, as illustrated in the following equation:

$$Na_2CO_3 + CO_2 + H_2O = 2\ HCO_3^- + 2Na^+$$

During CPR, Carbicarb administration resulted in a greater increase in arterial pH and smaller increases in $Paco_2$, lactate, and serum osmolality in animals.[63,198,199] However, Carbicarb was not superior to sodium bicarbonate when used for hypovolemic shock in rats.[200]

Dichloroacetate (DCA) increases the activity of pyruvate dehydrogenase, which facilitates the conversion of lactate to pyruvate.[201] When administered to patients with lactic acidosis, DCA decreased lactate concentration by half and increased bicarbonate concentration and pH.[202] In other studies, DCA improved cardiac output, possibly by increasing myocardial metabolism of lactate and carbohydrate.[203,204] In a multicenter trial of patients with lactic acidosis, DCA did not improve outcome when compared with sodium bicarbonate.[205]

Tromethamine (THAM; tris-hydroxymethyl-aminomethane) is an organic amine that combines with hydrogen ion, causing CO_2 and H_2O to combine to form bicarbonate and hydrogen ion. A dose of 3 mL/kg should raise the bicarbonate concentration by 3 mEq/L. Adverse effects of THAM include hyperkalemia, hypoglycemia, and acute hypocarbia resulting in apnea. In addition, peripheral vasodilation may occur after administration of THAM during CPR, which is an undesirable effect. THAM is contraindicated in patients with renal failure.

Calcium

Recommendations for use of calcium in CPR are restricted to a few specific situations, namely, hypocalcemia, hyperkalemia, hypermagnesemia, and calcium channel blocker overdose. These restrictions are based on the possibility that exogenously administered calcium may worsen ischemia/reperfusion

injury. Intracellular calcium overload occurs during cerebral ischemia by the influx of calcium through voltage- and agonist-dependent (e.g., *N*-methyl-D-aspartate) calcium channels. Calcium plays an important role in the process of cell death in many organs, possibly by activating intracellular enzymes such as nitric oxide synthase, phospholipase A and C, and others.[206,207] Calcium channel blockers improve blood flow and function after ischemia to the heart,[208] kidney,[209] and brain.[210] Calcium channel blockers also raise the threshold of the ischemic heart to VF.[211] For these reasons, it appears that the recommended restrictions for use of calcium during CPR are well founded. On the other hand, no studies have shown that elevation of plasma calcium concentration, which occurs after calcium administration, worsens outcome of cardiac arrest. Because the normal ratio of extracellular to intracellular calcium is on the order of 1000:1 to 10,000:1, it seems unlikely that the rate of influx of calcium into cells would be influenced by a relatively small increase in its extracellular concentration.

The calcium ion is essential in myocardial excitation-contraction coupling, in increasing ventricular contractility, and in enhancing ventricular automaticity during asystole. Ionized hypocalcemia is associated with decreased ventricular performance and peripheral blunting of the hemodynamic response to catecholamines.[212,213] In addition, severe ionized hypocalcemia has been documented in adults experiencing out-of-hospital cardiac arrest (mean Ca 0.67 mmol/L),[212] during sepsis,[214] and in animals during prolonged CPR.[215] Thus patients at risk for ionized hypocalcemia should be identified and treated as expeditiously as possible. Both total and ionized hypocalcemia may occur in patients with chronic or acute disease. Total body calcium depletion leading to total serum hypocalcemia occurs in patients with hypoparathyroidism, DiGeorge syndrome, renal failure, pancreatitis, and long-term use of loop diuretics. Ionized hypocalcemia occurs after massive or rapid transfusion of blood products, a result of citrate and other preservatives in stored blood products that bind calcium. The magnitude of hypocalcemia in this setting depends on the rate of blood administration, the total dose, and the hepatic and renal function of the patient. Administration of 2 mL/kg/min of citrated whole blood causes a significant decrease in ionized calcium concentration in anesthetized patients.

The pediatric dose of calcium chloride for resuscitation is 20 mg/kg. The adult dose is 200 mg (2 mL of the 10% solution). Calcium gluconate is as effective as calcium chloride in raising ionized calcium concentration during CPR. Calcium gluconate is given at a dose of 30 to 100 mg/kg, with a maximum dose of 2 g in pediatric patients. Calcium should be given slowly through a large-bore, free-flowing intravenous line, preferably a central venous line. Severe tissue necrosis occurs when calcium infiltrates into subcutaneous tissue. When administered too rapidly, calcium may cause bradycardia, heart block, or ventricular standstill.

Srinivasan et al.[216] reviewed 1477 consecutive pediatric cardiopulmonary events submitted to the National Registry of Cardiopulmonary Resuscitation and reported on the prevalence of calcium administration. Of the children in the registry, 659 were documented as receiving calcium. Calcium was more likely to be used in pediatric facilities, ICUs, and in the settings of cardiac surgery, CPR performed for more than 15 minutes, asystole, and concurrently with other advanced life support medications. After controlling for confounding factors (demographics, immediate precipitating causes, arrest rhythm, concurrent ACLS medications, and duration of CPR), calcium administration during CPR was independently associated with poor survival to discharge and unfavorable neurologic outcomes. They found that 21% of patients survived to hospital discharge when calcium was used, compared with 44% who survived when calcium was not used. Only 15% of patients had a favorable neurologic outcome when calcium was used, compared with 35% with a favorable outcome when calcium was not administered.[216]

Glucose

Administration of glucose during CPR should be restricted to patients with documented hypoglycemia because of the possible detrimental effects of hyperglycemia on the brain during or following ischemia. Myers[217] found that infant monkeys that received glucose before cardiac arrest were more likely to develop seizures, prolonged coma, and brain death with cerebral necrosis than were those that received saline solution. Siemkowicz and Hansen[218] confirmed this finding when they demonstrated that after 10 minutes of global brain ischemia, the neurologic recovery of hyperglycemic rats was worse than that of normoglycemic control subjects. The mechanism by which hyperglycemia exacerbates ischemic neurologic injury may be increased production of lactic acid in the brain by anaerobic metabolism. During ischemia under normoglycemic conditions, brain lactate concentration reaches a plateau. In a hyperglycemic milieu, however, brain lactate concentration continues to rise for the duration of the ischemic period. The severity of intracellular acidosis during ischemia is directly proportional to the preischemic glucose concentration.[219] The negative effect of hyperglycemia during brain ischemia is predicated on the presence of at least a small amount of blood flow to brain tissue. In one study, collaterally perfused but not end-arterial brain tissue had greater neuronal damage during hyperglycemic focal ischemia (Figure 33-19).[220]

Clinical studies show a direct correlation between the initial postcardiac arrest serum glucose concentration and poor neurologic outcome.[209,221] However, a higher glucose concentration may just be an endogenous response to severe stress and thus a marker and not the cause of more severe brain injury.[64] In piglets, postischemic administration of glucose did not worsen neurologic outcome after global hypoxia-ischemia.[222] However, given the likelihood of additional ischemic and hypoxic events in the postresuscitation period, it seems prudent to maintain serum glucose in the normal range. Administration of insulin to hyperglycemic rats after global brain ischemia improved neurologic outcome.[223] The effect of insulin may be independent of its ability to lower blood glucose, because these investigators later showed that normoglycemic insulin-treated rats had a better outcome than normoglycemic placebo-treated control subjects.[224]

Using intensive insulin therapy, Van den Bergh et al.[225,226] strictly controlled the blood glucose levels of adults in a surgical ICU, maintaining levels between 80 and 110 mg/dL. This control of blood glucose levels appeared to reduce mortality and protect the central and peripheral nervous systems. However, a subsequent study in a medical ICU showed no difference in mortality between the intensive insulin therapy and control groups.[227] Another study showed that the use of

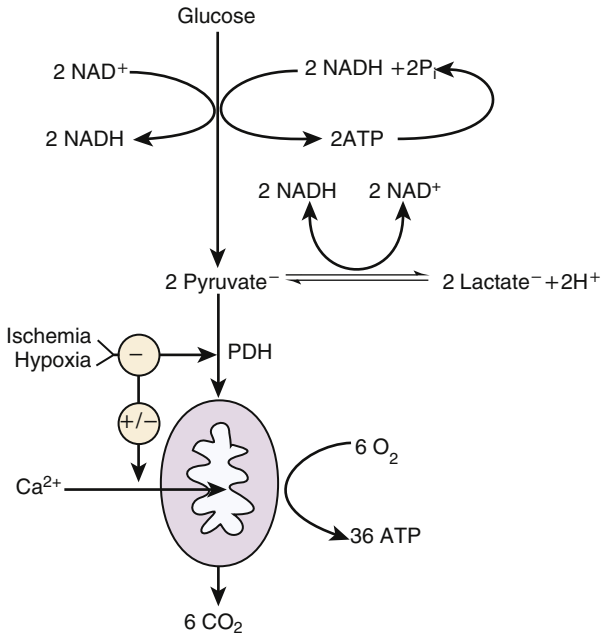

Figure 33–19. Schematic diagram illustrating the aerobic/anaerobic metabolism of glucose. Oxidation of pyruvate to CO_2 (and H_2O) by pyruvate dehydrogenase and citric acid cycle enzymes is retarded to blocked by oxygen deficiency, causing a reduction of pyruvate to lactate. If the adenosine triphosphate *(ATP)* formed during glycolysis is hydrolyzed (that is, if the ATP concentration stays constant), one molecule of H^+ is released for each molecule of lactate formed. If the mitochondria retain a membrane potential, they will sequester excess calcium entering the cell; however, if they deenergized (with collapse of their membrane potential), they will release their calcium content. *ADP,* Adenosine diphosphate; *NAD,* nicotinamide adenine dinucleotide; *NADH,* reduced nicotinamide adenine dinucleotide; P_i, intracellular phosphorus; *PDH,* pyruvate dehydrogenase.

intensive insulin therapy to maintain normoglycemia was associated with increased episodes of hypoglycemia.[228] Currently few pediatric data are available on the efficacy and safety of strict glucose control. Further study needs to be done to determine the blood glucose level at which to trigger intensive insulin therapy, as well as the optimal ranges at which to maintain blood glucose concentration.

Some groups of patients, including premature infants and debilitated patients with low endogenous glycogen stores, are more prone to the development of hypoglycemia during and after a physiologic stress (e.g., surgery).[229] Hypoglycemia poses a higher risk in the immature pediatric brain compared with the adult brain. Bedside monitoring of serum glucose is critical during and after a cardiac arrest and allows for intervention before the critical point of low substrate delivery is reached. The dose of glucose needed to correct hypoglycemia is 0.5 to 1.0 g/kg given as 10% dextrose in infants. The osmolarity of 50% dextrose is approximately 2700 Osm/L and is associated with intraventricular hemorrhage in neonates and infants.

Management of Ventricular Fibrillation

The management of lethal ventricular arrhythmias traditionally has not played a major role in resuscitation teaching or management for children because of the low incidence of these arrhythmias. Newer evidence gathered in the environment of rapid access defibrillation suggests that as many as 19% of the presenting rhythms in pediatric arrests are ventricular in origin, and represents as many as 5% to 15% of all pediatric victims of out-of-hospital cardiac arrest.[12,230] The incidence increases with age. Approximately 25% of children experiencing in-hospital cardiac arrest have ventricular tachycardia or fibrillation.[114] Moreover, the growing and aging population of children palliated for complex congenital heart disease in whom the occurrence of ventricular arrhythmias may be much higher than in the general pediatric population requires greater attention to ventricular arrhythmias than in the past. Other potential causes of ventricular arrhythmias include familial and acquired prolonged QT syndrome, other arrhythmogenic ventricular conditions,[231,232] cardiomyopathies, myocarditis, drug intoxications (such as illicit and accidental ingestion and therapeutic misadventures), electrolyte derangements (e.g., magnesium, calcium, potassium, or glucose), and hypothermia.

Advances have been made in the management of ventricular arrhythmias. Rapid access to defibrillation has been shown to reduce mortality in adults, and the development of public access defibrillation and AEDs has flowed from this knowledge. Initially AED devices had little utility for children, but the development of current-reducing electrodes and specific pediatric algorithms has made public access defibrillation a reality for children, and AEDs have been deployed in the many environments in which children would be the primary beneficiaries (e.g., schools and public swimming pools). When automated external defibrillators are used within 3 minutes of adult-witnessed ventricular fibrillation in children, long-term survival can occur in more than 70% of cases.[233,234] The technique of current delivery has undergone change with the development and deployment of biphasic defibrillators, which may offer increased efficacy with reduced risk of myocardial injury. Finally, amiodarone has started to replace lidocaine as the drug of choice for refractory ventricular arrhythmias and for atrial arrhythmias. The role of each of these factors in the resuscitation of pediatric arrest victims is discussed in the following section.

Defibrillation

VF is the chaotic electrical excitation of the ventricle, and the definitive treatment in accordance with the 2010 AHA guidelines is defibrillation.[39] The electrical mechanism is usually explained as a reentrant depolarization of the myocardium, initially in waves, that then take more circuitous routes and degenerate into smaller reentry circuits resulting in loss of the rhythmic contractile function of the ventricles.[235] This changing pattern of reentry circuits corresponds with the change from coarse to fine VF as the duration of fibrillation persists and may correlate with deterioration in energy stores associated with persistence of fibrillation.[236-238] Similarly, most cases of ventricular tachycardia are attributable to reentrant mechanisms, although increased automaticity is the likely mechanism in persons with drug-induced torsades de pointes and electrolyte disturbances such as hypokalemia and hypomagnesemia.[239] Nonpulsatile ventricular tachycardia with loss of effective contractile function of the heart rapidly deteriorates into VF. Loss of effective ventricular function with these arrhythmias requires emergent management.

The standard for management of VF and pulseless ventricular tachycardia is immediate defibrillation and high-quality CPR. Although the lowest energy dose for effective defibrillation and the upper limit for safe defibrillation in infants and children are not known, energy doses greater than 4 J/kg (up to 9 J/kg) have effectively defibrillated children.[112] The standard voltage dose for pediatric defibrillation is 2 J/kg. If unsuccessful, successive doses of defibrillation are repeated at 4 J/kg or more, not to exceed 10 J/kg or the maximum adult dose.[40] This dosage is based on data reported by Gutgesell et al.[240] in 1976. They reported 71 defibrillation attempts in 27 children. Efficacy was 91% with 2 J/kg and 100% with 4 J/kg. After initial defibrillation, CPR is performed for 2 minutes, followed by a rhythm check and then repeat shock if required. This sequence may then be repeated, with consideration given to initiate vasopressor therapy. Rhythms that fail to respond to three rounds are defined as "shock resistant." In this setting, the standard as defined in the AHA guidelines is amiodarone, 2 minutes, 5 mg/kg (or lidocaine, 2 minutes, if amiodarone is not available, or magnesium for torsades des pointes), followed by 2 minutes of CPR and continuation of the rhythm check-shock-CPR/vasopressor cycle (Figure 33-21). Reversible causes of VT/VF should also be investigated. Success in resuscitation is incumbent on immediate defibrillation with immediate CPR in between delivery of shocks.

It is important to continue to deliver appropriate CPR while gathering defibrillation equipment.[241,242] Additional important considerations when delivering shocks include paddle size, position, contact pressure, and use of electrode paste. Large paddles reduce thoracic impedance, and infants older than 1 year or weighing more than 10 kg should be treated with adult paddles.[243] Adhesive patch electrodes are an acceptable alternative to paddles[244-246] and can be used when available if their use does not cause a delay in therapy. Paddles should be positioned to achieve current flow through the heart, and an anterior-apex, or anterior-posterior placement is selected. Contact pressure has been demonstrated to reduce impedance. Firm pressure, which commonly is not properly applied, is required.[247] Proper electrode paste or gel is needed. Care is required to avoid smearing paste across the chest wall because doing so can lead to arcing of the circuit and a resultant short circuit. Bare paddles, ultrasound gel, pads soaked in saline solution, and alcohol pads are not acceptable alternatives to electrode cream or paste.[40]

The role of immediate defibrillation has come under question. The efficacy of defibrillation declines rapidly as fibrillation persists. When an arrest is witnessed and a defibrillator is immediately available, defibrillation likely will be successful. With any delay in resuscitation, the success of initial defibrillation declines at a rate estimated at between 7% and 10% per minute of continued fibrillation.[39] A number of studies have demonstrated in both animals and adults that if more than 3 to 5 minutes of fibrillation have occurred before institution of defibrillation, use of CPR for 90 to 180 seconds to restore myocardial energy stores will improve the likelihood of conversion to a perfusing rhythm with defibrillation.[2,4,248,249] Given the frequency of unwitnessed arrest in children and the relatively low frequency of ventricular arrhythmias, CPR first may be the appropriate response in children.

Use of biphasic defibrillators is another important advance in the management of tachyarrhythmias. Studies suggest that defibrillation with a biphasic waveform can be achieved with lower energy and less myocardial injury than with a standard monophasic defibrillator current.[250,251] The first commercially available devices were approved by the Food and Drug Administration in 1996. An evidence-based review was undertaken by the AHA and published in 1998.[252] The reviewers concluded that "low-energy, non-progressive biphasic waveform defibrillators may be used for both out-of-hospital and in-hospital VF arrest, including persistent or recurrent VF that does not respond to the initial low-energy shock." These conclusions were based on observational studies and case reports. Subsequently, Schneider et al.[253] reported a randomized controlled trial of biphasic versus monophasic defibrillation for out-of-hospital cardiac arrest. Of 338 arrests, 115 patients had VF and were shocked with an AED. Defibrillation in the initial shock series was successful in 98% of patients receiving biphasic shocks but in only 69% of those receiving monophasic shocks ($P < .0001$), providing further evidence that biphasic waveforms are more efficacious than monophasic waveforms (Figure 33-20).

Biphasic shocks appear to be at least as effective as monophasic shocks and less harmful. Published data on children are limited to case reports.[254] Animal data are supportive of the use of biphasic defibrillators in infants and children. Clark et al.[255] demonstrated in a piglet model that low-energy biphasic shocks were superior to monophasic shocks for converting catheter-induced VF. Both Tang et al.[256] and Berg et al.[236] studied the use of AEDs equipped with energy-reducing electrodes and found increased efficacy compared with monophasic waveforms. Berg et al. also demonstrated improved LV function 5 hours after resuscitation. Based primarily on adult data, these devices have come into widespread use in pediatric hospitals. According to the 2010 AHA recommendations, with a manual defibrillator, dosage recommendations for children remain 2 J/kg for the first attempt followed by 4 J/kg for subsequent attempts.[112,236,257]

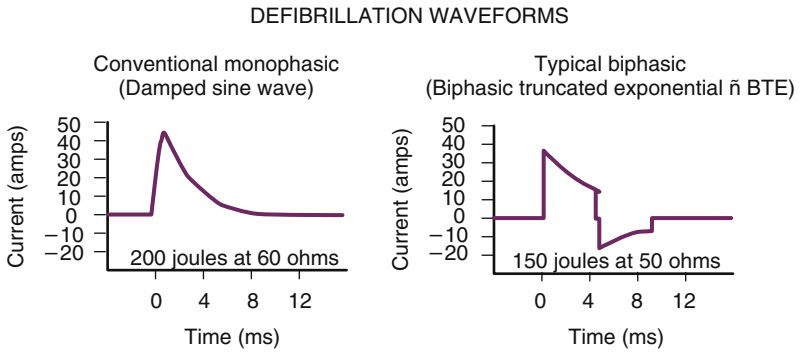

Figure 33–20. Schematic patterns of current flow for conventional monophasic and typical biphasic defibrillator waveforms.

In the early 1990s, as part of an AHA campaign to improve the abysmal rates of resuscitation from out-of-hospital cardiac arrest in adults, the development and deployment of AEDs was initiated. Both fixed and escalating dose devices were developed; however, the initial dose usually was at least 150 J in adults. Because of the high fixed energy doses, the devices were not recommended for use in children younger than 9 years. Moreover, use of these devices for young children was questioned because the arrhythmia detection algorithms used in these devices were developed for adults. Cecchin et al.[258] used the Agilent Herstream FR2 Patient Analysis System to analyze 696 five-second rhythms from 191 children younger than 12 years. Analysis revealed 100% accuracy for nonshockable rhythms and 96% accuracy for VF. This is similar to the accuracy reported for adults. In a more recent study, Atkinson et al.[239] tested the accuracy of the Lifepak 500 AED on 1561 fifteen-second rhythms from 203 children aged 1 day to 7 years. The device correctly identified 99% of coarse VF as shockable and 99.1% of nonshockable rhythms. A number of manufacturers (Zoll and Agilent) have developed energy-reducing electrodes that should allow use of these devices in young children.[239]

Since the 2000 AHA guidelines, data have shown that AEDs can be safely and effectively used in children of all ages. Current guidelines recommend use of an AED in children between the ages of 1 and 8 years who have no signs of circulation. The device should be adapted to deliver a pediatric dose with the use of a pediatric attenuator system that decreases the delivered energy to a dose suitable for children. When an attenuator system is not available, then the standard adult pads with corresponding dose should be delivered. In children younger than 1 year of age, a manual defibrillator is preferred; however, an AED with or without a pediatric attenuator may be used if necessary.[259]

Amiodarone

Amiodarone is an effective antiarrhythmic agent for both atrial and ventricular arrhythmias. The role of amiodarone in cardiac arrest was established after a series of studies demonstrated efficacy and superiority of amiodarone over lidocaine in the management of refractory VF and pulseless ventricular tachycardia in adults. Compared with lidocaine, amiodarone led to substantially higher rates of survival to hospital admission in patients with shock-resistant out-of-hospital VF.[260] These findings led to major changes in the AHA guidelines for management of ventricular arrhythmias (Table 33-1 and Figures 33-21 and 33-22).

Early reports on use of oral amiodarone in children were favorable.[261-263] Data on amiodarone use in children are limited to case reports and descriptive case series.[264-268] Nevertheless, it now is used widely for serious pediatric arrhythmias. It appears to be effective and have an acceptable short-term safety profile. In 2008, we examined the practice patterns of amiodarone use during in-hospital cardiac arrest. In this retrospective cohort study, it was noted that there has been a significant increase in amiodarone use for VF/ventricular tachycardia events during the past 5 years. It also was noted that the frequency of amiodarone use in adults correlated positively with the number of intensive care beds, suggesting that the emerging data and national guidelines affect resuscitation practice patterns.[269]

The growing pediatric experience among experts and inference from adult studies led to inclusion of amiodarone in the 2000 AHA pediatric advanced life support guidelines and continued in the 2010 AHA pediatric advanced life support guidelines as a drug of choice for pulseless ventricular tachycardia or VF, with class IIb level of evidence.[112] For hemodynamically stable ventricular tachycardia, it is also the drug of choice, with the level of evidence classified as IIb. Procainamide and lidocaine remain alternative drug choices. Amiodarone is commonly used for management of postoperative atrial and junctional ectopic tachycardia, especially in patients with ventricular pacing wires in place.

The wide range of effectiveness of amiodarone is demonstrated by the array of indications noted in the 2010 AHA guidelines for adults.[39] Its role in the management of atrial arrhythmias in adults includes the following: as an adjunct to electrical cardioversion of refractory paroxysmal

Table 33–1 Drug Therapy for Pulseless Arrest

Drug	Route of Administration	Dosage	How Applied
Epinephrine	IV, intraosseous, endotracheal	10 μg/kg	1:10,000 (0.1 mL/kg)
		100 μg/kg	1:1000 should be used for ETT
			(0.1 mL/kg)
Atropine	IV, intraosseous, endotracheal, subcutaneous	0.02 mg/kg (minimum dose = 0.15 mg)	
Sodium bicarbonate	IV, intraosseous	1 mEq/kg/dose	1 mEq/mL
		or	0.5 mEq/mL
		0.3 × weight (kg) × base deficit	
Calcium chloride	IV (intraosseous)	20 mg/kg	10% solution (100 mg/mL)
		0.2 mL/kg	
Lidocaine	IV (intraosseous), endotracheal	1 mg/kg	1%, 2%, 4% solution
Amiodarone	IV (intraosseous)	5 mg/kg	Dilute to 3 mg/mL
Magnesium	IV (intraosseous)	25–50 mg/kg for torsades des pointes or hypomagnesemia	50% solution

ETT, Endotracheal tube; *IV,* intravenous.

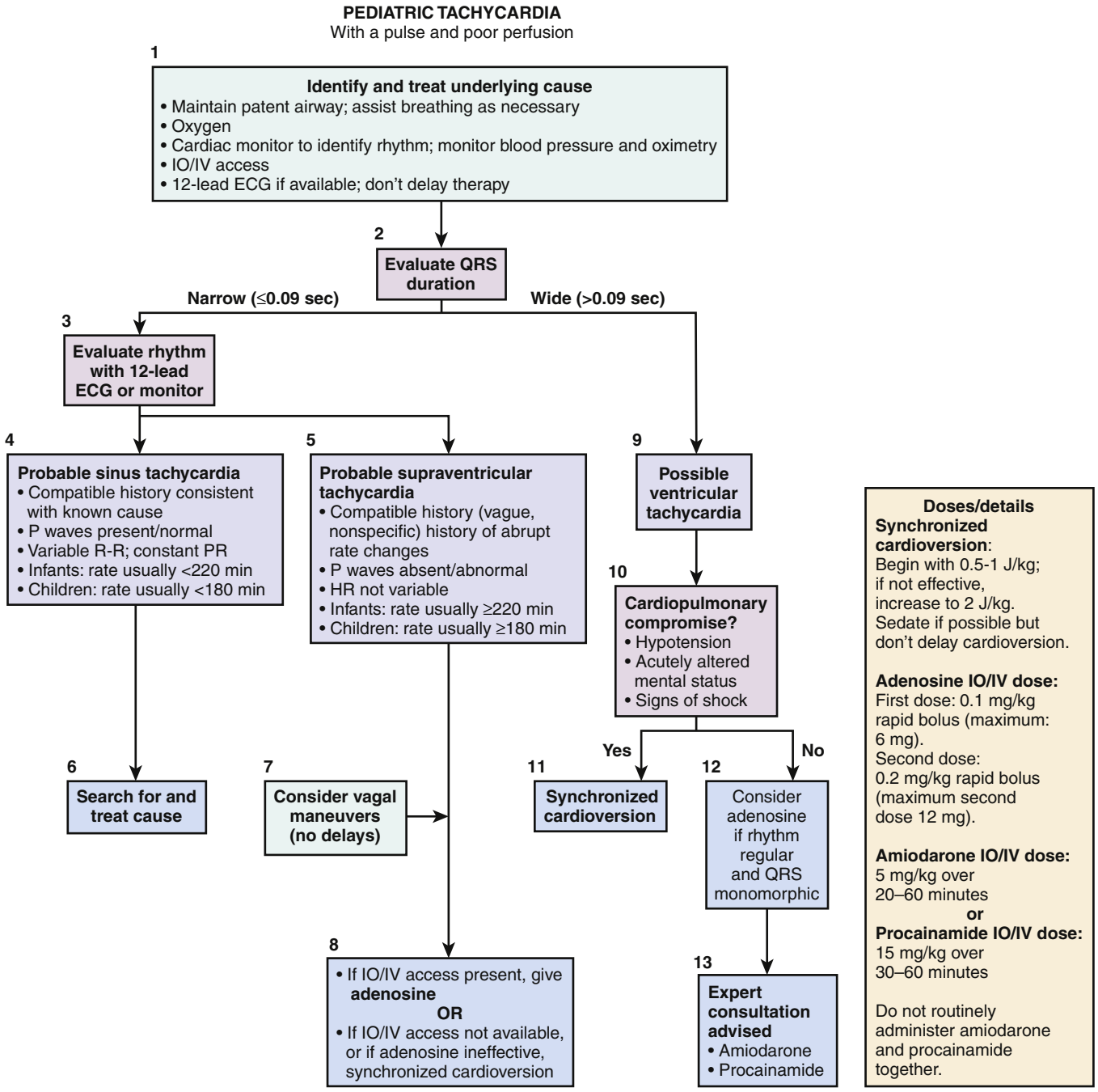

Figure 33–21. American Heart Association (AHA) guidelines for management of ventricular arrhythmias. *ABCs,* Airway, breathing, and circulation; *BLS,* basic life support; *CPR,* cardiopulmonary resuscitation; *ECG,* electrocardiogram; *IO,* intraosseous; *IV,* intravenous; *PEA,* pulseless electrical activity; *TT,* tracheal tube; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.

supraventricular tachycardia and atrial tachycardia, for rate control when digoxin has been ineffective, for pharmacologic conversion of atrial flutter, and for control of rapid ventricular response in preexcited atrial tachyarrhythmias. It is the drug of choice for junctional tachycardia with poor function. If function is preserved, amiodarone is an acceptable alternative to a β-blocker or calcium channel blocker. Its role in ventricular arrhythmias is outlined in Box 33-2.

The pharmacology of amiodarone is complex and may partially explain the wide range of efficacy. It is poorly absorbed orally and must be loaded intravenously in urgent situations. It is primarily classified as a Vaughn-Williams class III agent that blocks the ATP-sensitive outward potassium channels, causing prolongation of the action potential and refractory period. However, this effect requires intracellular accumulation. Upon intravenous loading, the antiarrhythmic effects primarily result from noncompetitive α- and β-adrenergic receptor blockade, calcium channel blockade, and effects on inward sodium current causing a decrease in anterograde conduction across the atrioventricular node and an increase in the effective atrioventricular refractory period. The full antiarrhythmic impact requires a loading period for up to 1 to 3 weeks to

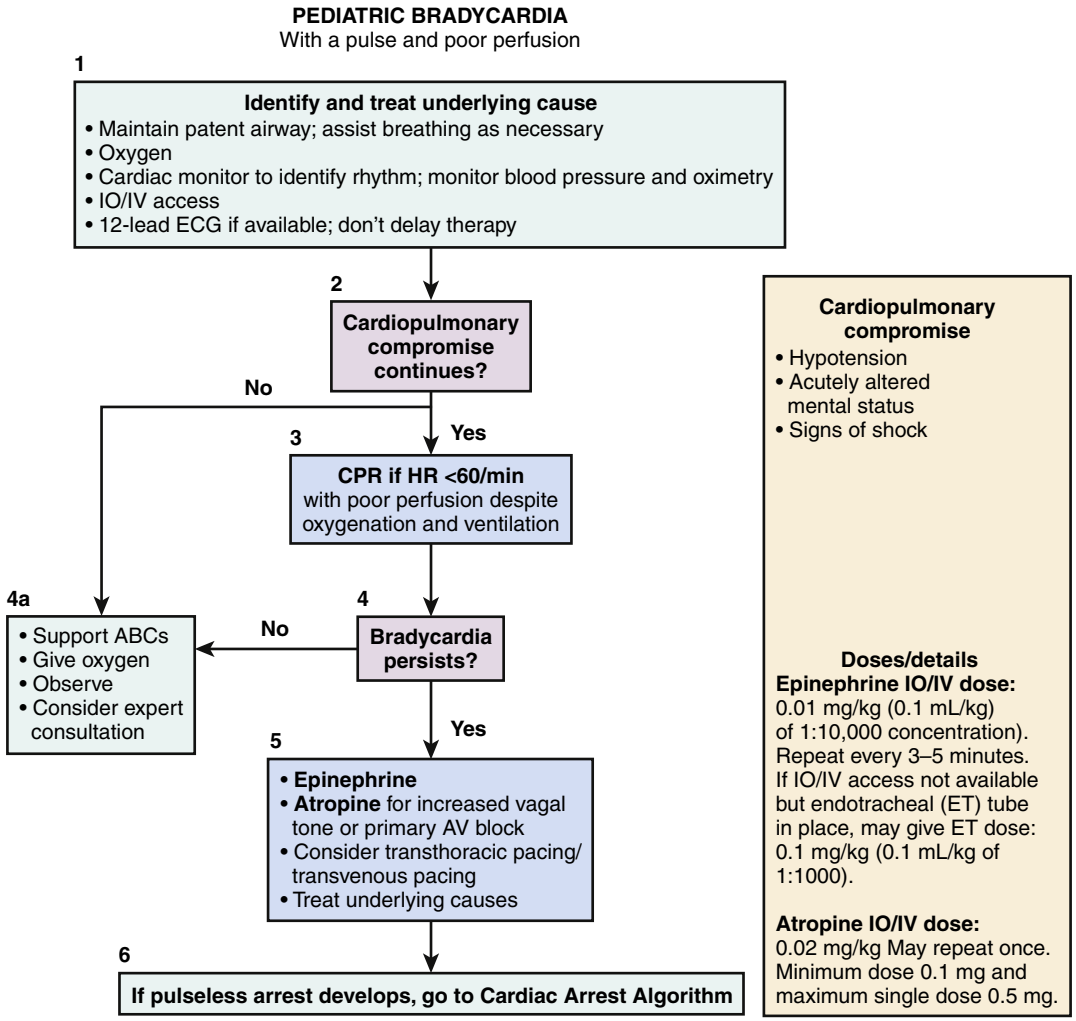

Figure 33–22. American Heart Association (AHA) guidelines for management of bradycardia. *ABCS,* Airway, breathing, and circulation; *ALS,* advanced life support; *AV,* atrioventricular; *BLS,* basic life support; *CPR,* cardiopulmonary resuscitation; *IO,* intraosseous; *IV,* intravenous.

achieve intracellular levels and full potassium channel blocking effects. Prolongation of the QT interval, an effect resulting from K-ATP channel blockade, is commonly described with amiodarone use; however, it does not manifest until several days into loading, underscoring its different effects during the acute period and after loading is accomplished. These effects are evident throughout all cardiac tissue, which may explain amiodarone's efficacy for so many arrhythmias, both atrial and ventricular. The α-adrenergic blockade leads to vasodilation, which may increase coronary blood flow.

Immediate hemodynamic effects of amiodarone are caused by the solubilizing agent Tween 80, which has both vasodilating and myocardial depressant effects.[270] Hypotension is commonly reported with intravenous administration and may limit the rate at which the drug can be given. The overall hemodynamic impact of intravenous administration depends on the balance of its effect on rate control, myocardial performance, and vasodilation. Cardiac output usually is unchanged or increases despite the decreased contractility because of both rate control and vasodilation. The effect on systemic vascular resistance and the limited impact on contractility make amiodarone the drug of choice for use in patients with impaired cardiac function.

The drug is highly lipid soluble, giving it a very large volume of distribution, which accounts for the need for loading over many days. Until all tissues are saturated, rapid redistribution out of the vascular compartment may lead to early recurrence of arrhythmias. Once tissue saturation has occurred, the half-life is estimated to be between 13 and 103 days.

Dosage recommendations for children are based on limited clinical studies and extrapolation of adult data. For life-threatening arrhythmias, the usual recommended dose is 5 mg/kg administered intravenously. This dose can be repeated if necessary to control the arrhythmia. Intravenous loading doses are followed by a continuous infusion of 10 to 20 mg/kg/day if there is a risk for arrhythmia recurrence. The ideal rate of bolus administration is unclear, but once diluted the drug is given by intravenous push in adults. The potential for profound vasodilation in children has led to concern by some pediatric intensivists and cardiologists, who recommend that amiodarone be given over 10 minutes as recommended in the package insert. This concern may not be valid in the pulseless arrest setting. Some delay always occurs with the current formulation of the intravenous drug because it must be diluted before it can be administered. Drug dilution should not delay

Box 33–2 Amiodarone (Intravenous)

- Intravenous amiodarone affects sodium, calcium channels, and α- and β-adrenergic blocking properties. The drug is useful for treatment of both atrial and ventricular arrhythmias.
- Amiodarone is also helpful for ventricular rate control of rapid atrial arrhythmias in patients with severely impaired LV function when digitalis has proved ineffective. Amiodarone is recommended after defibrillation and epinephrine in cardiac arrest with persistent VT or VF.
- Amiodarone is effective for control of hemodynamically stable VT, polymorphic VT, and wide-complex tachycardia of uncertain origin.
- Amiodarone is an adjunct to electrical cardioversion of refractory PSVTs, atrial tachycardia, and pharmacologic cardioversion of AF.
- Amiodarone can control rapid ventricular rate due to accessory pathway conduction in preexcited atrial arrhythmias.

AF, Atrial fibrillation; *LV,* left ventricular; *PSVT,* paroxysmal supraventricular tachycardia; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.
From Guidelines 2005 for cardiopulmonary resuscitation and emergency cardiovascular care part 7.2: management of cardiac arrest. American Heart Association in collaboration with International Liaison Committee on Resuscitation, *Circulation* 112(suppl I):IV-58-IV-66, 2005.

administration of additional shocks. An average of five shocks are delivered to adults with refractory VF before amiodarone is administered. An alternative dosing regimen for children is administration of 1 mg/kg pushes every 5 minutes up to 5 mg/kg. This dose can be repeated up to 10 mg/kg if the arrhythmia is not controlled. Use of the small-aliquot bolus technique may be particularly appropriate for infants younger than 6 to 12 months.

Amiodarone administered intravenously leaches plasticizers, particularly DEHP, from polyvinyl chloride. This effect is enhanced at low infusion rates and at higher drug concentrations and may be minimized by frequent intermittent boluses. Whether these plasticizers have any significant toxicity at these doses is unknown, although evidence indicates testicular vacuolization in rodents. Additional caution is warranted in neonates because the solution contains benzyl alcohol, which is associated with metabolic acidosis and death in premature infants (gasping syndrome). Identification of the potential for these adverse events has led the manufacturer to issue a statement to health care professionals stating that use of intravenously administered amiodarone in pediatrics is not recommended. The AHA has responded with a reiteration of the recommendation for intravenous amiodarone use in the 2010 guidelines for emergency cardiac care. In the recommendation it concludes that practitioners should obtain expert consultation because complications may include bradycardia, heart block, and torsades de pointes ventricular tachycardia. Adverse reactions to amiodarone can be life-threatening. The drug prolongs the QT interval. In a series by Etheridge et al.,[265] 29 of 50 infants and children experienced mild-to-moderate prolongation of the QTc. In the series by Burri et al.,[264] "most" infants experienced prolongation. Although none of the pediatric case series described the development of drug-induced arrhythmias in patients, amiodarone-induced torsades de pointes has been described in case reports,[271] and, although less common than in adults, caution is warranted. Use of amiodarone should be avoided in combination with other drugs that prolong the QT interval. In addition, caution should be exercised in the setting of hypomagnesemia and other electrolyte abnormalities that predispose to torsades de pointes. Severe bradycardia and heart block have been described, especially in the postoperative period, and ventricular pacing wires are recommended in this setting.

The manufacturer of the intravenous preparation (Pfizer, New York) reports in the product literature a series of 61 children receiving amiodarone, of whom 36% had hypotension, 20% had bradycardia, and 15% had atrioventricular block. These complications were severe or life-threatening in some cases. In the published case series of children, the incidence of adverse effects appears to be much lower. In a series reported by Etheridge et al.,[265] two of six patients who received intravenously administered amiodarone experienced hypotension. In several other series, the incidence of hypotension ranged from zero of 15 to four of 40.[264,266,268] All patients who were believed to require treatment responded to a saline solution infusion or calcium. One patient with symptomatic bradycardia responded to temporary pacing. Two other patients required a reduction in the rate of drug infusion for mild bradycardia.

Noncardiac adverse effects are often seen, especially with chronic dosing.[272] The most serious adverse effect is the development of interstitial pneumonitis, seen most often in patients with preexisting lung disease.[273] The incidence in children is unknown. Rarely an acute respiratory distress syndrome–like illness has been reported in both infants and adults at the initiation of treatment.[274,275] The lung disease may remit with early discontinuation of the drug. Thyroid disorders may occur with chronic use. Desethylamidarone, the major metabolite of amiodarone, appears to have an antithyroid effect by noncompetitive binding to the nuclear receptors. Both hyperthyroidism with thyrotoxicosis and hypothyroidism have occurred. This may be of particular concern in the management of fetal tachycardias. Although amiodarone appears to be effective in controlling refractory life-threatening fetal tachycardias, evidence of fetal hypothyroidism was present in 19% of neonates based on cord blood thyroid-stimulating hormone.[276] Other forms of toxicity include hepatotoxicity that may progress to cirrhosis, photosensitivity and skin discoloration, and local inflammation and cellulitis at the infusion site. Injection site reactions occurred in five of 20 patients who received amiodarone through a peripheral intravenous line. Corneal opacities are a common finding with chronic therapy but apparently do not affect vision.

Postresuscitation Care

Hemodynamic instability is common after cardiac arrest. A persistently low cardiac index may lead to multiorgan failure and is associated with early death within the first 24 hours after arrest.[277,278] Therapies to address low cardiac output states have included the use of inodilators. Inodilators (inamrinone and milrinone) augment cardiac output with little effect on myocardial oxygen demand. An inodilator can be used to treat myocardial dysfunction with increased systemic or pulmonary vascular resistance.[279,280] Administration of fluids may be required because of the vasodilatory effects.

Inodilators have a long half-life with a long delay in reaching a new steady-state hemodynamic effect after changing the infusion rate (18 hours with inamrinone and 4.5 hours with milrinone). In case of toxicity, adverse effects may persist for several hours after the infusion is discontinued.

Amelioration of neurologic injury after cardiac arrest has been a goal of many investigators over the past decades (Box 33-3). With the completion of two multicenter trials on mild hypothermia after cardiac arrest, one from Europe and the other from Australia, this goal appears to have been partially realized. In both studies, adult patients presenting with out-of-hospital VF who were resuscitated underwent rapid cooling to a target temperature between 32.8° C and 34.8° C. This temperature was maintained for 12 to 24 hours. Both neurologic outcome and mortality were improved compared with the control groups. The odds ratio for improved neurologic outcome were 1.4 in the European study, which included 275 patients, and 5.25 in the Australian study, which included 77 randomized patients. The hypothermia groups had lower mean blood pressure, required more frequent use of epinephrine, and had higher systemic vascular resistance. Although these studies have a limited target population, data from animal studies[281] and other smaller case series[282] suggest that therapeutic hypothermia is a useful tool after cardiac arrest from all causes and its use appears warranted, especially because the incidence of serious attributable complications is low. Fink et al.[283] studied the feasibility of achieving mild hypothermia after pediatric arrest and found that they were reliably able to achieve a target temperature of 32°C to 34°C in less than 3 hours. A multi-institutional randomized controlled trial of systemic hypothermia for 48 hours after nontraumatic cardiac arrest (Therapeutic Hypothermia After Pediatric Cardiac Arrest [THAPCA-]) is now underway.

Box 33–3 Experimental Cerebroprotective Therapy

- Calcium channel blockers
- Glutamate receptor antagonists
- Opiate receptor antagonists
- Central α_2-receptor antagonists
- β-Receptor antagonists
- Oxygen radical scavengers
- Iron chelators
- Xanthine oxidase inhibitors
- Inhibitors of arachidonic acid metabolism
- Thrombolytic agents
- Lazeroids
- Cerebral vasodilators
- Metabolic activators/inhibitors
- Hypothermia
- Nitric oxide synthase inhibitors
- Adenosine agonists
- Antiplatelet agents
- Antineutrophil strategies
- Protease inhibitors
- Growth factors

Future Directions

Despite the aforementioned therapeutic advances, continued efforts to clarify their applicability to infants and children is vital. Clinical trials have been hampered by the federal regulation know as the "final rule" for resuscitation research.[284] In 1996, as part of a broad-ranging effort to protect patients rights as human subjects, the standard of community consent for research that required immediate intervention was developed. Since that time, resuscitation research in both adults and children has been limited, with most trials conducted in Europe, Australia, and other countries, often with U.S. collaborators. The feasibility of defining a community standard to perform a hypothetical trial of hypothermia after postcardiac arrest in children was tested in 2004.[285] The relevant community was defined as hospital staff and the parents of ICU patients and parents of previously resuscitated children. They concluded that development of a study using an exemption from informed consent was feasible. However, in an accompanying editorial, Moler[284] reiterates that, despite feasibility, practicality is very different as evidenced by the complete lack of pediatric resuscitation trials since 1996. Whether revision of this rule will occur or techniques for acquiring community consent can be developed remains one of the major hurdles to future pediatric resuscitation research.

References are available online at http://www.expertconsult.com.

II

Chapter 34

Performance of Cardiopulmonary Resuscitation in Infants and Children

Robert M. Sutton, Robert A. Berg, and Vinay Nadkarni

PEARLS

- The four distinct phases of cardiac arrest and cardiopulmonary resuscitation (CPR) are:
  1. Prearrest
  2. No flow (untreated cardiac arrest)
  3. Low flow (CPR)
  4. Postresuscitation
- The most common precipitating event for cardiac arrests in children is respiratory insufficiency; adequate ventilation and oxygenation remain the first priority.
- High-quality CPR (i.e., push hard, push fast, allow full chest recoil, minimize interruptions, and don't overventilate) can improve cardiac arrest outcomes.
- Automated real-time corrective feedback devices improve CPR quality and short-term survival outcomes.
- Strategically focused therapies to specific phases of cardiac arrest and resuscitation can lead to more successful resuscitation in children.

Pediatric cardiac arrest is not a rare event. Approximately 16,000 American children (8-20/100,000 children/year) experience cardiopulmonary arrest each year.[1-5] Approximately half of these cardiac arrests occur in-hospital, and about half outside the hospital.[5,6] In times past, survival outcomes were not good and many children had severe neurological injury after their arrest event. With advances in resuscitation science and implementation techniques, survival from pediatric cardiac arrest has improved substantially over the past 25 years.[7] This chapter focuses on pediatric cardiac arrest, cardiopulmonary resuscitation (CPR), and other therapeutic interventions that have been specifically designed to improve outcomes from pediatric cardiac arrest.

Four Phases of Cardiac Arrest

The four distinct phases of cardiac arrest and CPR interventions are (1) prearrest, (2) no flow (untreated cardiac arrest), (3) low flow (CPR), and (4) postresuscitation. Interventions to improve the outcome of pediatric cardiac arrest should optimize therapies targeted to the time and phase of CPR, as suggested in Table 34-1.

Prearrest

The prearrest phase refers to relevant preexisting conditions of the child (e.g., neurologic, cardiac, respiratory, or metabolic problems) and precipitating events (e.g., respiratory failure or shock). It is known that pediatric patients who suffer an in-hospital cardiac arrest often have changes in their physiological status in the hours leading up to their arrest event.[8,9] Therefore, interventions during the prearrest phase focus on preventing the cardiac arrest, with special attention to early recognition and treatment of respiratory failure and shock. Rapid-response teams or medical emergency teams (METs) are in-hospital emergency teams designed specifically for this purpose. These teams respond to patients on general inpatient units who are at high risk of clinical decompensation and transfer these children to more acute care areas, with the goal to prevent progression to full cardiac arrest. Implementation of pediatric METs has been moderately successful; decreased cardiac arrest frequency and mortality have been demonstrated.[10-12] While METs cannot identify all children at risk for cardiac arrest, it seems reasonable to assume that transferring critically ill children to an intensive care unit (ICU) early in their disease process for better monitoring and more aggressive interventions can improve resuscitative care and clinical outcome.

No Flow/Low Flow

In order to improve outcomes from pediatric cardiac arrest, it is imperative to shorten the no-flow phase of untreated cardiac arrest. To that end, it is important to monitor high-risk patients to allow early recognition of the cardiac arrest and prompt initiation of basic and advanced life support. Effective CPR optimizes coronary perfusion pressure and cardiac output to critical organs to support vital organ viability during the low-flow phase. Important tenets of basic life support are push hard, push fast, allow full chest recoil between compressions,

Table 34–1 Phases of Cardiac Arrest and Targeted Interventions

Phase	Interventions
Prearrest phase: *Protect*	• Optimize community education regarding child safety • Optimize patient monitoring • Prioritize interventions to prevent progression to cardiac arrest • Early recognition and activation of medical emergency response teams
Arrest (no-flow): *Preserve*	• Minimize interval to BLS and ACLS phase • Organized 911/code blue response system • Preserve cardiac and cerebral substrate • Minimize interval to defibrillation, when indicated
Low-flow (CPR): *Resuscitate*	• Effective CPR to optimize myocardial blood flow and cardiac output • Avoid overventilation • Consider adjuncts to improve vital organ perfusion during CPR • Match oxygen delivery to oxygen demand • Consider extracorporeal CPR if standard CPR/ALS are not promptly successful
Postresuscitation: *Regenerate* Short-term	• Optimize cardiac output and cerebral perfusion • Treat arrhythmias, if indicated • Prevent hyper/hypoglycemia, hyperthermia • Consider mild resuscitative systemic hypothermia
Long-term	• Early intervention with occupational and physical therapy • Bioengineering and technology interface rehabilitation • Possible future role for stem cell transplantation

and minimize interruptions of chest compression. Achieving optimal coronary perfusion pressure, exhaled carbon dioxide concentration, and cardiac output during the low-flow phase of CPR is consistently associated with an improved chance for return of spontaneous circulation (ROSC) and improved short and long term outcome in both animal and human studies.[13-20] For ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), rapid detection and prompt defibrillation are vital for successful resuscitation. For cardiac arrests resulting from asphyxia and/or ischemia, provision of adequate myocardial perfusion and myocardial oxygen delivery are most important.

Postresuscitation

The postresuscitation phase includes management of the immediate postresuscitation stage, the next few hours to days, and long-term rehabilitation. The immediate postresuscitation stage is a high-risk period for ventricular arrhythmias and other reperfusion injuries. Interventions during the immediate postresuscitation stage and the next few days include adequate tissue oxygen delivery, treatment of postresuscitation myocardial dysfunction, and minimizing postresuscitation tissue injury (e.g., preventing postresuscitation hyperthermia, hyperglycemia/hypoglycemia and, perhaps, providing postresuscitation hypothermia). This postarrest phase may have the greatest potential for innovative advances in the understanding of cell injury and death, inflammation, apoptosis, and hibernation, ultimately leading to novel interventions. The rehabilitation stage concentrates on salvage of injured cells, recruitment of hibernating cells, and reengineering of reflex and voluntary communications of these cell and organ systems to improve functional outcome.

The specific phase of resuscitation dictates the focus of care. Interventions that improve outcome during one phase may be deleterious during another. For instance, intense vasoconstriction during the low-flow phase of cardiac arrest improves coronary perfusion pressure and the probability of ROSC. The same intense vasoconstriction during the postresuscitation phase increases left ventricular afterload and may worsen myocardial strain and dysfunction. Current understanding of the physiology of cardiac arrest and recovery allows us to only crudely manipulate blood pressure, oxygen delivery and consumption, body temperature, and other physiologic parameters in our attempts to optimize outcome. Future strategies likely will take advantage of increasing knowledge of cellular inflammation, thrombosis, reperfusion, mediator cascades, cellular markers of injury and recovery, and transplantation technology.

An overview of some of the pathophysiologic pathways perturbed by cardiac arrest and resuscitation, along with potential avenues for intervention, is shown in Figure 34-1.

Epidemiology of Pediatric Cardiac Arrest

Cardiovascular disease remains the most common cause of disease-related death in the United States, resulting in approximately 1 million deaths per year.[21] It is estimated that more than 400,000 Americans will have a cardiac arrest each year, nearly 90% in prehospital settings. While data regarding the incidence of childhood cardiopulmonary arrest are less robust, the best data suggest that about 16,000 American children suffer a cardiac arrest each year (annual incidence: 8 to 20 per 100,000 children per year).[1-5,22] For in-hospital arrests specifically, it is estimated that approximately 2% to 6% of all children admitted to pediatric intensive care units,[1,2,23] and 4% to 6% of children admitted to cardiac units will suffer a cardiac arrest.[24,25] In short, pediatric cardiac arrest is an important public health problem.

Outcomes from pediatric cardiac arrest have improved significantly over the past 20 years (Table 34-2). Nearly two thirds of children who have an in-hospital cardiac arrest are successfully resuscitated initially (i.e., attain sustained ROSC). Moreover, more than 25% of them will survive to hospital discharge, and many (nearly 75%) will have good neurologic function.[1-4,7,25-37] Factors that influence outcome from pediatric cardiac arrest include (1) the preexisting condition of the child, (2) the initial electrocardiographic (ECG) rhythm detected, (3) the duration of no-flow time (the time during an arrest without spontaneous circulation or provision of CPR), and (4) the quality of the life-supporting therapies provided during the resuscitation. With this knowledge, it is no surprise then that out-of-hospital pediatric arrests have worse outcomes compared to in-hospital arrests.[3,22,23,30,35,38-44] As many of these out-of-hospital events are not witnessed and bystander CPR is not common (less than 30% of children receive bystander CPR),[3] the duration of no-flow time can be

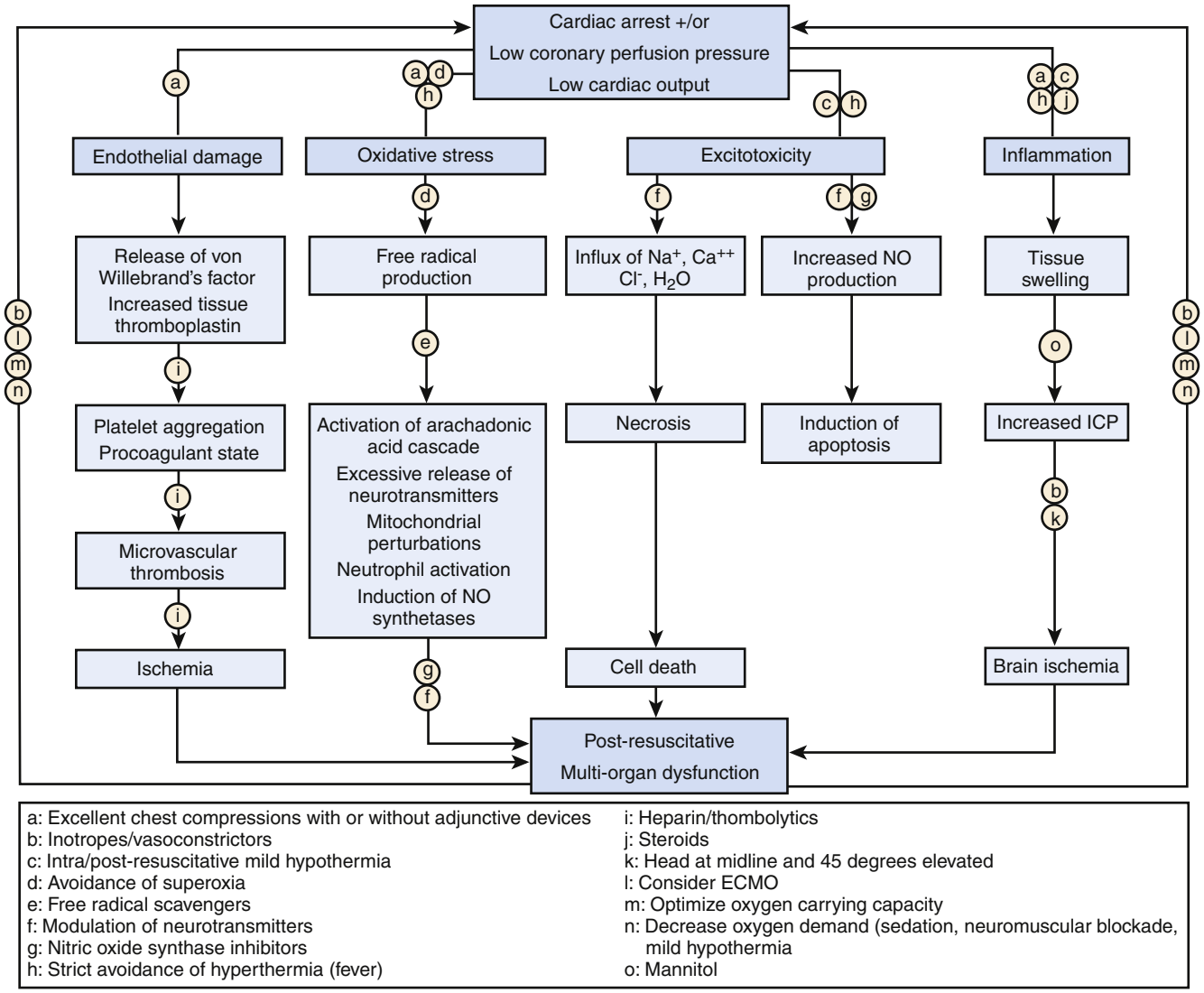

Figure 34–1. Schematic of physiologic processes that result from cardiac arrest and initial resuscitation, with some promising interventions indicated by lower case letters. Many complex interconnections and feedback loops among these processes are omitted from the schematic in order to generate an overview of the processes and potential interventions. *a,* Excellent chest compressions with or without adjunctive devices; *b,* inotropes/vasoconstrictors; *c,* intra-/postresuscitative mild hypothermia; *d,* avoidance of superoxia; *e,* free radical scavengers; *f,* modulation of neurotransmitters; *g,* nitric oxide (NO) synthase inhibitors; *h,* strict avoidance of hyperthermia (fever); *i,* heparin/thombolytics; *j,* steroids; *k,* head at midline and 45 degrees elevated; *l,* consider extracorporeal membrane oxygenation; *m,* optimize oxygen-carrying capacity; *n,* decrease oxygen demand (sedation, neuromuscular blockade, mild hypothermia); *o,* mannitol.

prolonged. As a result, less than 10% of these children survive their initial event, and in those that do survive, neurological injury is common. These findings are especially troublesome given that bystander CPR more than doubles patient survival rates.[45]

Compared to adults, superior survival rates are documented after pediatric cardiac arrest, specifically after in-hospital events; 27% of children survive to hospital discharge compared with only 17% of adults.[7] These findings may be in part due to differences in the initial ECG rhythm detected. While pediatric arrests are less commonly caused by arrythmias, such as ventricular tachycardia or ventricular fibrillation—10% of pediatric arrests versus 25% of adult arrests—the superior pediatric survival rate reflects a substantially higher survival rate among children with asystole or pulseless electrical activity compared with adults (24% vs. 11%). Moreover, the higher survival rate seen in children is mostly attributable to a much better survival rate among infants and preschool age children compared with older children.[26] Although this is speculative, the higher survival rates in children may be due to improved coronary and cerebral blood flow during CPR because of increased chest compliance in these younger arrest victims.[46,47]

Interventions During the Low-Flow Phase: Cardiopulmonary Resuscitation

Airway and Breathing

During the low-flow state of CPR, cardiac output and pulmonary blood flow are approximately 25% of that during normal sinus rhythm; therefore, much less ventilation is necessary for adequate gas exchange from the blood traversing the pulmonary circulation. Moreover, animal and adult data indicate

Table 34–2 Cardiac Arrest Outcomes for Both In-Hospital and Out-of-Hospital Pediatric Cardiac Arrest

Author (year)	Setting	No. Patients	ROSC (%)	Survival to Discharge (%)	Good Neurologic Survival (%)
Tibballs (2006)[32]	IH	147	73	36	NR
de Moss (2006)[37]	IH	91	82	25	11
Samson (2006)[28]	IH (VT/VF)	104	70	35	33
Nadkarni (2006)[7]	IH	880	52	27	18
Meaney (2006)[26]	IH (<21yr)	464	50	22	14
Donoghue (2005)[4]	OOH (systematic review)	5693	NR	12	4
Lopez-Herce (2005)[30]	IH/OOH	213	52	21	16
Berg (2005)[39]	OOH	13	100	0	0
Reis (2002)[27]	IH	129	64	16	15
Parra (2000)[25]	IH (Ped CICU)	32	63	44	25
Suominen (2000)[2]	IH	118	63	18	NR
Young (1999)[3]	IH (meta-analysis)	544	NR	24	NR
Young (1999)[3]	OOH (meta-analysis)	1568	NR	8	NR
Sirbaugh (1999)[42]	OOH	300	11	2	<1
Suominen (1998)[44]	OOH (posttrauma)	41	24	7	5
Suominen (1997)[43]	OOH	50	26	16	12
Torres (1997)[34]	IH	92	NR	10	8
Slonim (1997)[1]	IH (PICU)	205	NR	14	NR
Schindler (1996)[41]	OOH	80	54	8	0
Kuisma (1995)[23]	OOH	34	29	15	12
Dieckmann (1995)[40]	OOH	65	5	3	1.5
Zaritsky (1987)[36]	IH	53	NR	9	NR

IH, In-hospital; *OOH,* out-of-hospital.

that a rapid rate of assisted ventilation ("overventilation" from exuberant rescue breathing) during CPR is common and can substantially compromise venous return and cardiac output by increasing intrathoracic pressure.[48-50] Moreover, these detrimental hemodynamic effects are compounded when one considers the effect of interruptions in CPR to provide airway management and rescue breathing.[51-55] While overventilation is problematic, in light of the fact that most pediatric arrests are asphyxial in nature, provision of *adequate* ventilation is still important. The difference between arrythmogenic and asphyxial arrests lies in the physiology. In animal models of sudden VF cardiac arrest, acceptable PaO_2 and $PaCO_2$ persist for 4 to 8 minutes during chest compressions without rescue breathing.[56] This is in part because aortic oxygen and carbon dioxide concentrations at the onset of the arrest do not vary much from the prearrest state. As a result, the lungs act as a reservoir of oxygen during CPR, and adequate oxygenation and ventilation can continue without rescue breathing. However, during asphyxial arrest, blood continues to flow to tissues in the prearrest state, resulting in significant arterial and venous oxygen desaturation, elevated lactate levels, and depletion of the pulmonary oxygen reserve. Therefore, at the onset of resuscitation, there is substantial arterial hypoxemia and acidemia. In this circumstance, rescue breathing with controlled ventilation can be lifesaving. In contrast, the adverse hemodynamic effects from overventilation during CPR combined with the interruptions in chest compressions to open the airway and deliver rescue breathing are a lethal combination in certain circumstances such as VT/VF arrests. In short, the resuscitation technique should be titrated to the physiology of the patient to optimize patient outcome.

Circulation

Optimizing Blood Flow During Low-Flow Cardiopulmonary Resuscitation: Push Hard, Push Fast

When the heart arrests and no blood flows to the aorta, coronary blood flow ceases immediately.[57] At that point, provision of high-quality CPR (push hard, push fast) is necessary to reestablish flow. The goal during CPR is to maximize the myocardial perfusion pressure (MPP). Related by the following equation:

$$\text{MPP} = \text{Aortic diastolic blood pressure (AoDP)} - \text{Right atrial pressure (RAP)}$$

myocardial blood flow improves as the gradient between AoDP and RAP increases. During downward compression phase, aortic pressure rises at the same time as right atrial pressure with little change in the MPP. However, during the

decompression phase of chest compressions, the right atrial pressure falls faster and lower than the aortic pressure, which generates a pressure gradient perfusing the heart with oxygenated blood during this artificial period of "diastole." Several animal and human studies have demonstrated in both VT/VF and asphyxial models the importance of establishing MPP as a predictor for short term survival outcome (ROSC).[19,58-61]

Based on the equation above, MPP can be improved by strategies that increase the pressure gradient between the aorta and the right atrium. As an example, the inspiratory impedance threshold device (ITD) is a small, disposable valve that can be connected directly to the tracheal tube or face mask to augment negative intrathoracic pressure during the inspiratory phase of spontaneous breathing and the decompression phase of CPR by impeding airflow into the lungs. Application in animal and adult human trials of CPR has established the ability of the ITD to improve vital organ perfusion pressures and myocardial blood flow[51,62-65]; however, in the only randomized trial during adult CPR, mortality benefit was limited to the subgroup of patients with pulseless electrical activity.[66] Additional evidence that augmentation of negative intrathoracic pressure can improve perfusion pressures during CPR comes from the active compression-decompression device (ACD). The ACD is a handheld device that is fixed to the anterior chest of the victim by means of suction—think household plunger—that can be used to apply active decompression forces during the release phase, thereby creating a vacuum within the thorax. By actively pulling during the decompression phase, blood is drawn back into the heart by the negative pressure.[67] Animal and adult studies have demonstrated that the combination of ACD with ITD acts in concert to further improve perfusion pressures during CPR compared to ACD alone.[63] In the end, while novel interventions such as the ITD and ACD are promising to improve blood flow during CPR, the basic tenants of "push hard, push fast, minimize interruptions, and don't overventilate" are still the dominate factors to improve blood flow during CPR and chance of survival.

Chest Compression Depth

The pediatric chest compression depth recommendation of at least one-third anterior-posterior chest depth (approximately 4 cm in infants and 5 cm in children) is based largely upon expert clinical consensus, using data extrapolated from animal, adult, and limited pediatric data. Recently, Maher et al. published data from a case series of infants postcardiac surgery associating arterial blood pressure with qualitative chest compression depths. In this small study of 6 infants, chest compressions targeted to one-half anterior-posterior chest depth imparted improved systolic blood pressures compared to those at one-third anterior-posterior chest depth.[68] While a small series with qualitatively estimated chest compression depths, this is the first study to collect actual data from children supporting the existing chest compression depth guidelines. On the contrary, two recent studies using computer-automated tomography[69,70] suggest that depth recommendations based on a relative (%) anterior-posterior chest compression depth are deeper than those recommended for adults, and that a depth of one-half anterior-posterior chest depth is unattainable in most children. Future studies that collect data from actual children and that associate quantitatively measured chest compression depths with short- and long-term clinical outcomes (arterial blood pressure, end-tidal carbon dioxide, return of spontaneous circulation, survival) are needed.

Compression/Ventilation Ratios

The amount of ventilation provided during CPR should match, but not exceed, perfusion and should be titrated to the amount of circulation during the specific phase of resuscitation as well as the metabolic demand of the tissues. Therefore during the low-flow state of CPR when the amount of cardiac output is roughly 25% of normal, less ventilation is needed.[71] However, the best ratio of compressions to ventilations in pediatric patients is largely unknown and depends on many factors including the compression rate, the tidal volume, the blood flow generated by compressions, and the time that compressions are interrupted to perform ventilations. Recent evidence demonstrated that a compression/ventilation ratio of 15:2 delivers the same minute ventilation and increases the number of delivered chest compressions by 48% compared to CPR at a compression/ventilation ratio of 5:1 in a simulated pediatric arrest model.[72,73] This is important because when chest compressions cease, the aortic pressure rapidly decreases and coronary perfusion pressure falls rapidly.[57] Increasing the ratio of compressions to ventilations minimizes these interruptions, thus increasing coronary blood flow. These findings are in part the reason the American Heart Association (AHA) now recommends a pediatric compression/ventilation ratio of 15:2.

Duty Cycle

In a model of human adult cardiac arrest, cardiac output and coronary blood flow are optimized when chest compressions last for 30% of the total cycle time (approximately 1:2 ratio of time in compression to time in relaxation).[74] As the duration of CPR increases, the optimal duty cycle may increase to 50%. In a juvenile swine model, a relaxation period of 250 to 300 milliseconds (duty cycle of 40% to 50% at a compression rate of 120/min) correlates with improved cerebral perfusion pressures compared with shorter duty cycles of 30%.[75]

Circumferential Versus Focal Sternal Compressions

In adult and animal models of cardiac arrest, circumferential (vest) CPR has been demonstrated to improve CPR hemodynamics dramatically.[76] In smaller infants, it is often possible to encircle the chest with both hands and depress the sternum with the thumbs, while compressing the thorax circumferentially (thoracic squeeze). In an infant animal model of CPR, this "two-thumb" method of compression with thoracic squeeze resulted in higher systolic and diastolic blood pressures and a higher pulse pressure than traditional two-finger compression of the sternum.[77]

Open-Chest Cardiopulmonary Resuscitation

Excellent standard closed-chest CPR generates cerebral blood flow that is approximately 50% of normal. By contrast, open-chest CPR can generate cerebral blood flow that approaches normal. Whereas open-chest massage improves coronary perfusion pressure and increases the chance of successful defibrillation in animals and humans,[78-80] performing a thoracotomy to allow open-chest CPR is impractical in many situations. A retrospective review of 27 cases of CPR following pediatric blunt trauma (15 with open-chest CPR and 12 with closed-chest CPR) demonstrated that open-chest CPR increased hospital cost without altering rates of ROSC or survival to

discharge. However, survival in both groups was 0%, indicating that the population may have been too severely injured or too late in the process to benefit from this aggressive therapy.[81] Earlier institution of open-chest CPR may warrant reconsideration in selected special resuscitation circumstances.

Medications Used to Treat Cardiac Arrest

While animal studies have indicated that epinephrine can improve initial resuscitation success after both asphyxial and VF cardiac arrests, no single medication has been shown to improve survival outcome from pediatric cardiac arrest. A variety of medications are used during pediatric resuscitation attempts including vasopressors (epinephrine or vasopressin), antiarrhythmics (amiodarone or lidocaine), and other drugs such as calcium chloride and sodium bicarbonate. Each is discussed separately below.

Vasopressors

Epinephrine (adrenaline) is an endogenous catecholamine with potent α- and β-adrenergic stimulating properties. The α-adrenergic action (vasoconstriction) increases systemic and pulmonary vascular resistance. The resultant higher aortic diastolic blood pressure improves coronary perfusion pressure and myocardial blood flow even though it reduces global cardiac output during CPR. Adequacy of myocardial blood flow is a critical determinant of ROSC. Epinephrine also increases cerebral blood flow during CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation.[82-84] However, recent evidence suggests that epinephrine can decrease local cerebral microcirculatory blood flow at a time when global cerebral flow is increased.[85] The β-adrenergic effect increases myocardial contractility and heart rate and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi; however, the β-adrenergic effects are not observed in the peripheral vascular beds secondary to the high dose used in cardiac arrest. Epinephrine also increases the vigor and intensity of VF, increasing the likelihood of successful defibrillation.

High-dose epinephrine (0.05 to 0.2 mg/kg) improves myocardial and cerebral blood flow during CPR more than standard-dose epinephrine (0.01 to 0.02 mg/kg) in animal models of cardiac arrest and may increase the incidence of initial ROSC.[86,87] Administration of high-dose epinephrine, however, can worsen a patient's postresuscitation hemodynamic condition. Retrospective studies indicate that use of high-dose epinephrine in adults or children may be associated with a worse neurologic outcome.[88,89] A randomized, controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine following failed initial standard-dose epinephrine in pediatric in-hospital cardiac arrest demonstrated a worse 24-hour survival in the high-dose epinephrine group (1/27 vs. 6/23, $P < .05$).[90] Based on these clinical data, high-dose epinephrine cannot be recommended routinely for either initial or rescue therapy.

Vasopressin is a long-acting endogenous hormone that acts at specific receptors to mediate systemic vasoconstriction (V_1 receptor) and reabsorption of water in the renal tubule (V_2 receptor). The vasoconstriction is most intense in the skeletal muscle and skin vascular beds. Unlike epinephrine, vasopressin is not a pulmonary vasoconstrictor. In experimental models of cardiac arrest, vasopressin increases blood flow to the heart and brain and improves long term survival compared with epinephrine. However, vasopressin can decrease splanchnic blood flow during and following CPR and can increase afterload in the postresuscitation period.[91-95] Adult randomized controlled trials suggest that outcomes are similar after use of vasopressin or epinephrine during CPR.[96,97] During pediatric arrest, a case series of four children who received vasopressin during six prolonged cardiac arrest events suggested that the use of bolus vasopressin may result in ROSC when standard medications have failed.[98] However, a more recent retrospective study of 1293 consecutive pediatric arrests from the National Registry of CPR (NPCRP) found that vasopressin use, while infrequent (administered in only 5% of events), was associated with a lower likelihood of ROSC. Therefore, it is unlikely that vasopressin will replace epinephrine as a first-line agent in pediatric cardiac arrest. However, the available data suggest that its use in conjunction with epinephrine may deserve further investigation.

Calcium

Calcium is used frequently in cases of cardiac arrest, despite the lack of evidence for efficacy when it is administered routinely during resuscitation attempts. In the absence of a documented clinical indication (i.e., hypocalcemia, calcium channel blocker overdose, hypermagnesemia, or hyperkalemia), administration of calcium does not improve outcome from cardiac arrest.[37,99-107] To the contrary, three pediatric studies have suggested a potential for harm, as routine calcium administration was associated with decreased survival rates and/or worse neurological outcomes.[37,99,100]

Buffer Solutions

There are no randomized controlled studies in children examining the use of sodium bicarbonate for management of pediatric cardiac arrest. Two randomized controlled studies have examined the value of sodium bicarbonate in the management of adult cardiac arrest[108] and in neonates with respiratory arrest in the delivery room.[109] Neither was associated with improved survival. One multicenter retrospective in-hospital pediatric study found that sodium bicarbonate administered during cardiac arrest was associated with decreased survival, even after controlling for age, gender, and first documented cardiac rhythm.[99] Therefore, during pediatric cardiac arrest resuscitation, the routine use of sodium bicarbonate is NOT recommended.

Clinical trials involving critically ill adults with severe metabolic acidosis did not demonstrate a beneficial effect of sodium bicarbonate on hemodynamics despite correction of acidosis.[110,111] However, the presence of severe acidosis may depress the action of catecholamines, so the use of sodium bicarbonate may be considered in an acidemic child who is refractory to catecholamine administration.[112,113] Acidosis may increase the threshold for myocardial stimulation in a patient with an artificial cardiac pacemaker[114]; therefore administration of bicarbonate or another buffer is appropriate for management of severe documented acidosis in these children. Administration of sodium bicarbonate also is indicated in the patient with a tricyclic antidepressant overdose, hyperkalemia, hypermagnesemia, or sodium channel blocker poisoning. The buffering action of bicarbonate occurs when

a hydrogen cation and a bicarbonate anion combine to form carbon dioxide and water. If carbon dioxide is not effectively cleared through ventilation, its buildup counterbalances the buffering effect of bicarbonate. Because carbon dioxide readily penetrates cell membranes, intracellular acidosis may increase without adequate ventilation. Therefore, bicarbonate should not be used for management of respiratory acidosis.

Unlike sodium bicarbonate, tromethamine (THAM) buffers excess protons without generating carbon dioxide. Carbon dioxide is consumed following THAM administration. In a patient with limited ventilation, tromethamine may be preferable when buffering is necessary. Tromethamine undergoes renal elimination, and renal insufficiency may be a relative contraindication to its use. Carbicarb, an equimolar combination of sodium bicarbonate and sodium carbonate, is another buffering solution that generates less carbon dioxide than sodium bicarbonate. In a canine model of cardiac arrest comparing animals given normal saline, sodium bicarbonate, THAM, or Carbicarb, the animals given any buffer solution had a higher rate of ROSC than the animals given normal saline. In the animals given sodium bicarbonate or Carbicarb, the interval to ROSC was significantly shorter than in animals given normal saline. However, at the end of the 6-hour study period, all resuscitated animals were in a deep coma, so no inferences regarding meaningful survival can be drawn.[115] It is premature to recommend either THAM or Carbicarb during CPR at this time.

Postresuscitation Interventions

Temperature Management

Hyperthermia following cardiac arrest is common in children, and fever following cardiac arrest is associated with poor neurologic outcome.[116,117] Two seminal articles addressing adult out-of-hospital VF cardiac arrest have established that mild induced hypothermia (32° C to 34° C) is a clinically promising recent goal-directed postresuscitation therapy. In these randomized studies of comatose patients older than 18 years after VF cardiac arrest, outcomes were improved.[118,119] However, extrapolation of these findings to the pediatric arrest victim is difficult, as fever, trauma, stroke, and other ischemic conditions, common in pediatric cardiac arrest, are associated with poor neurologic outcome. Emerging neonatal trials of selective brain cooling and systemic cooling show promise in neonatal hypoxic-ischemic encephalopathy, suggesting that induced hypothermia may improve outcomes.[120,121] At a minimum, it is advisable to avoid hyperthermia in children following CPR. Using an approach of "therapeutic normothermia" with scheduled administration of antipyretic medications and the use of external cooling devices may be necessary to prevent hyperthermia in this population.

Glucose Control

Both hyperglycemia and hypoglycemia following cardiac arrest are associated with worse neurologic outcome.[122-125] While it seems intuitive that hypoglycemia would be associated with worse neurologic outcome, whether hyperglycemia per se is harmful or is simply a marker of the severity of the stress hormone response from prolonged ischemia is not clear. In critically ill adult patients, tight glucose control using an insulin infusion was associated with improved survival.[126,127] However, subsequent studies of nonsurgical adult populations and neonatal/pediatric trials have demonstrated no survival benefit and/or the potential for harm when rates of inadvertent hypoglycemia were high during treatment.[125,128-135] Using the available data, there is insufficient evidence to formulate a strong recommendation on the management of hyperglycemia in children with ROSC following cardiac arrest. If hyperglycemia is treated following ROSC in pediatric patients, blood glucose concentrations should be carefully monitored to avoid hypoglycemia.

Blood Pressure Management

Compared with healthy volunteers, adults resuscitated from cardiac arrest have impaired autoregulation of cerebral blood flow.[136] Hence they may not maintain adequate cerebral blood flow in the context of low systemic pressure and, likewise, may not be able to protect the brain from excessive blood flow and microvascular perfusion pressure in the context of systemic hypertension. However, in animal models, brief induced hypertension following resuscitation results in improved neurologic outcome compared with normotensive reperfusion.[137,138] Therefore, a practical approach to blood pressure management following cardiac arrest is to attempt to minimize blood pressure variability in this high-risk period following resuscitation.

Postresuscitation Myocardial Dysfunction

Postarrest myocardial stunning and arterial hypotension occur commonly after successful resuscitation in both animals and humans.[118,119,139-146] Animal studies demonstrate that postarrest myocardial stunning is a global phenomenon with biventricular systolic and diastolic dysfunction. This postarrest myocardial stunning is pathophysiologically and physiologically similar to sepsis-related myocardial dysfunction and post–cardiopulmonary bypass myocardial dysfunction, including increases in inflammatory mediators and nitric oxide production.[139,141,142,145] Because cardiac function is essential to reperfusion following cardiac arrest, management of postarrest myocardial dysfunction may be important to improving survival. The classes of agents used to maintain circulatory function (i.e., inotropes, vasopressors, and vasodilators) must be carefully titrated during the postresuscitation phase to the patient's cardiovascular physiology. Trials in animal models have shown that various vasoactive medications can effectively ameliorate postarrest myocardial dysfunction (e.g., dobutamine, milrinone, levosimendan).[147-151] Similarly, in human observational studies, fluid resuscitation and various vasoactive medications (i.e., epinephrine, dobutamine, and dopamine) have been provided for myocardial dysfunction syndrome.[118,119,140-144] In the end, optimal use of these agents involves close goal-directed titration, and the use of invasive hemodynamic monitoring may be appropriate.

Other Considerations

Quality of CPR

The quality of healthcare provider CPR during adult resuscitations typically does not comply with American Heart Association clinical practice guidelines. Long CPR-free intervals, shallow chest compressions, incorrect chest compression

rates, and overventilation are common.[152-155] Unfortunately, the quality of CPR performed during the resuscitation attempt is directly related to patient outcome.[52,152,156] Studies have shown in adults and in children that patients with a witnessed cardiac arrest[4] and those who receive bystander CPR[157] have an increased chance of survival. Those that suffer their in-hospital cardiac arrest at night or during weekends (presumably when the quality of resuscitation is not as good as in the daytime or on weekdays) have higher mortality.[158] Furthermore, pediatric outcomes are improved in hospitals staffed with highly trained pediatric specific providers.[22] Taken all together, these findings establish that the quality of resuscitative care, specifically early high-quality CPR, is an important determinate of patient survival.

In an effort to improve CPR quality, CPR-monitoring defibrillators with audiovisual feedback have been used during adult resuscitation, and improvements in CPR quality and clinical outcomes have been achieved.[156,159] In a recent pediatric article, the combination of focused bedside training and automated feedback defibrillators improved CPR guideline compliance of in-hospital providers.[154] However, there were still significant portions of the resuscitation that suffered from substandard resuscitative care. Future studies should continue to focus on novel ways to improve pediatric CPR during resuscitation attempts.

Extracorporeal Membrane Oxygenation Cardiopulmonary Resuscitation

Venoarterial extracorporeal membrane oxygenation (ECMO) has been increasingly used as a rescue therapy during CPR, especially for potentially reversible acute postoperative myocardial dysfunction or arrhythmias. Studies of extracorporeal CPR (E-CPR) have demonstrated favorable early survival outcomes in children with primary cardiac disease when E-CPR protocols were in place at the time of the arrest.[31,160-170] Interestingly, data has been mixed regarding the relationship between outcome and CPR duration before ECMO cannulation. CPR and ECMO are not curative treatments. They are simply cardiopulmonary supportive measures that restore tissue perfusion until recovery from the precipitating disease process is achieved. As such, they can be powerful tools. Thus E-CPR should be considered for children with cardiac arrest who have heart disease amenable to recovery or transplantation, if the arrest occurs in a highly supervised environment such as an intensive care unit with existing clinical protocols and available expertise and equipment to rapidly initiate extracorporeal life support (ECLS).

Ventricular Fibrillation and Ventricular Tachycardia in Children

Pediatric VF or VT has been an underappreciated pediatric problem. Recent studies indicate that VF and VT (i.e., shockable rhythms) occur in 27% of in-hospital cardiac arrests at some time during the resuscitation.[28] In a population of pediatric cardiac intensive care unit patients, as many as 41% of arrests were associated with VF or VT.[24] According to the National Registry of Cardiopulmonary Resuscitation (NRCPR) database, during in-hospital arrest, 10% of children had an initial rhythm of VF/VT. In all, 27% of the children had VF/VT at some time during the resuscitation.[28] The incidence of VF varies by setting and age.[171] In special circumstances, such as tricyclic antidepressant overdose, cardiomyopathy, status post–cardiac surgery, and prolonged QT syndromes, VF and pulseless VT are more likely.

The treatment of choice for short-duration VF is prompt defibrillation. In general, the mortality rate increases by 7% to 10% per minute of delay to defibrillation. Because VF must be considered before defibrillation can be provided, early determination of the rhythm by electrocardiography is critical. An attitude that VF is rare in children can be a self-fulfilling prophecy with a uniformly fatal outcome. The recommended defibrillation dose is 2 J/kg, but the data supporting this recommendation are not optimal and are based on old monophasic defibrillators. In the mid-1970s, authoritative sources recommended starting doses of 60 to 200 J for all children. Because of concerns for myocardial damage and animal data suggesting that shock doses ranging from 0.5 to 1 J/kg were adequate for defibrillation in a variety of species, Gutgesell et al. evaluated the efficacy of their strategy to defibrillate with 2 J/kg monophasic shocks. Seventy-one transthoracic defibrillations in 27 children were evaluated. Shocks within 10 J of 2 J/kg resulted in successful defibrillation in 91% of defibrillation attempts. The major determinant of successful defibrillation other than VF duration is countershock current. This current depends on the defibrillator energy and transthoracic impedance. Studies in children indicate that the transthoracic impedance of infants and children greatly overlap. Although there is a statistically significant correlation between size and transthoracic impedance, the correlation is weak. These studies provide only weak support for the present dogma that the defibrillator energy dose should vary directly with weight. Nevertheless, the present recommendation of 2 J/kg has stood the test of time.

Although the limited data regarding pediatric defibrillation used monophasic waveform shocks, most new defibrillators use biphasic waveform shocks. Defibrillation with these biphasic waveforms apparently is safer and more effective than monophasic waveform defibrillation. Therefore the use of 2 J/kg biphasic waveform shocks should be at least as effective as 2 J/kg monophasic shocks and possibly safer.

Antiarrhythmic Medications: Lidocaine and Amiodarone

Administration of antiarrhythmic medications should never delay administration of shocks to a patient with VF. However, after an unsuccessful attempt at electrical defibrillation, medications to increase the effectiveness of defibrillation should be considered. Epinephrine is the current first-line medication for both pediatric and adult patients in VF. If epinephrine and a subsequent repeat attempt to defibrillate are unsuccessful, lidocaine or amiodarone should be considered.

Lidocaine traditionally has been recommended for shock-resistant VF in adults and children. However, only amiodarone improved survival to hospital admission in the setting of shock-resistant VF compared with placebo.[172] In another study of shock-resistant out-of-hospital VF, patients receiving amiodarone had a higher rate of survival to hospital admission than patients receiving lidocaine.[173] Neither study included children. Because there is moderate experience with

amiodarone use as an antiarrhythmic agent in children and because of the adult studies, it is rational to use amiodarone similarly in children with shock-resistant VF/VT. The recommended dosage is 5 mg/kg by rapid intravenous bolus. There are no published comparisons of antiarrhythmic medications for pediatric refractory VF. Although extrapolation of adult data and electrophysiologic mechanistic information suggest that amiodarone may be preferable for pediatric shock-resistant VF, the optimal choice is not clear.

Pediatric Automated External Defibrillators

Automated external defibrillators (AEDs) have improved adult survival from VF.[174,175] AEDs are recommended for use in children 8 years or older with cardiac arrest.[176,177] The available data suggest that some AEDs can accurately diagnose VF in children of all ages, but many AEDs are limited because the defibrillation pads and energy dosage are geared for adults. Adapters having smaller defibrillation pads that dampen the amount of energy delivered have been developed as attachments to adult AEDs, allowing their use in children. However, it is important that the AED diagnostic algorithm is sensitive and specific for pediatric VF and VT. The diagnostic algorithms from several AED manufacturers have been tested for such sensitivity and specificity and therefore can be reasonably used in younger children.

Summary

Outcomes from pediatric cardiac arrest and CPR appear to be improving. Perhaps the evolving understanding of pathophysiologic events during and after pediatric cardiac arrest and the developing fields of pediatric critical care and pediatric emergency medicine have contributed to these apparent improvements. In addition, exciting breakthroughs in basic and applied science laboratories are on the immediate horizon for study in specific subpopulations of cardiac arrest victims. By strategically focusing therapies to specific phases of cardiac arrest, there is great promise that critical care interventions will lead the way to more successful cardiopulmonary and cerebral resuscitation in children.

References are available online at http://www.expertconsult.com.

Structure and Development of the Upper Respiratory System in Infants and Children

Linda Brodsky

PEARLS

- The upper airway and upper digestive tract are intimately related during embryogenesis and consequently have important anatomic relationships that must be considered in the context of one another. Failure to recognize and fully understand these relationships can lead to serious morbidity in the critically ill child.
- The structure of the upper airway undergoes enormous change from infancy through young adulthood. An understanding of the numerous variations, congenital anomalies, and resultant special vulnerabilities of the developing airway and how they relate to altered states of consciousness and underlying illness should result in better outcomes and a lower morbidity rate.
- The upper airway includes both the middle ear and connecting Eustachian tube and the paranasal sinuses, which drain into the nose. Iatrogenic manipulation of these connections, such as that which occurs with tube placement, may cause obstruction and secondary infection, complicating the clinical picture in a seriously ill child.

Respiration is vital to survival and is the first function that is protected in any critical medical situation. The respiratory tract can be divided into the upper or conducting airways and the lower or gaseous exchange airways. For the purposes of this chapter, the trachea down to the carina is included as part of the "upper" or conducting airways. The upper airway shares its development with that of the upper digestive tract, and the lower airway shares its development with the cardiovascular system.

The upper airway serves numerous functions, including air conduction, warming, purification, humidification, protection of the lower airways, and phonation, which is most often overlooked in the critical care setting.

In the fetus, the larynx allows fetal breathing (of amniotic fluid) until the moment of birth, when it assumes the role of protecting gas exchange between the environment and the newborn. Protection of the lower airway and phonation occur simultaneously. Thus the infant's first cry heralds its ability to sustain independent life. After breathing, eating becomes the infant's next priority, requiring some of the most complex neurologic coordination found in nature. When confronted with the challenges of maintaining a patent airway, deglutition, and vocalization, a well-functioning upper airway is of utmost importance.

Developmental Anatomy of the Upper Airway

The embryologic development of the nasal cavity, mouth, nasopharynx, oropharynx, and hypopharynx occurs in a separate developmental environment from that of the larynx, trachea, bronchi, and lung parenchyma. Early errors in development can affect both anatomic areas, but these errors are usually incompatible with life. Because the nose, mouth, pharynx, and part of the larynx develop from different embryonic structures than the rest of the larynx and lower respiratory tract, there are few coincident congenital anomalies between these two contiguous but developmentally distinct areas.

The branchial arches, which begin to appear during the fourth week of embryogenesis, give rise to most of the upper airway—nasal passages, pharynx, larynx, and striated muscles— involved in breathing and swallowing. The development of these structures is usually complete by week 14.

The respiratory system, including parts of the larynx, the trachea, and the lungs, also begins to appear during week 14, when the laryngotracheal groove develops into a diverticulum that subsequently separates from the pharynx. In the fourth and fifth weeks, the longitudinal tracheoesophageal folds fuse, forming the tracheoesophageal septum and dividing the foregut into ventral and dorsal portions. The ventral portion becomes the larynx, trachea, bronchi, and lungs, and the dorsal portion becomes the esophagus.

The embryogenesis of the larynx is complex. The cartilages and muscles are derived from the fourth and sixth branchial arches, and the epithelium is derived from the endoderm of

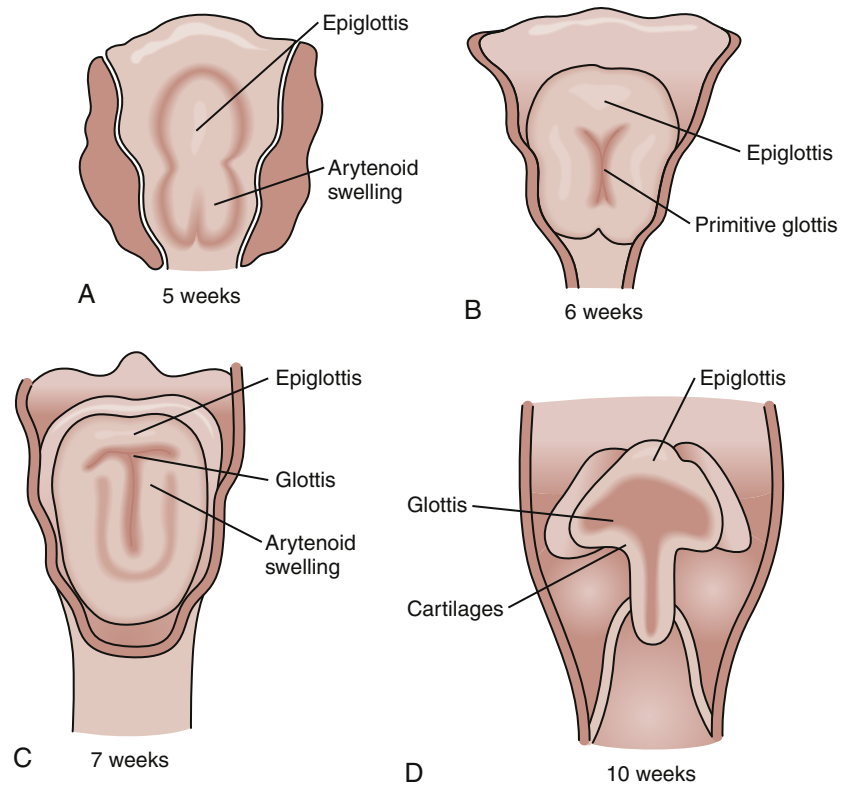

Figure 35–1. The embryologic development of the larynx. *(Modified from Arvedson J, Brodsky L:* Pediatric feeding and swallowing: management and assessment, *ed 2, Andover, United Kingdom, 2002, Thomson Learning.)*

the laryngotracheal tube. As this epithelium rapidly proliferates, the larynx is temporarily occluded until the 10th week, when recanalization occurs. Failure to recanalize can result in laryngeal webs, stenosis, or, rarely, atresia. The epiglottis forms by mesenchymal proliferation of the third and fourth branchial arches (Figure 35-1).

The tracheobronchial tree also has several embryonic origins. Its epithelium is derived from the laryngotracheal tube, and its connective tissue, cartilages, and muscles are derived from the surrounding splanchnic mesenchyme. All the cartilages of the trachea are C-shaped and thus are incomplete posteriorly, giving the airway flexibility to expand, except for the cricoid cartilage immediately below the true vocal folds. The cricoid cartilage is anatomically considered part of the larynx. It is the only cartilage in the airway to form a complete ring. Because of its inflexibility, edema from intubation and inflammation can result in serious, often avoidable injury.

Anatomy and Physiology of the Upper Airway

Nasal Passages

The upper airways begin at the tip of the nose and the vermilion border of the lips. Both the nasal and oral passages allow air stream from the environment through the larynx into the lungs where oxygen and carbon dioxide are exchanged through the alveoli into the cardiovascular system via capillaries. The mouth, oral cavity, and pharynx (oropharynx and hypopharynx) have the additional function of ingesting adequate amounts of food for growth and development.

The structure of the upper airways differs in the infant (Figure 35-2), young child, and young adult (Figure 35-3). Preferential nasal breathing is present in neonates and persists up until 6 months of age due to the high riding larynx in the neck with the soft palate and vallecula in close anatomic approximation.

The nasal tip and, in particular, the nasal valve area is the area of highest resistance in the upper airway. Infants who require enteral feeds are better served with an orogastric tube than a nasogastric tube and oxygen delivered by mask rather than by nasal prongs to avoid obstruction and injury to this area. The nasal cavity courses posteriorly until it meets the nasopharynx, a box-shaped structure where the oropharynx and nasopharynx meet.

The purpose of the nasopharynx is to serve as a conduit for air, a drainage area for the nose, paranasal sinuses, and middle ear via the Eustachian tube, and a resonator for speech. As growth occurs, the angle of the nasopharynx at the base of the skull becomes more acute, approximating 90 degrees in the adult. Elongation of the nasopharynx has implications not only for the placement of airway and feeding tubes but also for the production of a wide variety of sounds. The adenoid pad is located in the nasopharynx and sits against the muscles covering the cervical spine at the base of the skull. During the first years of life the adenoids may enlarge, but in most instances they begin to involute at about age 8 years extending through puberty unless ongoing inflammation from allergy, infection, or gastrointestinal reflux causes stimulation and growth.

The nasal passage is divided by the nasal septum, which is cartilaginous anteriorly and bony posteriorly. Injury to the anterior nasal septum is not uncommon with the use of nasal tubes, nasal prongs, or nonhumidified oxygen because of the thin epithelium overlying the cartilage anteriorly. Bacterial colonization frequently occurs when the nasal passages become dry and stasis of secretions occur. In the critically ill

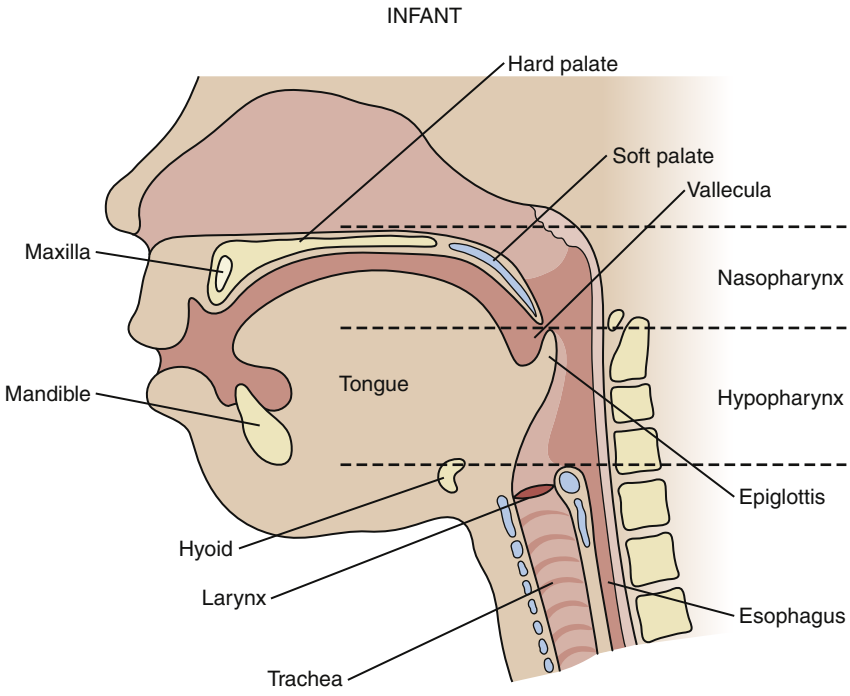

Figure 35–2. Lateral view of the infant's upper airway. The soft palate and vallecula form a tongue and groove relationship that effectively separates the oral cavity from the nasal cavity during the first 6 months of infancy when most children are primarily nasal breathers. This anatomic proximity effectively separates the oral route for ingestion from the nasal route for respiration. Anterior placement of the larynx has implications for intubation technique. *(Modified from Arvedson J, Brodsky L:* Pediatric feeding and swallowing: management and assessment, *ed 2, Andover, United Kingdom, 2002, Thomson Learning.)*

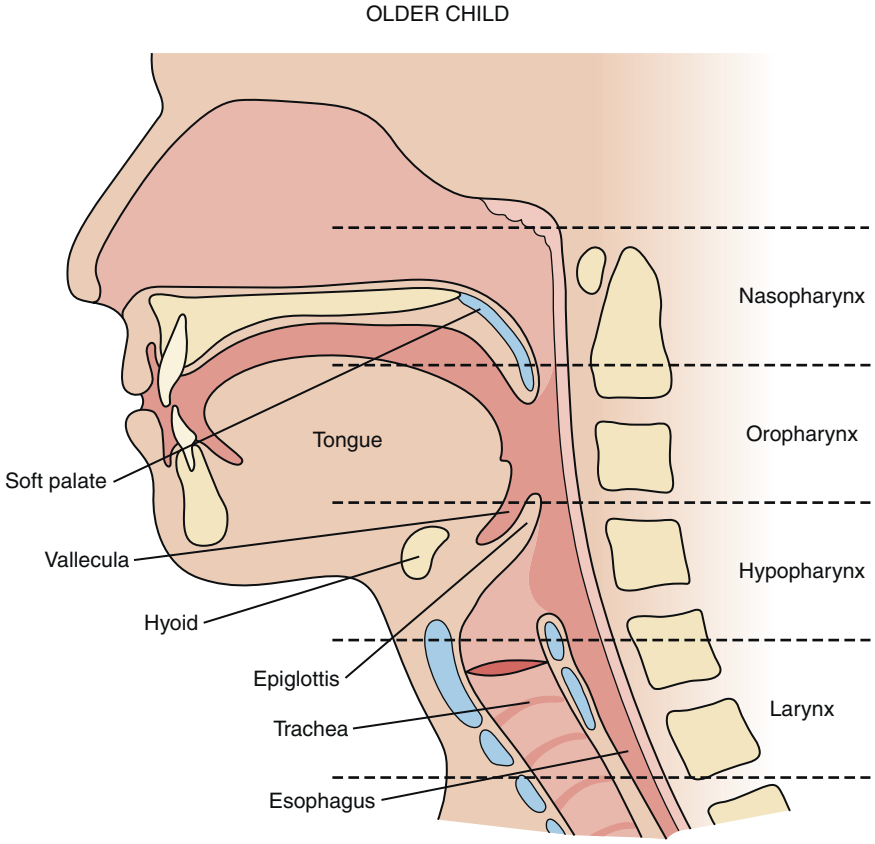

Figure 35–3. Lateral view of the older child's upper airway. Note the development of the oropharynx, a shared passage for eating and breathing. The tongue occupies less of the oral cavity. The larynx sits lower in the neck, which is unique to humans and has allowed for the development of human speech production. However, the shared passageway with the digestive system creates challenges in airway protection, particularly during intubation. *(Modified from Arvedson J, Brodsky L:* Pediatric feeding and swallowing: management and assessment, *ed 2, Andover, United Kingdom, 2002, Thomson Learning.)*

patient these conditions often are present, and further injury to this area increases the risk of epistaxis. Close attention to nasal hygiene may prevent these injuries.

Often overlooked are the ostia of the paranasal sinuses that drain into the nasal cavity and, like the Eustachian tube orifices (which drain into the nasopharynx), are considered part of the upper airways. However, their roles in air conduction are poorly understood. Iatrogenic nasal obstruction may lead to obstruction of ostia of the paranasal sinuses and Eustachian tube resulting in secondary infections in the middle ear and sinuses. Frequent assessments of the middle ear and nasal cavities are helpful.

The nose and paranasal sinuses are involved in respiration, humidification, and purification of inspired air. Except for the nasal vestibule and parts of the oral cavity, the pharynx, and the edges of the true vocal folds, ciliated, pseudo-stratified columnar epithelium lines the nasal passages, upper airway surfaces, and lower airway to the second order bronchi. The lateral nasal walls consist of bony prominences with specialized epithelium and submucosa called the nasal turbinates. The nasal turbinates are structured both to increase the surface area and to create turbulence to enhance the nasal functions of humidification, purification, and warming of the inspired nasal air. When these structures are bypassed, some of these functions are compromised, most notably humidification and purification. Close attention to humidity and "clean" air delivered by ventilators requires nursing vigilance and physician oversight.

Seromucinous glands are found throughout the entire upper airway from the sinonasal passages to the bronchi. Rich in immunoglobulins and other immune mediators, mucociliary clearance is always in the direction of the hypopharynx, where these secretions are swallowed. Therefore, movement of mucous is caudad in the nose and cephalad in the trachea and bronchi.

Mouth and Pharynx

The structures of the oral cavity include the lips, teeth, tongue, tonsils, and palate. The anterior structures are primarily involved in food bolus preparation and speech. However, the tongue may be absolutely or relatively enlarged for the space allotted. Children with Beckwith-Wideman syndrome have macroglossia; their tongue often sticks out of the mouth and may require reduction or airway bypass. Some craniofacial anomalies are characterized by micrognathia or retrognathia, when even a normal or smaller sized tongue may be posteriorly placed, causing laryngeal obstruction. Sometimes glossoptosis, by anatomic or physiologic mechanisms, can produce airway obstruction that prevents ventilation by natural or mechanical means unless an endotracheal tube bypasses the obstruction. Patients with Down syndrome can present with multilevel airway problems as a result of mid-face hypoplasia, a small nasopharynx, relatively large tongues, and a congenitally narrowed subglottic space.

The oropharynx begins posterior to the posterior tonsillar pillars with its superior border at the edge of the soft palate and its inferior border at the superior tip of the epiglottis. With growth and development the pharynx elongates so that an oropharynx develops between ages 2 and 3 years. The lateral walls of the pharynx consist of the three pairs of constrictor muscles that are innervated by cranial nerves V, IX, and X. Many of these nerves are also important in protection of the lower airways. The muscle tone of the constrictors is often compromised in neurologically impaired children and may cause airway collapse and obstruction, even in the absence of enlarged tonsils and adenoids or glossoptosis. The tonsils are found laterally, and when chronically or severely inflamed, they may enlarge and cause upper airway obstruction similar to that found in the adenoids at the nasopharyngeal level. Often, but not always, enlargement of the tonsils and the adenoids occur together.

The posterior structure, the oropharynx, is the crossroads for the nasopharynx from above and the hypopharynx from below. In infants, no oropharynx exists because the nasopharynx is blended directly into the hypopharynx as a result of the uvula being situated in the vallecula. At the base of the tongue, located in the vallecula (a wedge-shaped structure posterior to the epiglottis), are the lingual tonsils. When enlarged, they can cause airway obstruction and interfere with visualization of the glottis.

The hypopharynx is the most inferior of the shared passageways for respiration and deglutition. Superiorly it is defined by the tip of the epiglottis, which in the adult is at the level of the hyoid bone in the neck, a relationship that is variable in the infant and child. The inferior border of the hypopharynx is at the level of the cricopharyngeus muscle, which is the introitus of the esophagus and is located directly posteriorly to the cricoid cartilage (see Figures 35-2 and 35-3). Protection of the airway occurs in this area, particularly during deglutition. The anterior boundary of the hypopharynx is the larynx.

Larynx

The larynx is a complex organ that serves in respiration, protection of the lower airways, and phonation. There are no fewer than eight cartilages (excluding the cricoid cartilage), two ligaments, and almost a dozen paired and unpaired muscles that have various roles in the three primary functions of the larynx (Figure 35-4). The larynx begins at the level of the true vocal folds and extends to the inferior border of the cricoid cartilage.

Proper airflow requires that the larynx have functioning vocal folds so that during inspiration there is abduction of the true vocal folds, allowing the least restrictive inflow of air. During expiration, slight adduction occurs and the false vocal folds (also known as the ventricular folds) modulate the expiratory airflow.

Protection of the lower airways is key to survival. Prevention of aspiration of secretions or ingested food requires multilevel coordination of several sphincters. The most superior level is the epiglottis, which has a flattened lingual surface directing secretions laterally and posteriorly as it folds into the larynx during deglutition. The paired arytenoid cartilages sit at the posterior aspect of the larynx and provide the next level of protection. These cartilages, along with the coordination of the aryepiglottic folds (reinforced by the smaller cuneiform and corniculate cartilages) contract medially to close the glottis.

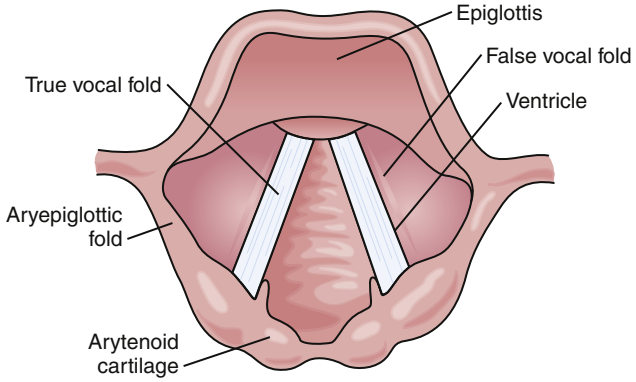

Figure 35–4. Superior (endoscopic) view of the endolarynx. *(Modified from Arvedson J, Brodsky L:* Pediatric feeding and swallowing: management and assessment, *ed 2, Andover, United Kingdom, 2002, Thomson Learning.)*

Table 35–1 Anatomic Airway Difference Between Infants and Children

Anatomic Location	Infant	Older Child
Oral cavity	Tongue fills mouth Edentulous Tongue rests between lips and sits against palate Relatively smaller mandible Uvula sits in vallecula separating oral from nasal cavity resulting in preferential nasal breathing	Mouth is larger, tongue rests on the floor of the mouth Dentulous Tongue rests behind teeth and not up against palate Mandibular-maxillary relationship relatively normal Uvula sits above epiglottis with respirations occurring through mouth and nose
Pharynx	No definite/distinct oropharynx Obtuse at skull base in nasopharynx	Elongation from nasopharynx through hypopharynx with distinct oropharynx 90-degree angle at skull base
Larynx/ tracheobronchial tree	One third adult size at laryngeal inlet Half of true vocal fold is cartilage Narrow, vertical epiglottis Subglottis size is 4-5 mm Tracheal rings more compliant	Less than one third of true vocal fold is cartilage Flat, wide epiglottis Subglottis enlarges with age

Modified from Arvedson J, Brodsky L: *Pediatric feeding and swallowing: management and assessment*, ed 2, Andover, United Kingdom, 2002, Thomson Learning.

Simultaneously, the larynx is elevated under the tongue and provides the airway with further protection during swallowing. Finally, the paired true and false vocal folds abduct and provide yet another level of protection. During quiet respiration, the highly innervated larynx repels unwanted secretions by the highly sensitive cough reflex, mediated primarily through cranial nerves IX and X. In the intubated, often sedated, or paralyzed child, these protective mechanisms are absent and the dangers of aspiration of secretions become of great concern. Frequent suctioning of oral cavity secretions may reduce this risk but is unlikely to eliminate aspiration completely.

Innervation of the larynx for its protective and respiratory functions is located centrally in the brainstem and is thus reflexive. The sensory and motor innervations to this area are key to proper function. Thus, following prolonged intubation, immediate return of function is unrealistic and a cautionary approach to the re-establishment oral feeds is prudent. Another issue to consider is that intubation may cause recurrent laryngeal nerve injury with vocal fold paralysis. The mechanism for this injury is believed to result from pressure on the cricoarytenoid joint close to where the nerve enters the larynx.

Interestingly, the most highly innervated areas of the larynx are the epiglottis and the posterior surfaces of the arytenoids. The chemical and thermal receptors are particularly sensitive to temperature and humidity in infants and young children. Cool mist can slow the rate of respiration and increase tidal volume, thereby having a positive effect on respiration. Other receptors in the larynx include joint, aortic, baroreceptors, and stretch receptors, the clinical significance of which has received little study in children.

Anatomic differences between the upper aerodigestive tracts of infants and children are listed in Table 35-1.

Trachea and Bronchi

Inferior to the larynx is the trachea, which conducts air to the bronchi, which then branch to ever smaller lumen tubes that eventually become alveoli, the anatomic location of gas exchange. The trachea is made of cartilaginous rings that are essentially the same diameter until they reach the carina, where the trachea splits into left and right main stem bronchi.

The right main stem bronchus is shorter, wider, and takes off at a less acute angle than does the left main stem bronchus and thus is the site of bronchial foreign body aspiration more often than is the left main stem bronchus. Bronchial intubation is more often encountered on the right. The right main stem bronchus leads to the right upper, middle, and lower lobes.

The left main stem bronchus is longer, narrower, and more acutely angled than the right main stem bronchus. Its bronchi lead to the lower and upper lobes and to the lingula. As mentioned previously, these airways are lined by pseudostratified, ciliated columnar epithelium. This epithelium is readily injured through suctioning. Prolonged intubation, particularly after tracheotomy, results in diffuse squamous metaplasia. Without functioning cilia, airway secretions remain in the airway and can be the source of irritation, inflammation, and atelectasis, all complicating factors in the management of the upper airway during a critical illness.

References are available online at http://www.expertconsult.com.

III

Chapter 36

Structure of the Respiratory System: Lower Respiratory Tract

Christopher A. D'Angelis, Jacqueline J. Coalson, and Rita M. Ryan

PEARLS

- Lungs increase in volume from about 250 mL at birth to 6000 mL in the adult.
- At birth, the pulmonary artery and aorta are comparable in medial thickness and configuration and are the same size; by age 2 years, elastic tissue decreases in the pulmonary artery and its thickness is only about 60% that of the aorta.
- Each bronchopulmonary segment is divided by connective tissue septa that define the smallest surgically resectable portions of the lung.
- The airway branching pattern in the lung undergoes multiple generations, yielding a total of 27 or 28 divisions when counting begins from the primary bronchus.
- The bronchial mucosa contains several epithelial cell types, with the ciliated cell comprising more than 90% of the epithelial cell population in the conducting airways, but the proportion and number of cilia per cell decrease from the proximal to distal airways.
- The acinus, which is approximately spherical in shape and has a diameter of about 7 mm and a length of 0.5 to 1 cm, is the gas exchange portion of the lung.
- Although there is disparity concerning the time alveolarization is completed, alveoli in a normal adult number from 300 to 500 million and have a diameter of 150 to 200 μm.
- The two epithelial cells of the alveolus are the gas-exchanging type I cell and the surfactant-producing type II cell that is responsible for epithelial repair.
- The alveolar-capillary unit is comprised of three major constituents: the epithelial lining of the alveolus, capillary endothelial cells, and a mixture of cellular and extracellular interstitial components.
- The large pulmonary arteries traverse with the cartilaginous airways and extend from the hilum to nearly halfway in the bronchial tree.
- Smaller pulmonary arteries measure between 100 and 1000 μm in diameter, branch with the bronchial tree, and lie close to bronchi and bronchioles.
- The pulmonary veins do not course with the bronchial tree and instead are seen within the interlobular septa.
- The diaphragm, the principal muscle of respiration, is essential during deep anesthesia because other muscles of respiration become inactive.

Lower Respiratory System

Lungs

Lung weights of children from birth to age 12 years have been published.[1-13] At birth, the lungs weigh about 40 g and double in weight by 6 months. Mature respiratory alveoli appear at approximately 36 weeks of gestation and continue to develop until about 2 years of age. By age 2 years, when most of the alveolarization process is completed, total lung weight is approximately 170 g. In the normal adult, the lungs weigh approximately 1000 g.[9] Lung volume increases from about 250 mL at birth to 6000 mL in the adult. The height of a normal adult lung is 27 cm at total lung capacity, but in the range of normal breathing it is approximately 24 cm in height. Externally, the lungs are paired structures that, with the mediastinum, fill the thoracic cavity. Normally the right lung is comprised of three lobes and the left lung consists of two lobes and the lingula, which arises from the left upper lobe. The lobes are separated by fissures and have hili that receive a primary lobar bronchus, pulmonary artery and veins, bronchial arteries and veins, lymphatics, and nerves (Figure 36-1).[14] The lobes are further subdivided into 19 bronchopulmonary segments that receive a primary segmental bronchi and a tertiary pulmonary artery branch and are drained by pulmonary veins. The pulmonary veins do not course with the airway and pulmonary artery dyad; instead, they course midway between the dyads and can be readily identified in the septa that run within the intersegmental septa. The connective tissue septa that demarcate each bronchopulmonary segment define the smallest surgically resectable portions of the lung.

Airways and Bronchus-Associated Lymphoid Tissue

The airway branching pattern in the lung undergoes multiple generations, yielding a total of 27 or 28 divisions when counting begins from the primary bronchus. The bronchi are the larger intrinsic cartilaginous airways and comprise nine to 12 generations starting with the primary bronchus and terminating in bronchi having a diameter of approximately 1 mm. Bronchioles, sometimes called membranous bronchioles or distal noncartilaginous airways, are the last of the conducting system. They comprise an additional 12 generations before ending as terminal bronchioles, the last purely conducting

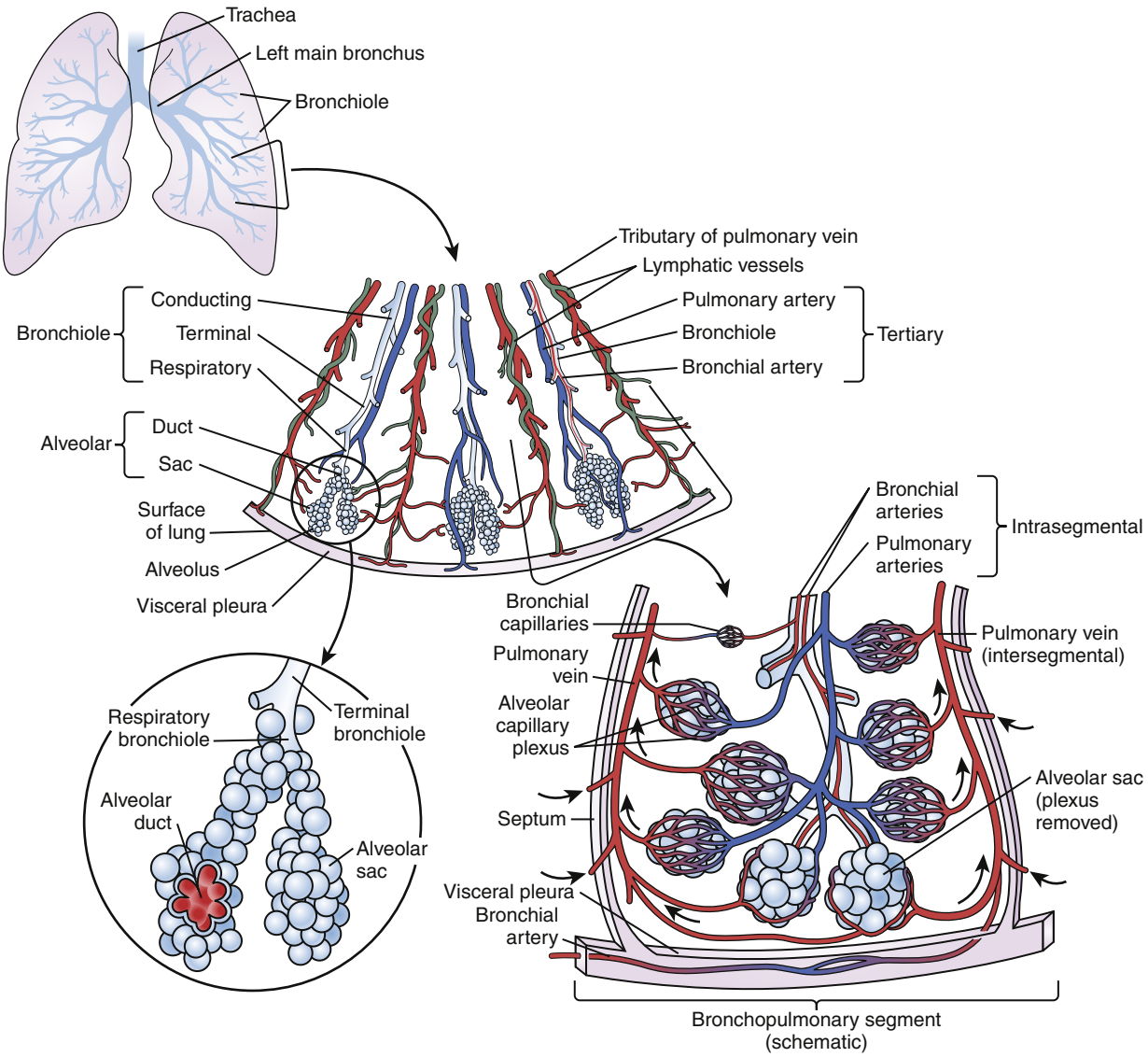

Figure 36–1. Internal structure and organization of lungs. Within the lungs, the bronchi and pulmonary arteries are paired and branch in unison. Segmental (tertiary) branches supply the bronchopulmonary segments. Each intrasegmental pulmonary artery ends in a capillary plexus in the walls of the alveolar sacs and alveoli. The pulmonary veins arise from the pulmonary capillaries and drain toward and then course within the septa between adjacent segments. Bronchial arteries are distributed along and supply the bronchial tree. Their distal-most branches supply capillary beds drained by the pulmonary veins, such as those of the visceral pleura (even though this small amount of blood is poorly oxygenated). *(Modified from Moore KL, Dalley, Arthur F:* Clinically oriented anatomy, *ed 5, 2006, Lippincott Williams & Wilkins.)*

structure in the lung. Horsfield[4] showed that the course from the trachea to the alveolar level may be as few as eight or as many as 24 airway branch points. This finding points out that a particular airway diameter may occur at various points along the distribution of the bronchial wall. Determination of the total cross section of airways is important in understanding the distribution of airway resistance. Weibel[12] showed that as the peripheral generations of the airways are approached, the total cross-sectional area of the lung is markedly increased, suggesting that peripheral airways account for only a small proportion of total airway resistance. In the adult, the asymmetrical dichotomous branching pattern results with each daughter branch decreasing an average of 0.75% of its parent branch, but an increase results from the combined cross-sectional area of the two daughter branches. It is well known, however, that peripheral airway resistance in children's lungs is disproportionately high. The size of the conducting airways is related to stature, so the airways' cross-sectional area in children increases at a slow rate with growth and aging. Because the peripheral airways make up a significant portion of the total respiratory resistance in children, disease in the bronchioles can be serious.

The bronchi maintain the histologic appearance of the trachea in that a mucosa, submucosa, muscularis, adventitia, and cartilaginous support are present. As the bronchi branch deeper into the lung parenchyma, the cartilage rings become plates and less regular, and the muscularis becomes continuous, being located between the submucosa and the cartilage plates. Also contained within the bronchial submucosa are mucus-secreting submucosal glands, nerves, ganglia, and bronchial arterial branches (Figure 36-2). As the bronchi decrease in diameter, the pseudostratified columnar epithelium becomes lower and the mucoserous glands become fewer in number. Although the glands wane in number in the

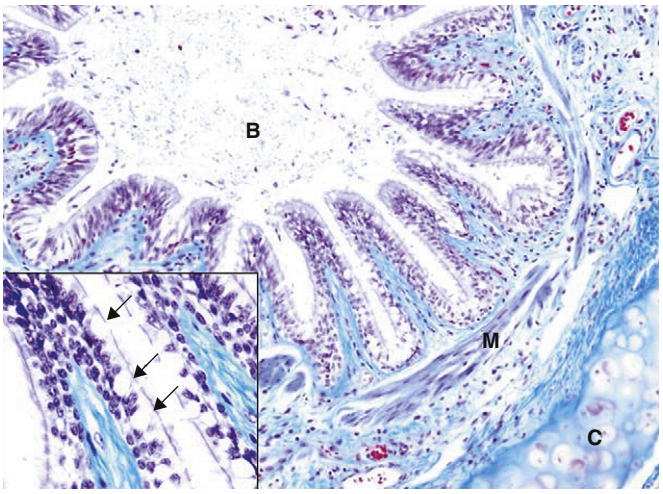

Figure 36–2. Bronchus (*B*) with surrounding smooth muscle (*M*) and cartilage (*C*). The airway mucosa (*insert*) is composed of ciliated epithelial cells and vacuolated goblet cells (*arrowheads*). (Gomori trichrome; ×40 and ×400.)

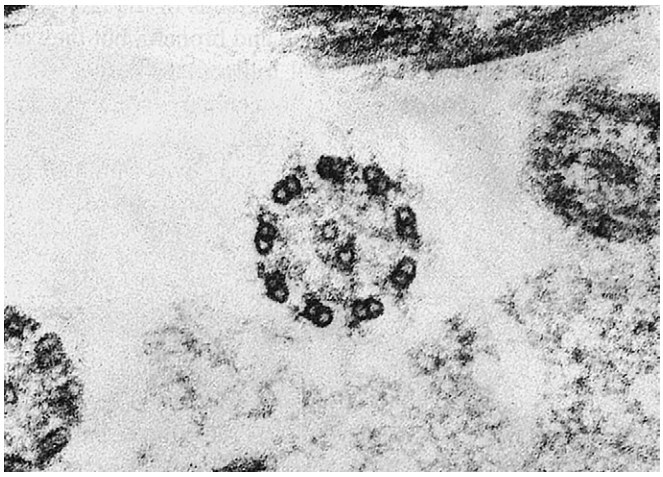

Figure 36–3. Internal structure of a cilium (no cell membrane evident) in which two axial tubules and nine peripheral duplex tubules are seen. Dynein arms are attached to several of the peripheral duplex tubules (×13,500).

more distal parts of the lung, mucous cells persist and can be found in very small bronchi and in some of the membranous bronchioles.

The bronchial mucosa contains several epithelial cell types: ciliated, mucus producing (goblet cells), basal, brush, and neuroendocrine. The ciliated cell constitutes more than 90% of the epithelial cell population in the conducting airways, but the proportion and number of cilia per cell decrease from the proximal to distal airways. The 9+2 microtubular structure within the cilia has been shown to be altered in the primary ciliary syndromes (Figure 36-3). In addition to its ciliary beating movement, the ciliated columnar cells regulate the depth of the composition of the periciliary fluid and transport ions across the epithelium. The basal cell has a progenitor cell role and also functions to maintain adherence of columnar cells to the basement membrane. The brush cell, thought to have a role in fluid absorption and/or chemoreceptor function, is found rarely in the tracheobronchial and alveolar epithelia.

The mucociliary apparatus is the primary defense mechanism in the respiratory system. Although mucous goblet cells secrete mucin, it is the submucosal glands that produce more than 90% of the mucus needed for mucociliary function. The glandular unit of the bronchial submucosa is comprised of mucous, serous, myoepithelial cells, collecting duct cells, and occasional neuroendocrine (Kulchitsky) cells. The physical characteristics of the mucous layer reveal that the superficial layer is more viscous than the deeper layer. This difference in consistency of the mucous layer allows the cilia to function properly, allowing a power and recovery stroke mechanism. The secretions include lysozyme, antileukoprotease, lactoferrin, and IgA. The secretory component of IgA is synthesized in bronchial gland cells and expressed on their basolateral cell surfaces to which IgA dimers synthesized by plasma cells bind. The complex is endocytosed by the glandular cell and then is secreted from its luminal surface.

Neuroendocrine cells can be solitary near the basal lamina between columnar cells or in collections called neuroepithelial bodies that occur near branch points of bronchi. A number of neural markers are expressed (e.g., 5-hydroxytryptamine, chromogranin A, neuron-specific enolase, synaptophysin) and a number of hormones are produced (e.g., endothelin, calcitonin, and bombesin [gastrin-releasing peptide]). They are more abundant in the fetus and likely have a role in lung growth or maturation.

Mast cells are an important population of cells found in great abundance in the submucosa and connective tissue in lungs. They contain cytoplasmic granules and produce two neutral proteases: chymase and tryptase. They release lysosomal enzymes (arylsulfatase, B-glucuronidase, myeloperoxidase) and various mediators (e.g., histamine, eosinophil chemotactic factor of anaphylaxis, and heparin), and they help mediate important physiologic events, such as IgE-dependent bronchial asthma.

Bronchus-associated lymphoid tissue (BALT) appears as isolated nodules in the connective tissue of the lamina propria of the bronchial tree and produces primarily IgG and secretory IgA. Collections of BALT cells tend to occur at airway bifurcations and are covered by a special epithelium that can undergo pinocytosis and transport solutes and particulate antigens. BALT is sparse at birth but starts accumulating thereafter. It is prominent in lungs of children and in diseased lungs of smokers and patients with bronchiectasis. Although more than 50% of the cells are B lymphocytes, T lymphocytes also are found (18%), along with follicular dendritic cells.[15] Sometimes these nodules bulge into the bronchial lumen. Additional lymphoid tissue in the lung is a rich supply of lymph nodes within the lung, at the carina, and along the trachea.

Although originally defined as having a lumen diameter less than 2 mm, the term "small airway" usually refers to a bronchiole. Histologically, the bronchiole is characterized by a transition from pseudostratified tall columnar epithelium to a more cuboidal ciliated form. In addition, the mucous goblet cell is replaced by the nonciliated Clara cell (Figures 36-4 and 36-5). In the bronchiolar epithelium, a ratio of about three ciliated cells to two nonciliated cells lines the lower airways. The Clara cell is identified as a dome- or tongue-shaped cell that protrudes into the bronchiolar lumen among the shorter ciliated cells. The Clara cell has varying features according to species but possesses an abundance of agranular reticulum and secretory granules. Clara cells synthesize and secrete Clara cell secretory protein (CC10, CC16), a unique 10-kDa protein similar to rabbit uteroglobin that has antiinflammatory and

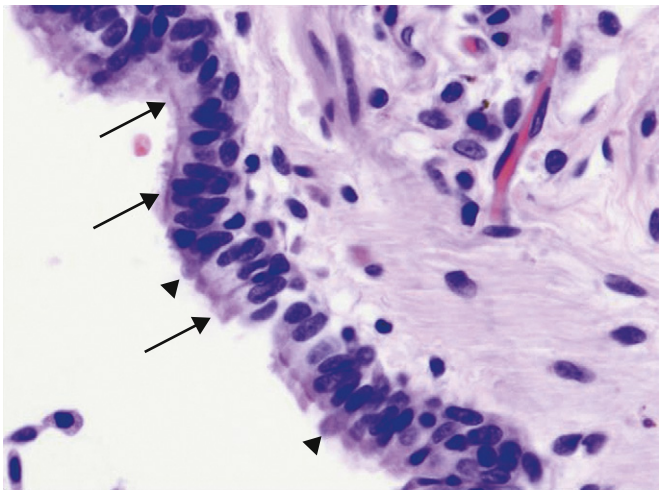

Figure 36–4. Distal conducting airway mucosa composed of some ciliated epithelial cells showing a terminal bar (*arrows*) and a noncilicated Clara cell (*arrowheads*). (Hematoxylin-eosin stain; ×400.)

immunoregulatory functions.[16] In addition, Clara cells secrete surfactant-associated proteins A, B, and D. Importantly, the Clara cell also functions as a progenitor cell that differentiates into ciliated cells following injury, and some investigators have shown that the Clara cell can differentiate into a type II epithelial cell.[17]

Within the wall of the bronchiole, the muscular layer becomes more prominent and submucosal glands and cartilage are absent. The bronchiole segment ends as a terminal bronchiole that marks the terminus of the conducting portion of the airway. The terminal bronchiole branches into two generations of respiratory bronchioles, which through further divisions give rise to additional respiratory bronchioles that have more alveoli in their walls, so-called second- and third-order respiratory bronchioles. By definition, respiratory bronchioles are alveolated, and they branch into two to three generations of alveolar ducts. The alveolar ducts are defined as those channels from which a series of alveoli open and are histologically characterized by having small clublike ends that contain muscle sphincters and elastic fibers. The ducts open

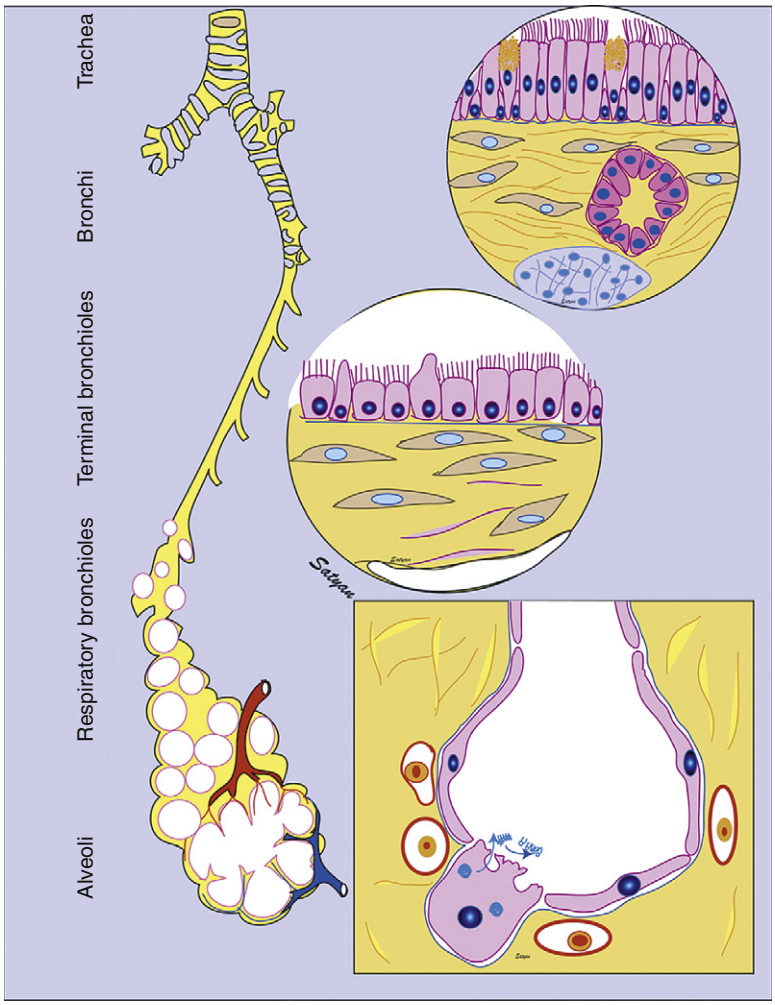

Figure 36–5. Respiratory tract epithelia. There is a progression from pseudostratified columnar epithelium with ciliated, goblet, and basal cells in the large conducting airways (*top circle*) to a more cuboidal ciliated epithelium in the small conducting airways with nonciliated Clara cells (*middle circle*). In the alveolar epithelium, flattened type I pneumocytes and cuboidal type II pneumocytes are present and are associated with an extensive capillary network (*box*). (Copyright Satyan Lakshminrusimha.)

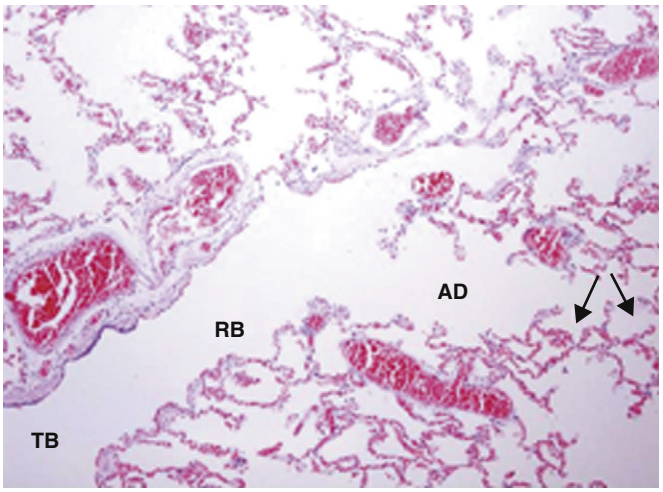

Figure 36–6. Distal conducting airway with transition to respiratory airway. *AD,* Alveolar duct; *RB,* respiratory bronchiole; *TB,* terminal bronchiole. Individual alveoli are indicated by *arrows*. (Hematoxylin-eosin stain; ×40.)

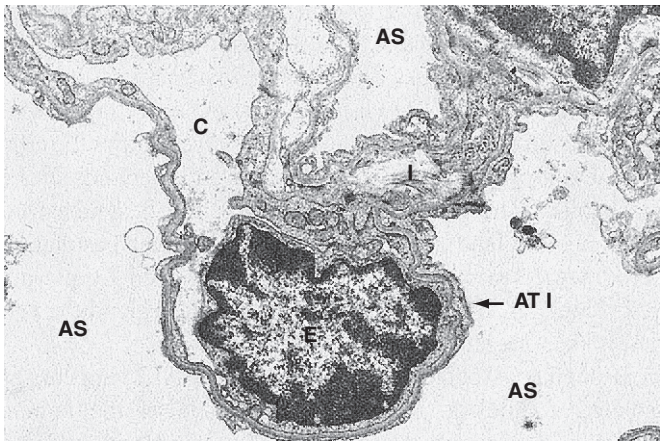

Figure 36–7. Both surfaces of the alveolar wall that separates the alveolar spaces (*AS*) are covered by thin extensions of alveolar type I epithelial cells (*ATI*). The capillary (*C*) is lined by endothelium (*E*). The epithelium and endothelium rest on a fused basement membrane on the thin portion of the alveolar wall and are separated by an interstitial space (*I*) in the thick portion of the alveolar wall (×5500).

into a final generation of alveolus-lined spaces, the multiloculated cup-shaped alveolar sacs (Figure 36-6).

Definitions of Special Lung Unit and Alveolar Formation

Each bronchopulmonary segment is further compartmentalized into smaller units termed *pulmonary lobules*. Each pulmonary lobule is supplied by a bronchiole that divides into a cluster of three to five terminal bronchioles and their associated respiratory tissue situated at the end of a bronchial pathway. The pulmonary lobule is roughly 1 to 2 cm in diameter, pyramidal in shape, and is bound by delicate connective tissue septa in which small proximal branches of pulmonary veins travel. The portion of the pulmonary lobule distal to the terminal bronchioles and consisting of several respiratory bronchioles, alveolar ducts, and ultimately alveoli is termed the pulmonary acinus. The acinus, which is approximately spherical in shape and has a diameter of about 7 mm and a length of 0.5 to 1 cm, is the gas exchange portion of the lung.

At the alveolar level, many changes occur in the postnatal period.[18-23] Although there is disparity concerning the time alveolarization is completed, evidence links the postnatal development of alveoli with elastic tissue fiber deposition.[20] At birth, primitive alveoli called saccules are evident, but approximately 50 million alveoli are already formed.[19] The number of alveoli in a normal adult can vary from 300 to 500 million, and they have a diameter of 150 to 200 μm. The early work by Dunnell[18] suggesting that new alveolar formation ceased at about age 8 years has been challenged by Thurlbeck,[22] who has shown that alveolarization appears to be nearly complete at about age 2 years. Lung volume correlates with body size, but alveolar surface area correlates with metabolic activity; thus alveoli become more complex in shape during maturation and as increasing levels of oxygen are required.

Alveolar-Capillary Unit

The alveolar-capillary unit is highly specialized to maximize diffusion between the blood and air gases (Figure 36-7).[24,25] The alveolar-capillary unit is comprised of three major constituents: the epithelial lining of the alveolus, capillary endothelial cells, and a mixture of cellular and extracellular intersitial components. This alveolar-capillary bed is the most extensive in the body and is contained within the epithelium-lined walls of adjacent alveoli, forming a gridlike network. The internal surface area of the adult lung is 70 to 80 m^2, of which 90% covers the pulmonary capillaries; thus the air-blood surface available for gas exchange is 60 to 70 m^2. The endothelial cells, which constitute about 30% of the total lung cells, contain few intracelluar organelles that are clustered together within the cytoplasm, allowing the cell to maximize its surface area. A number of adenine nucleotides, vasoactive amines, prostaglandins, vasoactive peptides, and lipoproteins can be metabolized and taken up within the numerous pinocytotic vesicles characteristic of pulmonary endothelial cells.

In addition to gas exchange, endothelial cells synthesize and secrete various locally acting substances such as nitric oxide, endothelins, prostacylin, tissue plasminogen activator, and thrombomodulin. Other functions include liquid and solid exchange and enzyme activity within the walls of the caveolae. At the ultrastructural level the blood-air barrier consists of a 0.1 to 0.2 μm thick septum comprised of a capillary endothelial cell and the type I pneumocyte with their intervening fused basal laminae. Within thicker portions of the alveolar wall, the alveolar epithelium and capillary endothelium are separated by the interstitial space.

The connective tissue space, or interstitium of the lung at the alveolar level, does not have lymphatics, but it can accumulate fluid that can be absorbed into the lymphatic system, which ends usually at the respiratory bronchiolar level. The interstitial cell population includes resident and migratory cell populations. Normally the interstitium contains macrophages, pericytes, myofibroblasts, mast cells, infrequent lymphocytes, and a few cells that are best termed undifferentiated, mesenchymal, or pluripotential because in disease they can differentiate into various cell types including fibroblasts, smooth muscle cells, and others. More than 25% of the interstitial cells cannot be identified definitively with the electron microscope, so it is understandable why most of the cells cannot be identified by light microscopy without special cell marker stains.

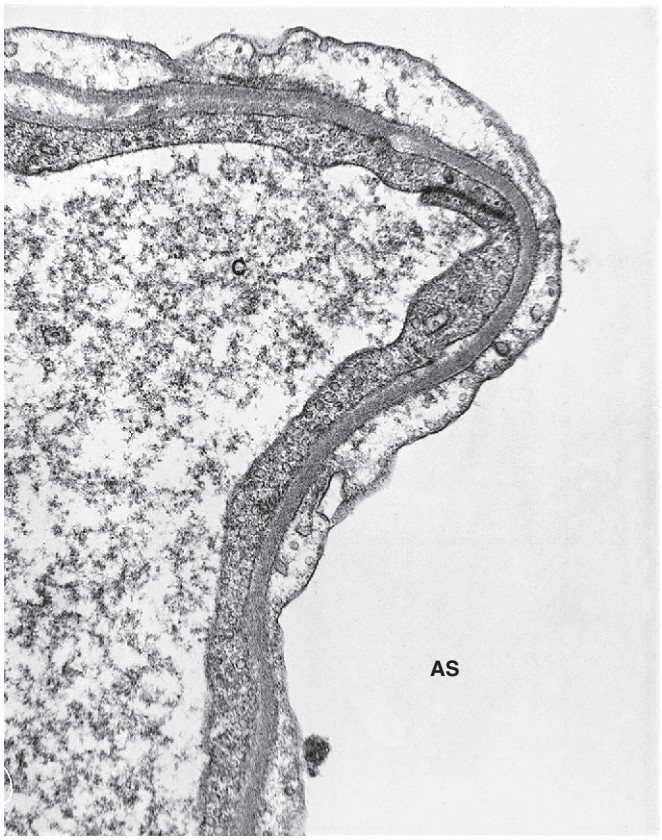

Figure 36–8. Electron micrograph showing the thin side of the air-blood barrier. The thin cytoplasmic extension of the type I epithelium contains only a few vesicles and shares a fused basement membrane with the endothelium that contains many caveolae (×18,000). *AS,* Alveolar space; *C,* capillary.

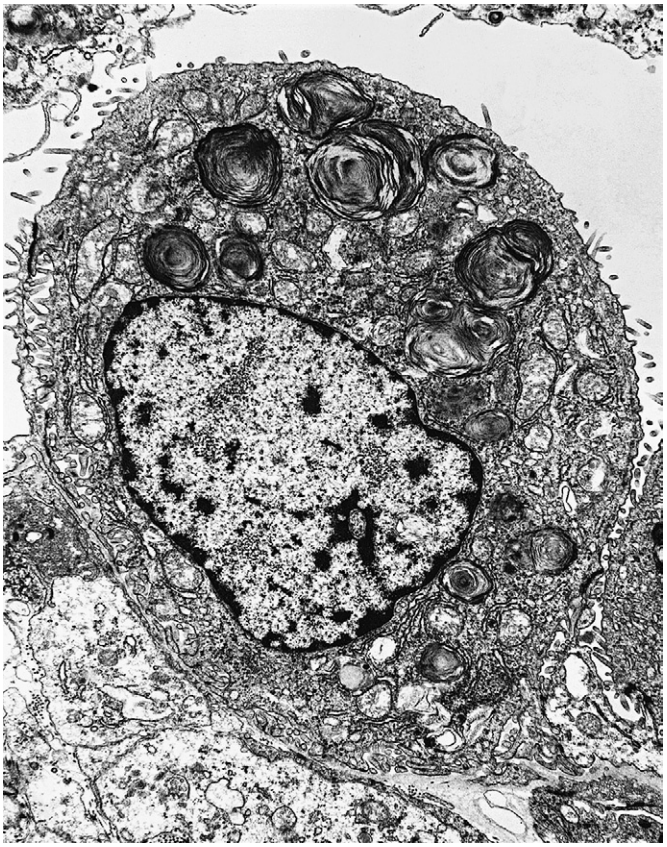

Figure 36–9. Cytoplasm of the alveolar type II cell has abundant lamellar inclusion bodies and surface membrane microvilli (×7500).

Two epithelial cell types line the alveoli. Type I cells have thin cytoplasmic extensions and have a very large surface area covering approximately 90% of the total alveolar surface (Figure 36-8). Numerically they form only about 40% of the epithelial cells, whereas the type II cell, which is cuboidal, constitutes 60% of the total number of epithelial cells but contributes less than 10% of the total alveolar surface area. Type I cells are exquisitely well adapted to allow for the rapid exchange of gases, and their micropinocytotic system probably plays a major role in the transport of solutes, such as albumin and immunoglobulin, in small quantities. They can be induced to ingest some particulates and can increase their number of pinocytotic vesicles, but they are not active in surfactant uptake.

The type II cell is the regenerative cell of the alveolar epithelium, serving as the stem cell following injury. It can repopulate the alveolar surface in about 5 days. It is cuboidal in shape and only numbers about one per alveolus. Ultrastructurally the type II cell has characteristic surface microvilli and cytoplasmic lamellar inclusions, which are the intracellular cytoplasmic storage forms of pulmonary surfactant (Figure 36-9). The inclusions evolve from multivesicular bodies or lysosomal granules, which progressively acquire the characteristic lamellae. In addition to its roles in the synthesis, secretion, and reuptake of surfactant, the type II cell synthesizes arachidonic acid metabolites, synthesizes and secretes connective tissue components of the basement membrane including fibronectin, synthesizes and secretes components of the complement system, expresses class II proteins of the major histocompatibility complex, among others, and has been found to be a critical source of many different growth factors during injury and repair.

Considerable data demonstrate clearly that several populations of macrophages exist: intraalveolar (pulmonary alveolar macrophage), septal (interstitial), pulmonary intravascular, and airway. Within the alveolar spaces, alveolar macrophages are abundant and form an important arm of the defense mechanism of the lung (Figures 36-10 and 36-11). They number approximately 23×10^9 in the lung (10% of the total cells of the alveolar compartment), and 50 to 100 are estimated per alveolus. They derive from three sources: bone marrow via blood monocyte, the interstitial macrophage pool, and proliferation of macrophages in the alveolar space. They are actively phagocytic and scavenge the surface of the alveoli for respired particulates (macrophages as so-called "dust cells"). Although seen free-floating in alveolar spaces in light microscopic preparations, the alveolar macrophage crawls along the surface of the epithelium, adhering with its filopodia. The macrophage has remarkable metabolic activities, has known immune functions, and is involved in lung injury and repair phenomena. Alveolar macrophages also play a role in surfactant uptake, removal, or catabolism. More than 100 macrophage-synthesized mediators have been identified, including many proinflammatory cytokines, and numerous ligands have been demonstrated. In normal bronchoalveolar lavage fluid, 90% of the cells are alveolar macrophages and 1% to 5% are lymphocytes (T-cell lymphocytes constituting 60% to 70% and B cells constituting 5% to 10%).

Lung Circulation

Pulmonary Vascular System

The pulmonary circulation is furnished by the pulmonary and the bronchial vascular systems.[26,27] During gestation, branches of the pulmonary arterial system are thick-walled and contain a medial layer of smooth muscle. At birth, the pulmonary artery and aorta are comparable in medial thickness and configuration. Elastic fibers tend to be long, uniform, unbranched, and parallel with one another. Following birth, the pulmonary vasculature undergoes extensive remodeling and by 2 years of age shows a media composed of short, branched, and loosely arranged elastic fibers. When fully matured, the pulmonary artery and its thickness is only about 60% that of the aorta. Only a few muscular arteries are seen accompanying terminal bronchioles at birth. Following birth, when pulmonary arterial pressures fall to normal levels, the muscle fibers diminish. Initially new vessels without muscle are formed, along with new respiratory units during lung growth. Smooth muscle extends peripherally into small arteries slowly, reaching arterioles at the respiratory bronchiolar level at 4 months, at the alveolar duct level at 3 years, and some alveoli at age 10 years.[28]

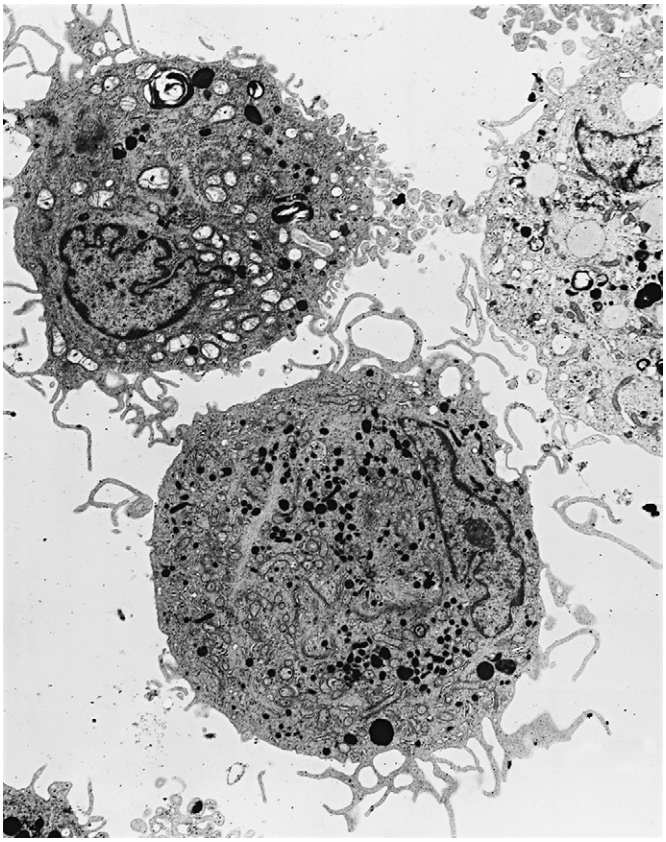

Figure 36–10. Alveolar macrophages recovered from bronchoalveolar lavage fluid contain abundant lysosomes and other cytoplasmic contents, including lipid droplets and surfactant remnants (×5300).

The criteria for recognizing various types of pulmonary vessels were put forth by Brenner[29] in 1935. The pulmonary arteries, which exceed 1000 μm in external diameter, are called elastic pulmonary arteries and traverse with the cartilaginous airways. They extend from the hilum to nearly halfway in the bronchial tree of the newborn, a pattern completed by week 16 of gestation and retained into adulthood. Pulmonary arteries measure between 100 and 1000 μm in diameter and have a distinct muscular media and internal and external limiting elastic membranes. The muscular arteries of the lung have thinner media than do their counterparts in the systemic circulation. Muscular pulmonary arteries branch with the bronchial tree and lie close to bronchi and bronchioles (Figure 36-12). Pulmonary arterioles are vessels that measure 100 μm in diameter and have only an endothelial lining and a single elastic lamina with little, if any, muscular media. These vessels usually are seen at the level of the alveolar ducts and in certain sites within the alveolar walls. Pulmonary capillaries are nonfenestrated, whereas bronchial capillaries are fenestrated. The appearance of pulmonary venules is identical to that of pulmonary arterioles, and serial sections are required to differentiate the two. In contrast with the pulmonary arteries, the larger branches of pulmonary veins do not course with the bronchial tree and instead are seen within the interlobular septa. The media of larger veins is composed of smooth muscle fibers, collagen,

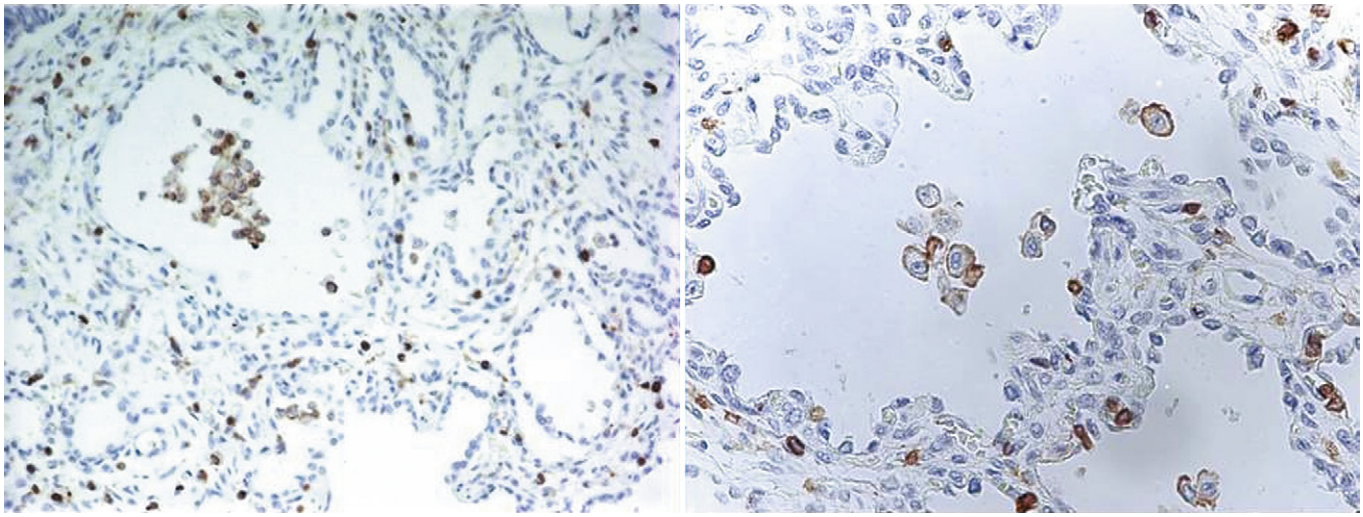

Figure 36–11. Sections obtained from infants who died with bronchopulmonary dysplasia. Pulmonary macrophages present within air spaces were immmunostained (brown stain) with anti-CD45, a general leukocyte marker. Leukocytes are also identified within the alveolar walls and capillaries (hematoxylin counterstain; ×200 *left,* ×400 *right). (Courtesy Dr. Gloria Pryhuber.)*

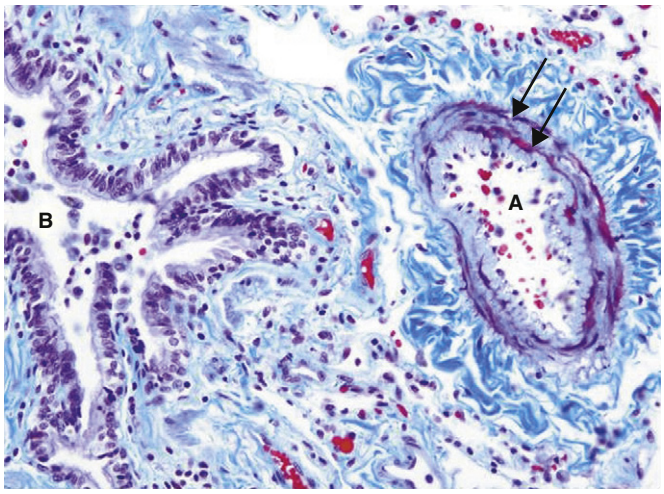

Figure 36–12. Small muscular pulmonary artery (*A*) traveling with a bronchiole (*B*). Two layers of smooth muscle cells are present in the vascular media (*arrows*). (Gomori trichrome; ×200.)

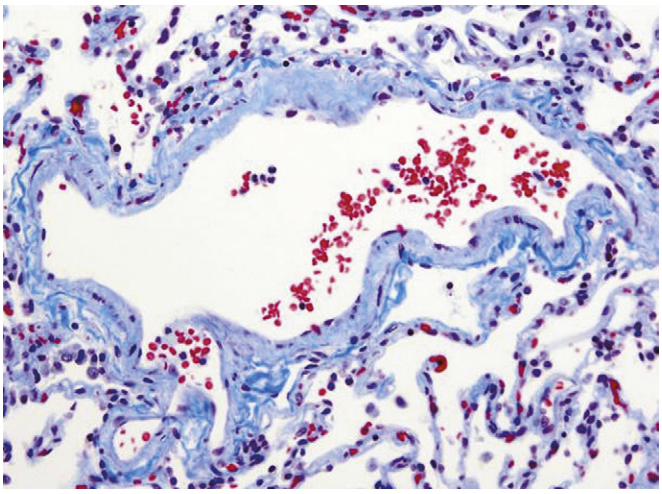

Figure 36–13. Pulmonary vein. The media is composed of loose, pale, blue-staining collage fibers with scarce smooth muscle present. (Gomori tricrome, ×200.)

and elastin, and unlike their arterial counterpart, show no clear internal and external elastic lamina (Figure 36-13).

Bronchial Vascular System

Whereas the pulmonary circulation returns all venous blood to the lung and serves some nutritive function to peripheral capillaries, the bronchial circulation is the primary blood source for the lung. Although two major bronchial arteries for each lung is a common pattern, this pattern is present less than 40% of the time. There usually are two bronchial arteries in the left lung and one in the right lung. Although variable, the left bronchial arteries usually arise from the upper portion of the descending aorta. The right bronchial artery arises from the descending aorta, one of the right intercostal branches, or subclavian or internal thoracic arteries. The bronchial arteries traverse along the dorsal portion of each bronchus. They lose their distinctness along the respiratory bronchioles and drain with the alveolar capillaries into the peribronchiolar venous network. They form a capillary plexus in the bronchi that supplies the submucosa and muscle. The capillary plexus communicates with branches of the pulmonary artery that empty into pulmonary veins. Other bronchial arteries supply the interlobular tissue and the pleura. They drain into the bronchial veins. The diameter of the bronchial artery is much smaller than that of the accompanying pulmonary artery. It has an internal elastic lamina and media but no external elastic lamina.

Pulmonary Lymphatics

Pulmonary lymphatics invariably have less elastic tissue in their walls than either arteries or veins.[11,30] They are lined by endothelium, and valves are present, especially near and in the visceral pleura. There are two lymphatic systems in the human lung: a superficial network in the pleura and a deep network around the bronchi and pulmonary arteries and veins and in the connective tissue septa between the pulmonary lobules. The two separate systems have anastomoses, both in the pleura and near the hilum. Lymphatics can be demonstrated to the level of the septal walls but are not found at the alveolar level. Lymph flow from both lower lobes drains into the infratracheal lymph nodes. The remaining right and left lung lobes drain into the tracheobronchial lymph nodes on each side of the trachea, respectively. Lymph from the right tracheobronchial nodes drains into the right bronchomediastinal trunk, whereas the left tracheobronchial nodes drain into thoracic duct.

Understanding the lymphatic drainage of the pleura is of clinical value. All lymph from the visceral pleura eventually reaches parabronchial and hilar lymph nodes by flowing either on the surface or in lymphatic trunks that course through the lung. Lymphatic vessels in the parietal pleura are in communication with the pleural space via 2- to 6-mm stomas found on the mediastinal pleura or the intercostal surfaces of the lower thorax. Because the parasternal nodes in the second and third interspaces receive lymph from a significant portion of the parietal pleura, biopsy of these nodes may reveal an etiology of the pleural effusion. The portion of lymph that drains caudally from the lower parietal pleural region into retroperitoneal nodes can explain metastases of tumor to the adrenals and kidneys.

Diaphragm

Although the diaphragm is the principal muscle of respiration, it is not essential for breathing in the awake state. It becomes essential during deep anesthesia because other muscles of respiration become inactive. The diaphragm is a musculotendinous sheet that is the main source of inspiratory muscle force. Anatomically it separates the thoracic from the abdominal cavity. It has two distinct muscular components: the sternocostal portion and the crural portion. These two portions have distinct embryologic origins and have separate segmental innervations and varying muscle fiber composition. Following birth, changes in fiber composition occur. The muscle fibers vary morphologically, physiologically, and cytochemically. The diaphragm has three openings near its central portion for the aorta, inferior vena cava, and esophagus. The vagus nerve passes through the esophageal hiatus, whereas the azygos vein and thoracic duct pass through the aortic hiatus. There are small paravertebral perforations for

splanchnic nerves. Because of the way the fibers originate from the bones and traverse to the central tendon, triangular areas may result in spaces or clefts in the diaphragm. Anteriorly these spaces or clefts are called Morgagni foramina, and posteriorly they are known as the foramina of Bochdalek. Both are potential sites for hernias. The phrenic nerve innervates the diaphragm.

During contraction in adults, the dome of the diaphragm descends and the lower ribs elevate. In infants, because of their very compliant rib cage, descent opposes elevation of the lower ribs and results in the subcostal retractions. Other muscles of respiration include the intercostals, the majority of which are arranged to enhance inspiration by elevating the lower ribs, and the abdominal muscles, which are powerful muscles of expiration but do not participate in expiration during quiet breathing. Scalenes act to elevate the first two ribs and are active even during quiet breathing. Although the sternocleidomastoid muscles usually are not active in quiet breathing, when inspiratory efforts are marked, they become the most important accessory muscles of inspiration. This phenomenon is well seen in infants with respiratory distress who elevate the upper portion of their sterna.

Summary

The respiratory portion of the lung is a complex organ with more than 40 cell types. It undergoes remodeling over the first few years of life. Altered structure, whether due to congenital abnormalities or due to injury and repair, is a critical determinant of survival and quality of life. Understanding the structure of the lung is critical to the management and treatment of lung disease in critically ill children.

References are available online at http://www.expertconsult.com.

Physiology of the Respiratory System

Mark J. Heulitt and Katherine C. Clement

PEARLS

- During childhood, the most important chest diseases have obstructive pictures that are best measured utilizing interrupter and oscillation techniques.
- Wheezing is a sound heard when there is flow limitation in a compliant tube. It is a sign of expiratory flow limitation. The wheezing is caused by "flutter" of the walls at the site of flow limitation secondary to the conservation of energy in the system.
- The respiratory system is not a linear system; resistance and compliance are not constants. They are dependent upon volume, volume history, and flow.
- The equation of motion changes when a spontaneously breathing patient is placed on positive pressure mechanical ventilator support. The pressure applied to the airway (P_{APP}) equals the sum of pressure generated by the patient's muscles (P_{mus}) plus the ventilator pressure (P_{vent}). Thus:

$$(P_{mus} + P_{vent} = \left(\frac{1}{C}\right)\dot{V} + RV)$$

Physiology of the Respiratory System

Because of the increasing emphasis on molecular biology today, many physicians currently in training have received limited exposure to physiologic principles that form the basis of clinical medicine. However, a resurgence of interest in translational research has occurred recently with a reemphasis on molecular research and applied animal physiology before these principles are utilized in clinical research.[1] In a recent editorial in the *European Journal of Physiology*, Rossier[1a] stated that research is refocusing itself to make a change from the past, where its mantra was "from function to the gene," to the future, where the focus must be on the "gene to function." The focus of this chapter will be to expose the reader to the important basic principles of respiratory physiology and to serve as a primer to other chapters in this book that utilize these principles.

The main function of the lungs is (rapid) gas exchange. This process is accomplished by a well-coordinated interaction of the lungs with the central nervous system, the diaphragm and chest wall musculature, and the circulatory system.

Gas exchange occurs in the alveolus, where the thin laminar blood flow and inspired air are separated only by a thin tissue layer. Gas exchange takes 0.25 seconds or one third of the total transit time of a red cell. The entire blood volume of the body passes through the lungs each minute in the resting state, approximately 5 L/min. The total surface area of the lung is about 80 meters square, equivalent to the size of a tennis court. The primary function of the lungs is to supply oxygen (O_2) and to remove carbon dioxide (CO_2) from the tissues of the body. For the lungs to do this, two interrelated processes must occur: ventilation, which is the movement of air between the outside body and the alveoli, and gas exchange, which is the transfer of O_2 and CO_2 between the alveolar gas and the mixed venous blood entering the lungs.

Approximately 10% of the lung is occupied by solid tissue, whereas the remainder is filled with air and blood. However, it should be noted that changes occur with development. A gram of lung from an infant probably represents more airway tissue and less parenchymal (alveolar and interstitial) tissue than the same amount of lung from an adult. Supporting structures of the lung must be delicate enough to allow gas exchange yet strong enough to maintain the architectural integrity needed to sustain alveolar structure. The functional structure of the lung can be divided into (1) the conducting airways (dead air space) and (2) the gas exchange portions. The two plumbing systems are airways for ventilation and the circulatory system for perfusion. Both systems are under low pressure.

Conducting Airways

The diameter of the lower airways is maintained by a balance of forces. Sympathetic impulses relax and parasympathetic impulses constrict the muscles. Airway dilatation may occur as a result of sympathomimetic agents (e.g., epinephrine or adrenaline). Narrowing forces are bronchial smooth-muscle contraction, mediated by efferent autonomic nerve control. Constriction also can occur as a result of irritants (e.g., dust, smoke, or cold), hyperventilation, and vasoactive agents (e.g., acetylcholine, histamine, or bradykinin).

Additional narrowing occurs during forced expiration, when there is dynamic airway compression caused by pleural and peribronchial pressures. This narrowing is counteracted by the intraluminal pressure and the tethering action of the surrounding lung. The luminal diameter of a branch

is related to the number of alveoli at the end of that branch (axial and lateral pathways). Because the longer airways with more branches and more alveoli usually have a wider lumen that allows greater airflow, newly inspired air reaches all of the alveoli throughout both lungs at the same time and in approximately the same amount, that is, an even distribution of inspired air throughout all lobes in a given period of time. There are approximately 23 airway divisions to the level of the alveoli. The divisions include main bronchi, lobar bronchi, segmental bronchi (to designated bronchopulmonary segments), and so on to the smallest bronchioles, which do not have alveoli and are lined completely by bronchial epithelium. These are the terminal bronchioles. Although the base airway diameter decreases with branching, the overall or total cross-sectional diameter increases tremendously so that peripheral airway resistance decreases.

Model of the Respiratory System

The respiratory system can be represented by a collection of physical components interacting with one another and with their environment. Although in vivo analysis demonstrates that the lungs do not function as a single compartment, analyzing the respiratory system in a linear model simplifies the presentation.

A single balloon on a pipe is the simplest model, although this model has its deficiencies because the airway is more complex than a simple pipe. Also, it now appears that the alveolus is not simply a single balloon or group of balloons similar to a cluster of grapes. It is now known that the alveoli are not physically independent structures but are actually interconnected.[2] An excellent review of the structure of the alveoli and the role of surfactant is offered by Gatto et al.[3] However, to lay the ground work for our understanding of respiratory mechanics, we will consider the simple model of a balloon on a pipe.

The relationship at any moment (t) between the pressure applied at the opening of the model (P(t)) and the volume in the model (V(t)) during emptying of this balloon can be described as a first-order model:

$$P(t) = E \bullet V(t) + R + \dot{V}$$

where *E* is the elastance of the balloon, *R* is the resistance of the pipe, and $\dot{V}$ is the flow through the opening. Using regression analysis, E and R can be calculated from P(t), V(t), and V′(t).

The values of R and E, as applied to the respiratory system, reflect the resistance of the airways and the elastance of the respiratory system, whereas V(t) is the volume increase from functional residual capacity (FRC) when the mouth pressure is zero.

The three important components of this linear model are the time constant (τ), compliance (C) or elastance (E), and resistance (R). The relationship of these is given by the equations:

$$\tau = C \times R \text{ or } \tau = R/E$$

Each of these components will be discussed separately.

Elastic Properties of the Respiratory System

The respiratory system is composed of a collection of elastic structures. The response to a force applied to the elastic structure of the respiratory system is to resist deformation by producing an opposing force, known as elastic recoil, to return the structure to its relaxed state.[4] In the respiratory system this opposing force produces a pressure known as the elastic recoil pressure (P_{EL}). The force required to stretch an elastic structure depends on the volume at which the outward recoil of the chest wall balances the inward recoil known as the elastic equilibrium volume. The pressure of the elastic recoil or P_{EL} divided by the lung volume (V) gives a measure of the elastic properties of respiratory system and is called elastance (E):

$$E = P_{EL} / V$$

When lung volume is plotted on the ordinate and P_{EL} is plotted on the abscissa, the slope of the static pressure-volume curve is equivalent to the reciprocal of elastance, called *compliance*.

For ventilation of the lungs to occur, the forces necessary to overcome the elastic, flow-resistive, and inertial properties of the lungs and the chest wall must be produced to create motion of the respiratory system. In normal circumstances, respiratory muscles produce these forces.

Overcoming forces to move gas into the airway can be exemplified by moving a block of wood over a surface. The movement of the block is determined by the friction between the block of wood and the surface and how fast the wood is moving. It is irrelevant what the block's position is. Similarly, the pressure required to produce a flow of gas between the atmosphere and the alveoli must overcome the frictional resistance of the airways. This pressure is proportional to the rate at which volume is changing or flow ($\dot{V}$) as follows:

$$P_{mouth} - P_{alv} = P_{fr} \alpha \dot{V} \text{ or } P_{ao} - P_A = P_{fr} \alpha \dot{V}$$

where P_{ao} is pressure at the airway opening (usually atmospheric pressure), P_A is the alveolar pressure, and P_{fr} is the pressure required to overcome frictional resistance. The pressure required to produce a unit of flow is known as flow resistance (R):

$$R = P_{fr} / \dot{V}$$

If the respiratory system is modeled as a single compartment with a single constant elastance (E) and a single constant resistance (R), then the equation of motion describes the balance of forces acting on the system is as follows:

$$P = EV + R\dot{V} + I\dot{V}$$

The inertia (*I*) is usually negligible and therefore ignored. Of the pressure produced during normal tidal respiration, most is required to overcome the elastic forces, and a minimal amount is required to overcome the flow-resistant forces.

Traditionally it was thought that little energy was dissipated by the tissues of the respiratory system and that the majority of the force developed during breathing was required to move gas through the airways. The lung parenchyma is a complex system consisting of alveolar walls composed of collagen, elastin, and proteoglycan macromolecules; an air liquid interface of surfactant; and cells that have the capacity to act in a contractile fashion, called interstitial cells. The viscoelastic behavior of the pulmonary parenchyma could potentially explain this behavior. In addition, this action is difficult to study because it is unclear where the boundary of the airways end and parenchyma begins. Airway smooth muscle exists in the terminal bronchioles and alveolar ducts, and the behavior of these structures may well influence parenchymal mechanics.

The energy expended moving the tissue is called the tissue viscance or resistance, although it is a non-Newtonian resistance. In other words, the viscosity depends upon the force applied. When measured during inspiration, the tissue resistance increases with increasing lung volume, whereas airway resistance falls. Tissue resistance comprises approximately 65% of respiratory system resistance at FRC in mechanically ventilated animals and increases as much as 95% at higher lung volumes.[5] The contribution of tissue resistance to respiratory system resistance in humans under the same circumstances is unknown.

Resistance is expressed as changes in pressure divided by changes in flow:

$$R = \Delta P / \Delta \dot{V}$$

The other part of elastic recoil depends upon the surface tension at the alveolar gas-liquid interface (surface forces). Surface tension is produced by the interface between air in the alveolus and the thin film of liquid that covers the alveolar surface. Surface tension in the alveolus is created by interacting water molecules that direct a force inward and could cause the alveoli to collapse. This action is described by La Place's equation where the pressure inside a bubble exceeds the pressure outside the bubble by twice the surface tension, divided by the radius. In other words, the smaller a bubble, the more the pressure inside exceeds the pressure on the outside. La Place's equation is defined as:

$$P = 2T / r$$

where *P* is the internal pressure, *T* is the tension in the wall of the structure, and *r* is the radius. When comparing two different alveoli with the same surface tension, the smaller the radius, the greater the pressure created by a given surface tension. Air will flow from high pressure (small alveoli) to lower pressure (larger alveoli). Thus smaller alveoli are more likely to collapse. The surface tension of the alveoli is affected by a substance produced in the alveoli called surfactant. Surfactant contains a mixture of lipids and proteins, is manufactured by alveolar type II cells, and exists as a monolayer on top of the alveolar subphase. Three surfactant-associated protein groups have been identified.[6] Surfactant acts to lower surface tension at the alveolar air-liquid interface and thereby decreases elastic recoil of the lungs.[7] Another action of surfactant is to reduce the development of pulmonary edema by diminishing one component of the pressure gradient driving transudation. In the lung there is a gradient between pulmonary capillary pressure and the interstitial pressure that surrounds the capillary. In most of the lung, the pulmonary capillary pressure is greater than the interstitial pressure; thus pulmonary edema would develop if not checked by the oncotic pressure of the plasma proteins. By reducing surface tension, the surfactant reduces the interstitial pressure and transcapillary gradient, but if there is a deficiency of surfactant and thus a rise in surface tension, pulmonary edema may develop.[8] Also, surfactant has been described as an anti-wetting agent that helps to keep the lungs dry.[9] Currently there is agreement on the fact that surfactant plays an essential role in alveolar mechanics, but its mechanism is debated. The aforementioned description outlines the classic discussion on the role of surfactant, but diverse opinions exist on its true role. Scapelli[10] has described the role of the surfactant foam bubbles within the alveoli as "inner tubes." In contrast, Hills proposes that surfactant coats the alveolar walls as a "biologic wax."[11,12] The clinical implications of a deficiency of surfactant has been described in a famous editorial by Lachman entitled "Open up the Lung and Keep the Lung Open."[13]

Compliance and Elastance

Compliance is how much a compartment will expand if the pressure in that compartment is changed. An elastic balloon has a high compliance because a small pressure increase inside the balloon will greatly expand the balloon. A rigid tube has a low compliance because a small pressure increase inside the rigid tube will not result in a significant increase in the volume of the rigid tube. Two major forces contribute to lung compliance: tissue elastic forces and surface tension forces. The compliance (C) is determined by the change in elastic recoil pressure (ΔP) produced by a change in volume (ΔV):

$$C = \Delta V / \Delta P$$

The compliance of the lungs (C_L), chest wall (C_{CW}), and respiratory system (C_{RS}) can be determined by measuring the change in distending pressure and the associated change in volume. The distending pressure represents the pressure change across the structure, where P_{ao}, P_{pl}, and P_{bs} represent the pressure measured at the airway opening, pleural pressure, and pressure at the body surface (atmospheric pressure), respectively:

$$C_L = \Delta V / \Delta (P_{ao} - P_{pl})$$
$$C_{CW} = \Delta V / \Delta (P_{pl} - P_{bs})$$
$$C_{RS} = \Delta V / \Delta (P_{ao} - P_{bs})$$

Lung volume and volume-pressure relationships (e.g., compliance) reflect parenchymal (air space) development, whereas airflow and pressure-flow relationships (resistance and conductance) predominantly reflect airway development. The lungs become stiffer (compliance decreases) at higher lung volumes.

Pulmonary compliance changes with growth and maturation depending upon the number of expanded air spaces, the size and geometry of the air spaces, the characteristics of the surface lining layer, the properties of the lung parenchyma. This shift is represented by changes in the shape of the volume-pressure curve. When these curves are corrected by expressing the volumes as a percentage of the maximal observed lung volume, they are more curved in infants than in older children (Figure 37-1).[14] It is important to note that there may be boundaries for dynamic changes in alveolar size and shape during ventilation because of the tensile forces of the connective tissue and surface tension supporting the alveoli and alveolar ducts.

The developmental change in shape of the volume pressure curve represents the maturation of alveoli and hence differences in the elastin-collagen ratio with age.[14] The lung volume (as a percent of maximal lung volume) at which airway closure occurs is higher in children younger than 7 years[15] and is closer to their functional residual volume. Pressure-volume relationships are also more curvilinear in infants.[16] Chest wall compliance is 50% greater in infants.

Elastance is defined as the change in distending pressure divided by the associated change in volume:

$$E = \Delta P / \Delta V$$

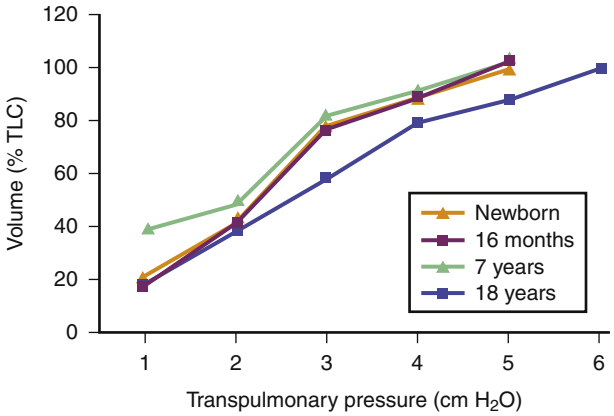

Figure 37–1. Deflation volume-pressure curves of the lung at different ages (obtained from studies on excised lungs).[8] With increasing age up to young adulthood, the curves become straighter and, at a given lung volume, elastic recoil pressure is greater. The curve from elderly individuals resembles that from a 7-year-old respiratory system. *TLC,* Total lung capacity.

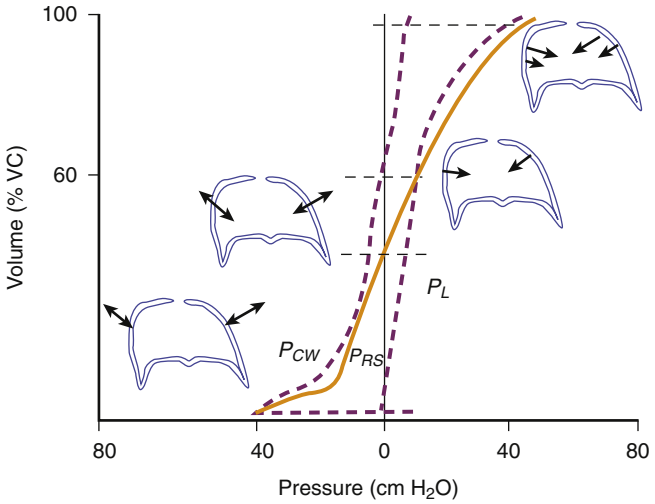

Figure 37–2. Pressure-volume relationship of the lung (P_L), chest wall (P_{CW}), and entire respiratory system (P_{RS}). *Large arrows* represent the elastic recoil of the lungs and the chest wall. *(Modified from Agostoni E, Mead J: Statics of the respiratory system. In Fenn WO, Rahn H, editors:* Handbook of physiology, respiration, vol 1, *Washington, DC, 1964, American Physiological Society, p 392.*

Elastance is therefore the reciprocal of compliance; thus stiff lungs have a high elastance.

Elastic Recoil of the Respiratory System

In the intact thorax, the inward recoil of the lungs is opposed by the outward recoil of the chest wall (when it is below its resting volume). Both the lungs and the chest wall recoil inward when chest volume exceeds its resting volume. These recoil forces act as though arranged in series.

The pressure required to balance the elastic recoil of the lungs, chest wall, and respiratory system (elastic recoil pressure) may be determined by having a subject exhale in increments from total lung capacity (TLC) to residual volume. At each volume, the subject relaxes against a fixed obstruction with glottis open, and the pressure difference across the lung, chest wall, and entire respiratory system is recorded. Pressure volume curves are derived in this way for the respiratory system, and its components are shown in Figure 37-2.[17] The static pressure-volume curves of the respiratory system, lung, and chest wall are different during inspiration and expiration. Thus lung volume at a given transpulmonary pressure is higher during deflation than during inflation. This phenomenon is called hysteresis. Hysteresis is the failure of a system to follow identical paths of response on application and withdrawal of a forcing agent, as occurs during inspiration and expiration. Hysteresis in the respiratory system depends on viscoelasticity, such as stress adaptation (i.e., rate-dependent phenomenon), and on plasticity (i.e., a rate-independent phenomenon). In the lungs, hysteresis is due primarily to surface properties and alveolar recruitment-derecruitment. In comparison, the chest wall hysteresis is related to the action of both muscles and ligaments because both skeletal muscles and elastic fibers exhibit hysteresis. Hysteresis is negligible when volume changes are minimal, such as during quiet breathing. This phenomenon is important because the area of the hysteresis loop represents energy lost from the system.

The resting volume of the respiratory system, the FRC, is the volume at which the elastic recoil of the lungs and the chest wall exactly balances each other. Above and below this equilibrium point, progressively increasing pressure is required to change the volume of the respiratory system. The total pressure required at each volume is the sum of the pressures required to overcome the elastic recoil of the lungs and chest wall.

Flow Resistance of the Respiratory System

The response of the lung to movement is governed by its response to the physical impedance of the respiratory system. The impedance can be categorized into (1) elastic resistance between the alveolar gas/liquid interface and tissue and (2) frictional resistance to gas flow. Under static conditions, pressure is required only to oppose the elastic recoil of the respiratory system. However, when the lungs and chest wall are in motion and movement of air into and out of the lungs occurs, pressure also must be provided to overcome the frictional or viscous forces. The ratio of this additional pressure (P) and the rate of air flow that it produces ($\dot{V}$) is defined as the resistance:

$$R = P / \dot{V}$$

In other words, the flow ($\dot{V}$) measured at the mouth depends on the driving pressure (i.e., the pressure difference between alveoli [P_{alv}] and mouth [P_{mo}]) and the airway resistance (R_{aw}):

$$\dot{V} = (P_{mo} - P_{alv}) / R_{aw}$$

If the mouth pressure is zero (i.e., atmospheric pressure), the driving pressure is the alveolar pressure.

Airways resistance (R_{aw}) is the sum of the peripheral airways resistance (peripheral intrathoracic airways <2 mm diameter; R_{awp}), the central airways resistance (large intrathoracic airways >2 mm diameter; R_{awc}), and the extrathoracic airways resistance (especially glottis; R_{ext}). In healthy people, R_{ext} accounts for 50% of the total R_{aw} and R_{awp} for about 15%. R_{awp} and R_{awc} are influenced by lung volume. Higher lung volumes give higher P_{el} and therefore increase airway diameter. With increasing volumes during inspiration, the increased

P_{el} is counteracted by P_{pl}, resulting in increased radial distending force. This distending force is the transmural pressure and is the difference between pressure in (P_{in}) and pressure outside (P_{out}) the airway.

At zero airflow the pressure inside the airways (P_{in}) equals atmospheric pressure and transmural pressure (P_{tm}) equals the elastic recoil pressure (P_{el}):

$$P_{in} = P_{mo},\ P_{tm} - P_{el}$$

The total respiratory resistance (R_{rs}) consists of the resistance of the airways (R_{aw}), the resistance of the lung (R_L), and the resistance of the chest wall (R_{cw}):

$$R_{rs} = R_{cw} + R_L + R_{aw}$$

In older children, R_{cw} and R_L represent only 10% to 20% of R_{rs},[18] but in newborns, R_L could be higher.[19]

Airway diameter of the intrathoracic airways approximates to a sigmoidal relationship with P_{tm}. This relationship results in volume dependency of R_{aw}. At higher lung volumes R_{awp} decreases. The specific relation between R_{awp} (or its reciprocal conductance G_{aw} [$=1/R_{aw}$]) and volume is mirrored by the specific R_{aw} (sR_{aw}) and specific G_{aw} (sG_{aw}):

$$sR_{aw} = R_{aw} / V$$

The resistance of the airways (R_{aw}), lungs (airway and parenchyma) (R_L), chest wall (R_{cw}), and entire respiratory system (R_{RS}) can be calculated by measuring the rate of air flow and the associated transstructural pressure by subtracting from the total pressure the amount required to overcome elastic recoil:

$$R_{aw} = (P_{ao} - P_{alv}) / \dot{V}$$
$$R_L = (P_{ao} - P_{pl}) / \dot{V}$$
$$R_{cw} = (P_{pl} - P_{bs}) / \dot{V}$$
$$R_{RS} = (P_{ao} - P_{bs}) / \dot{V}$$

where P_{ao}, P_{alv}, P_{pl}, and P_{bs} represent the pressure at the airways opening, alveolar pressure, pleural pressure, and pressure at the body surface, respectively. The resistance of the lung parenchyma may be derived by subtracting airway from total lung resistance.

The relationship between the flow rate and the airway pressure gradient is nonlinear because of the relative contribution of the various components of the respiratory system to the total pressure required to overcome the viscous forces and its dependence upon volume, volume history, and flow. The viscous forces increase disproportionately as the flow rate increases and as airway resistance increases. In contrast, the resistance of the chest wall and lung parenchyma remains constant over a wide range of flow rates.[20] During quiet breathing by mouth, airway resistance accounts for greater than 50% of the total respiratory system resistance.[21] However, as flow rate increases, the contribution of the airways to total resistance progressively increases.

Changing patterns of airflow result in the nonlinear flow-resistance characteristic of the airways. Subsequently, as the flow rate to the airway increases, airflow becomes progressively more turbulent. The more turbulent the flow, the greater the pressure required to overcome the viscous forces. Turbulence occurs at lower flow rates in the upper airway compared with the lower (intrathoracic) airways because of the tortuous geometry of the upper (extrathoracic) airway and the narrow glottic aperture. Therefore, the upper airway is responsible for most of the increase in airway resistance with an increase in flow rate. Studies have shown the resistance of the lower airways to be nearly constant up to flow rates of 2L per second.[20] For patients who are breathing quietly by mouth, total airway resistance is divided almost equally between the upper and lower airways. As their effort increases, flow rate increases, and the ratio of upper to lower airway resistance progressively increases as previously described.

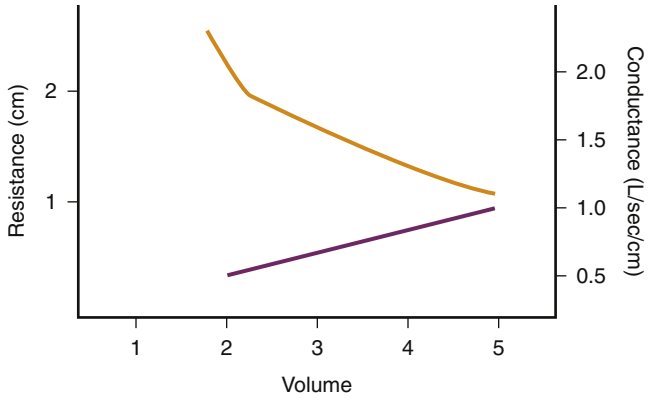

Figure 37–3. Relationship between lung volume and airway resistance (*solid line*) and conductance (*dashed line*). *(Modified from Briscoe WA, Dubois AB: The relationship between airway resistance, airway conductance, and lung volume in subjects of different age and body size,* J Clin Invest *37:1280, 1958.)*

Depending on whether laminar or turbulent flow predominates, resistance to airflow varies inversely with either the fourth or the fifth power of airway radius.[22] Therefore major changes in airway resistance are caused by factors that affect airway diameter.[23] During spontaneous lung inflation, airway diameter increases as airway resistance decreases. This change is produced by two mechanisms. First, as lung volume increases, the increasing elastic recoil of the pulmonary parenchyma provides a tethering effect that dilates the intrapulmonary airways. Second, extrapulmonary and large intrapulmonary airways are surrounded by pleural pressure, which becomes increasingly negative during inspiration. This phenomenon leads to an increasing pressure gradient across the airway wall and therefore to an increasing diameter. The change in airway resistance with lung volume is curvilinear and is illustrated in Figure 37-3.[23] When the reciprocal of airway resistance, airway conductance (G_{AW}) is plotted against lung volume, this relationship is nearly linear.

Dynamic Change in Airway Caliber During Respiration

Airway caliber is partially dependent on the transmural pressure. The transmural pressure is the difference between the interstitial pressure and the atmospheric pressure. The external airway wall for the intrathoracic airways is subjected to the interstitial pressure, which is approximately equal to the pleural pressure. In contrast, the external walls of extrathoracic airways are subjected to atmospheric pressure. The intraluminal pressure is dependent upon the generation of the airway. During inspiration, pleural pressure is negative relative to atmospheric pressure. Alveolar pressure is approximately equal to pleural pressure, and pressure at the mouth is equal to

atmospheric pressure. This pressure difference creates a gradient from the mouth to the alveoli. Extrathoracic airways tend to narrow during inspiration because the transmural pressure is positive. In contrast, the transmural pressure in the intrathoracic airways is negative, causing a tendency for these airways to dilate during inspiration. The degree of airway caliber change during inspiration depends on both the magnitude of the transmural pressure and the airway wall compliance. At the end of inspiration there is a relaxation of the inspiratory muscles, and the elastic recoil of the respiratory system produces, relative to atmospheric pressure, a positive pleural and alveolar pressure. Because of the dynamic pressure changes previously described, there is a tendency for intrathoracic airways to narrow and extrathoracic airways to dilate during expiration.

Applied Forces

Ventilation of the lungs involves motion of the respiratory system, which is produced by the forces required to overcome the flow resistive, inertial, and elastic properties of the lungs and chest wall. Under normal circumstances, these forces are produced by the respiratory muscles.

If ventilation is to occur, opposing forces must be overcome by a pressure applied to the respiratory system to create motion. At each instant, the applied pressure (P_{APP}) must equal the sum of the pressure required to balance elastic recoil (P_{ER}) and the pressure lost to viscous (resistive) forces (P_R). The maximal pressures that can be generated by the respiratory muscles are determined by both lung volume and gas flow:

$$P_{APP} = P_{ER} + P_R$$

With use of the aforementioned equations, this may be converted to:

$$P_{APP} = (1/C)V + R\dot{V}$$

This equation is known as the *equation of motion of the respiratory system.*

Figure 37-4 illustrates the pressure involved in respiration. Gradients must occur to allow for gas to flow into the lungs.

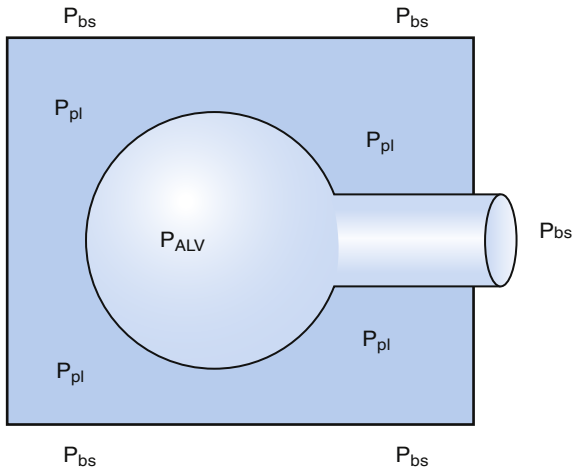

Figure 34–4. Illustration of the pressure involved in respiration. Gradients must occur to allow for gas to flow into the lungs. P_{ALV}, Alveolar pressure; P_{bs}, pressure at the body surface; P_{PL}, intrapleural pressure.

The airway pressure gradient that drives airflow into the lungs is defined as:

$$P_M - P_{ALV}$$

where P_M is the pressure at the mouth, which is normally atmospheric, and P_{ALV} is the alveolar pressure. Transpulmonary pressure (P_{TP}) is defined as:

$$P_{TP} = P_{ALV} - P_{pl}$$

where P_{ALV} is the alveolar pressure and P_{pl} is the intrapleural pressure. P_{TP} is equal to elastic recoil of the lungs when there is no airflow. P_{TP} increases and decreases with lung volume. Transchest wall pressure (P_{TC}) is defined as:

$$P_{TC} = P_{pl} - P_{bs}$$

where P_{pl} is the intrapleural pressure and P_{bs} is the pressure at the body surface that is usually atmospheric. P_{TC} and P_{pl} are equal in magnitude to the elastic recoil of the chest when there is no airflow and, like P_{TP}, increases and decreases with lung volume.

The transmural pressure (P_{RS}) is defined as:

$$P_{RS} = P_{ALV} - P_{bs}$$

where P_{ALV} is the alveolar pressure and P_{bs} is the pressure at the body surface. P_{RS} represents the transmural pressure across the entire respiratory system, including the lungs and the chest wall, and is equal to the net passive elastic recoil pressure of the whole respiratory system when airflow is zero.

During inspiration the respiratory muscles provide the applied pressure that expands the chest wall and the lungs, causing the alveolar and airway pressure to fall. The net result is that the alveolar pressure becomes less than atmospheric pressure. Once alveolar pressure is less than atmospheric pressure, air flows into the lungs along a pressure gradient and the lungs inflate, storing potential energy in the elastic structures for expiration. In order for gas flow to occur, there must be a balance of forces. Table 37-1 illustrates these forces (expressed as pressures).

Expiration is usually passive (excluding disease states where the patient actively tries to empty their lungs). That is, the energy stored in the elastic recoil of the lungs and the chest wall produces the positive alveolar and airway pressure needed to overcome flow resistance and air is forced from the lungs.

In order to inflate the lungs there must be an increase in alveolar pressure, which is usually done with positive pressure ventilation or a decrease in body surface pressure, such as in negative pressure ventilation (iron lung), or the respiratory muscles must be activated (normal breathing).

Under resting conditions, expiration is usually passive. At times of increased ventilatory requirements, such as during exercise, contraction of the abdominal and internal intercostals muscles can aid expiration.

Table 37–1 Balance of Forces

$P_{RS} + P_{MUS}$	=	$P_L + P_{CW}$
$P_{ALV} - P_{bs} + P_{MUS}$	=	$P_L + P_{CW}$
Inspiratory muscle contraction		Lung, chest wall elastic recoil
Outward acting forces when positive		Inward acting forces when positive

Interactions Between Lungs and Chest Wall

The lungs and the chest wall operate in series, and their compliance adds reciprocally to make total compliance:

$$1/C_T = 1/C_L + 1/C_{CW}$$

The chest wall is like a spring that may either be compressed or distended. Transthoracic pressure is negative at residual volume and at FRC, meaning the chest wall is smaller than its unstressed volume and its tendency is to spring out. Normal tidal breathing is entirely in the negative pressure range for transthoracic pressure. When examining the compliance curve of the chest wall (lung volume versus transthoracic pressure), pressure is 0 at about 65% of TLC. Thus the chest is at its unstressed volume and has no tendency to collapse or expand. Transthoracic pressure is positive at volumes above 65% TLC. The chest tends to collapse above its unstressed volume.

Volume-pressure loops observed during breathing are based on the flow resistance of gas and tissue. It had been previously suggested that the static volume-pressure relationship is represented by a single line, suggesting that the static pressures depend only on volume. However, the static pressure will vary depending upon the volume history of the lung. Thus if the lung is fully expanded, at deep inspiration, static pressures will be lower. This concept is important because of the hysteresis of the lungs and the tendency not to follow identical paths of response upon the application and withdrawal of forces on the lung. Hysteresis applies both to the lung and to the chest wall.

Time Constant of Emptying

The time taken for volume in the respiratory system to be reduced by 63% when the respiratory system is allowed to empty passively and the volume-time profile is measured is known as the time constant (τ) of the respiratory system.[24] If we use a model of the respiratory system with a single compartment and a single, constant elastance and a single, constant resistance, then the following occurs:

$$\tau = R/E$$

In a single compartment model the volume-time profile can be represented by a single exponential decay.

In healthy adults the time constant of the passive respiratory system is short—approximately 0.5 seconds. Such a short time constant allows the lungs to empty to the end expiratory volume (EEV) at the end of each expiration. Thus the FRC and EEV are equal. Since the respiratory system is relaxed at the end of expiration, inspiration can begin as soon as inspiratory muscle activity is initiated. The expiratory time constant is shorter in children, with values approximating 0.3 seconds reported in infants with normal lungs.[25] Infants with hyaline membrane disease have stiffer than normal lungs with expiratory time constants reported as low as 0.1 seconds. In the case of patients with obstructive airway diseases such as asthma, resistance is increased and the expiratory time constant is longer. Therefore, a longer time is required for the lungs to empty and return the respiratory system to EEV. Patients with chronic airway obstruction frequently have carbon dioxide retention and an increased respiratory drive. This phenomenon results in an increased respiratory rate with a shorter respiratory cycle and less time available for expiration. In this situation the respiratory system frequently does not have time to return to EEV before the next inspiration starts; thus FRC occurs at a volume higher than EEV, not equal to EEV, which prevents relaxation of the respiratory system at the end of expiration. This lack of relaxation of the respiratory system at the end of expiration causes a positive recoil pressure. This pressure is called intrinsic positive end expiratory pressure, or $PEEP_i$. Before inspiratory flow can begin, the patient's inspiratory muscle must produce enough force to overcome the $PEEP_i$; thus this force is "lost" to produce inspiratory flow and represents a load that must be overcome by the inspiratory muscle. In patients with severe airway obstruction, this pressure can be as high as 15 to 20 cm H_2O.

Physiology of Positive Pressure Mechanical Ventilation

Up to this point our discussion has focused on patients breathing spontaneously without artificial support. To understand the respiratory physiology principles that apply to the critically ill pediatric patients, we must briefly examine the effects of positive pressure breathing on the pediatric respiratory system.

The respiratory system, like most biological systems, is closely associated with exponential functions. An exponential function is a mathematical expression that describes an event where the rate of change of one variable is proportional to its magnitude.

For example, in a passive breath, expiratory flow will be higher at the beginning of expiration than at the end, as the lung volume decreases toward FRC.

There are various forms of exponential functions, but the two most important ones for the clinician in mechanical ventilation are the rising and the decaying exponential functions.

Rising exponential function expresses an increase of one variable as a function of time—for example, flow, pressure, or volume versus time. A rising exponential function expresses the behavior of a physical system where the rate of change of one variable is proportional to its magnitude and a constant. In this relationship, the largest rate of change is always observed at the beginning of the event, and the smallest rate of change is always observed at the end of the event.

Decaying exponential function expresses a decrease of one variable as a function of time: flow, pressure, or volume versus time. An example of this relationship can be seen with the pressure decrease during lung deflation in a passive expiration. Flow returns to a baseline during a passive expiration, reflecting a negative decaying function. This expression of a physical system is expressed where the rate is proportional to its magnitude only. Therefore the rate of change will always have the largest value at the beginning of the event, and the smallest value at the end of the event. The rate of decay is not constant over time.

As previously discussed, the respiratory system is governed by various laws of physics that describe the various dynamic forces involved in the movement of the system. In physiology, force is measured as Pressure = Force/Area, displacement is measured as Volume = Area × Displacement, and the relevant rate of change is measured as flow (e.g., Average flow

= ΔV/ΔTime; Instantaneous flow = dv/dt [the derivative of volume with respect to time]). The pressure necessary to cause flow of gas into the airway and increase the volume of the gas in the lung is the key component in positive pressure mechanical ventilation. The volume of gas (ΔV) to any lung unit and the gas flow ($\dot{V}$) is related to the applied pressure (ΔP) by:

$$\Delta P = \frac{\Delta V}{C} + \dot{V} \bullet R + K$$

where *R* is the airway resistance and *C* is the lung compliance. This equation is the same one previously described as Newton's equation of motion for the respiratory system. The applied pressure to the respiratory system measured at the inlet is the sum of the muscle pressures P_{mus} (pressure generated by the patient's spontaneous muscular forces) and the ventilator pressure $P_{applied}$ (pressure generated by ventilator). Muscle pressure is patient generated but cannot be directly measured. Muscle pressure represents the pressure generated by the patient to expand the thoracic cage and lungs. In contrast, ventilator pressure is the transrespiratory pressure generated by the ventilator during inspiration. Combinations of these pressures are generated when a patient is breathing on a positive pressure ventilator. In spontaneously breathing patients, the pressure measured at the patient's airway is a mix of the two pressures dependent upon the mode of ventilator support utilized. For example, in continuous positive airway pressure, all pressure generated will be by the patient muscles, whereas in pressure support, the pressure generated will be a mix of the pressure generated by the patient's respiratory muscles and that generated by the ventilator. When respiratory muscles are at complete rest, the muscle pressure is zero; therefore the ventilator must generate all the pressure necessary to deliver the tidal volume and inspiratory flow. The reverse is also true, and there are degrees of support depending upon the amount of force generated by the patient's respiratory muscles. The application of the equation of motion to the generation of gas flow is the next important step. Total pressure applied to the respiratory system (P_{RS}) of a patient undergoing ventilation is the sum of the pressure generated by the ventilator (measured at the airway) (P_{AO}) and the pressure generated by the respiratory muscles (P_{MUS}). Therefore:

$$P_{RS} = P_{Applied} + P_{MUS} = (V/C) + \dot{V} \times R + K$$

where P_{RS} is the respiratory system pressure, $P_{Applied}$ is the applied pressure by the ventilator, P_{MUS} is the pressure developed by the respiratory muscles, $\dot{V}$ is flow, *R* is airway resistance, *V/C* is respiratory system compliance, and *K* is the pressure. $P_{Applied}$ and $\dot{V}$ can be measured by the pressure and flow transducer in the ventilator. Volume is derived mathematically from the integration of the flow waveform.

To generate a volume displacement, the total forces have to overcome elastic and resistive elements of the lung and airway/chest wall represented by V/C and V × R, respectively. V/C depends on both the volume insufflated in excess of resting volume and the respiratory system compliance. To generate gas flow, the total forces must overcome the resistive forces of the airway and the endotracheal tube against the driving pressure gradients. At any moment during inspiration, there must be a balance of forces opposing lung and chest wall expansion measured as the airway pressure (P_{AO}). The opposing pressure can be summarized as the sum of elastic recoil pressure ($P_{elastic}$), flow-resistive pressure ($P_{resistive}$), and inertial pressure ($P_{resistance}$) of the respiratory system. Therefore:

$$P_{AO} = P_{elastic} + P_{resistive} + P_{inertance}$$

Inertial forces are usually negligible during conventional ventilation, which depends on bulk convective flow—unlike in high-frequency ventilation, where volumes are at the level of dead space. Therefore, for conventional ventilation, the forces exemplified in the equation of motion can expressed as:

$$P_{AO} = P_{elastic} + P_{resistive}$$

If elastic forces are recognized as the product of elastance and volume ($P_{elastic} = E \times V$) and the resistive forces as the product of flow and resistance (Resistive $\dot{V} \times R$), the formula can be written as:

$$P_{AO} = (\text{Elastance} \times \text{Volume}) + (\text{Resistance} \times \text{Flow})$$

If compliance (the inverse of elastance) is substituted for elastance, the equation of motion, as described in the preceding text, becomes:

$$P_{AO} = \text{Volume} / \text{Compliance} + \text{Resistance} \times \text{Flow}$$

The quotient of volume displacement over compliance of the respiratory system represents the pressure necessary to overcome the elastic forces above the resting lung volume or FRC. The resting lung represents the quantity of air remaining in the lungs at the end of a spontaneous expiration. Pressure, flow, and volume are all measured relative to their baseline values. The pressure necessary to cause inspiration is measured as the change in airway pressure above PEEP. For example, in a patient breathing spontaneously on continuous positive airway pressure, the ventilator pressure is zero; the patient must utilize his or her respiratory muscles to generate all the work of breathing. The same can be applied to the volume during inspiration or the tidal volume, which is the change in volume above FRC. The pressure necessary to overcome the resistive forces of the respiratory system is the product of the maximum airway resistance (R_{MAX}) and inspiratory flow. Flow is measured relative to its end-expiratory value, which is usually zero, unless a $PEEP_i$ is present. The ultimate result of the gas movement or flow is to allow gas to reach and be exchanged at the alveolar unit.

Gas Exchange

The basic function of the respiratory system is to supply oxygen to the body and to remove excess carbon dioxide. The following are the essential steps involved in this process:

1. Ventilation, the exchange of gas between the atmosphere and the alveoli
2. Diffusion across the alveolar-capillary membrane
3. Transport of gases in the blood
4. Diffusion of the gases from the capillaries of the systemic circulation to the cells of the body
5. Use of the oxygen and production of carbon dioxide within the cells as a by-product of metabolism

During the process of ventilation, air is transported back and forth between the outside of the body and the terminal respiratory units of the lungs. In the alveoli, the air is exposed to a thin film of blood. O_2 diffuses across the alveolar-capillary membrane, enters the blood, and combines with hemoglobin. Simultaneously, CO_2 diffuses from the blood and enters the

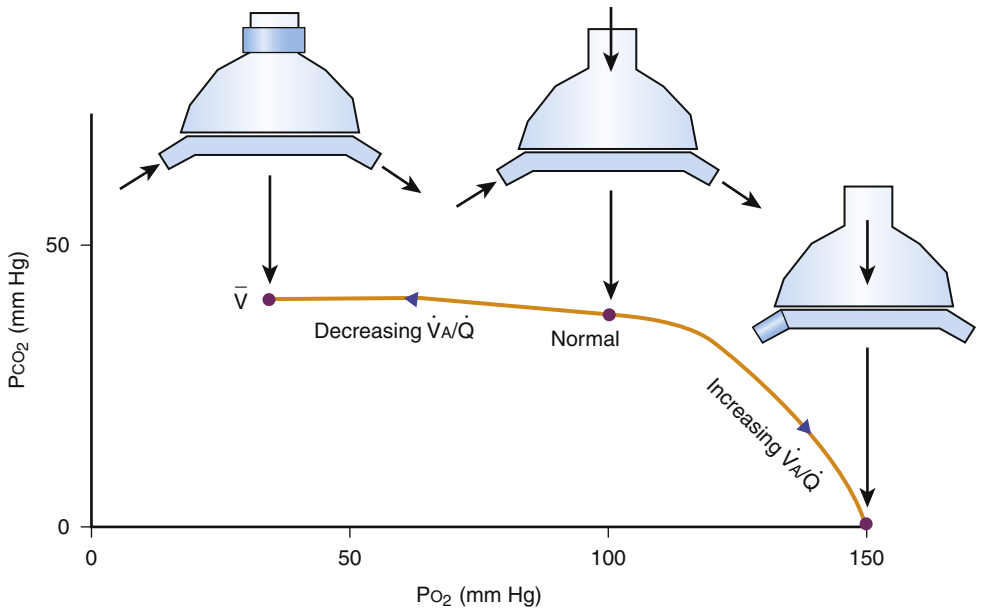

Figure 37-5. Relationship between the ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) of an alveolus and the P_{O_2} and P_{CO_2} of the alveolar gas and end-capillary blood. The P_{O_2} and P_{CO_2} vary from the mixed venous blood ($\bar{V}$) to inspired air (I) as $\dot{V}_A/\dot{Q}$ changes from zero to infinity. *(Modified from West JB:* Ventilation blood flow and gas exchange, *ed 3, Oxford, 1977, Blackwell Scientific, p 37.)*

alveolar gas. In this way, the mixed venous blood entering the lungs is altered through the addition of O_2 and the removal of CO_2. This is the process of gas exchange.

The partial pressure of O_2 (Pa_{O_2}) and CO_2 (Pa_{CO_2}) in the arterial blood, and therefore the adequacy of gas exchange, are dependent on a number of factors. These factors include the composition of the alveolar gas and the extent to which equilibrium is reached between the alveolar gas and the pulmonary capillary blood. The alveolar gas composition is, in turn, dependent upon the content of the inspired air and the mixed venous blood, the quantity of air (ventilation) and blood (perfusion) reaching the alveoli, and the ratio of alveolar ventilation to perfusion ($\dot{V}_A/\dot{Q}$). Of the factors determining the adequacy of gas exchange, the structure and function of the lungs primarily influence the ventilation-perfusion relationships, alveolar ventilation, and diffusion of O_2 and CO_2.

Ventilation Perfusion Relationships

In the normal, upright lung, both alveolar ventilation and perfusion increase from the apex to the bases largely because of the effects of gravity. Blood flow increases more rapidly from apex to base than ventilation, and therefore $\dot{V}_A/\dot{Q}$ ratios are high at the apex and decrease progressively toward the base of the lungs. The regional differences in perfusion are called *West's zones of perfusion*.[26-28] West's zone I occurs when mean pulmonary arterial pressure is less than or equal to alveolar pressure; thus no blood flow occurs. In zone I, the apices of the lung of an upright adult, there are unperfused yet ventilated alveoli, which is dead space ventilation. (Bronchial arterial flow nourishes the lung.) In zone II, which consists of the mid lung, pulmonary artery pressure is greater than alveolar pressure. Conditions in this zone are governed by the fact that blood flow is not influenced by venous pressure but by the difference between arterial and alveolar pressures, which is a function of (hydrostatic) height. In zone III, the lower zone of the lung, pressure at the alveolus is exceeded by the pressures in both pulmonary artery and vein. Flow in this zone is a function of pulmonary artery and pulmonary venous pressures and is independent of height. At the very base of the lung, because of higher perivascular pressures and reduced lung expansion, flow again is diminished.[29]

Any disorder affecting the airways or the parenchyma of the lung will result in an increased imbalance between ventilation and perfusion and therefore a greater than normal range of $\dot{V}_A/\dot{Q}$ ratios. The presence of varying $\dot{V}_A/\dot{Q}$ ratios, whether in the normal or the diseased lung, has several important effects on gas exchange. The P_{O_2} and the P_{CO_2} of an alveolus, and therefore of the capillary blood leaving it, is dependent on the ratio of ventilation to perfusion. As this ratio decreases, the P_{O_2} decreases and the P_{CO_2} increases. The opposite occurs as the $\dot{V}_A/\dot{Q}$ ratio increases. Figure 37-5 demonstrates the relationship between the ventilation/perfusion ratios P_AO_2 and P_ACO_2.

Lung units with low $\dot{V}_A/\dot{Q}$ ratios therefore decrease arterial P_{O_2} and increase arterial P_{CO_2}. In the extreme cases in which no ventilation reaches a lung unit, $\dot{V}_A/\dot{Q}$ is zero and mixed venous blood is added unchanged to the arterial circulation. A right-to-left shut occurs. The contribution of low $\dot{V}_A/\dot{Q}$ units and shunts to arterial blood may be determined through the calculation of the venous admixture $\dot{Q}_S/\dot{Q}_T$:

$$\dot{Q}_S/\dot{Q}_T = (C_C - C_a)/(C_C - C\bar{V}),$$

where C_c, C_a, and $C\bar{V}$ are the O_2 contents of pulmonary end-capillary, arterial, and mixed venous blood, respectively. This contribution also may be assessed by calculating the difference between the alveolar and arterial P_{O_2} ($A-aDO_2$), which varies directly with the extent of venous admixture. Because of difficulties in accurately measuring it, the mean alveolar P_{O_2} (P_AO_2) is calculated from the alveolar air equation:

$$P_AO_2 = P_IO_2 - PCO_2/R,$$

where P_IO_2 represents the P_{O_2} of inspired air and R is the respiratory exchange quotient—the ratio of CO_2 production

to O_2 consumption. In healthy young subjects, the A – aDO_2 averages 8 mm Hg.[30]

When ventilation to a lung unit exceeds its perfusion (that is, $\dot{V}_A/\dot{Q} > 1$), the excess ventilation is considered to be "wasted" because it does not participate in gas exchange. The sum of the excess ventilation contributed by lung units with high $\dot{V}_A/\dot{Q}$ ratios is referred to as *alveolar dead space*.

The effects of increasing ventilation/perfusion imbalance on gas exchange is that as the amount of inequality increases, both the ratio of physiologic dead space to tidal volume and venous admixture increase and arterial P_{O_2} falls. Arterial P_{CO_2} also progressively increases.

Alveolar Ventilation

The volume of air entering the lungs each minute that actually participates in gas exchange is called the alveolar ventilation ($\dot{V}_A$). It is therefore the difference between the total volume of air entering the lungs each minute (minute ventilation, $\dot{V}_E$) and the volume of air entering the lungs that does not participate in gas exchange (dead space: $\dot{V}_D$): $\dot{V}_A = \dot{V}_E - \dot{V}_D$.

The type of dead space ($\dot{V}_D$) depends on the location of the volume not exchanged, either in the anatomic airways or in the alveolus. The anatomic dead space is equal to the volume of airways proximal to the terminal respiratory units. Approximately 25% of each tidal volume is lost in these conducting airways. The ultimate volume is dependent on body size and equals approximately 1 mL/lb.[31] This volume is divided almost equally between the upper and lower airways. An alveolar dead space is produced by all alveoli that are overventilated relative to their perfusion. Thus more gas is available then blood for diffusion. The physiologic dead space is usually expressed as a fraction of the tidal volume (V_D/V_T).

The alveolar ventilation is an important determinant of gas exchange because it, along with the rate at which tissue metabolism produces CO_2 ($\dot{V}_{CO2}$), determines the P_{CO_2} of arterial blood:

$$PCO_2 = \dot{V}_{CO\,2} / \dot{V}_A$$

When $\dot{V}_{CO2}$ is constant, P_{CO_2} varies inversely with $\dot{V}_A$. It is evident that at given minute ventilation, the P_{CO_2} will vary directly with the amount of physiologic dead space. As dead space changes, the P_{CO_2} can be kept constant only by increasing or decreasing $\dot{V}_E$ by an identical amount.

The measurement of dead space has evolved from the original description by Bohr in 1891 when dead space was considered simply the gas from the conducting airways. One can calculate the physiologic dead space as:

$$V_D/V_T = (Pa_{CO2} - P\dot{E}_{CO2})/Pa_{CO2}$$

where $P\dot{E}_{CO2}$ is end-tidal P_{CO_2}.

Diffusion of Oxygen and Carbon Dioxide

Gas must travel through a number of barriers between the alveolus and blood. These barriers include the alveolar epithelial lining, basement membrane, capillary endothelial lining, plasma, and the red blood cell. The amount of gas (Q) diffusing through a membrane is directly proportional to the surface area available for diffusion (S), the pressure difference for the gas on either side of the membrane (p1 – p2), and a constant (K) that depends on the solubility coefficient of the gas, membrane characteristics, and liquid used. This association is defined by the Fick principle of the diffusion state as follows:

$$Q/\min = K\lambda(p1 - p2)/d$$

where Q is inversely proportional to the distance it has to diffuse, whereas K is proportional to the solubility of the gas and inversely proportional to the square root of the molecular weight.

In healthy subjects at rest, equilibration of the P_{O_2} and P_{CO_2} of the alveolar gas and the pulmonary capillary blood is achieved in approximately 0.75 seconds.[32] This is about one third of the time spent by the blood in the capillary network. The rate of pulmonary blood flow can increased greatly, to the point that it prevents equilibration. For this reason, diffusion disequilibrium has been demonstrated in healthy persons, but only during strenuous exercise at high altitudes.

In the presence of parenchymal disease, diffusion impairment may occur solely as a result of thickening of the alveolar-capillary membrane. Much more commonly, however, diffusion disequilibrium is associated with destruction of the pulmonary capillary bed. This destruction results in a greatly increased blood flow velocity in the remaining capillaries, which may allow insufficient time for equilibration. Even when parenchymal disease is severe, however, diffusion disequilibrium usually occurs only when cardiac output, and therefore rate of flow, is markedly increased.

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Control of Breathing and Acute Respiratory Failure

Robert K. Kanter

PEARLS

- Powerful neural regulation of breathing maintains a constant supply of oxygen to the tissue, despite wide variations of metabolic rate and respiratory system disorders, until an advanced stage of respiratory failure is reached.
- Impaired controls of breathing may interfere with respiratory cycle timing, respiratory effort, or functional patency of the airway. In some cases a disorder of respiratory regulation may be the patient's primary problem. Other patients have secondary impairment of respiratory regulation as a result of acute or chronic systemic illness.
- Sick or injured patients usually hyperventilate in compensation for their stressful disorder. Stressed patients with irregular breathing or inappropriately comfortable effort to breathe have a severely depressed respiratory drive. In these cases, immediate ventilatory support usually is warranted.
- Respiratory depression or apnea may be the clue that an underlying systemic illness requires specific treatment.

Because of the brain's ability to regulate breathing, homeostasis normally is maintained with respect to oxygen, carbon dioxide, and pH despite the presence of serious cardiorespiratory or metabolic disorders. Derangements of respiratory controls may be the primary cause of acute respiratory failure or one of a number of multifactorial causes in a critically ill or injured patient. In other patients, disorders of respiratory regulation prolong dependence on mechanical ventilation.

Respiratory control disorders may be acute or chronic. Longstanding disorders of respiratory controls may be acquired or congenital. When the patient is apneic or has a very slow respiratory rate, the depression of respiratory controls is obvious to the clinician. Functional obstruction of the upper airway may be a clue that neural controls of breathing are impaired. However, many disorders of respiratory controls depress the intensity of respiratory motor neural activity in a more subtle way. Neural depression of breathing may be difficult to distinguish from hypoventilation because of peripheral neuromuscular disease or primary respiratory tract disorders. Recognition of respiratory control disorders may allow specific interventions or, when these disorders cannot be reversed, may enable close monitoring and timely administration of general supportive care, including mechanical ventilation.

This chapter will describe normal respiratory controls, how respiratory controls may fail, and a practical clinical approach to recognition of failed respiratory controls and intervention.

Normal Regulation of Breathing

Rhythmic discharges whose timing corresponds to inspiratory and expiratory phases are generated in motor neurons of the medulla oblongata.[1] During comfortable unstimulated breathing, inspiratory motor activity includes diaphragm flattening as well as a mild increase in pharyngeal muscle tone and vocal cord abduction that keep the upper airway patent during inspiratory airflow. When inspiratory muscles relax, resting expiration is passive, driven by elastic recoil of the lung and chest wall. The respiratory rate and motor intensity are modified by a variety of neural, chemical, and mechanical stimuli (Figure 38-1). With high-intensity stimulation, accessory muscles are activated, including intercostals and neck muscles. Nasal flaring occurs. Stimulated breathing also may include end-inspiratory vocal cord closure that acts to prolong lung inflation with little energy expenditure, clinically evident as grunting when the vocal cords open at the beginning of expiration. In highly stimulated breathing, abdominal muscles contract to force expiratory airflow.

Other normal respiratory control behaviors include periodic deep inspirations, sneezing, and coughing to maintain expansion of basal lung areas and clear secretions from the respiratory tract. Breathing is normally coordinated with swallowing and airway protective reflexes to prevent aspiration. Pharyngeal muscle tone is also adjusted with neck flexion and extension to maintain airway patency.

Hypoxemia is a powerful stimulus to ventilation mediated by sensory input originating in the carotid body chemoreceptor. Peripheral chemoreceptor activity and ventilation increase slightly as Pao_2 falls below 500 mm Hg. Ventilation rises steeply as Pao_2 falls below 50 mm Hg (Figure 38-2, *A*). Low oxygen tension, rather than low oxygen, content is the ventilatory stimulus. Little carotid body response results from profound anemia. Hydrogen ion concentration and carbon dioxide tension independently activate chemoreceptors in the carotid body and in the brainstem (Figure 38-2, *B*). The simultaneous presence of hypoxia augments the hypercapnic ventilatory response (Figure 38-2, *C*).

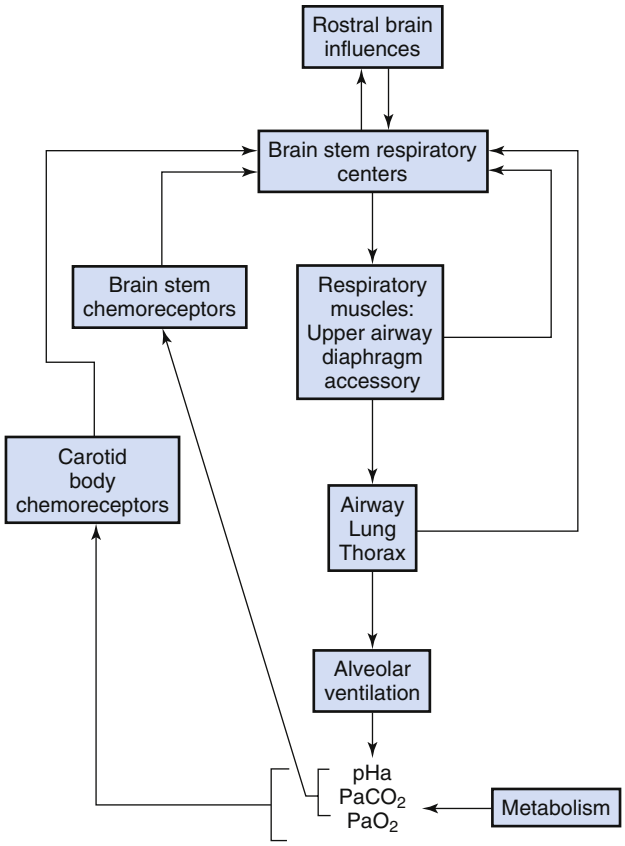

Figure 38–1. Elements of the respiratory control system.

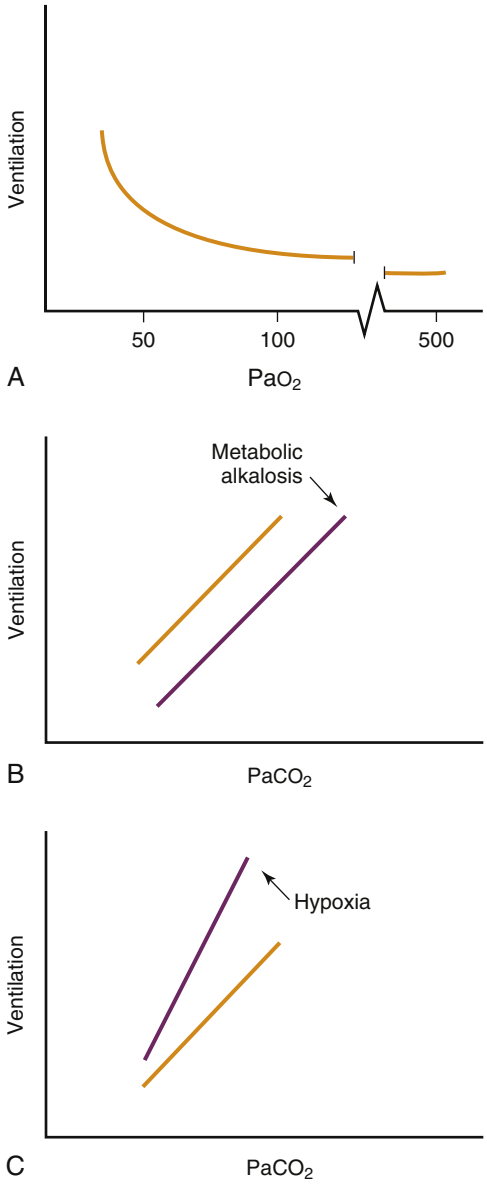

Figure 38–2. Chemoreceptor activity, as reflected by minute ventilation, varies as a function of Pao_2 (**A**), $Paco_2$ (**B**) (superimposed metabolic alkalosis inhibits breathing), and $Paco_2$ (**C**) (superimposed hypoxia stimulates breathing).

Mechanical loads on breathing influence respiratory efforts independent of chemical stimuli. Sensors for load-compensating reflexes are located in respiratory muscles and the chest wall. Reduction in lung volume also is detected by pulmonary stretch receptors. Afferent signals travel via the spinal cord, vagus nerves, and perhaps the phrenic nerves. Both conscious and reflex responses are involved in compensatory increases of effort, including the recruitment of accessory muscles in response to increased respiratory resistance or to a decrease in compliance. Stimulation to breathe is further augmented by hypercapnia or hypoxia when loaded breathing reduces ventilation. Respiratory compensation for mechanical loads accounts for the increased respiratory effort in patients who have normal blood gas tension despite acute lung disease. Dyspnea and anxiety may exacerbate the tendency to hyperventilate even without a chemical ventilatory stimulus.

Sleep modifies breathing, and compensation for respiratory illness is most likely to fail during sleep.[2] In some persons ventilatory responses to hypercapnia and hypoxia diminish during sleep. Sleep-induced reduction in upper airway tone and cough reflexes worsens the risk of obstruction and aspiration. In infants, whose thorax is compliant, awake lung volume is maintained by thoracic muscle tone and breathing at sufficiently high frequencies that expiration seldom reaches the passive resting lung volume. During sleep, inspiratory muscle tone diminishes and respiratory rate decreases, with resulting reduction in infants' expiratory lung volume. Infants' compensation for mechanical loads is compromised during the rapid eye movement stage of sleep more than during quiet sleep. Although sleep is a period of high risk for the sick infant, depriving the patient of sleep is counterproductive. Obstructive and central apnea are worsened by sleep deprivation in healthy infants.[3]

Genetic factors may account for some variation in respiratory regulation in a normal population,[4] but the clinical importance of this variation in predisposing individuals to acute respiratory failure is not clear. Although apnea is common in the premature infant, immaturity of respiratory controls does not otherwise appear to be a risk factor for respiratory failure in infant populations.

Failure of Respiratory Controls

Acute Disorders of Respiratory Controls

Patients with a critical illness or injury generally hyperventilate. At least some of the increased respiratory drive can be attributed to a higher metabolic rate. Pain, discomfort, and

fear also stimulate ventilation. When a stressed patient fails to hyperventilate, depressed respiratory controls and impending respiratory failure should be suspected.

Moderate brain injuries typically are associated with hyperventilation (Figure 38-3, *B*), whether the injury is traumatic, infectious, or hypoxic-ischemic. The hypermetabolic state, lung pathology, and loss of inhibitory cortical influences probably combine to augment ventilation. Even when the brain-injured patient does hyperventilate, airway protective reflexes usually are impaired, seizures may ensue, and subtle progression of the brain lesion may lead to hypoventilation (Figure 38-3, *A, C to E*). Resulting hypoxia may exacerbate the brain injury.

Seizures impair breathing in various ways. Apnea or slowing of respiratory rate, impairment of upper airway protective reflexes, and poor inspiratory effort are common. The clinician must have a high index of suspicion to recognize occult seizures. The seizure-induced respiratory depression may be difficult to distinguish from the brain pathology that may have caused the seizure, as well as the respiratory-depressing effects of anticonvulsant medications.

Respiratory depression by analgesic drugs, sedative agents, anticonvulsant medications, and anesthetic drugs is common. Opiates, benzodiazepines, barbiturates, and propofol all have respiratory-depressing effects. Relative effects on upper airway patency and hypoxic, hypercapnic, and loading responses may be dissociated. For example, Chloral hydrate has little effect on chemosensitivity but reduces genioglossus muscle tone and predisposes to obstructive apnea. Concern regarding respiratory depression does not warrant withholding analgesia. Rather, monitoring should be appropriate. In fact, episodic hypoxia during treatment procedures may be reduced when appropriate analgesia is provided.[5] Sedative agents and analgesic drugs that are rapidly cleared after a single dose may have a more prolonged duration of action when given repeatedly or continuously. Clearance rates for medications may vary with systemic disease, immaturity, or genetic factors. Sedation and analgesic-induced respiratory depression may prolong the need for mechanical ventilation. Substituting an agent that clears rapidly (such as remifentanil) for longer acting agents several hours before a planned extubation may facilitate weaning from mechanical ventilation. Dexmedetomidine, an α_2 adrenergic agonist, may provide sedation with less respiratory depression than other agents.

Opioid-induced respiratory depression can be reversed with naloxone. In patients with cardiovascular compromise (e.g., those who have had cardiac surgery), naloxone should be avoided in the immediate postoperative period because the stress of abruptly eliminating opioid anesthesia would be hazardous. In the patient with multiple chronic drug ingestions, naloxone may induce vomiting without improving airway protective reflexes, predisposing the patient to aspiration. The benzodiazepine antagonist flumazenil reduces the respiratory depression that results from taking benzodiazepines, but little pediatric experience with this agent has been reported. Flumazenil lowers the threshold for seizures and may cause a more hazardous condition than the initial respiratory depression. The duration of action of antagonists may be shorter than the agent that is depressing breathing. Close monitoring of the patient is essential, and repeated doses of antagonists may be necessary. In other cases of drug-induced respiratory depression, mechanical ventilation provides greater safety than do pharmacologic antagonists. This is the case with multifactorial central depression or in severely ill patients.

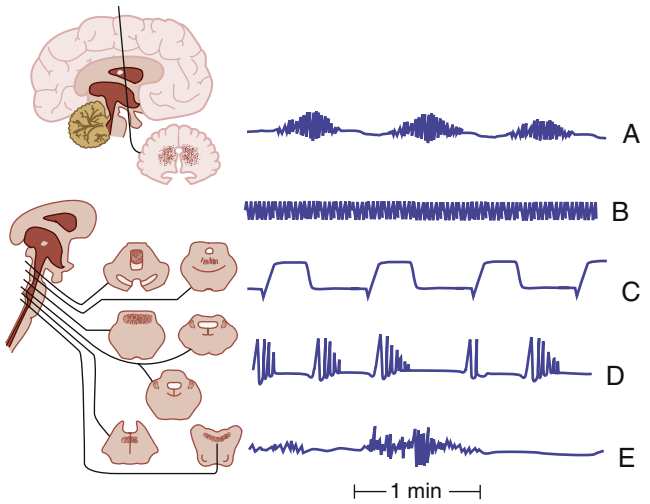

Figure 38–3. Abnormal respiratory patterns associated with lesions (shaded areas) at various levels of the brain. Inspiration reads up. **A,** Cheyne-Stokes respiration. **B,** Central neurogenic hyperventilation. **C,** Apneusis. **D,** Cluster breathing. **E,** Ataxic breathing. *(Modified from Plum F, Posner JB:* The diagnosis of stupor and coma, *ed 3, Philadelphia, 1980, FA Davis.)*

Other medications may depress breathing without alteration of consciousness. For example, prostaglandin E_1, which is given to maintain patency of the ductus arteriosus in infants with congenital heart disease, is frequently associated with respiratory depression.[6]

The respiratory inhibitory action of metabolic alkalosis may account for hypoventilation. The impact of alkalosis on breathing in sick children has not been systematically studied but may contribute to prolonged dependence on mechanical ventilation in children receiving chronic doses of diuretic agents. When metabolic alkalosis accompanies prolonged recovery from respiratory failure, correction of the alkalosis with potassium chloride and occasionally acetazolamide may promote ventilator weaning.

In the advanced stages of respiratory failure, the vigorous respiratory effort of the dyspneic patient may become counterproductive. Agitation increases oxygen consumption, and forced respiratory efforts may cause dynamic obstruction of airways. Dynamic airway obstruction in the dyspneic child may account for rapid progression of respiratory failure in some cases.

As the severely dyspneic patient decompensates, exhausted efforts may rapidly give way to periodic breathing and apnea. While this phenomenon is commonly observed in infants with lower respiratory infections[7] and pertussis,[8] observations in adults with near-fatal asthma reveal a similar tendency for respiratory arrest to precede cardiovascular collapse.[9] The mechanism of this preterminal respiratory depression is not well understood, but it appears to occur in some patients prior to the development of hypoxia and hypercapnia.

Acute Life-Threatening Events

Patients may be admitted to the pediatric intensive care unit for observation after an apparent life-threatening event (ALTE) in which caregivers perceived the need to stimulate

an infant during a sudden episode of irregular breathing or apnea, cyanosis, pallor, altered level of consciousness, or hypotonia. When the history or physical examination suggests a specific cause, diagnostic confirmation is warranted. Confirmatory studies may include a blood cell count and chemistries; screening for respiratory, bloodstream, urinary, or central nervous system infection; metabolic screening; screening for gastroesophageal reflux; a chest radiograph; brain neuroimaging; a skeletal survey; an electroencephalogram; or an echocardiogram. Studies that sometimes reveal the cause when history and physical examination are nonspecific include screening for urinary infection, brain neuroimaging, screening for gastroesophageal reflux, a chest radiograph, and a white blood cell count. In one series of patients with ALTE, 33% had infections, 28% had gastrointestinal problems, 13% had neurological disorders, 3% had airway causes, 3% had other congenital problems, 4% had other noncongenital problems, and for 16%, the cause was unknown.[10] See Box 38-1 for causes of apnea requiring specific therapy. In one sample, infants with ALTE who were more likely to have another subsequent severe event tended to be younger than 43 weeks' postconceptional age, premature, and had an upper respiratory infection.[11] The epidemiological characteristics of infants with ALTE differ from those who experience Sudden Infant Death Syndrome (SIDS). ALTE and SIDS should be regarded as distinct entities.[12] The causes and strategies to prevent SIDS continue to be an active area of investigation.

Box 38–1 Systemic Causes of Apnea that Require Specific Therapy

Central Nervous System
- Head injury, child abuse
- Seizure
- Meningitis, encephalitis
- Hydrocephalus
- Posterior fossa mass

Circulation
- Dysrhythmia
- Congestive heart failure

Infection
- Sepsis

Gastrointestinal
- Gastroesophageal reflux

Metabolic
- Poisons
- Hypoglycemia
- Many inborn errors of metabolism

Chronic Disorders of Respiratory Controls

Congenital or long-standing acquired disorders of the central nervous system may impair respiratory centers, leading to respiratory failure. Acute respiratory insufficiency may accompany progression of a central lesion. A static regulatory impairment may be revealed by failure to compensate for acute systemic illness. Primary disorders of respiratory controls may present with the following symptoms: impaired respiratory cycle generation (central apnea), deficient responses to respiratory stimuli (hypoventilation during stress and failure to arouse from sleep hypoxia), or inadequate motor control of the vocal cords or pharynx (stertor, stridor, poor swallowing, or obstructive apnea). These patterns of regulatory dysfunction may occur individually or in combination. Respiratory compromise usually is worst during sleep. Sedating medications may have an exaggerated impact on patients with primary disorders of respiratory controls. Pulmonary hypertension as a result of recurrent hypoxia, or aspiration pneumonia associated with impaired airway protective reflexes, complicate the clinical situation in some cases.

Structural Brain Disorders

Recognition of structural brain lesions as the cause of impaired respiratory regulation is important because some of the lesions are correctable. Congenital structural neurologic malformations may manifest as apnea or profound hypoventilation at birth or may be recognized later if respiratory impairment is mild. In particular, patients with Arnold-Chiari malformation often have central and obstructive sleep apnea. Surgical decompression may be associated with improvement[13] even when performed in adults.[14] Acquired lesions such as posterior fossa tumors may interfere with respiratory regulation before or after[15] surgical resection.

Nonstructural Congenital Disorders

Some genetic conditions are associated with derangements in regulation of breathing. Children with congenital central hypoventilation syndrome[16] have characteristic mutations in the *PHOX2B* gene. These patients may first come to medical attention because of growth failure, neurodevelopmental disabilities, or cor pulmonale. Abnormalities include autonomic dysfunction and cardiovascular instability as well as impaired controls of breathing. The syndrome may be recognized in the newborn period, later in childhood, and occasionally in adults. Sleep hypoventilation predominates in persons with congenital central hypoventilation syndrome, although some patients also experience respiratory insufficiency while awake. The disorder often is fatal without mechanical ventilation. Early mechanical ventilation may reduce the sequelae and improve long-term neurodevelopmental outcome.

Prader-Willi syndrome is a multigenic disorder initially presenting with hypotonia and then with progressive obesity, growth failure, neurodevelopmental disabilities, reduced ventilatory response to hypoxia and hypercapnia, sleep hypoventilation, and apnea.[17]

Rett syndrome is an X-linked disorder affecting development, behavior, and autonomic and respiratory regulation. Many patients with Rett syndrome have seizures. Abnormalities often are present in the *MECP2* gene, although some patients with characteristic clinical features have other genetic findings.[18] Multiple phenotypes exist in regard to the respiratory control disorder, with hyperventilation, hypoventilation, and apneustic breathing seen in subgroups.[19]

Many other genetic syndromes with severe neurological manifestations have impaired upper airway motor function, respiratory cycle timing, and respiratory effort nonspecifically associated with their brain disorder. Nongenetic congenital

disorders may impair respiratory controls. For example, children with cerebral palsy occasionally have neurologic deficits of pharyngeal tone, although the central drive to breathe usually is intact.

Nonstructural Acquired Chronic Disorders

Some patients with severe chronic respiratory disease have blunted ventilatory responses to hypoxia, hypercapnia, or respiratory mechanical loads. A concern regarding supplemental oxygen is sometimes raised in the care of patients with acute exacerbations of chronic respiratory disease. It is sometimes argued that administration of supplemental oxygen causes respiratory failure in patients with chronic CO_2 insensitivity who might depend on hypoxic drive to breathe. Of greater concern are the adverse effects of hypoxia. Because the hypoxic drive to breathe only increases substantially at oxygen tension below 50 mm Hg (see Figure 38-2, *A*), it is virtually impossible to maintain stable respiratory stimulation with mild and "safe" hypoxia without risking episodic life-threatening hypoxia. If a patient is so poorly compensated that removal of hypoxic drive results in hypoventilation, then mechanical ventilation may be the safest management strategy, unless end-of-life plans specifically exclude mechanical ventilation.

Obesity causes hypoventilation by a complex interaction of factors including mechanical loads on the respiratory system, reduction of lung volume, upper airway obstruction, and impaired respiratory regulation.[20] In obese patients, weight loss often improves hypoventilation.

Apparently healthy preterm infants may have postanesthetic apnea until the age of 60 weeks' postconceptional age.[21,22] Apneic events occurred within 2 hours of surgery in 72% of patients, but in the remainder, respiratory irregularity began as late as 12 hours postoperatively. Both obstructive and central mechanisms of apnea were observed. Continuous monitoring for at least 12 hours after anesthesia is warranted when surgery is required for infants born prematurely who are still younger than 60 weeks' postconceptional age.

Sleep hypoventilation tends to occur in adults with hypothyroidism and diabetes mellitus.[23] Little information is available regarding the pediatric patient or the specific role of the endocrine disorder versus obesity.

Recognition and Treatment

The Deteriorating Patient

In a patient who is sick and stressed, hyperventilation is the typical compensatory response for physiological derangements, with increased respiratory frequency and obvious use of accessory muscles of breathing. The clinician should recognize thoracic retraction, grunting respiratory sounds, nasal flaring, head bobbing, and active use of expiratory abdominal muscles as signs of increased respiratory drive.

Controls of upper airway patency and protective reflexes should be assumed to be absent in the comatose patient or the critically ill drowsy patient with stertor (i.e., snoring sounds of pharyngeal obstruction). Prompt efforts to secure the airway may avert aspiration and obstruction.

If time allows, arterial blood gas analysis may confirm suspicion of hypoventilation in a crisis. If moderate respiratory effort and hypocapnia ($Paco_2$ <35 mm Hg) accompany an acute respiratory disorder, it can be inferred that ventilatory drive is (at least temporarily) sufficient and alveolar ventilation relative to CO_2 production is satisfactory. If $Paco_2$ exceeds 40 to 45 mm Hg in a patient with an acute respiratory disorder, then lung function, the respiratory pump, or the drive to breathe is compromised. This scenario may represent a rapidly worsening trend. Close monitoring is essential, and immediate intervention may be warranted. In a sick, stressed patient with irregular breathing or inappropriately slow comfortable respiratory effort, respiratory drive is probably severely impaired, and arterial blood gas analysis is unnecessary. Immediate airway protection and ventilatory support usually is indicated.

Evaluation of patients during respiratory decompensation often is limited by their rapidly evolving state. Given the safety and effectiveness of endotracheal intubation and mechanical ventilation, support should be initiated promptly when there is substantial suspicion concerning impaired regulation of breathing in the critically ill patient. Apnea may suggest the presence of a systemic disorder requiring specific treatment (Box 38-1).

Evaluation During Recovery

Impairment of respiratory controls may contribute to prolonged dependence on mechanical ventilation during recovery from critical illness. In contrast to the limited evaluation of respiratory controls in patients during respiratory emergencies, careful study of specific ventilatory responses is feasible and may be warranted in the patient with slow recovery from respiratory failure.

Coordination of the upper airway is assessed by testing the gag reflex. If the gag reflex is vigorous in the alert patient, upper airway control will seldom be a limiting factor in the patient's recovery.

In attempting to decide whether to discontinue mechanical ventilation and remove an endotracheal tube, a trial of unassisted spontaneous breathing with the endotracheal tube still in place provides important insights. Continuous positive airway pressure may be maintained to avoid loss of functional residual capacity during the trial. Once $Paco_2$ exceeds the apneic threshold of 30 to 35 mm Hg, respiration should become regular and comfortable without apnea. $Paco_2$ less than 45 mm Hg, pH greater than 7.35, and safe oxygenation with a comfortable effort suggest that drive and other components of the respiratory system are adequate to withdraw mechanical ventilation.

If tachypnea develops or the patient breathes laboriously or complains of dyspnea, respiratory tract disease or impaired respiratory muscle strength probably is a limiting factor. Failure to cough, to at least double resting tidal volume, and to generate peak inspiratory negative pressures of at least 30 cmH_2O all suggest that respiratory muscle strength is inadequate to accomplish the necessary work of breathing. When pulmonary disease and muscle weakness are present, independent evaluation of respiratory drive is difficult.

Finally, some patients fail to increase effort despite hypercapnia and hypoxia during the trial of spontaneous breathing. Others lack a gag response. In these cases, obvious deficiency of neural controls of breathing contributes to persistence of their respiratory insufficiency.

Measuring Respiratory Drive

Except for observation of breathing pattern and rate, respiratory neural output cannot be directly measured. Interpreting baseline ventilation as a measure of the intensity of drive to breathe is confounded by dependence of ventilation on muscle weakness, respiratory system compliance, and resistance, as well as intensity of respiratory neural motor output.

However, useful and clinically feasible measurements of respiratory drive are possible. Whatever the baseline ventilation, an increase in ventilation in response to hypercapnia is evidence of at least partially intact chemosensitivity.[24,25] The pressure generated at the airway in the first 0.1 seconds of inspiration against an occluded airway (P0.1) parallels experimental direct measures of respiratory center output. Increase in P0.1 with hypercapnia indicates at least partially intact chemosensitivity. In one study, augmented P0.1 response to hypercapnia was associated with more successful extubation in a group of patients with brainstem tumors who were at risk for depressed respiratory controls.[26] These techniques are feasible for application in the pediatric critical care population, but published data are not available.

Therapy Related to Respiratory Controls

Patients with known disorders of respiratory controls should be monitored continuously during periods of severe stress and especially during sleep. Mechanical ventilation may be necessary after anesthesia and should be initiated when hypoventilation poses a substantial threat.

When tonsillar or adenoidal hypertrophy contributes to hypoventilation, surgical removal may improve ventilation. However, underlying neurological deficits of pharyngeal motor control often persist despite tonsillectomy and adenoidectomy. Noninvasive mask positive pressure may relieve upper airway obstruction resulting from pharyngeal motor dysfunction. In some cases, a tracheostomy tube may be warranted to bypass intractable upper airway obstruction in a patient with neurological motor deficits. In other cases, relief of upper airway obstruction will eliminate the need for mechanical ventilation.

Although theophylline and doxapram have been successful in alleviating apnea of prematurity, there is little evidence for the effectiveness of respiratory-stimulating drugs in other pediatric critical care applications. If a trial of respiratory stimulant therapy is used in a patient with a life-threatening disorder of respiratory regulation, such therapeutic trials should be undertaken with close observation.

Long-term management of uncorrectable disorders of respiratory controls may include home apnea monitors, positive or negative pressure ventilation, and diaphragm pacing.

References are available online at http://www.expertconsult.com.

Assessment and Monitoring of Respiratory Function

Emily L. Dobyns

PEARLS

- Clinical assessment of respiratory function remains invaluable in the diagnosis and management of patients with respiratory failure.
- Initial evaluation should include assessment of child's comfort and activity level and observation of child's body position, respiratory pattern, and body habitus.
- Chest x-ray films can be used to identify cardiac, vascular, bone, and lung abnormalities and to assess device placement (i.e., endotracheal tube) and the need for intervention.
- Chest computed tomography guidance can be used to drain fluid collections and obtain biopsies.
- Simple observation of the ventilator displays of an intubated patient undergoing ventilation with use of a microprocessor-equipped ventilator provides information about the respiratory mechanics of the patient.
- Flexible bronchoscopy is used to evaluate the size, patency, and compression of the airway during respiration, to evaluate the anatomy/structure of the airway, and for removing or obtaining secretions from the lung.
- Rigid bronchoscopy is used for better evaluation of vocal cord paralysis, laryngeoesophageal clefts, and H-type tracheoesophageal fistulas. Removal of foreign bodies is performed more easily and safely with a rigid bronchoscope.

The majority of children admitted to the pediatric intensive care unit (PICU) present with cardiorespiratory disease or with an acute illness that may progress to involve the respiratory system, emphasizing the need for careful monitoring of respiratory parameters. Close respiratory examination and monitoring allow titration of therapies to minimize ventilator-induced injury, optimize patient-ventilator interaction, and aid in weaning from the ventilator.[1]

Physical Examination of the Respiratory System

Clinical assessment of respiratory function remains invaluable in the diagnosis and management of patients with respiratory failure despite all the technologic advances that have occurred in monitoring. Initial evaluation begins with assessment of the child's comfort and activity level. Coexisting nonpulmonary conditions such as pain and anxiety may make this assessment difficult. Observation of the child's body position, respiratory pattern, and body habitus provides important information as to his or her level of respiratory distress.

Often children in respiratory distress assume a body position that helps them breathe more comfortably. This position may be splinting of the chest in a patient with pneumonia or assuming the "sniffing position" to maintain an open airway in a child with an upper airway obstruction. An infant is less independent and therefore often is held in position by his or her caregivers, irrespective of comfort.

The respiratory pattern provides information regarding the work of breathing in a distressed child. The respiratory rate varies with age, but an early sign of distress is tachypnea. Additional signs of increased work of breathing include grunting or irregular respirations, nasal flaring, use of accessory muscles of respiration (strap muscles of the neck), and retractions.

Inspection of the shape of the chest wall may reveal abnormalities that affect pulmonary function. Increased anteroposterior diameter can be seen in conditions associated with hyperinflation (e.g., asthma or cystic fibrosis). Scoliosis in severe cases can cause a reduction in lung volume. Neuromuscular disorders may be associated with an "A-shaped" chest and lung hypoplasia/dysplasia. Thoracic asymmetry may be associated with neuromuscular or skeletal deformities, pneumothorax, or a paralyzed diaphragm. Fingers and toes should be examined for evidence of clubbing (painless enlargement of the connective tissues of the distal phalanges), which is nonspecific but may be indicative of chronic hypoxemia. Growth parameters and neurodevelopment should be obtained and compared with age-appropriate normal subjects to assist in evaluation of long-standing or associated diseases.

Detection of cyanosis centrally (lips, tongue) or peripherally (nail beds) may be difficult. Arterial oxygen tension must drop below 80 mm Hg before cyanosis can be detected clinically. Cyanosis may be absent in patients with severe anemia or missed when lighting is poor. It also may be intermittent and be seen only with exercise or change in position. Cyanosis that does not resolve with oxygen therapy may indicate right-to-left shunting of blood in the lungs or heart or the formation of methemoglobin or sulfhemoglobin following the ingestion of certain drugs.

Evaluation of breath sounds provides assessment of airflow through the tracheobronchial tree, the presence of fluid in or

obstruction of the airways, and conditions outside the lung and pleural space. The child's chest wall is thinner than that of the adult, which allows better access to breath sounds but impedes localization of the lesion because the breath sounds can be referred. Upper airway abnormalities may present with stridor or muffling of the voice. Bronchial breath sounds suggest consolidation, whereas wheezes result from narrowed airways. Crackles may be fine or coarse. They represent air bubbling through secretions and the reopening of closed airways. A friction rub may be heard when the inflamed surfaces of the pleura move against each other through the respiratory cycle. Breath sounds may be absent if there is a significant pleural effusion or complete lobar collapse resulting from a mucus plug or pneumothorax. Heart tones often are shifted away from the pneumothorax and toward the atelectasis because of complete airway obstruction. Assessment for pulsus paradoxus (i.e., exaggerated decrease in the pulse or systolic blood pressure with inspiration) should be made during the evaluation of severe airway obstruction or pulmonary embolus.

Although each assessment should include observation and a limited physical examination, it is recognized that interobserver repeatability of physical signs is poor and independent of the experience of the observer.[2] The assessments of clubbing, wheezes, friction rub, and crackles are the most reliable and reproducible.[2,3] The lack of accuracy of repeated physical examinations and the complexity of critically ill pediatric patients require adjunctive tests/assessments to monitor these patients.

Radiography

Portable chest x-ray films are the most common films taken in the PICU. The technical quality of the chest radiograph affects the interpretation; therefore, it is important to assess the film for adequacy of penetration, degree and symmetry of lung inflation, and degree of chest rotation. Chest x-ray films can be used to evaluate for cardiac, vascular, bone, and lung abnormalities, to assess for device placement (e.g., an endotracheal tube), and to determine the need for intervention.[4] Lateral decubitus films help identify and quantify pleural effusions, pneumothorax, and the position of chest tubes/lines. Cross-table lateral films also may be used for these purposes but are harder to interpret. A chest computed tomography (CT) scan is used when details on the plain film are obscured by the superimposition of structures or an opaque hemithorax. A chest CT scan also can be used to guide drainage of fluid collections and assist in obtaining biopsy specimens. A high-resolution chest CT scan examines 1- to 1.5-mm slices at 10-mm intervals; therefore it can be used to illustrate lung parenchymal details better than a conventional CT scan, which examines 7- to 10-mm slices at 10-mm intervals.[5] This detail can be helpful in distinguishing the pathologic process causing diffuse lung diseases that appear as diffuse lung shadowing on chest x-ray films. Chest ultrasound, ventilation/perfusion scanning, spiral CT, and magnetic resonance imaging may be useful adjutants depending on the disease process.

Evaluation of Gas Exchange

Episodic hypoxemia is common in critically ill adults and has been associated with increased mortality. The frequency and impact of episodic hypoxemia in pediatrics has not been studied. Additionally, whether monitoring and early treatment of episodic hypoxemia will improve patient outcome remains unanswered, but continuous monitoring of oxygen saturation in the PICU has become the standard of care.

Noninvasive Respiratory Monitoring

Transcutaneous Oxygen and Carbon Dioxide Monitoring

Transcutaneous measurements reflect both gas exchange and skin perfusion. In this technique, a probe composed of a heater, an electrode, and a thermistor is applied to the patient's skin. The skin is warmed and softened to improve diffusion and permeability. This step also causes capillaries to dilate, resulting in better approximation of arterial oxygen values. Several disadvantages limit the use of transcutaneous monitoring to the newborn population. Skin thickness increases with age, making transcutaneous measurements less predictable. Frequent electrode site changes are required to prevent local burns. Relatively frequent calibration and comparison with arterial blood gases are necessary. Because of these limitations and the ease of application of pulse oximetry and end-tidal carbon dioxide monitoring, transcutaneous monitoring has nearly been replaced by other monitoring methods.

Pulse Oximetry

Pulse oximetry is considered a significant technologic advance that has improved patient safety.[1,6-9] Its ease of application and accuracy have resulted in widespread use. Pulse oximetry is commonly used to detect hypoxemia and to wean the oxygen concentration in patients undergoing mechanical ventilation.

Pulse oximetry is based on the principles that (1) the pulsatile absorbance detected is arterial blood and (2) oxyhemoglobin and reduced hemoglobin have different absorption spectra.[6] Red (660-nm) and infrared (940-nm) wavelengths of light are used to determine the ratio of oxygenated to deoxygenated blood. Deoxygenated blood absorbs more red light, whereas oxygenated blood absorbs more infrared light. The two wavelengths are passed through an arterial bed, and the ratio of infrared and red light transmitted to the photodetector is determined. The ratio is calibrated against measurements of arterial oxygen saturations from human volunteers and their absorbance ratios.

Several factors may affect the accuracy of pulse oximetry. Pulse oximetry measures oxygen saturation (Sao_2). Sao_2 and Pao_2 are not linearly related; the oxyhemoglobin dissociation curve is sigmoid in shape (Figure 39-1). Large changes in Pao_2 at high levels of oxygen, the upper flat portion of the oxyhemoglobin dissociation curve, may occur with little change in saturation. Additionally, a reduction in oxygenation on the steep portion of the curve may not be appreciated as significant because only a small change in saturations will have occurred.[6,7] The accuracy of pulse oximetry falls with arterial oxygen saturations less than 70%.[1,6] At arterial oxygen saturations below 70%, pulse oximetry may be more appropriate for showing trends.[6]

Abnormal hemoglobin levels (carboxyhemoglobin, methemoglobin) that have similar absorbance spectra can lead to overestimation of the true Sao_2.[6] Intravenous dyes and certain colors of nail polish may falsely lower pulse oximetry readings.

Pulse oximetry sensors may be unable to distinguish a true signal from background in low perfusion states that result in diminished pulsations (e.g., vasoconstriction, low cardiac output, and hypothermia). This situation usually is displayed as an inadequate pulse message.[1] Low peripheral perfusion and motion artifact are the most common causes of inaccurate pulse oximetry readings.[9-11] Newer designs of pulse oximeters with signal-progressing algorithms that detect and ignore motion and pulse rate interferences may overcome these limitations.[10,11]

The complications of pulse oximetry are rare. They include skin burns and pressure necrosis in newborns.[1,6] Limited understanding of pulse oximetry by health care providers may be an underrecognized problem, along with time spent determining whether alarms are false.[9,12]

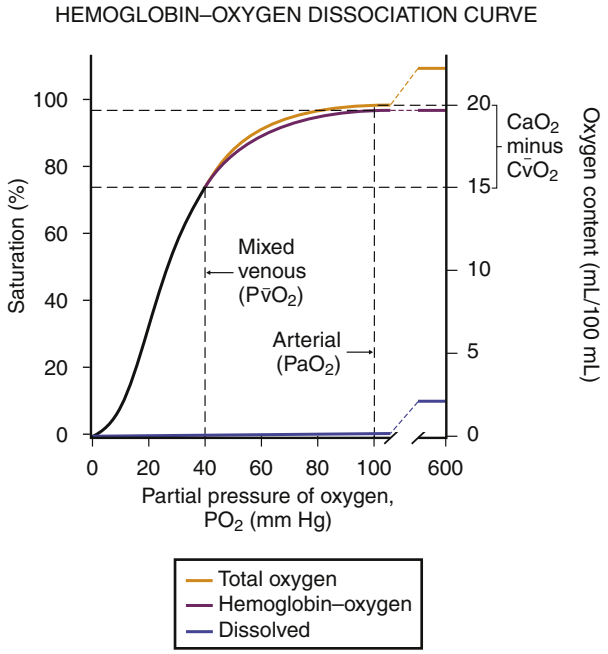

Figure 39–1. Hemoglobin-oxygen ($Hb\text{-}O_2$) dissociation curve shows the percentage saturation of hemoglobin at each P_{O_2}. When the hemoglobin concentration is known, the content of oxygen can be calculated. The total content includes the small additional content of oxygen in solution, which becomes significant at high levels of P_{O_2}. The saturation scale on the *left* applies only to the $Hb\text{-}O_2$ line. The scale on the *right* shows content values for a normal hemoglobin level of 15 g/100 mL blood. *(Modified from Hlastala MP: Blood gas transport. In Culver BH, editor:* The respiratory system, *Seattle, 1997, ASUW Publications. Redrawn in Albert RK, Spiro SG, Jett R, editors:* Clinical respiratory medicine, *ed 2, St. Louis, 2004, Mosby Elsevier.)*

Capnography

End-tidal carbon dioxide monitoring is the noninvasive measurement of exhaled carbon dioxide at the plateau of the carbon dioxide waveform (Figure 39-2). End-tidal carbon dioxide concentration reflects $Paco_2$, cardiac output, percentage of dead space, and airway time constants. In healthy subjects, the end-tidal carbon dioxide concentration is 1 to 5 mm Hg less than the $Paco_2$.[13] End-tidal carbon dioxide concentration represents the Pco_2 of all ventilated alveoli, whether or not they are perfused. Therefore any condition that reduces pulmonary perfusion of ventilated alveoli increases the difference between $Paco_2$ and end-tidal carbon dioxide. Comparison between end-tidal carbon dioxide concentration and $Paco_2$ helps to differentiate between change in alveolar ventilation, CO_2 production, or pulmonary perfusion as a cause of the change in end-tidal carbon dioxide concentration. Additionally, end-tidal carbon dioxide monitoring can be used to verify tracheal intubation, detect complete airway obstruction, and monitor ventilation during sedation.[13-16]

Sampling of exhaled carbon dioxide can be at the patient-ventilator interface (mainstream), diverted to a monitor (sidestream), or an intermediate connection.[16] The exhaled gas sample is exposed to various wavelengths of infrared light. The relative amount of light absorbed by the exhaled sample is compared with the amount of light absorbed by a sample that does not contain carbon dioxide. The difference between the

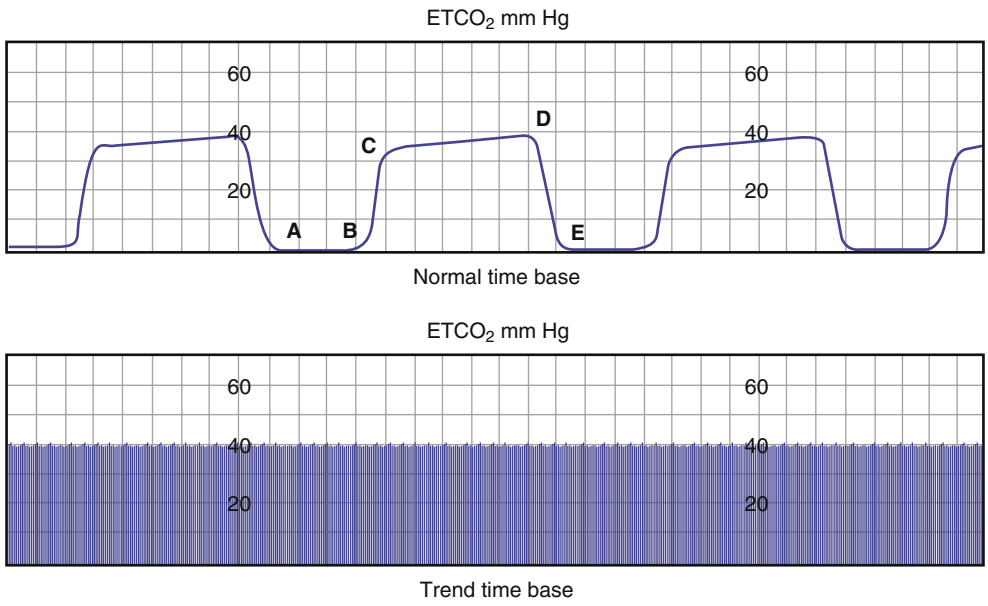

Figure 39–2. Normal capnograph. *A* to *B* is dead space, *B* to *C* is start of expiration (mix of dead space and alveolar gas), *C* to *D* is the alveolar plateau with point *D* representing the end-tidal value, and *D* to *E* is the start of inhalation.

two samples is the concentration of carbon dioxide. Carbon dioxide also can be measured semiquantitatively using a pH-sensitive indicator that changes from purple to yellow when exposed to carbon dioxide.[14]

Arterial Blood Gas Monitoring

Intermittent samples of arterial blood can be obtained from a single arterial puncture or an indwelling arterial line. Although convenient and frequently used, they offer isolated data points of continuous physiologic changes. Because of limitations such as the spontaneous variability in patients over time, the fact that blood gas is often obtained after an event has occurred, and the significant amount of lag time in therapeutic decisions that may ensue, interest in the development and use of continuous arterial blood gas monitoring exists.[17]

Evaluation of arterial blood gas provides information on the uptake of oxygen and disposal of carbon dioxide by the lung. In diseased lungs, additional information may be necessary to better understand and treat problems with gas exchange. Therefore indexes of oxygenation have been developed that use the data obtained from a blood gas to better define the efficiency of gas exchange and the causes of hypoxemia.

Venous blood that enters the arterial system without participating in gas exchange is termed "shunt." Shunt flow may be intrapulmonary or extrapulmonary. Intrapulmonary shunt occurs when alveoli are being perfused but there is no inspired alveolar ventilation because the alveolus is collapsed or filled with fluid. Extrapulmonary shunting occurs when there is drainage of venous blood into the postcapillary pulmonary circulation through either anomalous (intracardiac right to left shunts) or normal (thebesian and bronchial veins) pathways. Approximately 3% of cardiac output is shunted in a healthy individual. Most shunt flow is intrapulmonary in persons with pulmonary disease. The magnitude of the shunt can be calculated by using the following equation:

$$\frac{Q_s}{Q_t} = \frac{Cc_{O_2} - Ca_{O_2}}{Cc_{O_2} - Cv_{O_2}}$$

where Q_s is shunt, Q_t is total flow, Cc_{O_2} is pulmonary capillary oxygen content, Ca_{O_2} is arterial oxygen content, and Cv_{O_2} is mixed venous oxygen content. Applying this equation requires measurement of a mixed venous sample collected from the right ventricle or the pulmonary outflow track (i.e., placement of a pulmonary artery catheter). This equation does not identify the site or cause of the shunt.

Calculation of the alveolar-arterial oxygen tension difference ($AaD_{O_2} = PA_{O_2} - Pa_{O_2}$) helps to differentiate hypoxemia caused by hypoventilation from diffusion abnormalities, ventilation/perfusion (V/Q) mismatch, or shunt. It has the advantage of not requiring mixed venous blood sampling, but it does require alveolar $P_{A O_2}$, which is difficult to measure. Instead of direct measurement, $P_{A O_2}$ is approximated to be equal to $PA_{O_2} \sim P_{I O_2} - Pa_{CO_2}/R$, where $P_{I O_2}$ is partial pressure of inspired oxygen, Pa_{CO_2} is partial pressure of arterial carbon dioxide, and R is respiratory exchange ratio (generally assumed to be 0.8). Normally, $A_{aD O_2}$ is less than 10 mm Hg. $A_{aD O_2}$ tends to change with age and increasing fraction of inspired oxygen, and it may vary unpredictably with V/Q inequality.[18-20]

The easiest index to calculate is the arterial inspired oxygen concentration ratio ($Pa_{O_2}/F_{I O_2}$). It has been used as the basis for the definition of acute lung injury/acute respiratory distress syndrome (ALI/ARDS). One of the disadvantages of the $Pa_{O_2}/F_{I O_2}$ ratio is that it changes as a function of $F_{I O_2}$, raising the concern that it is not a precise enough measure to be used to define ALI/ARDS. That said, it remains an integral part of the ALI/ARDS definition for now.[18,20]

Respiratory Mechanics

Institution of mechanical ventilation in a patient with acute respiratory failure may result in improvement and even normalization of blood gases and measures of ventilation without improving the underlying disease process. Assessment of respiratory mechanics can provide information on the status and progression of the disease process and information that is useful for minimizing ventilator-induced lung injury.

The development of microprocessor-equipped ventilators has simplified the measurement of respiratory mechanics.[21] Simple observation of the displays of an intubated patient who is undergoing ventilation with a microprocessor-equipped ventilator provides significant information about the respiratory mechanics of the patient. Failure of expiratory flow to fall to zero (on the flow-time trace) before the onset of inspiration is the hallmark of breath-stacking, also termed autoPEEP. Inability of the patient to trigger the ventilator can be seen as "bumps" during expiration.

The simple maneuver of a rapid airway occlusion using the ventilator buttons can provide further information. The end-expiratory occlusion gives a direct measure of autoPEEP once a plateau in the airway pressure is reached.[21] The occlusion of the airway at end-inspiration for 5 seconds will measure the inspiratory plateau pressure, which approximates alveolar pressure. The risk of barotrauma is thought to increase at inspiratory plateau pressures greater than 35 cm H_2O. The inspiratory plateau pressure also can be used to calculate the static compliance. Static compliance is the change in volume over the pressure change when flow has stopped in the airways and lung, measured as plateau pressure. Therefore the calculation of static compliance is

$$C_{static} = V_t / (Pinsp_{Plateau} - PEEP)$$

where V_t is tidal volume and *PEEP* is positive end-expiratory pressure. Dynamic compliance is the change in volume divided by the change in pressure when flow in the upper airway is zero but flow continues in the lung. It can be calculated at the bedside as

$$C_{dyn} = V_t / (PIP - PEEP)$$

where *PIP* is peak inspiratory pressure. Dynamic and static compliance should be similar. Compliance may be markedly reduced in patients with ALI/ARDS because of the presence of pulmonary edema and alveolar flooding.

Studies that have used pressure-volume curves to set ventilator parameters and compared survival outcome have generated interest in the clinical application of pressure-volume curves. Three methods can be used to generate these curves.[22] All methods require that the patient be deeply sedated and usually medically relaxed. This step is necessary to eliminate the influence of the respiratory muscles. The first method used was the super syringe method.[22] In this method, the lungs are inflated in a stepwise manner using a calibrated syringe of a known volume (1.5 to 2 L) from the resting volume to a

maximum of 40 to 50 cm H_2O. The limitations of the method are that it takes a long time, the patient must be repeatedly disconnected from the ventilator, and the results may be influenced by oxygen consumption, changes in gas temperature, and humidity. Because of these limitations, its use is mainly limited to research.

The second method is the multiple occlusion technique.[22] The ventilator system is checked to ensure the absence of leaks. Multiple end-inspiratory occlusions are used to achieve different inflating volumes, each starting at the same lung volume. After several seconds of pause, the static pressure values are obtained and the exhaled volume is read off the ventilator after the occlusion is released. The volumes are plotted against the static pressures to make the pressure-volume curve. This procedure is fairly complex and may not be well tolerated by the patient. In addition, the sequential inflations at different tidal breaths may modify the lung volume history and influence the shape of the curve.

The third method is the low-flow technique.[22] This method is based on the concept that the rate of airway pressure change is inversely related to the compliance of the respiratory system during a passive lung inflation with constant inspiratory flow (15 L/min). This method is rapid and reproducible and does not require that the patient be disconnected from the ventilator.

However generated, the pressure-volume curve is an S-shaped inspiratory curve of three segments (Figure 39-3). The lower inflection point is at the transition from the initial flat segment and the linear part of the curve. It is thought to reflect reopening of collapsed airways. The upper inflection point is at the transition of the linear part of the curve and the final portion of the curve. It is thought to reflect the start of overinflation. The portion of the curve between the upper and lower inflection points represents the target for ventilation in patients with ARDS to reduce the potential for ventilator-induced lung injury.[21]

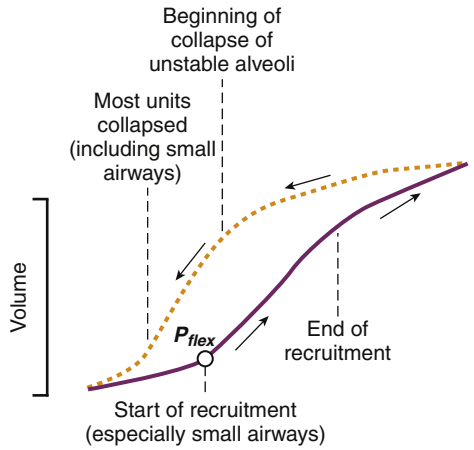

Figure 39–3. Thepressure-volume curve is an S-shaped inspiratory curve that can be divided into three sections. The lower inflection point (*P-flex*) is at the transition from the initial flat segment and the linear part of the curve. It is thought to reflect reopening of collapsed airways. The upper inflection point is at the transition of the linear part of the curve and the final portion of the curve. It is thought to reflect the end of recruitment and the start of overinflation. The portion of the curve between the upper and lower inflection points represents the target for ventilation in patients with ARDS to reduce the potential for further lung injury. *(From Albert RK, Spiro SG, Jett JR, editors:* Clinical respiratory medicine, *ed 2, St. Louis, 2004, Mosby Elsevier.)*

Endoscopy

Bronchoscopy and laryngoscopy are sometimes used in the PICU to visually examine the airway. Direct endoscopy can be performed with a flexible or rigid bronchoscope.[23,24] Flexible bronchoscopy offers the advantages of requiring little sedation and can be done through the endotracheal tube. Flexible bronchoscopy is used to evaluate the size, patency, and compression of the airway during respiration. It also is useful for evaluating the anatomy/structure of the airway and for removing or obtaining secretions from the lung. Rigid bronchoscopy continues to have a role for several reasons. Visualization of the posterior aspects of the larynx and cervical trachea is difficult using a flexible bronchoscope. Therefore better evaluation of vocal cord paralysis, laryngeoesophageal clefts, and H-type tracheoesophageal fistulas are obtained with a rigid bronchoscope. Removal of foreign bodies is performed more easily and safely with a rigid bronchoscope.

Summary

A variety of methods for assessing pulmonary status and function have been reviewed. Use of the derived information may allow ventilator settings to be altered and better matched to patient demands and comfort. Better understanding and interpretation of respiratory monitoring may result in improved patient care.

References are available online at http://www.expertconsult.com.

III

Chapter 40

Overview of Breathing Failure

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PEARLS

- Three pathways to breathing failure are (1) impaired neural control, (2) failure of the muscles of breathing, and (3) dysfunction of the mechanics of breathing.
- Though diverse stimuli drive respiratory cycling and effort, all must be processed by the brain to affect respiratory muscles.
- Volitional control of breathing is supratentorial and may dominate automatic control in the awake state, but may be lost in brain injury with or without loss of automatic control.
- Automatic control of breathing is integrated in the medulla and involves numerous separate brainstem regions, which are so widely dispersed that some evidence of respiratory drive may persist even after near total loss of brain function.
- Muscles of breathing include the diaphragm, intercostals, and accessory muscles. The diaphragm works like a piston to expand the thorax and displace abdominal organs caudad. Intercostal muscles participate in both inspiration and expiration. The thoracic accessory muscles (scalenes, sternocleidomastoids, pectoralis minor, and erector spinae) all elevate the ribs and facilitate inspiration. The abdominal muscles (rectus abdominis, transverse abdominis, and the obliques) facilitate expiration.
- The respiratory muscles can fail from overwork (as might occur in asthma) or from inadequate supply of blood flow, oxygen, or nutrients (as might occur in shock or sepsis, even when there is no evidence of lung disease).
- Dysfunction of the mechanics of breathing can contribute significantly to respiratory muscle workload. Abdominal distension, for example, worsens the angle of contraction of the diaphragm from the vertical, and opposes its descent.
- Assisted ventilation can (1) prevent breathing failure from progressing to respiratory arrest, (2) improve gas exchange, and (3) reduce metabolic expenditure for muscle work in the patient with limited reserve.

Respiration involves movement of air (breathing), diffusion of gases between alveolus and pulmonary circulation, circulation of blood between tissue and lung, and tissue energy metabolism. This chapter will provide an overview of spontaneous breathing and breathing gone awry, and will set the stage for later chapters on respiratory disorders. The term "breathing failure" is used in this chapter to limit consideration to mechanical failure of the respiratory pump that drives air movement. Breathing failure is arguably the most common cause of arrest in infants and children.

Physiology of Breathing

Diaphragm (Structure and Function)

The diaphragm arises from the embryologic pleuroperitoneal fold. Myoblasts migrate from cervical somites to the pleuroperitoneal fold where they arrange themselves into a sheet on a mesenchymal substrate that separates the peritoneum from the abdomen. Once fully formed, the diaphragm originates from bilateral tendinous crura attached to the spinal column and inserts as a costal tendon attached to the chest wall between the sixth and twelfth ribs. The dome of the diaphragm remains largely tendinous. This structure, a circular attachment to the thoracic wall, vertical muscle orientation adjacent to the thorax, and attachment to a flattened central tendinous dome (Figure 40-1), works like a piston during breathing to enlarge the thorax and displace abdominal contents downward.

Approximately 50% of the diaphragm consists of type I fast twitch muscle fibers, which have high endurance and are resistant to fatigue. The remainder of the diaphragm is made up of type IIA and type IIB fibers, which have different properties.[1] Type IIA fibers are important in achieving high levels of minute ventilation quickly, have good endurance, and can contract rapidly, but are not able to sustain long-term power output. Type IIB fibers cannot sustain their force of contraction because they possess lower oxidative capacity and are more susceptible to fatigue. The greater the force of contraction required, the more motor units of the diaphragm are recruited. There appears to be little difference between the activity of costal muscles and crural muscles, either during normal breathing or in response to hypoxia and hypercapnia.

When a patient lies supine, the diaphragm rests against the inner surface of the rib cage. When the diaphragm contracts and its muscle fibers shorten, the whole diaphragm moves down, lowering pleural pressure and increasing intra-abdominal pressure. The increase in intra-abdominal pressure generated by descent of the diaphragm acts as a caval pump to enhance cardiac filling.[2] Because of its alignment against the lower ribs (zone of apposition), descent of the diaphragm also expands the caudal portion of the rib cage.

The muscle of the diaphragm extends from the costal insertion onto the dome of the diaphragm. When the diaphragm is "high," it is loaded for greater force of contraction. When it is "low" or "flat," it is unloaded and disadvantaged.

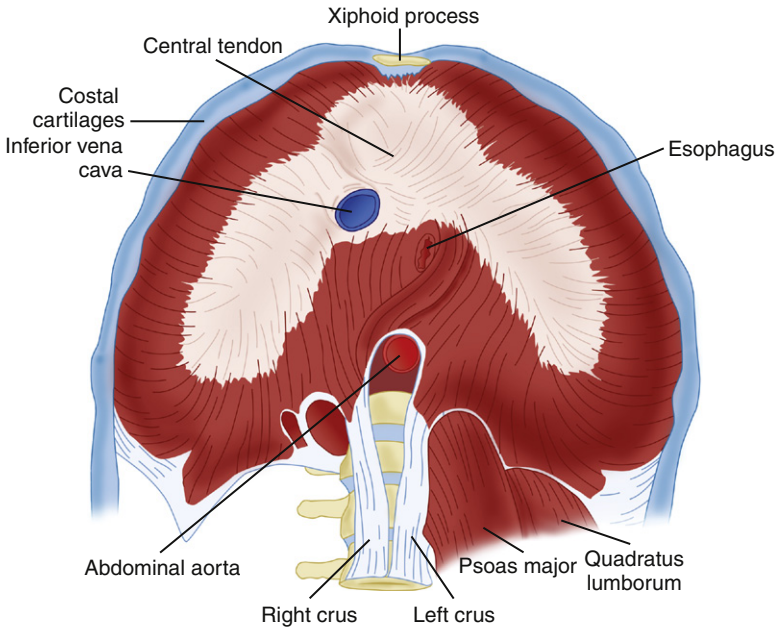

Figure 40–1. The diaphragm is attached circumferentially to the thoracic wall. Its muscular portion extends onto the dome, where it is tendinous and flattened. When the muscle contracts, the dome descends like a piston, enlarging the thorax and displacing abdominal contents downward.

The diaphragm is the major inspiratory muscle of the neonate. It increases in thickness with age (as its muscle mass increases). It also becomes appositional to a longer segment of chest wall with growth, enhancing its effectiveness as an inspiratory piston.[3] In the neonate, the muscular diaphragm has a greater angle from the vertical than that of the adult, which reduces its effectiveness as an air pump (Figure 40-2). This angle approaches zero with growth, increasing the diaphragm's effectiveness with advancing age. The importance of this angle as an impediment to diaphragmatic effectiveness becomes exaggerated at total lung capacity, with air trapping, and when the abdomen is distended, all of which flatten and unload the diaphragmatic muscle (Figure 40-3).

Intercostal Muscles

The rib cage is fixed to the spine and to the sternum. Thoracic volume is modified during breathing primarily by changing the angle of the anterior ribs to the horizontal. At rest, the ribs slope caudad from their spinal attachments. The rib cage tilts upward during inspiration. The intercostals muscles form three functional sheets. The outermost (external) sheet and the parasternal sheet act to displace the ribs cephalad as they shorten. This increases both the anteroposterior and lateral dimensions of the thorax. There is also a deep (internal) layer of intercostal muscle at right angles to the external sheet that acts to displace the ribs caudad when it contracts. Thus, the intercostals muscles play both inspiratory and expiratory roles in breathing by reshaping the thorax.

Accessory Muscles of Respiration

Though quiet expiration is largely passive, resulting mostly from elastic recoil of the lung, active expiration may be assisted by contraction of abdominal muscles (rectus abdominis, transverse abdominis, and the obliques). During quiet breathing, abdominal muscle tone elevates the diaphragm during expiration, increasing the zone of apposition and loading the diaphragm for greater inspiratory contractile efficiency.

Accessory muscles of inspiration include the scalenes, sternocleidomastoids, pectoralis minor, and erector spinae, all of which elevate the ribs during contraction. During quiet breathing, accessory muscles play a minor role, but during respiratory exertion, they may play a major role and may act to unload and unburden the diaphragm and intercostals. Even profoundly neurologically impaired children, who exhibit little volitional activity, can use accessory muscles of breathing when distressed. Children with dysfunction of the primary muscles of respiration may rely on their accessory muscles even at rest.

Integrated Control of Breathing

Control of breathing involves numerous afferent and efferent neural arcs, including volitional, sensory, and biochemical input and motor output to respiratory muscles, facial structures, and airway effectors. All of these signals are integrated, modulated, and emitted to effector organs by the brain. It is for this reason that brain death eliminates all breathing function.

The phrenic nerve arises from the cervical spinal cord (C3-C5) and migrates with the myoblasts to the pleuroperitoneal fold. Separate branches innervate the crural and costal regions of the diaphragm, and both regions include slow and fast twitch muscle fibers. These nerves secrete acetylcholine and transmission may be blocked by many drugs and toxins, including the clinically useful neuromuscular blocking agents. Phrenic motor neurons and muscle fibers continue to grow postnatally. The intercostal muscles are innervated by thoracic intercostals nerves.

The diaphragm and intercostal muscles work in unison, but also have individualized functions in breathing. When their functions are separately impaired, as in quadriplegia or

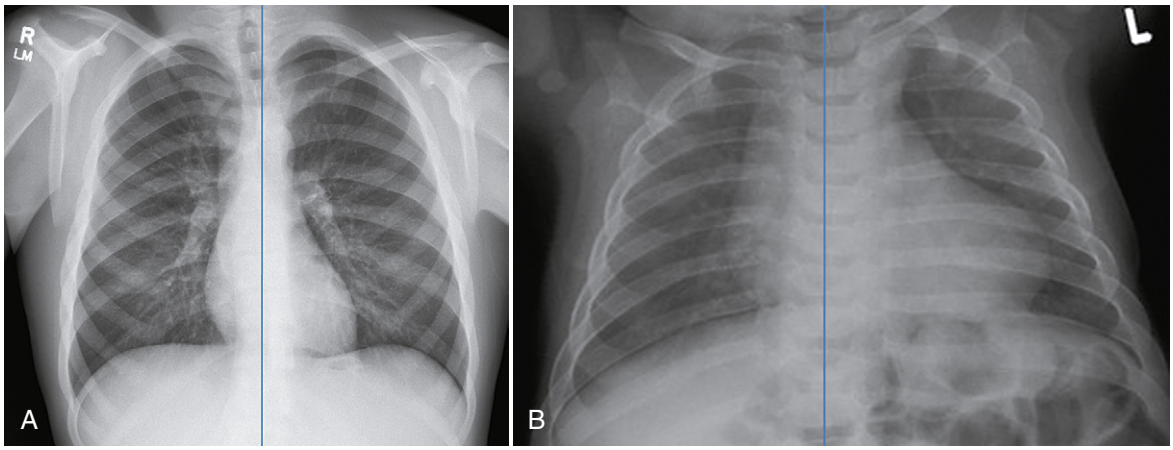

Figure 40–2. The angle of the muscular diaphragm to the vertical is narrow in the older child (**A**) and adult than it is in the infant (**B**). This more horizontal traction on the dome may be disadvantageous when the muscle of the infant diaphragm contracts. *(Courtesy Women & Children's Hospital of Buffalo, NY.)*

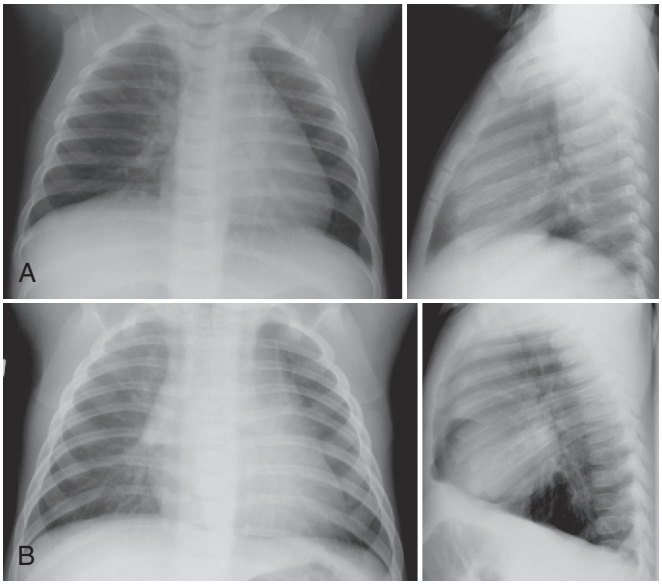

Figure 40–3. The normal position of the diaphragm (**A**) allows it to stretch or "load" during expiration. In inspiration, its muscular attachment to the thorax pulls it vertically downward. Air trapping (**B**), abdominal distension, or other disorders that cause flattening of the diaphragm interfere with "loading" and with the direction of contraction. *(Courtesy Women & Children's Hospital of Buffalo, NY.)*

diaphragm paralysis, abnormalities of gas exchange occur. DiMarco et al[4] showed that ventilation to basal lung regions is generally preserved when intercostal function alone is impaired, whereas, with isolated diaphragmatic paralysis, ventilation of more cephalad regions of the lung is relatively preserved. Costal and crural portions of the diaphragm are both responsive to hypercarbia and hypoxia.[5]

Neural Automatic Control of Breathing

The generation of respiratory patterns resides in the brainstem, in a respiratory complex consisting of the dorsal and ventral medullary and pontine respiratory groups.[6] These three neural groups coordinate and control inspiration and expiration. They modulate input from chemoreceptors, mechanoreceptors, and lung stretch receptors. In this manner, they integrate blood gas stimuli, chest wall tension, and lung stretch signals to generate and modulate an oscillatory pattern of breathing.[7]

Innervation of the laryngeal muscles modulates airway dilation and constriction. Neurons in the hypoglossal nucleus, which is the motor nucleus for the tongue, provide breath-by-breath signals to protruder muscles of the tongue to enlarge the oral airway. The trigeminal motor nucleus also plays a role in tensing the tensor palate muscle of the nasopharynx, which helps to minimize airway resistance. The alae nasi muscles, controlled by the facial motor nucleus, can actively enlarge the nostrils to facilitate inflow of breath.

The ventral medullary group functions in sleep, anesthetized, and awake states, but how organization of activity differs in these distinct states is not known. Blood pressure is tied into excitatory or depressant respiratory activity. This is thought to occur in the rostral ventromedullary area. It is also suggested that this area mediates responses to carbon dioxide (through both tidal volume and rate control), and responses to resistive breathing.[8] Lesions in the ventral medulla have been implicated in the etiology of sudden infant death syndrome and apneic episodes.[9]

Automatic control of breathing is so widely dispersed within the brainstem that it is no wonder that elements of respiratory cycling persist in many patients severely devastated by brain injury. Use of accessory muscles of respiration and motor components of respiratory distress may persist even when supratentorial function and most brainstem reflexes are absent. In the awake state, breathing patterns may be dominated by voluntary cortical activity that reaches the muscles of respiration by way of the corticospinal motor tract. Specific brain lesions may independently impair either automatic or spontaneous breathing controls.

Chemoregulation in the Physiology of Breathing

The aortic arch and the bifurcation of the common carotid artery house chemoreceptors that respond to both hypercapnia and hypoxemia. Changes in carbon dioxide are recognized by both central and peripheral chemoreceptors. The brainstem may distinguish acute from chronic hypercapnia

by sensing the acid base status of the cerebrospinal fluid. Sustained hypoxia evokes a cascade of ventilatory, neurochemical, and metabolic responses. Responses in immature animals are characterized by earlier and more marked depression of ventilation than is found in fully mature animals. Ventilation during hypoxia incorporates a number of compensatory mechanisms (stimulation or depression) from multiple systems. The time course of these responses is developmentally regulated. When hypercapnia is combined with hypoxia, the ventilatory responses are exaggerated.

The predominant drive to breathe during hypoxia and hypercarbia is mediated by stimulation of chemoreceptors of the carotid and aortic bodies. Hypercapneic drive predominates under most circumstances, but hypoxic drive may persist and predominate if the response to carbon dioxide is blunted (as in chronic respiratory acidosis). These chemoreceptors then stimulate the respiratory center in the medulla to increase minute ventilation. In the absence of brainstem function, there is no respiratory response to either hypercarbia or hypoxia.

Breathing Failure

When challenged, muscle tension can be increased either by increasing the frequency of firing or by increasing the number of motor units being fired. At low muscle tension, the *number* of motor units participating in contraction may be increased before frequency is raised. Recruitment is used to increase work. To achieve an even greater increase in force, the *frequency* of firing of individual motor units may be raised, such that while the number of motor units is held constant the *work* of each motor unit is increased.

Working skeletal muscles rely on a continuous supply of oxygenated blood. Diaphragmatic function can be impaired if blood flow or oxygenation is reduced. Diaphragmatic muscle cannot operate at optimal length (force-length relationship) to generate the appropriate contraction (force-velocity relationship) if energy demand outstrips energy supply. The combination of suboptimal force-length and force velocity relationships causes rapid, shallow breathing, largely from dysfunction of Type II B fast-twitch glycolic fibers.

Respiratory muscle fatigue develops during exhaustive exercise. Prolonged malnutrition has also been shown to affect the diaphragm's muscle structure and to impair its ability to generate force. On the other hand, it has been shown that respiratory muscle training can lessen the development of respiratory muscle fatigue.[10] Training of the diaphragm can increase capillary density, myoglobin content, mitochondrial enzyme concentration, and the concentration of glycogen, but persistent mechanical ventilation (particularly during deep sedation or paralysis) decreases muscle strength by allowing disuse muscle atrophy.

In acute illness, breathing fails if respiratory muscle demand for blood flow, metabolic substrate, and oxygen delivery outstrips supply, just as it does in exhaustive exercise.[11] The point at which this occurs is influenced by many factors, including the energy cost of breathing, duration of contraction per breath, velocity of contraction, operational length of muscle fibers, energy supply, efficiency of muscles, and state of muscle training.[12] Respiration can also fail if control of breathing is impaired. In any event, breathing failure, if untreated, may cause respiratory arrest and death.

Final Common Pathways to Breathing Failure

There are several discrete mechanisms that may cause breathing failure (Table 40-1). Each of these final common pathways may be triggered or compounded by other discrete adversities, and independent pathways of breathing failure may converge to cause respiratory arrest (or need for mechanical support of breathing).

Failure of Neural Control

The brain may fail to drive rhythmic breathing for a variety of reasons. The brain is susceptible to injury, ischemic stroke, central nervous system hemorrhage, suppression of brain function by cold, structural dysfunction, chemical suppression, signal disruption, and intrinsic disorders of respiratory control. Efferent neural pathways may be blocked by spinal cord lesions, spinal anesthesia, phrenic nerve injury, or neuromuscular disorders. Examples are cited in Table 40-2.

Table 40–1 Failure of Breathing

Mechanism	Examples
Failure of neural control	Uncal herniation, central hypoventilation
Failure of muscles of breathing	Insufficient muscle blood flow, hypoxemia
Failure of mechanics of breathing	Flail chest, diaphragmatic paralysis

Table 40–2 Causes of Failure of Neural Control of Breathing

Mechanism	Example
Brain injury	Closed head trauma
	Ischemic stroke
Severe supratentorial stroke	"Locked-in" syndrome (loss of volitional control of breathing)
Lateral medullary stroke	Ondine's curse (loss of automatic control)
Subarachnoid hemorrhage	Intracranial hypertension with uncal herniation
Brain suppression by cold	Cold water drowning
Structural brain dysfunction	Brain stem glioma
Chemical suppression	Narcotic overdose
Signal disruption	Seizure
INTRINSIC DISORDERS	
Idiopathic	Ondine's curse
Immaturity	Apnea of prematurity
Spinal cord lesion	Poliomyelitis, traumatic cord transection
Spinal anesthesia	Inadvertent spinal anesthesia
Phrenic nerve injury	Cardiac surgical phrenic nerve injury
Neuromuscular disorder	Curare poisoning, botulinum and many snake venoms

Note that volitional and automatic control of breathing may be separately and independently affected. In Ondine's curse (resulting from stroke involving the lateral medulla), automatic control is impaired, whereas volitional control may persist in the awake state. Supratentorial stroke may impair volitional control of breathing, though automatic control of breathing may be preserved. Central hypoventilation is abnormal respiratory control by the brain and results in hypercapnia. Patients with central hypoventilation may have otherwise normal neurologic functioning or concomitant neurologic injury. Unless mixed with peripheral neuromuscular disease, patients have normal muscle strength, but the essential feature is altered responses to respiratory acidosis.[13] Respiratory patterns may also be abnormal. Central hypoventilation is most apparent when patients are sleeping. Apnea of prematurity, which may persist beyond term, is still not well understood, but is clearly aggravated by concomitant infection.

Peripheral (extracranial) neural disorders include spinal cord injury, myasthenia gravis, anticholinesterase poisoning, and Guillain Barré syndrome. The hallmark of these diseases is muscle paresis or paralysis. Hypercapnia is a common feature. Depending on the extent of weakness, patients will be unable to increase their work of breathing in the face of lung disease. Clinical signs such as tachypnea and accessory muscle usage cannot be relied on. Abnormal arterial blood gases may be the only indications of worsening breathing failure, especially in patients with altered sensorium. Patients with spinal cord lesions develop muscle weakness below the level of injury. For instance, patients with lower cervical cord injury may have preservation of suprasternal muscle action but have loss of other accessory muscle function as well as diaphragmatic dysfunction or paresis. These patients will have vigorous suprasternal retractions that expand the lung apices, but have little other movement.

Failure of Muscles of Breathing

Causes of breathing muscle failure are listed in Table 40-3, along with examples. They may be crudely divided into causes of muscle exhaustion and causes of muscle plegia or paralysis and causes of muscle tetany.

In pediatric critical care, the most common cause of failure of the muscles of breathing is exhaustion. The respiratory muscles may become exhausted when responding to excessive workload. Airway obstruction (fixed or functional), lung stiffness, thoracic stiffness (e.g., anasarca), abdominal distension, air trapping, and inefficient ventilation-perfusion matching (e.g., high ventilation-perfusion mismatch, which functionally wastes ventilation) are examples. Respiratory muscles may also become exhausted if their effort is not supported by adequate nutrition, blood supply, and oxygen delivery. Respiratory distress can be likened to running a marathon. There can be a "wall" beyond which respiratory muscle metabolism is not able to sustain further respiratory effort. Without assistance, after these muscles reach their "wall," respiratory arrest occurs.

In both shock and hypoxemia, oxygen delivery to respiratory muscle may prove inadequate to meet demand on a minute by minute basis.[14] Skeletal muscle may sustain a transient oxygen debt by unloading oxygen from myoglobin, but such reserve is limited. It can also perform anaerobic metabolism to generate ATP using the Kreb cycle, but only until levels of reducing substances (diphosphopyridine nucleotide), unable to participate in oxidative phosphorylation, build up to such a degree that they inhibit the activity of Kreb cycle enzymes. Over a range of oxygen delivery, metabolic use of oxygen is insensitive to rates of supply (delivery), but below some threshold, muscle aerobic metabolism must inevitably be reduced.[15]

Mitochondrial dysfunction may aggravate deficient muscle metabolism in sepsis. Impaired oxygen utilization may contribute to failure of breathing in other mitochondrial crises as well. One of the indications for intubation and mechanical ventilation in patients with septic shock is to avert respiratory arrest from loss of oxidative metabolism with exhaustion and failure of the muscles of breathing.

There are a few conditions in which muscle contraction may be impaired by dysfunction of the myocyte. Tetrodotoxin (puffer fish) blocks the fast voltage-gated sodium channel of the muscle cell, thereby causing paralysis. Hypokalemia may impair muscle contraction and hypokalemic periodic paralysis has similar effects. Tetanus and hypocalcemia are capable of causing tetanic contraction that can impair breathing.

Failure of Mechanics of Breathing

Mechanical factors may pose acute or chronic impediments to breathing. Some place such a burden on respiratory muscles that they become exhausted (e.g., flail chest, severe thoracic dystrophy, deformity). Others cannot be overcome by any effort (e.g., foreign body, pneumothorax). Chest and spinal deformities, diaphragmatic eventration, prune belly syndrome (in which abdominal musculature is virtually absent), and deformities that flatten the diaphragm may either cause chronic respiratory insufficiency or may contribute to intolerance of intercurrent processes such as pneumonia.

Table 40–3 Causes of Muscle Failure

Mechanism	Example
Muscle exhaustion	
Overwork	Lung dysfunction, airway obstruction
Inadequate substrate	Shock, hypoxemia
Muscle plegia	Hypokalemia
Muscle tetany	Tetanus, hypocalcemia

Breathing Failure from Lung Disease

Acute lung disease may progress to breathing failure along one of several pathways. The primary mechanism is respiratory muscle exhaustion. Both excessive demand and impaired supply may come into play, and, in many children, poor thoracic mechanics and neurologic impairment contribute to breathing failure from acute lung disease.

Typically, lung disease increases the work of breathing. Hypoxia and hypercarbia drive the respiratory muscles toward exhaustion. Efficiency of the respiratory system is impaired by lung regions of high ventilation-perfusion ratio. Because these regions see scant blood flow, they actually waste ventilation and breathing effort. On the other hand, low ventilation-perfusion ratio segments cause hypoxemia, which impairs oxygen delivery to tissue and makes circulation inefficient. When oxygen delivery is too low, muscle oxygen utilization becomes

delivery dependent, and muscle work capacity declines. Add to these factors others, such as the compliance of the infant chest (which wastes breathing effort), the deformity of kyphoscoliosis (which makes breathing less efficient), the inefficiency of the infant diaphragm that operates at a wide angle to the chest wall, abdominal distension (which further widens that angle and opposes descent of the diaphragm), and the nutritional issues of chronic illness, and progression toward respiratory arrest is accelerated. Superimposed immaturity, neuromuscular dysfunction, or other comorbid conditions may also exacerbate breathing failure.

As breathing failure worsens, fatigue causes the patient's respiratory effort to deteriorate. Patients use accessory muscles less, they develop brief respiratory pauses, and they progress to apnea followed by respiratory arrest. Respiratory pauses are a subtle but helpful warning sign that should be interpreted as impending respiratory arrest. Pauses warn that respiratory support is indicated. Another helpful sign is grunting. Grunting is a low-pitched sound produced by partial or total closure of the glottis in expiration. Grunting is thought to augment expiratory lung volume (FRC) and increase arterial oxygen tension much like positive end-expiratory pressure (PEEP).[16] Grunting is also a warning of possible impending arrest in children and adults with respiratory failure,[17] though it also often occurs immediately after birth and may quickly resolve as the neonate successfully navigates transition. Patients may appear anxious and describe a feeling of air hunger. Mental status changes ranging from panic to obtundation may occur. Abrupt respiratory slowing and gasping are harbingers of respiratory arrest.

Ventilator induced lung injury (VILI) and the acute respiratory distress syndrome are histologically inseparable. Two of the mechanisms of VILI are excessive tidal volume and repeated opening and closing of diseased lung units (see Chapter 51). The distress of breathing failure drives breathing. This exertion may overdistend some lung units while contributing to closure and reopening of others. The ausculatory finding of rales in patients with pneumonia supports the contention that closure and reopening of lung units is characteristic of parenchymal lung disease. Ventilation-perfusion mismatch suggests the presence of both overdistended and collapsed alveoli. One must ask: can spontaneous breathing during respiratory failure promote an injury identical to VILI? Can spontaneous breathing of the patient with severe lung disease and breathing failure worsen lung mechanics and accelerate breathing failure?

After a patient has been intubated for breathing failure, tidal volume can be controlled, alveoli can be stinted open by PEEP, and the risk that superimposed secondary lung injury may worsen lung disease may actually be reduced (compared with the risk of an analogous injury by spontaneous breathing). Intubation also interrupts the progression from breathing failure to respiratory arrest.

Restrictive Versus Obstructive Respiratory Disease

Though restrictive and obstructive pulmonary processes act through the same final common pathways of breathing failure, their mechanics and clinical manifestations often differ. Restrictive diseases are those that limit lung expansion. These include processes that (1) fill alveoli with blood, infectious material, edema, or other debris; (2) involve expansion or swelling of the alveolar interstitium; (3) compress the lung, as with pneumothorax or effusion; or (4) impair excursion of the chest wall or thoracoabdominal region because of neuromuscular dysfunction, skeletal deformity, abdominal distension, ascites, or anasarca. These processes are characterized by a reduction in vital capacity, small resting lung volumes, but normal or near-normal airways resistance. The physical examination reflects these processes. Patients are tachypneic, taking rapid, shallow breaths. Auscultation of the chest may reveal fine inspiratory crepitations (crackles) or rales, evidence of parenchymal lung disease. Poor excursion of the chest wall is usually readily appreciated. Retractions (subcostal and intercostal) are common and indicate significant respiratory effort.

Obstructive diseases of the lung are common in childhood and are characterized by obstruction to flow in airways. Obstructive diseases may be classified as extrathoracic (above the thoracic inlet) or intrathoracic (below). Obstruction may be the result of occluding material or tissue in airways, elevated tone of the smooth muscle of airway walls (reducing caliber of the lumen), weakness of the airway wall causing collapse and impeding gas flow, or fixed extrinsic compression of airways. In some diseases, several of these processes occur simultaneously. Indeed, secondary obstruction is a common phenomenon. Obstruction in a proximal airway may cause turbulent gas flow downstream in distal airways. Turbulent gas flow causes the wall of the still developing airway to flutter, further weakening the wall's structure and exacerbating overall obstruction.

The hallmark of extrathoracic obstruction is inspiratory noise (stridor or stertor). The affected airway segment lies between the nose and the proximal trachea. Inspiratory stridor is a vibratory sound heard because the reduction of intrathoracic pressure during inspiration narrows the extrathoracic (subglottic) airway, generating an inspiratory noise. Stertor is a snoring noise generated in the nasopharynx. Airways with severe obstruction flutter in both inspiration and exhalation, causing biphasic stridor or noise heard in both phases of the respiratory cycle. Other characteristic sounds may help to identify the obstructed airway segment (Table 40-4). In extreme obstruction, patients may position themselves to maximize airway caliber (remaining upright, leaning slightly forward, and holding the head in the "sniffing position" to enhance alignment of the pharynx and larynx). It should be noted that generation of noise requires air flow. With very severe obstruction, there is little air flow and little noise is generated. Loss of noise, despite increased effort, is an

Table 40–4 Abnormal Sounds Indicative or Extrathoracic Airway Obstruction

Sound	Condition
Hoarseness	Unilateral vocal cord paralysis
Muffled voice	Supraglottic or infraglottic processes, including epiglottitis
"Hot potato" voice	Oral, retropharyngeal abscess
	Ludwig's angina
"Barking" cough	Laryngotracheobronchitis (croup)
Monotone, hurried sentences	Bilateral vocal cord paresis

ominous sign and is indicative of complete obstruction and impending respiratory arrest.

The hallmark of intrathoracic obstruction is an expiratory sound. In intrathoracic obstruction, forced expiration compresses soft airways, causing a musical wheeze. This obstruction may be largely relieved by inspiration, which tends to dilate intrathoracic airways. In severe intrathoracic obstruction, sounds may be heard during both phases of the respiratory cycle. In the classic pediatric disease of intrathoracic obstruction is asthma, high-pitched wheezes on exhalation are heard early in the episode. As airway obstruction worsens, wheezes are heard in inspiration as well. With severe obstruction, wheezes diminish because there is little gas flow.

The character of the voice and ability to speak (in words, phrases, or sentences) may be helpful in the evaluation of airway obstruction. Observation of the respiratory rate can be revealing in obstructive disease. With mild obstruction, the respiratory rate is often slower than normal, but may rise as ventilation perfusion inequality develops and increases respiratory drive. Physical examination will often reveal the use of accessory muscles of breathing.

Compensatory Mechanisms in Breathing Failure

A patient may try to compensate for the functional effects of lung disease. These compensatory mechanisms generally come into play before there is evidence of breathing failure. Many of the clinical signs of respiratory distress, discussed previously, are evidence of compensatory mechanisms. Understanding these mechanisms improves recognition of impending failure.

Compensatory Mechanisms in Restrictive Lung Disease

Tachypnea is the patient's primary compensation for the small lung volume of restrictive lung disease and is the earliest detectable clinical sign. Additional compensation is achieved by recruitment of accessory muscles. Patients with restrictive disease may take periodic sigh breaths, which are larger than tidal breaths, to recruit collapsing units. Compensatory mechanisms also operate to maximize gas exchange in diseased lungs. Hypoxic pulmonary vasoconstriction is an important mechanism to improve gas exchange in normal lungs. Hypoxic pulmonary vasoconstriction is a direct response of the vascular smooth muscle to low PaO_2 alveolar units. The precapillary arteriole of such units constricts in response to low O_2 tension in the adjacent postcapillary venule, thereby directing blood away from poorly functioning alveoli. In a lung with patchy disease, the overall effect of the hypoxic pulmonary vasoconstriction response is to shunt blood away from diseased segments and to allow flow to healthier areas. This may, paradoxically, increase pulmonary vascular resistance and oppose right ventricular ejection. Inhaled nitric oxide provides an exogenous means to improve ventilation perfusion matching (by preferentially dilating vessels to ventilated lung segments) without afterloading the right ventricle.

Compensatory Mechanisms with Obstructive Lung Disease

The major compensations in obstructive disease focus on maximizing airflow. As previously stated, patients naturally position themselves to maximize opening of their airway. If this is the case, repositioning patients, especially to the supine position, may worsen airflow. For the infant, carefully monitored prone positioning may aid gas exchange and assist spontaneous breathing.[18] Control of respiratory rate provides another means of compensation. In mild obstructive disease, the respiratory rate is lower than normal. As resistance to airflow rises, total work of breathing also rises greatly. To maximize efficiency, the respiratory rate falls. Longer respiratory cycle times allow longer times for gas flow. Having said this, the clinician will recognize that many patients with obstructive lung disease present with tachypnea, not decreased respiratory rates. The causes of tachypnea are (1) ventilation/perfusion mismatching with hypoxemia and sometimes hypercarbia driving the respiratory rate and (2) development of atelectasis in unventilated lung segments resulting in the superimposition of a restrictive process on an obstructive one. Tachypnea in such patients is counterproductive, greatly increasing the work of breathing and further diminishing gas flow.

Special Conditions

There are several conditions deserving of special note. In these, physical findings may reflect specific aberrations that generate specific compensatory mechanisms.

Infancy

The configuration of the infant's chest wall differs from that of adults. Orientation of the ribs is more horizontal in infants than in adults and they move less during breathing. The chest wall is more compliant and is composed of more cartilaginous tissues. Strength of intercostals muscles is less. In the absence of muscular action, FRC is determined by the elastic forces of the lung and the chest wall, which oppose each other. Accordingly, the infant's more compliant chest wall and weaker musculature results in lower FRC. Infants with lung disease use expiratory braking (grunting), which involves constriction of pharyngeal muscles and glottis, to increase end-expiratory lung volume. Although this promotes higher FRC, it imposes a disadvantageous increase in muscular work.

Infant respiratory muscle fibers differ from those of adults. The infant diaphragm contains a greater proportion of type II fibers, which are unable to sustain repeat strenuous activity. Hence, the infant's diaphragm fatigues more quickly than that of the adult.[19] The infant's diaphragmatic anatomy is also disadvantageous. The reduced appositional area and greater diaphragmatic angle of the infant results in lesser lung volume expansion with diaphragmatic contraction. Because pulling the rib cage cephalad produces less outward chest displacement in the infant than in the adult, the infant's tidal volume is, in the aggregate, more dependent on diaphragmatic contraction than that of the adult.

Superimposition of breathing failure on infant respiratory function exacerbates these mechanical disadvantages. In normal respiration, the chest wall and abdomen move inward and outward in synchrony. With restrictive lung disease, the respiratory pattern may be out of phase, called paradoxical breathing. Contraction of the diaphragm pulls the compliant infant chest wall inward during inspiration and pushes abdominal contents outward. This respiratory pattern is greatly exaggerated by severe restrictive lung disease. With decreased lung compliance, the pleural pressure swing is exaggerated, pulling the chest wall further inward. Prolonged respiration in

this manner can cause inward deformation of the sternum, or acquired *pectus excavatum*, and is a clinical sign of prolonged respiratory insufficiency. In the infant with severe restrictive disease, recruitment of additional diaphragmatic and accessory muscles, use of compensatory braking and grunting maneuvers, and increases in respiratory rate may be insufficient to maintain a normal FRC. Fatigue comes quickly to the stressed infant with a highly elastic rib cage and at a greatly accelerated respiratory rate. Moreover, such work is extremely energy expensive. Infants with chronic respiratory insufficiency can use as much as 50% of their caloric intake for breathing, leaving few calories for growth and other functions, and resulting in failure to thrive.

Infants are also disadvantaged with respect to obstructive lung disease. In infants and young children, a greater percent of total airways resistance is apportioned to large airways than in adults. Infants are particularly susceptible to nasal obstruction, as occurs during upper respiratory infection, because the nose may comprise as much as 50% of total airway resistance. Moreover, resistance to airflow is proportional to the inverse of the airway radius to the fourth power:

$$R = 8\eta L / \pi r^4$$

where η is gas viscosity, L is airway length, and r is radius of the airways. Resistance is greater in infants and young children because of their intrinsically small airways. Further reduction in airways caliber with obstructive disease (e.g., bronchiolitis) magnifies this problem.

The infant's airways are also less endowed with cartilage than are those of the adult and may be subject to flow limitation during active expiration. The trachea and bronchi may be pathologically compressed during expiration, causing severe obstruction that is worsened by expiratory effort. Such regions of severe and pathologic flow limitation (tracheomalacia and bronchomalacia) may be localized. Similarly, the larynx may be compressed (by atmosphere) during forced inspiration (laryngomalacia) if there is proximal (supraglottic) obstruction.

Thoracic Dysfunction

Neuromuscular disorders generally result in restrictive lung defects. Coexisting obstructive lung disease can be seen with some thoracic defects or with scoliosis. Persistent atelectasis and longstanding lung hypoplasia may lead to atrophy and may destroy supporting airway architecture resulting in air trapping. Deformities of the rib cage and spinal column result in restriction to lung expansion as occurs with isolated scoliosis.[20,21] The most severe of these are classified as "asphyxiating thoracic dystrophies" in which the chest fails to expand at all during breathing. As with the other forms of neuromuscular diseases, hypercapnia predominates. Muscle strength may be normal, but abnormal configuration of intrathoracic muscles and diaphragm may make muscle work inefficient.

With many of these disorders, patients live in a chronic state of increased work of breathing and muscle fatigue. Growth failure is common. They tend to have little ability to meet the added demands of acute respiratory processes, such as respiratory infections, and total breathing failure often ensues. They may have frequent and recurring need for positive pressure support. Yet, the usual signs of impending breathing failure may be absent in patients who are weak, nonresponsive, or have chest wall distortions. In such cases, close monitoring and measurement of arterial blood gases are essential.

Altered Nutritional States: Malnutrition and Obesity

A major functional consequence of malnutrition is altered muscle function. Protein-calorie malnutrition results in decreased muscle energetics. Protein deficiencies alone may have the same effect. Catabolism of skeletal muscle to meet body protein needs results in decreased muscle mass. Malnourished states are easy to recognize when they are the result of longstanding inadequate caloric intake, as in marasmus, but this is rarely seen in developed countries. More common are subtler forms of insufficient nutrition in children who live in a chronically high metabolic state, such as chronic congestive heart failure. Such patients may be unable to consume enough calories for effective positive nitrogen balance. Catabolism is ongoing, sacrificing muscle mass and function. Chronic respiratory insufficiency results in a cycle of progressive breathing failure, increasing work of breathing, and worsening imbalance between calorie intake and expenditure. Recognition of this cycle is imperative; metabolic demands must be decreased by treating the underlying condition, and caloric intake must be increased. In the young child, reversal of this cycle is signaled by resumption of somatic growth. The clinician should also note that in patients with malnutrition, the superimposition of an acute respiratory process, such as an intercurrent respiratory infection, will result in more rapid progression to breathing failure. The patient has little or no reserve for the added metabolic demands and added work of breathing.

At the other end of the nutritional spectrum, obesity has major respiratory consequences. As with obese adults, obese children are at risk from obstructive sleep apnea syndrome. Obstructive sleep apnea syndrome may cause frequent obstructive events. Hypercarbia and hypoxemia may occur. Obstructive sleep apnea syndrome is diagnosed by polysomnography. Treatment includes weight loss, removal of tonsils and adenoids, palatoplasty procedures in some patients, and nightly positive pressure support in others. Additionally, obesity alters lung volumes, especially when children are supine. With abdominal contents pushing up on the diaphragm, FRC and total lung capacity are reduced, representing another form of chronic restrictive disease. This effect is exaggerated in the supine (as opposed to upright) position.

Conclusion

Breathing failure occurs when neural, muscular, or mechanical challenges cannot be overcome by compensatory mechanisms. A common final pathway is muscle exhaustion, either from excessive demand on respiratory muscles or from inadequate supply to these muscles of blood flow, oxygen, or nutrients. Assisted ventilation is important, not only to improve gas exchange, but to also to prevent respiratory arrest from breathing failure. This is true both in lung disease, and in other conditions that impair neural, muscular, or mechanical breathing capacity.

References are available online at http://www.expertconsult.com.

III

Chapter 41

Ventilation/Perfusion Inequality

Thomas V. Brogan and David J. Vaughan

PEARLS

- Gravity affects the distribution of pulmonary perfusion. Both perfusion and ventilation increase down the lung. Despite these changes, perfusion is tightly matched to ventilation.
- Recent studies have shown that there is significant heterogeneity of pulmonary blood flow and ventilation in isogravitation fields. The pattern of both perfusion and ventilation is fractal in nature.
- The primary ventilation/perfusion abnormality in acute respiratory distress syndrome is intrapulmonary shunt.
- In persons with asthma, ventilation/perfusion mismatch is responsible for hypoxemia, but there is no correlation between measurements of overall airway obstruction and V/Q mismatch.
- Although positive end-expiratory pressure decreases the proportion of shunt, at high levels it also increases dead space.

The primary function of the lung is to exchange oxygen and carbon dioxide between inspired air and blood. Efficient gas exchange requires the close matching of regional ventilation and perfusion (V_A/Q). However, as the largest organ in the body, the lung is influenced by external and internal factors that affect ventilation/perfusion relationships. In children, V_A/Q mismatch and intrapulmonary shunt cause most gas exchange abnormalities (Table 41-1). Lung units that are poorly ventilated in relation to blood flow (low V_A/Q) produce blood with low oxygen content (desaturated blood), but units with high V_A/Q ratios cannot compensate, because the oxygen content of blood leaving these areas has nearly the same oxygen content as that from normal V_A/Q regions as a result of the sigmoid shape of the hemoglobin oxygen dissociation curve (Figure 41-1). Early studies supported the concept that vertical gradients of both ventilation and perfusion produced V_A/Q matching. Newer studies that achieved greater spatial resolution demonstrated that perfusion and ventilation are rather heterogeneous and that this heterogeneity serves to match ventilation and perfusion.

The alveolar gas equation helps us understand the pathophysiology of abnormal gas exchange by providing information on alveolar oxygen tension. According to the Fick equation, under steady state conditions, the quantity of O_2 taken up by the lungs equals the amount of O_2 removed from inhaled air:

$$O_2 = {}_A(F_{IO_2} - F_{AO_2}) \quad (1)$$

where O_2 is O_2 consumption, F_{IO_2} is the fraction of inspired O_2, A represents alveolar ventilation, and F_{AO_2} is the fraction of alveolar O_2. This equation can be rearranged to read:

$$F_{AO_2} = F_{IO_2} - O_2/_A \quad (2)$$

Then, by changing the fraction of gases to their partial pressures, the equation takes the following form:

$$P_{AO_2} = P_{IO_2} - (O_2/_A)(P_B - 47 \text{ mm Hg}) \quad (3)$$

where P_{IO_2} is the inspired P_{O_2} and P_B is barometric pressure. The concept underlying this equation is that alveolar oxygen level (P_{AO_2}) is the difference between what comes in (P_{IO_2}) and the amount taken up by the pulmonary capillaries $[(O_2/_A)(P_B - 47 \text{ mm Hg})]$. The ratio $O_2/_A$ can be estimated from a surrogate for the ratio between O_2 and ${}_A$. By using P_{CO_2} in arterial blood as an estimate of alveolar CO_2, $CO_2/_A$ as an estimator of F_{ACO_2}, and the respiratory quotient $R = CO_2/O_2$, the second term of Equation 3 can be estimated by P_{ACO_2}/R. The alveolar gas equation can then be derived as follows:

$$P_{AO_2} = F_{IO_2} \times (P_B - 47 \text{ mm Hg}) - (CO_2/R/_A) \times (P_B - 47 \text{ mm Hg}) \quad (4)$$

$$P_{AO_2} = F_{IO_2} \times (P_B - 47 \text{ mm Hg}) - (F_{ACO_2}/R) \times (PB - 47 \text{ mm Hg}) \quad (5)$$

$$P_{AO_2} = F_{IO_2} \times (P_B - 47 \text{ mm Hg}) - (P_{ACO_2}/R) \quad (6)$$

Table 41–1 Causes of Hypoxemia

Intrapulmonary Factors	Extrapulmonary Factors
PRIMARY	**PRIMARY**
Ventilation/perfusion mismatch	Decreased minute ventilation
Shunt	Decreased cardiac output
Alveolar-end capillary diffusion limitation	Decreased Fio_2
	SECONDARY
	Decreased P_{50}
	Decreased hemoglobin concentration
	Alkalosis

Distribution of Ventilation

Ventilation of the lung is heterogeneous and is influenced by multiple factors, including gravity, posture, and even experimental technique. Gravity has been considered predominant because of the variation in pleural pressure from the apex to the base of the lung. The lung is a viscoelastic structure encased in the supporting chest wall, with gravity imposing a globular shape on the lung. Pleural pressure is more negative at the apex of the lung compared with the base, increasing approximately 0.25 cm H_2O per centimeter of vertical distance toward the lung base. Thus transpulmonary pressure is more marked at the apex, so apical alveoli are large and at the upper end of the normal pressure volume curve. They distend less for a given pressure change, that is, they are less compliant. In the spontaneously breathing upright human, maximal gas distribution occurs at the base and progressively diminishes toward the lung apex.[1,2] This gradient also exists when inhalation occurs in the supine or lateral decubitus position, although to a lesser degree. Fast inspirations from functional residual capacity (at supranormal flow rates >1.5 L/s) may reverse this distribution with preferential ventilation of the upper parts of the lung.[3]

Heterogeneous ventilation also may occur independent of the aforementioned factors. The time constant (the product of resistance and compliance) is defined as the time required for inflation to 63% of final lung volume, inflation being indefinitely prolonged. Therefore, a given lung unit with a slow time constant will fill more slowly than one with a fast time constant and also empty more slowly. Should the time constants of different lung units vary, as frequently happens in pulmonary illness, gas distribution will be determined in part by the rate, duration, and frequency of inhalation.

Distribution of Perfusion

The predominant characteristic of the pulmonary circulation is that it is a low-pressure system. The mean pulmonary artery pressure (P_{PA}) is approximately 15 mm Hg, whereas the mean systemic arterial pressure is on the order of 100 mm Hg. This finding implies that external pressures play a greater role in determining blood flow within the lung. According to the classical model of lung perfusion, gravity affects pulmonary blood flow (PBF) in a similar fashion and to a much greater extent. In general, the dependent areas of lung receive more blood flow. The pulmonary artery pressure decreases by 1 cm H_2O per centimeter of vertical distance up the lung, so the driving pressure rapidly approaches zero with minimal blood flow to the apices, and indeed P_{PA} may become negative. In the erect human, blood flow progressively increases from apex to base.[4]

The three-zone model of PBF has been widely used to explain the heterogeneity of perfusion within the lung (Figure 41-2).[4] Three variables comprise the components of this model: pulmonary arterial (P_{PA}), alveolar (P_A), and pulmonary venous (P_V) pressures. The degree of blood flow within the lung depends on the relative magnitudes of these pressures within that zone. Zone 1 ($P_A > P_{PA} > Pv$) has negligible blood flow, as the higher alveolar pressure is believed to compress collapsible capillaries. This region is one of minimal gas exchange and "wasted" ventilation. Zone 1 conditions are rare except in cases of diminished pulmonary blood flow (e.g., hypotension or cardiac failure) or increased P_A encountered during positive pressure ventilation. Zone 2 consists of the mid portions of the lungs in which $P_{PA} > P_A > P_V$, where flow rate is determined by the difference between pulmonary arterial and alveolar pressure. Venous pressure does not influence the flow rate. Blood flow progressively increases with descent through this zone as P_a increases, whereas P_{PA} remains relatively constant.

In the lowest zone of the lung described by West et al.,[4] zone 3, $P_{PA} > P_V > P_A$, therefore the arteriovenous pressure gradient ($P_{PA} - P_V$) determines flow rate. This gradient remains relatively constant as it descends through this zone, although because pleural pressures increase less, blood flow is greater in more dependent areas of zone 3. A zone 4 region in the most dependent areas of lung also has been described. In this region, transudated pulmonary interstitial fluid increases interstitial pressures, thereby reducing blood flow; this effect is exaggerated as lung volume diminishes from total lung capacity to residual volume.

PBF in immature animals differs in several important ways from that in adult animals. Studies in piglets suggest that the pulmonary vascular bed may be fully recruited,[5,6] with no

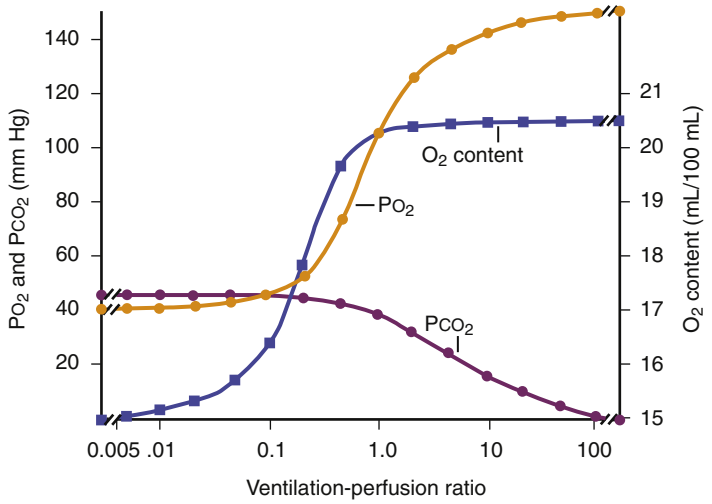

Figure 41–1. Gas exchange in a single lung unit. Changes in P_{O_2}, P_{CO_2}, and end-capillary O_2 content in a lung unit as its ventilation/perfusion ratio is increased from shunt (V/Q = 0) to dead space (V/Q = ∞). Hemoglobin concentration is 14.8 g/dL.

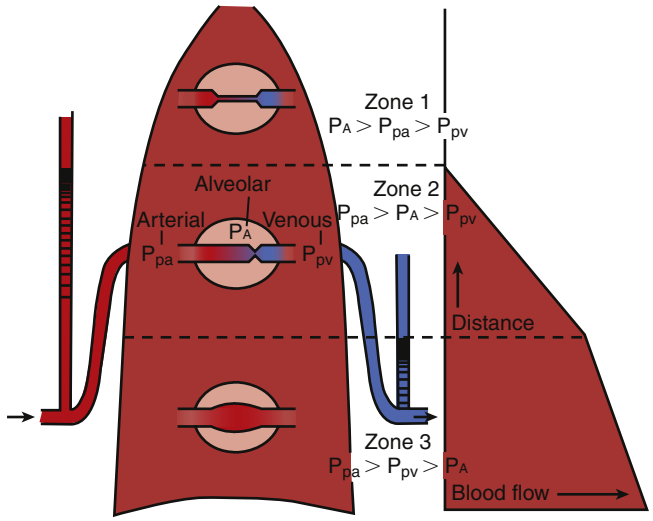

Figure 41–2. Normal distribution of pulmonary blood flow: gravitational model. According to the model, the gravitational driving force for pulmonary blood flow increases down the lung. At the apex (zone 1), flow is absent as alveolar pressure (P_A) exceeds pulmonary artery (P_{PA}) and pulmonary venous (P_V) pressures. In *zone 2,* flow is determined by the driving pressure ($P_{PA} - P_A$). Flow is constant and maximal in *zone 3* because both P_{PA} and P_V exceed P_A where the driving pressure is $P_{PA} - P_V$.

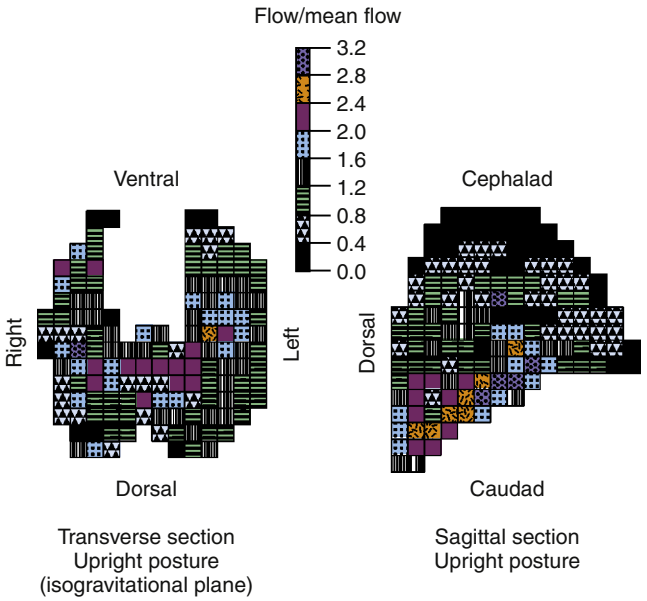

Figure 41–3. Isogravitational heterogeneity of pulmonary blood flow. Reconstruction of transverse and sagittal plane from a single baboon animal during upright posture. Each *square* depicts location and relative blood flow to a piece of lung in a given plane. Heterogeneity of blood flow is present in isogravitational planes. Flow is not random; rather, neighboring pieces tend to have similar magnitudes of flow. Cephalad-caudad (gravitational) gradient is apparent in the sagittal section.

contribution of Starling resistors in the pulmonary circulation during exposure to acute or chronic hypoxia. Furthermore, neonatal piglets show a relative hypoxemia and an increased dispersion of PBF (by the multiple inert gas elimination technique [MIGET]). This dispersion is measured as the standard deviation of PBF and is the second moment on a log scale of distribution about the blood flow mean among both high and low V_A/Q units compared with mature animals. In general, an increase in the standard deviation of PBF also occurs with lung disease.

Fractal Model of Pulmonary Blood Flow and Ventilation

The gravitational model provided a useful and accurate model of PBF. However, as studies employed increasing power of resolution, PBF was shown to have greater heterogeneity than was described by the gravitational model.[7-9] Blood flow in isogravitational planes was shown to be nearly as heterogeneous as the entire lung, yet the gravitational model predicted uniform flow in such planes (Figure 41-3). This heterogeneity in PBF was initially considered random, but the regional flow distributions were shown to be correlated with neighboring regions.[9] Thus high-flow regions were adjacent to other high-flow regions and low-flow regions bordered other low-flow regions. The distribution of PBF was shown to be independent of the scale of measurement, suggesting a fractal nature of PBF.

A fractal structure or process can be described as having a characteristic form that remains constant over a magnitude of scales (Figure 41-4).[9] This concept of self-similarity has been recognized within the topology of the bronchial and pulmonary vascular trees. The height up the lung was shown to account for only a minority of the total variability in regional perfusion.[10] In both dogs and upright baboons, gravity's contribution to overall perfusion heterogeneity was of secondary importance, although more important in upright primates than in dogs.[11] Indirect measurements of perfusion in humans under microgravity conditions showed substantial isogravitational heterogeneity of pulmonary perfusion with a hilar to peripheral gradient.[12] The asymmetry of flow at branches within the pulmonary arterial tree accounts for the heterogeneity of flow within isogravitational planes. Thus regions that share a parent or grandparent branch have more similar flows than do branches that are separated by a greater distance. This fractal pattern of PBF extends down to the subacinar level of gas exchange and is stable with growth.[13,14]

Fractal Model of the Pulmonary Ventilation

The close correlation between regional ventilation and perfusion suggests that ventilation has spatial characteristics similar to regional perfusion. Newer methods of measuring regional ventilation showed a similar pattern with similar heterogeneity to regional perfusion.[15-18] The correlation of regional heterogeneities of ventilation to those of perfusion ensures a narrow distribution of V_A/Q distributions in normal animals. Fractals possess a large area-to-volume ratio that ensures that all cells are serviced by capillaries, and hence they are well suited to the task of diffusion exchange and substrate delivery no matter what the organism's size. The high correlation between regional ventilation and perfusion may be explained by the close correlation of the developing bronchial tree and pulmonary arterial tree during organogenesis.[19]

Under normal circumstances, regional perfusion is tightly matched to ventilation.[20] Hence the innate structure of the lung itself appears to underlie the precision of V_A/Q matching. Lung basal pulmonary vascular tone is minimal, suggesting

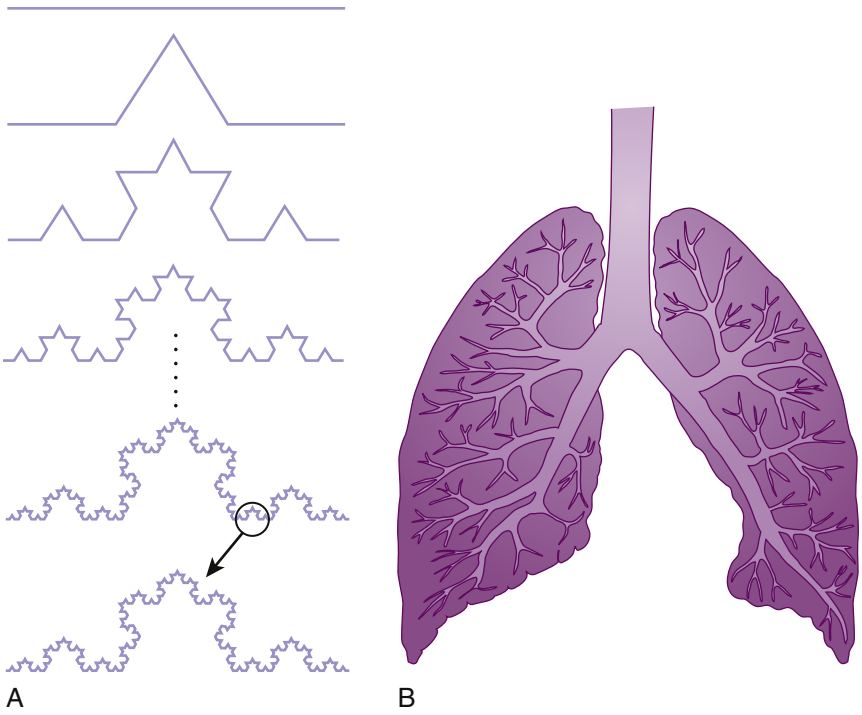

Figure 41–4. Fractal structures. **A,** This curve is produced by a simple iterative transformation beginning with a straight line. At each step the middle third of all lines is replaced with two segments, one-third length of the line, forming part of an equilateral triangle. An infinite number of iterations can be performed. Thus as increasing magnification reveals more detail, the overall appearance of the new segment remains similar to that of the previous segment. **B,** The pulmonary vascular (and bronchial) tree is a repetitive pattern of dichotomous branches that become progressively smaller and fill a predetermined area.

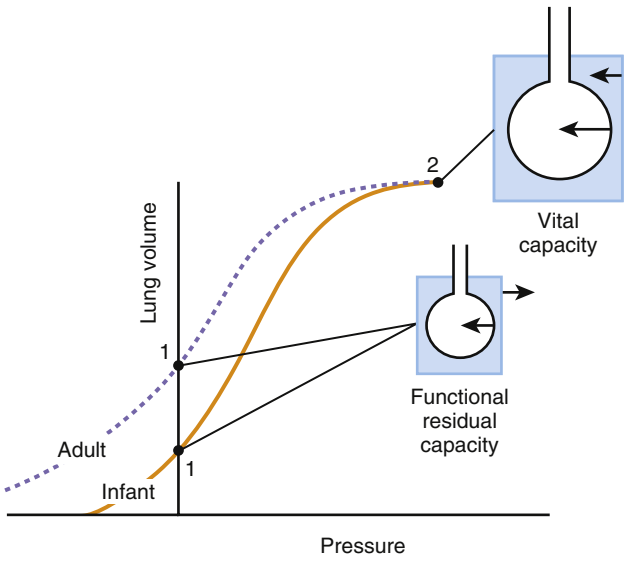

Figure 41–5. Relative ventilation and perfusion maps. Regional ventilation and perfusion scaled to the measured minute ventilation and cardiac output in the pig. Both regional ventilation and perfusion show clustering in which adjacent units have similar flows. There is strong correlation in which areas of high ventilation receive high perfusion and areas of low ventilation receive low perfusion. (These pig lungs were examined in cubes of 1.5–2.0 cm^3 volume.)

that vasoregulation is of minor importance for maintaining close V_A/Q matching in the uninjured lungs.[21,22] This concept was supported by animal and human experiments employing a variety of agents to alter baseline pulmonary vascular tone that showed little effect on ventilation/perfusion matching.[23]

Passive matching of perfusion and ventilation by pulmonary structure suggests an optimally engineered system because it requires no active feedback mechanism during normal function, which tends to develop fewer complications (Figure 41-5).[24] Furthermore, a fractal system delivers substrate with a minimum of energy expended because the fractal structure minimizes the total hydrodynamic resistance of the system. Additionally, the fractal structure appears to reduce the amount of biologic material to construct the vascular and bronchial trees while still filling the space occupied by the lung.[24] Finally, the fractal structure efficient uses the amount of genetic code to construct the vascular and bronchial structure by using a recursive construction mechanism that requires only a handful of proteins. A much greater amount of genetic code would exist if each branch in the bronchial and vascular system required unique genetic code.

V_A/Q Abnormalities in Pulmonary Disease

Hypoxemia

As previously mentioned, the primary causes of hypoxemia in children are shunt and V/Q mismatch. Shunt differs from V/Q mismatch in that it does not respond to increases in inspired O_2. Oxygen content of arterial blood represents a weighted average of the O_2 content of shunted blood (fraction of shunted blood flow within total blood flow [Q_s/Q_t]) and the remaining fraction ($1-Q_s/Q_t$) times the O_2 content of blood that participates in gas exchange (C_cO_2 or pulmonary capillary blood):

$$C_aO_2 = Q_s/Q_t \times C_vO_2 + (1 - Q_s/Q_t) \times C_cO_2 \qquad (7)$$

Q_s and Q_t represent shunt and total lung blood flow, respectively. This equation can then be rearranged to solve for shunt fraction:

$$Q_s / Q_t = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2} \quad (8)$$

By measuring arterial (C_aO_2) and venous (C_vO_2) O_2 content and by estimating C_cO_2 from the alveolar gas equation, the fraction of shunted blood can be estimated.

Regional alveolar hypoxia causes pulmonary vasoconstriction that restricts blood flow to the area.[25,26] (A similar though less robust response is seen with decreased mixed venous partial pressure of oxygen [$P_{\bar{V}}O_2$].) The response to a local decrease in Po_2 can restore the local Po_2 only to approximately half its normal level, and its efficiency is best when the alveolar Po_2 is in the 70 to 90 mm Hg range.[26] The degree of hypoxic pulmonary vasoconstriction (HPV) varies across the lung and may be affected by sepsis, vasodilators, anesthetics, and changes in inspired oxygen. Inspiration of 100% O_2 worsens V_A/Q mismatch substantially.[27] In neonatal piglets, exposure to chronic hypoxia with resultant pulmonary hypertension did not significantly alter V_A/Q matching during room air or acute hypoxic gas breathing.[5,6]

Alterations in inspired or arterial CO_2 tensions also have been shown to effect V_A/Q ratios. Low concentrations of inspired CO_2 (3% to 5%) improve V_A/Q matching and perfusion heterogeneity in normal lungs, while hypocapnia produces the opposite effect.[28,29] These changes in V_A/Q heterogeneity appear to be dependent upon changes in pH. Hypercapnia appears to improve oxygenation in injured lungs as well, but detailed analysis of V_A/Q relationships remains to be performed.[30]

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is marked by gas exchange abnormalities that include profound hypoxemia refractory to high concentrations of inspired O_2.[31] Patients were found to have a bimodal distribution of lung units, one with essentially normal V_A/Q and another smaller distribution representing shunt that was proportional to cardiac output.[31] In some patients a fraction of units with very low V_A/Q ratios also was found. Areas of high V_A/Q may be observed and correlated with the level of alveolar pressure due to mechanical ventilation and the mechanical properties of the lung. The increase in shunt demonstrated with inhalation of 100% O_2 remained elevated 1 hour after returning to the original FIo_2. Inhibition of HPV in shunt units also may occur as a result of an increase in mixed venous Po_2.

The large intrapulmonary shunt accounts for the lack of response of hypoxemia in patients with ARDS to increases in inspired oxygen. The shunt results from alveolar flooding, atelectasis, and right-to-left shunt through a patent foramen ovale. The low V_A/Q units explain the increase in venous admixture with decreasing inspired fractional concentration of oxygen and may represent transient events that occur when alveoli are in the process of collapsing or reexpanding.[32] Units with low V_A/Q deteriorate to shunt as a result of absorption atelectasis, especially when exposed to high levels of inspired O_2. Diffusion impairment contributes substantially to the gas exchange abnormalities in patients with ARDS.

Pneumonia

Hypoxemia found in patients with pneumonia is multifactorial. Pure shunt was demonstrated in a canine model of pneumococcal lobar pneumonia in the first 48 hours of infection.[33] After 2 days, shunt resolved and perfusion was largely concentrated in alveoli with low V_A/Q ratios. The most common pattern of V_A/Q mismatching in patients with bacterial pneumonia severe enough to require mechanical ventilation was a combination of intrapulmonary shunt and increased perfusion to units with low V_A/Q ratios.[34] High levels of inspired O_2 did not increase in patients with intrapulmonary shunt. Similar findings also were observed in spontaneously breathing patients who had less severe cases of pneumonia.[35] MIGET studies suggested no role for other factors such as intrapulmonary oxygen consumption, diffusion abnormalities, or postcapillary shunt due to increased bronchial blood flow.

Asthma

Ventilation/perfusion abnormalities have been found across the spectrum of patients with asthma, from those in clinical remission to those who are acutely ill. Patients with asthma usually show a bimodal distribution of blood flow with normal units and large areas of low V_A/Q.[36] Patients with asthma experience little intrapulmonary shunt, indicating that collateral ventilation keeps the lung units behind severely obstructed bronchioles open. In these patients, elevated levels of cardiac output augment Svo_2, preserving arterial oxygenation.

Interestingly, patients with asthma demonstrate almost no correlation between measurements of airway obstruction and respiratory and inert gas exchange.[37] A study of serial changes of V_A/Q inequalities and spirometric measurements in patients with acute severe asthma showed that no significant inter-individual correlations existed between maximum airflow rates and V_A/Q inequalities.[37] This finding suggests that spirometric changes predominantly reflect bronchoconstriction in larger and medium-sized airways, whereas V_A/Q abnormalities are mainly related to events, edema, and/or mucus formation occurring in the distal small airways. High inspired oxygen concentrations may prevent HPV and place low V_A/Q regions at risk for absorption atelectasis, and high doses of bronchodilators may enhance the perfusion of low V_A/Q areas, exacerbating V_A/Q mismatch. However, the beneficial effects of bronchodilators on airway resistance generally outweigh the worsening in V_A/Q mismatch.

Pulmonary Embolism

By using inert beads to create a pulmonary embolism, Altemeier et al.[23] demonstrated the nature of ventilation/perfusion abnormalities in a pulmonary embolism. The embolized beads distributed preferentially to high-flow regions of the pulmonary vasculature. They produced a shift of blood toward regions that previously had been low flow. Before the embolization, the regions with high blood flow were matched with high-ventilation regions. After the embolization, regional ventilation changed little. Consequently, the areas to which blood flow shifted now became low V/Q regions, resulting in hypoxemia.

Primary Pulmonary Hypertension

V_A/Q inequalities tend to be moderate even in late stages of pulmonary hypertension.[38] Much of the cardiac output is distributed to lung units with almost normal V_A/Q ratios, while less than 10% perfused underventilated or unventilated areas. When Q is reduced, hypoxemia often occurs because of low mixed venous Po_2. Oxygen, sodium nitroprusside, isoproterenol, and nifedipine worsened V_A/Q matching, but Pao_2 did not decrease because of increased Q. The resultant increase in Svo_2 raised the end capillary Po_2.

Therapeutic Considerations

Positive End-Expiratory Pressure

Positive end-expiratory pressure (PEEP) decreases the proportion of shunt units by recruiting the nonfunctional gas exchanging units, thereby improving functional residual capacity and arterial oxygenation. Additionally, by decreasing cardiac output (Q), PEEP produces a parallel fall in intrapulmonary shunt. However, even when Q is preserved, application of PEEP results in decreased shunt due to the redistribution of blood flow from shunt units to normal units because of alveolar recruitment.[32] With constant Q, PEEP decreases venous admixture and increases mixed venous Po_2. Yet PEEP tends to increase zone 1 and 2 regions within the lung, possibly increasing the vertical gradient of perfusion.

PEEP also affects dead space. Low levels of PEEP decrease dead space by reductions in shunt and mid-range V_A/Q heterogeneity, but high levels of PEEP increase dead space. The increase in dead space with high PEEP results from overinflation of some lung units, leading to compression of capillaries and increases in anatomic dead space by distention.

Prone Positioning

The matching of perfusion and ventilation appears to be improved in the prone position.[39] MIGET analysis has suggested that the improvement in arterial blood oxygenation often seen in the prone position in normal and injured lungs is to the result of improved V_A/Q matching.[39] With use of simultaneous aerosolized and injectable fluorescent microspheres, Mure et al.[40] showed that more evenly distributed ventilation and an increase in the correlation between ventilation and perfusion occurred in the prone position. Studies in humans have demonstrated similar findings.[41]

In ARDS and other lung injury models, nonaerated or poorly aerated portions of the lung are found mainly in the dependent areas. Perfusion is largely gravity independent, especially in zone 3 conditions.[4] The majority of perfusion goes through dorsal lung regions, whether in the prone or supine position. As previously mentioned, positive pressure, especially PEEP, redistributes perfusion toward the dependent portion of the lungs by creating conditions of zones 2 and 1.[4,32] This redistribution may increase the vertical perfusion gradient in the supine position but may reduce it in the prone position.

Nitric Oxide

Nitric oxide (NO) improves gas exchange in persons with acute lung diseases by preferentially increasing blood flow to well-ventilated regions of the lung. NO reaches the well-ventilated units, producing vasodilation and reducing shunt fraction.[42] Beneficial effects appear over a wide range of doses. NO does not appear to be beneficial in persons with chronic lung diseases, possibly because the structural damage precludes rapid vascular changes or because shunt usually is not found in such diseases.

References are available online at http://www.expertconsult.com.

III

Chapter 42

Mechanical Dysfunction of the Respiratory System

J. Julio Pérez Fontán and Joel B. Steinberg

PEARLS

- The work done by the respiratory muscles and, by extension, the energy that must be supplied to these muscles are both defined by the volume-pressure relations of the lungs and the chest wall.
- Volume changes within the respiratory system are dictated primarily by the body's need to take up oxygen and eliminate carbon dioxide and therefore are determined by factors such as physical activity or metabolic rate, which are relatively independent of the condition of the lungs and chest wall. Pressure changes, on the other hand, depend on physical processes that take place in the respiratory system's constituents.
- The respiratory system has a surprising ability to compensate for mechanical dysfunction. However, compensation does not come cheap. It raises the work of breathing in almost every instance, usually by combining increases in the force of contraction of the respiratory muscles with changes in ventilatory pattern. If the increase in work is sufficient to overcome the additional restrictive and obstructive loads applied on the respiratory system, minute alveolar ventilation and arterial P_{CO_2} are maintained within normal limits and respiratory failure is averted. In contrast, if the metabolic and contractile machinery of the respiratory muscles cannot meet the greater work demands, alveolar ventilation becomes insufficient to support gas exchange and respiratory failure ensues.
- It is a common clinical observation that different types of mechanical derangement result in distinctive patterns of breathing. These patterns generally agree with the principle of minimal power expenditure and can be useful to categorize the type of derangement the patient has during the initial evaluation.

From a mechanical perspective, the mammalian respiratory system functions like a reciprocating pump that moves fresh air into the pulmonary alveoli and exhausts spent alveolar gases into the atmosphere. The pump is powered by a specialized group of skeletal muscles (the respiratory muscles) that, through their insertions on the skeletal structures of the chest and abdomen, create movements that expand and sometimes compress the lungs. As often happens with systems that contain moving parts, the respiratory system is particularly vulnerable to mechanical dysfunction. The inefficiencies imposed by this dysfunction and the attempts that the organism makes to compensate for them are indeed responsible for the majority of the signs and symptoms of respiratory disease. Moreover, whether the respiratory system overcomes the effects of disease or, on the contrary, stops fulfilling its basic gas exchange functions (respiratory failure) is a matter that can be analyzed in the pure thermodynamic terms of a balance between the work that must be done and the energy that is available to do it.

This chapter provides a basic understanding of the mechanical function of the respiratory system in health and disease, focusing on the factors that determine both respiratory work and energy expenditure. The first portion of the chapter discusses the forces responsible for the volume-pressure behavior of the lungs and chest wall and how this behavior relates to the work of breathing in both normal and disease conditions. The second portion analyzes the elements that influence the translation of the work of breathing into energy expenditure, with special attention to the factors that define the efficiency of the respiratory system. Throughout the chapter, the unique characteristics of the developing respiratory system and the mechanical features that are relevant for the diagnosis and management of respiratory disease are highlighted.

Work, Power, and Energy Expenditure in the Respiratory System

In simple intuitive terms, the variable that best sums up the function of a muscle-powered pump is the mechanical load that the contraction of the powering muscles must overcome with each pump cycle. Over time, mechanical load translates into power (the product of work by the time that it takes to carry it out) and energy expenditure. Accordingly, whether the respiratory muscles can carry a given mechanical load is ultimately determined by their ability to generate work from the limited amount of energy that they receive from their blood supply. The first law of thermodynamics stipulates that when a certain amount of energy is added to a closed system by an external source (in this case the metabolism of fuels supplied by the circulation to the respiratory muscles), the resultant change in the system's internal energy may either be applied to perform external work (W) over a period of time (t) or is dissipated as heat (Q). Implicit in this statement is the fact that only a portion of the energy that the respiratory muscles derive from metabolic substrates is transformed into respiratory work. This

proportion varies depending on the system's efficiency (E), defined as:

$$E = \frac{W \cdot t}{W \cdot t + Q} \quad (1)$$

Thus workload and efficiency define the demands that the contractile machinery of the respiratory muscles must meet and therefore are the relevant variables in the analysis of the mechanical function of the respiratory system.

Determinants of Respiratory Work

Every high school physics student learns to calculate the external work done to move an object between two points as the product of the force needed to overcome all resistances to the movement by the distance between the points. Because the force may change along the way, the same student may learn at some point that it is more precise to break the movement into many elementary components and then add up all the work components by integration, as shown in Figure 42-1, *A*.

The calculation of the external work during breathing follows the same general principle, with one caveat: allowances must be made for the fact that the lungs and the chest wall move in all the dimensions of space. In other words, their displacements are measured in terms of volume, not distance, and determined by pressure, not force.

The mathematical subtleties of this distinction may become a little clearer if we compare the breath to the action of a syringe, where, by pushing or pulling on the plunger, we create a pressure (P), positive or negative, that has the effect of changing the volume contained in the barrel (V). The work done in this process can be determined by integrating the product $P \cdot dV$, as shown in Figure 42-1, *B*. The obvious corollary is that the work done by the respiratory muscles and, by extension, the energy that must be supplied to these muscles are both defined by the volume-pressure relationships of the lungs and the chest wall.

Volume-Pressure Relationships

Before analyzing the volume-pressure behavior of the various components of the respiratory system, it is helpful to clarify the terminology. Throughout this chapter, the term "thorax" is used in reference to all the moving components of the respiratory system, including the walls of the thoracic cavity (the skeletal rib cage and its soft attachments), the abdomen, and the lungs themselves. Similarly, the term "chest wall" is used to indicate all the structures that form the enclosure of the lungs, including the thoracic wall, the diaphragm, the abdominal wall, and the abdominal organs.

The volume changes of the respiratory system can be easily measured with the help of devices such as spirometers or plethysmographs. For any breath, the thorax (defined by the suffix TH), the lungs (L), and the chest wall (W) all undergo the same change in volume, or:

$$\Delta V_{TH} = \Delta V_L = \Delta V_W \quad (2)$$

The reason for this identity is the existence of a noncompressible and nonexpandable boundary, the pleural space, which links lungs to chest wall and prevents them from changing volume independently of each other.

The pressures needed to inflate the thorax, the lungs, and the chest wall are, however, different from each other. Respiratory physiologists have traditionally approached the analysis of these pressures by taking an imaginary walk from the mouth down the airways to the alveolus, across the lung tissue and visceral pleura to the pleural space, and finally across the chest wall to the surface of the chest (Figure 42-2). The difference between the pressures measured at two consecutive stops is the driving pressure needed to cause or maintain a certain volume displacement:

$$P_{AW} = P_M - P_A \quad (3)$$

$$P_L = P_A - P_{pl} \quad (4)$$

$$P_W = P_{pl} - P_B \quad (5)$$

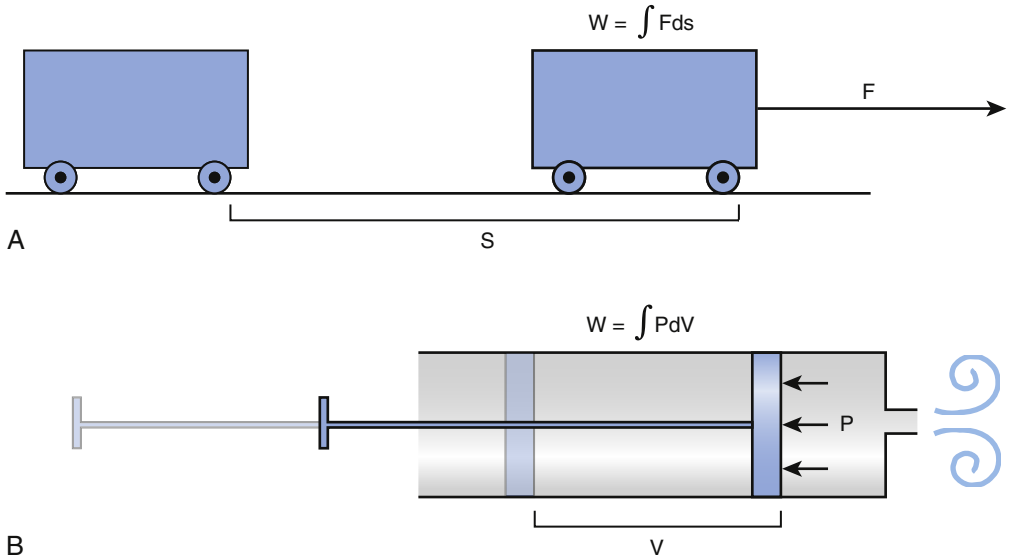

Figure 42–1. A. The amount of work that a force (*F*) must perform to move an object over a linear distance *s* is equivalent to the product $F \times s$. If the force varies during the displacement, then it is more precise to integrate the product of F by the change in *s* (*ds*). **B.** The work needed to produce a volume displacement *V* in a syringe, a better analogy for the respiratory pump, is determined as the integral of the product of the pressure inside the pump (the tridimensional analog of *F*) by *dV* (the tridimensional analog of *ds*).

where P_{AW} is the pressure gradient across the airways, P_M the pressure measured at the mouth (or, for that matter, at the connector of an endotracheal tube), P_L the lung transmural pressure or transpulmonary pressure, P_W the chest wall transmural pressure, P_A the alveolar pressure, P_{pl} the average pressure at the pleural surface, and P_B the atmospheric pressure (conventionally considered to be zero or reference).

Consider first a situation in which the lungs undergo passive distention, without participation of the respiratory muscles. This is what happens during positive airway pressure ventilation, when the pressure drive for inflation of the thorax is provided by P_M. By performing a series of substitutions in equations 3through 5 and assuming $P_B = 0$, we can easily arrive to the following equality:

$$P_M = P_{AW} + P_L + P_W \quad (6)$$

which reveals that, from a mechanical point of view, the components of the respiratory system form a *series* arrangement, whereby the total pressure needed to generate a movement is the sum of the pressures generated in the airways, the lungs, and the chest wall. Respiratory physiologists have often borrowed from electrical theory, assuming, perhaps to the dismay of many readers, that the black and white simplicity of electrical circuitry is less intimidating than the complexities of Newtonian mechanics. When speaking of electrical circuits, the term *series* indicates that every element in the circuit experiences the same current as the circuit as a whole, but the total voltage across the circuit is the sum of the voltages across the individual elements. Because current is the electrical analog of flow (volume per unit of time) and voltage is the analog of pressure, it is easy to see how Equations 2 and 6 justify the overall electrical analogy, even though many readers may be less impressed by how much conceptual clarity it sheds for them.

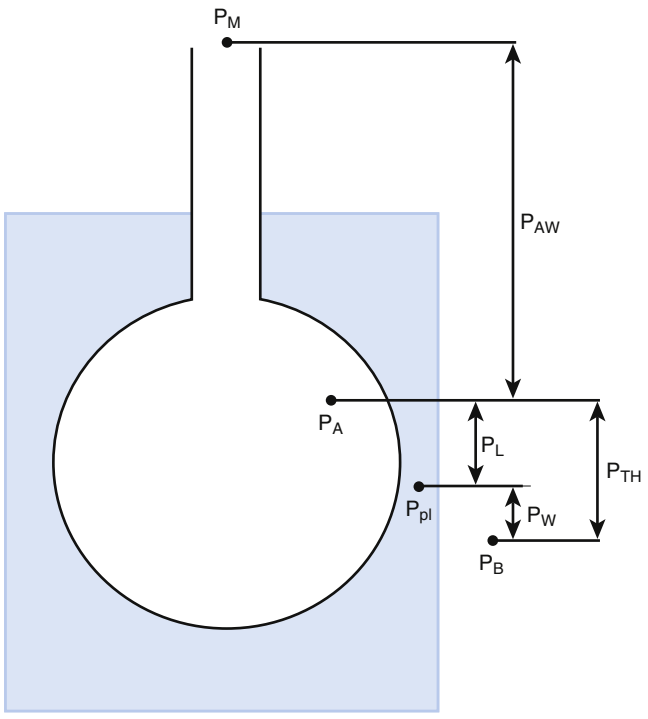

Figure 42–2. Schematic representation of the thorax demonstrating the relevant pressure gradients generated during breathing (these are the gradients that one would encounter during an imaginary walk from the mouth, through the airways, and across the walls of the lungs and the chest wall). The difference (P_{AW}) between the pressure at the mouth (P_M) and the pressure at the alveoli (P_A) drives gas flow between the airspaces and the atmosphere. The transpulmonary pressure (P_L) is the pressure that distends the lungs and is calculated as the difference between P_A and pleural pressure (P_{pl}). The transmural pressure of the chest wall (P_W) is the effective pressure distending the rib cage and abdomen defined as the difference between P_{pl} and atmospheric pressure (P_B). The transmural pressure of the thorax as a whole (P_{TH}) is the difference between P_A and P_B.

The mechanical behavior of the airways and the lungs does not change substantially during muscle-powered breathing. The behavior of the chest wall, on the other hand, is greatly influenced by the contraction of the respiratory muscles. Because the muscles not only act on the wall but are also part of the wall itself, any attempt to define mathematically the behavior of the chest wall during a spontaneous breath becomes a futile exercise. For our purposes here, however, it may suffice to say that, during spontaneous breathing, equation 6 can be modified as:

$$P_{mus} = P_{AW} + P_L + P_W \quad (7)$$

where P_{mus} represents the pressure generated by the muscles' contraction, inclusive of the effects that this contraction has on the behavior of the chest wall itself. Thus every time we take a breath, the neural output to the respiratory muscles is adjusted to overcome as precisely as possible the opposing pressures generated by the respiratory system.

Nature of the Mechanical Forces Acting on the Respiratory Pump

Volume changes within the respiratory system are dictated primarily by the body's need to take up oxygen and eliminate carbon dioxide and therefore are determined by factors such as physical activity or metabolic rate, which are relatively independent of the condition of the lungs and chest wall. Pressure changes, on the other hand, depend on physical processes that take place in the respiratory system's constituents. For instance, elastic pressures result primarily from the tendency of tissue components such as collagen and elastin fibers to recover their original shape after being stretched during lung inflation. Airway resistive pressures relate to friction and overcome the adherence of the moving gas molecules to the airway walls (viscous pressures) and, to a lesser extent, compensate for the loss in gas kinetic energy at points where the movement and direction of the gas vary randomly (turbulence). Tissue-resistive pressures are applied primarily to produce molecular rearrangements in the tissue and at the gas/liquid alveolar interface as the lungs inflate and deflate. Finally, inertial pressures derive from the acceleration and deceleration of the gas and tissue contained in the thorax during breathing. (Inertial pressure losses are negligible in children during normal breathing and therefore need no more than a passing reference here.)

Disease induces alterations in these physical processes and therefore also in the forces and pressures that result from them. To relate these alterations to the disease's clinical manifestations, it is helpful to classify both processes and pressures into nondissipative and dissipative, depending on whether the energy consumed stays in or leaves the system. For instance, elasticity is typically a nondissipative process because the energy needed to produce elastic deformation during inspiration is accumulated in the tissues and then used to empty

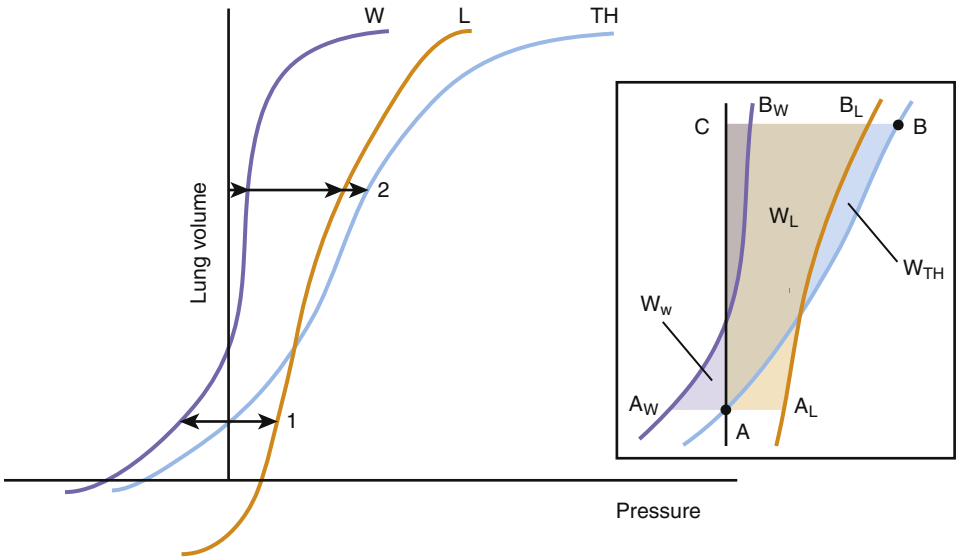

Figure 42–3. Idealized representation of the static volume-pressure relationships of the thorax (TH), lungs (L), and chest wall (W). Pressure, on the abscissa, represents the pressure across the thorax as a whole ($P_{TH} = P_A - P_B$), lungs ($P_L = P_A - P_L$), and chest wall ($P_W = P_{pl} - P_B$; see Figure 42-2). The *arrows* indicate the magnitude and direction of the pressures acting on the thorax and its components at two volumes: (1) the relaxation volume of the thorax, where the recoils of the lung and the chest wall neutralize each other; and (2) an arbitrary volume where the recoils of the lungs and the chest wall act both in the direction of reducing thoracic volume. *Inset:* Detail of the same curves, indicating the elastic work done on the thorax as a whole and each of its components for a volume displacement starting at a volume *A* (the relaxation volume of the thorax) and ending at a volume *C*. The work done on the thorax as a whole is represented by the area *A-B-C*; the work done on the lungs by $A\text{-}A_L\text{-}B_L\text{-}C$; and the work done on the chest wall by $A_W\text{-}A\text{-}B_W\text{-}C$. A portion of the work done on the chest wall (the *triangular area in purple* between A_W and the ordinate axis) is contributed by the recoil of the chest wall, which between those points facilitates the action of the respiratory muscles.

the lungs during expiration. In contrast, all resistive processes are dissipative: the energy liberated by the friction of the gas against the airway walls or by the molecular interactions within the tissue is transformed into heat and transported outside of the system by the blood or the expired gas.

Nondissipative Phenomena: Elastic Behavior of the Respiratory System

Elastic pressures result from the tendency of the components of the lungs and chest wall to recover their original shape after undergoing deformation. Because this tendency increases proportionally to the magnitude of the deformation, elastic pressures are volume-dependent. Thus they are most easily studied when the volume of the thorax is kept constant, a situation in which the absence of movement renders all resistive pressures irrelevant. This can be accomplished by inflating the lungs passively to the desired level or by asking the subject to inspire to a given volume and then to close the glottis while relaxing the respiratory muscles (something that a trained individual can do). In such circumstances, $P_{AW} = 0$, and

$$P_A = P_L + P_W \tag{8}$$

By obtaining measurements at various volumes and then plotting volume against P_A, P_L, and P_W, we can compare the volume-pressure relationships of the thorax as a whole with those of the lungs and the chest wall. Not unexpectedly given the heterogeneous composition of the structures involved, the relationships are complex and cannot be described in a simple mathematical equation (Figure 42-3). In all three cases, the plotted curve has a sigmoidlike shape, with pressure increasing rapidly relative to volume at low and high volumes and more slowly at middle volumes.[1]

Being a continuous function, each volume-pressure relationship has a defined slope at any given volume (dV/dP). This slope defines the *compliance* of the thorax, lungs, or chest wall for that particular volume, depending on whether dP is replaced by dP_A, dP_L, or dP_W. Although a cursory examination of Figure 42-3 reveals that both the lung and chest wall compliances defined in this manner vary markedly over the entire range of volumes, on closer inspection, the ratio dV/dP is relatively constant at normal breathing volumes. Thus for these volumes, it is safe to write:

$$\Delta P_{el} = \Delta V/C \tag{9}$$

where ΔP_{el} represents the change in elastic recoil pressure of the thorax (ΔP_A), lungs (ΔP_L), or chest wall (ΔP_W) for a lung volume excursion ΔV, and C is the compliance of the corresponding component. As lung volume decreases or increases beyond this linear range, dV/dP starts to decrease in a volume-dependent manner, and the respiratory muscles must generate progressively larger pressures to produce the same volume change. Disease frequently causes the lungs to operate outside of their linear volume-pressure range, thereby increasing both the work of breathing and the energy needed to do it.

At any given volume, the lungs, the chest wall, and the thorax each generate a certain elastic pressure or recoil. This recoil can act to increase or decrease volume (as indicated by the direction of the arrows in Figure 42-4). By definition, elastic recoil drives the thorax and its individual components to adopt a volume, known as the *relaxation volume,* at which recoil itself is extinguished. The relaxation volumes of the lungs and the chest wall are the volumes that each of these

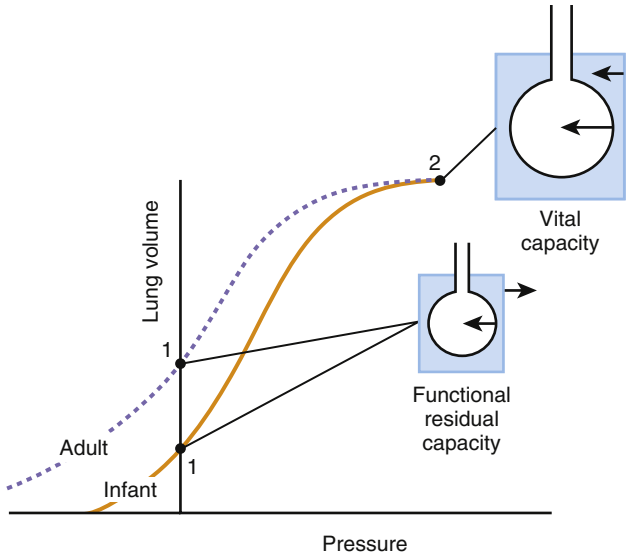

Figure 42–4. Idealized volume pressure relationships illustrating the differences in the elastic behaviors of the infant and adult thoraxes (normalized for vital capacity). The difference between the two points (labeled *1*) highlights the effect of maturation on the relaxation volume of the thorax. In the infant the chest wall is considerably more compliant than in the adult and, as a result, the opposite recoils of the lungs and the chest wall neutralize each other at a lower relaxation volume. Thus infants tend to have a lower functional residual capacity (*FRC*) than do adults. At volumes higher than the relaxation volume of the chest wall, the recoils of the lungs and the chest wall act in the same direction, opposing further increases in volume (as highlighted here at vital capacity, labeled *2*).

components would adopt if all the mechanical constraints imposed by their mutual attachments and interactions were removed. The relaxation volume of the thorax, in contrast, is defined by the mechanical interaction of the lungs and the chest wall. It coincides with the point at which the opposing elastic recoils of these two components neutralize each other (as shown by the equal magnitude but opposite pressure vectors in Figure 42-4).

In the adult, the relaxation volume of the lungs is lower than the residual volume (the volume of gas contained in the lungs at the end of a forced expiration). The relaxation volume of the chest wall, by contrast, exceeds 50% of the vital capacity (the maximal volume of gas that can be inhaled from residual volume). This discrepancy in the relaxation volumes of the lungs and chest wall has three important consequences. First, it forces the relaxation volume of the thorax as a whole to occupy a position intermediate between the relaxation volumes of the lungs and the chest wall (at approximately 35% of vital capacity). Under most circumstances, this volume coincides with the functional residual capacity (FRC), which is the volume contained in the lungs at the end of a tidal expiration. Second, as the thorax starts to rise above its relaxation volume during inspiration, the outward recoil of the chest wall contributes to the expansion of the lungs, thereby reducing the work that the respiratory muscles need to perform during normal breathing (see Figure 42-3, *inset*, where the work done by the chest wall at the beginning of a breath is represented by W_W). Finally, at normal breathing volumes, the opposing actions of the lungs and chest wall recoils create a negative pressure at the boundaries of the lung tissue with the chest wall and the other intrathoracic structures. This negative pressure is an important contributor to the return of venous blood to the chest. The static volume-pressure relationships of the lungs and chest wall vary depending on their state of maturation and health (see Figure 42-4). In the infant, the chest wall generates remarkably little outward recoil within the normal range of breathing volumes.[2-5] Because the inward recoil of the lungs varies little with respect to lung size and age during development,[6-8] the relaxation volume of the infant's thorax is proportionally smaller than that of the adult (as shown in Figure 42-4 by the lower intercept of the volume-pressure relationship of the thorax and the ordinate axis). If, as occurs in the adult, the FRC coincided with this relaxation volume (15% of vital capacity compared with 35% in the adult), then the infant would be at a definite disadvantage in terms of alveolar stability and oxygenation. The newborns of most mammalian species, however, have developed physiologic strategies to maintain their FRC above the relaxation volume of the thorax.[9] These strategies are generally directed at interrupting expiratory flow before expiration is complete and include shortening of the expiratory time,[10] contraction of adductor muscles of the glottis to retard exhalation,[11,12] and persistence of the tonic activity of the inspiratory muscles during expiration.[13] Being so dependent on the pattern of breathing, the FRC of the newborn and small infant is very vulnerable to changes in muscle coordination and tone. As an example, the decrease of tonic activity of the respiratory and laryngeal muscles associated with rapid eye movement sleep[13] may cause a substantial reduction in thoracic lung volume at these ages. Similarly, muscle weakness, anesthesia, deep sedation, and central nervous system depression in general tend to lower FRC below levels compatible with alveolar stability. Under such circumstances, alveoli close, and both the shunt fraction and the work of breathing increase.

In addition to its effects on the FRC, the reduced outward recoil of the chest wall in the infant reduces the chest wall's contribution to lung expansion. It also limits the amplitude of the pleural pressure variations as the lungs expand, an effect that helps to explain the surprising cardiovascular tolerance of many infants to the application of high levels of positive airway pressure.

Lungs/Chest Wall Interactions

Although, considered in isolation, the lungs and the chest wall have different volume-pressure relationships, their mechanical linkage at the pleural space prevents them from changing volume independently. By sharing a common boundary, the lungs and chest wall are also influenced simultaneously by variations in the pressure at this boundary. The resultant interplay is well illustrated by the effects of a pneumothorax, a complication that is quite familiar to readers who practice intensive care medicine. When a certain volume of air enters the pleural space, the most immediate effect is an increase in the pleural pressure (ΔP). This increase causes the effective transmural pressures of the lungs and chest wall to change by the same absolute amount, but in opposite direction: transpulmonary pressure ($P_A - P_{pl}$) decreases by $-\Delta P$, whereas chest wall transmural pressure (P_{pl}) increases by ΔP. No longer held together by a rigid boundary, the lungs and the chest wall respond to the change in transmural pressure by decreasing and increasing volume along their respective volume-pressure relationships (Figure 42-5). Consequently, one could say that the volume of air originally introduced in

the pleural cavity is partitioned into two components, one the volume by which the lungs collapse and the other the volume by which the chest wall expands. The relative sizes of the lung collapse and the chest wall expansion are dictated by the volume-pressure relationships of the lungs and chest wall. If the compliance of the chest wall exceeds the compliance of the lungs (as is usually the case in the infant), then the chest wall expands more than the lungs collapse. The difference is even greater when lung compliance is reduced by disease (Figure 42-5, *B*). Then the chest wall absorbs the majority of the volume change while the lungs barely decrease their volume. This simple analysis explains why noncompliant lungs show surprisingly little collapse when a pneumothorax develops, a finding that is often mistakenly attributed to the "stiffness" of the lung parenchyma. It also provides an opportunity to point out that the magnitude of the chest wall expansion, although frequently overlooked in radiographs, relates more directly to the true malignancy of a pneumothorax (compression of vascular structures) than does the usually more apparent collapse of the lungs.

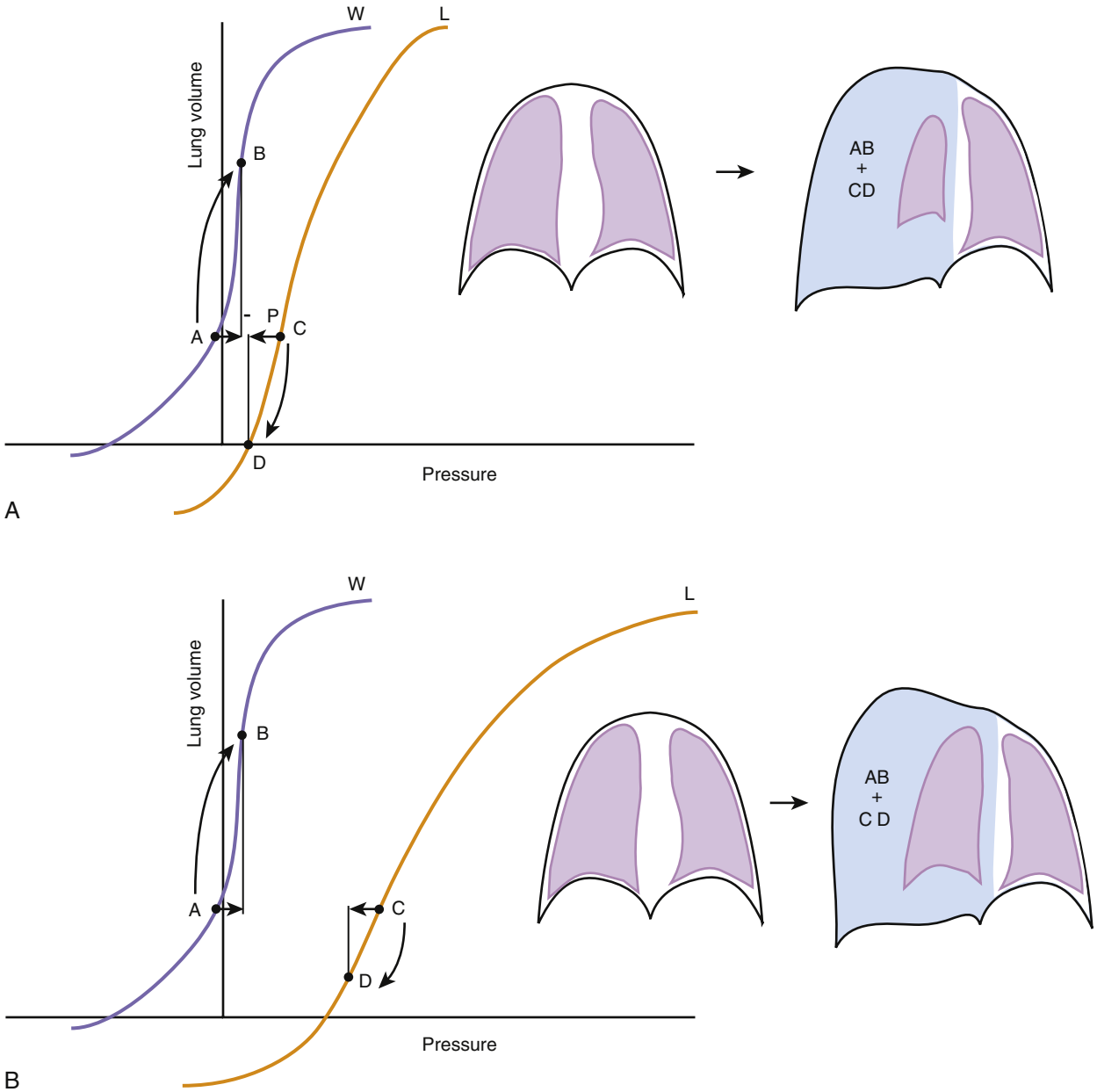

Figure 42–5. **A,** The effects of a pneumothorax are used here to illustrate the interdependence between the elastic recoils of the lungs and the chest wall. Pressures, on the abscissa, represent the transmural pressures of the lungs (*L*, $P_A - P_{pl}$, see Figures 42-2 and 42-3) and chest wall (*W*, $P_{pl} - P_B$). The introduction of a volume of gas into the pleural space raises pleural pressure by a magnitude ΔP, which changes both transmural pressures by the same absolute magnitude, but in opposite directions. Lungs and chest wall respond to the change in transmural pressure by decreasing (*C*→*D*) and increasing their volume (*A*→*B*) along their respective volume-pressure relationships. The volume of the pneumothorax is thus partitioned between the lungs and the chest wall according to their relative compliances. **B,** When lung compliance is decreased by disease, the volume pressure relationship of the lungs is displaced to the right and has a lower slope. Under these circumstances, the chest wall is forced to accommodate the majority of the volume change introduced by the pneumothorax (*AB* >> *C'D'*), giving perhaps the wrong impression that the stiffness of the lungs prevents them from collapsing further.

One important idea to emerge from these considerations is that, respiratory muscle activity aside, the pressure inside the pleural space is really determined by the elastic recoil of the chest wall and the volume of the thoracic contents. As long as lung volume is not forced above its normal range and chest wall compliance is unaltered by disease, pleural pressure (and thus the pressure around the major vessels and the heart) remains low, regardless of the airway pressures. Conversely, excessive lung distension (e.g., in asthma) is always associated with a high pleural pressure and is, for that reason, less well tolerated from a cardiovascular point of view. The dependence of pleural pressure on chest wall compliance explains why premature infants and newborns, who have very large chest wall compliance, have limited changes in this pressure during positive pressure ventilation, even if physiologic lung volumes are exceeded. Disease-induced reductions in chest wall compliance, on the other hand, always increase pleural pressure and reduce venous return to the heart. This is one reason why patients with abdominal distension typically have low cardiac output and why relief of the distension (e.g., by paracentesis in patients with ascites) reduces pleural pressure and increases cardiac output.

Dissipative Forces

Dynamic Volume-Pressure Relationships

Analysis of the volume-pressure relationships of the thorax and its components becomes more complicated when we consider the pressure changes generated by gas flow and by the movement of the lung and chest wall tissue as the lungs inflate and deflate. These pressure changes result from molecular interactions between the gas and the airway walls, within the gas stream itself, and among the components of the gas-liquid interface and the tissue. The same interactions are responsible for well-known physical phenomena such as viscosity (the internal resistance of a fluid to flow), turbulence (the development of chaotic movements within a flowing fluid), or viscoelasticity (a property of tissues and fluids that causes their deformations to be time-dependent rather than instantaneous; ketchup provides a good example when it hangs stubbornly to the bottle before being released after multiple taps).[14-17]

Regardless of their ultimate physical nature, all the phenomena that occupy our attention at this point have two characteristics in common. The first is that they always result in a net loss or dissipation of energy from the respiratory system. The lost energy can no longer be used to perform work, and consequently dissipative pressure losses cause the volume-pressure relationships of the respiratory system to follow a different trajectory depending on the direction of the volume change. This property, known as *hysteresis*, is responsible for the development of loops when the volume-pressure relationships are plotted continuously during a breath (Figure 42-6). In this graphic representation, the dissipative pressures can be easily identified as the horizontal distance between the volume-pressure tracing and the corresponding point on the elastic volume-pressure relationship. The work done against these pressures can be quantified as the area enclosed by the loop.

The second common characteristic of dissipative pressures losses is that they occur only when there is volume change or flow in or out of the lungs (flow is the first derivative of volume with respect to time, dV/dt, and is usually represented with the engineering symbol $\dot{V}$). The relationship between resistive pressure loss (P_{res}) and $\dot{V}$ is, under many circumstances, simple enough to be summarized with a linear equation:

$$P_{res} = R \times \dot{V} \qquad (10)$$

where the coefficient R defines the flow resistance of the thorax, lungs, or chest wall. While the concept of resistance is useful as a pulmonary function assessment and reporting tool, the idea of assigning a fix value to R involves a gross oversimplification. Indeed, resistive pressure losses are influenced by factors other than the absolute flow rate, including among others lung volume, flow direction (inspiratory or expiratory), and breathing pattern. An understanding of the role played by these factors during normal breathing provides valuable insights for the recognition and treatment of airway obstruction.

Effect of Flow Rate and Pattern on the Dynamics of the Gas Stream

The airway tree is a complex fractal structure. A particle traveling in the gas stream from the mouth to the alveolus would be likely to encounter obstacles and bifurcations and to experience periods of acceleration and deceleration along the way. Thus in real life, the pressure losses, and thus the amount of work that needs to be done to sustain these losses, is a complex function of flow and geometry. In the simplest of circumstances, a tube with a uniform diameter, gas flow tends to adopt a *laminar* arrangement with a *parabolic velocity profile*, whereby the gas molecules in the middle move faster than the ones near the wall, which are slowed down by their viscous interaction with the wall (in fact, the molecules next to the wall do not move at all). Under these

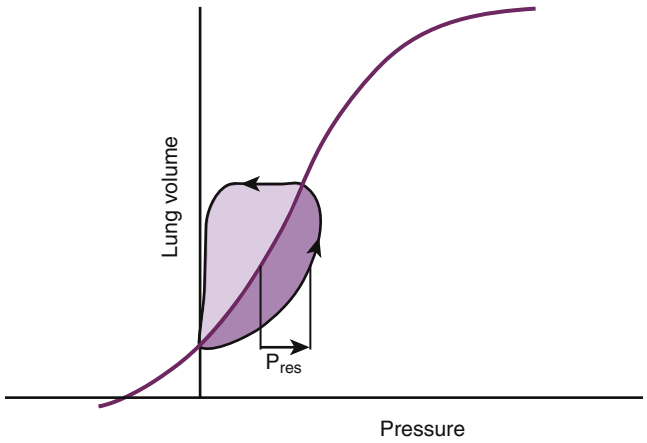

Figure 42–6. Idealized representation of the dynamic or real-time volume-pressure relationship of the respiratory system during a single breath (the *arrows* indicate the direction of the movement). Because energy is dissipated as the lungs change volume, the relationship follows a different trajectory during inspiration and expiration, forming a loop (hysteresis). The horizontal distance between any point in the loop and the line describing the elastic volume-pressure relationship of the respiratory system (*black*) is the pressure needed to overcome the dissipative forces present at the point in the breath (P_{res}). The area enclosed by the loop (*shaded area*) is the amount of energy in overcoming these forces. The inspiratory portion of this work (*darker shading* between the loop and the elastic volume-pressure relationship) must be performed by the respiratory muscles. The expiratory portion of the work (lighter shading) is typically done by the elastic recoil of the lungs and chest wall and requires no muscle effort or energy consumption. The resistance of the respiratory system is calculated by dividing P_{res} by the airway flow.

circumstances, energy dissipation is minimal and the pressure loss in the tube can be estimated with Pouiselle's law:

$$P_{res} = \frac{128 \times \mu \times L}{\pi \times d} \times \dot{V} \quad (11)$$

where μ is the viscosity of the gas, L the length, and d the diameter of the tube. It is easy to see that the fraction on the right side of this equation corresponds to the coefficient R in Equation 10.

Considerable theoretical and empirical evidence exists that although laminar flow is common, Pouiselle flow conditions are rare in the airways. The reason for this phenomenon is that airway segments are generally too short to allow the development of velocity differences between layers and thus the establishment of a parabolic profile. The resultant blunt velocity profile (i.e., the molecules move at similar speed in the center lines as in the vicinity of the airway wall) results in greater friction and causes the relationship between P_{res} and $\dot{V}$ to become nonlinear. Or, put in a different way, the value of R becomes dependent on $\dot{V}$.

The dependence of R on $\dot{V}$ becomes even more pronounced when an obstacle disturbs the laminar organization of the flow stream. Under these circumstances, the velocity and direction of the gas molecules can vary vigorously and randomly and a turbulent flow pattern is created. When this pattern is created, energy dissipation increases exponentially with flow and the density of the gas becomes more relevant than its viscosity in determining both pressure losses and work. This is the reason why helium, which has a much lower density than air, can decrease the work of breathing substantially in patients with some forms of airway obstruction (even though its viscosity is slightly greater than the viscosity of air). The development of turbulence in pipe systems and airway casts has been the subject of considerable study. Turbulence can be predicted when the ratio of inertial (density-dependent) to viscous (viscosity-dependent) forces acting in the flow stream exceed a certain value. This value is best exemplified by the Reynolds number (Re), a dimensionless quantity calculated as $\varrho \times d \times \dot{V}/\mu \times A$, where ϱ is the density of the gas. In general, Reynolds numbers lower than 2300 are associated with laminar flow and those greater than 4000 are associated with turbulent flow.

Airway Dynamics

The airways provide a distribution network to transport gas to and from the gas-exchanging units of the lungs. Although often idealized as a system of passive pipes, the airway network is in reality a highly specialized organ. Each airway segment, from the nose to the alveoli, has evolved not only to serve specific functions such as humidification and phonation but also to ensure maximal patency under the changing mechanical conditions present during breathing.

Indeed, the activity of the respiratory muscles exposes the airways to nonnegligible transmural stresses (or pressures) during breathing (Figure 42-7). The caliber and length of the airways change in response to these stresses in a manner that is only limited by the passive rigidity of its wall tissues and by the tone of the airway intrinsic muscle. Thus airway transmural pressure (the difference between the pressures measured on the inside and outside surface of the airway wall) and airway wall compliance (defined both as compressibility and distensibility) are the two determinants of airway caliber and ultimately also the determinants of airway resistance.

Airway transmural pressure varies during breathing. Its variations result from the fact that inspiration and expiration have very different effects on the pressures inside and outside the airways. The pressure inside all airways undergoes qualitatively similar changes during each phase of the breathing cycle. During inspiration, for instance, there is a gradient of increasingly negative pressures from the mouth, where pressure is atmospheric (or the zero reference), to the alveolar spaces, where the pressure must be negative (or subatmospheric) for gas to flow in. This negative pressure is of course driven by the actions of the respiratory muscles and transmitted to the lungs via the link between the chest wall and lungs at the pleural space. During expiration, alveolar pressure becomes positive and the gradient is inverted, with the pressures inside the airways being always positive but diminishing toward the mouth.

The pressure outside the airways is influenced in a different fashion by inspiration or expiration depending on whether the airways are extrathoracic or intrathoracic. Extrathoracic airways are included in the tissues of the neck, where the pressure can be considered to be atmospheric (at least in nonobese individuals, in whom tissue gravitational forces are neutralized by the skeletal support of the neck). Most of the intrathoracic airways are embedded in the lung tissue, where multiple tethering elements transmit the stresses (or pressures) generated by the tissue recoil to the airway wall (a phenomenon known as *pulmonary interdependence,*[18,19] which is explained visually in Figure 42-8). Therefore the pressure outside the intrapulmonary airways approximates the pleural pressure and, as we have seen, relates to lung volume in a manner that depends on the pressure-volume characteristics of the chest wall (see the section on Lungs/Chest Wall Interactions).

Taking these considerations altogether, it follows that the effect of inspiration and expiration on airway caliber is very different depending on whether the airway is outside or inside the chest cavity. During inspiration, the extrathoracic airways (i.e., the pharynx, larynx, and extrathoracic portion of the trachea) become narrower because the pressure inside their lumen decreases while the pressure immediately outside their walls is constant (pulling the airway wall in, as shown by the direction of the arrow acting on the wall of the trachea in Figure 42-7, *top panel A*). The intrathoracic airways, however, become dilated because the pressure outside their walls (the pleural pressure) decreases more than the pressure inside their lumen (Figure 42-7, *top panel B, C,* and *D*). Conversely, during expiration the extrathoracic airways increase their caliber as their inside pressure becomes positive with respect to atmospheric pressure (pushing the wall out, as also shown by the direction of the arrow in Figure 42-7, *bottom panel A*) and the intrathoracic airways narrow as their inside pressure decreases with respect to pleural pressure (Figure 42-7, *bottom panel B, C,* and *D*).

It is important to understand that the narrowing of the intrathoracic airways during expiration is contingent on the existence of a pressure gradient from the alveoli to the mouth. As predicted by Equation 4, alveolar pressure (P_A) must always exceed pleural pressure (P_{pl}) by a magnitude equivalent to the elastic recoil of the lungs. As the gas progresses downstream during expiration, frictional pressure losses lower the pressure inside the airways. Eventually the cumulative pressure losses can be as large as the pulmonary elastic recoil, and the

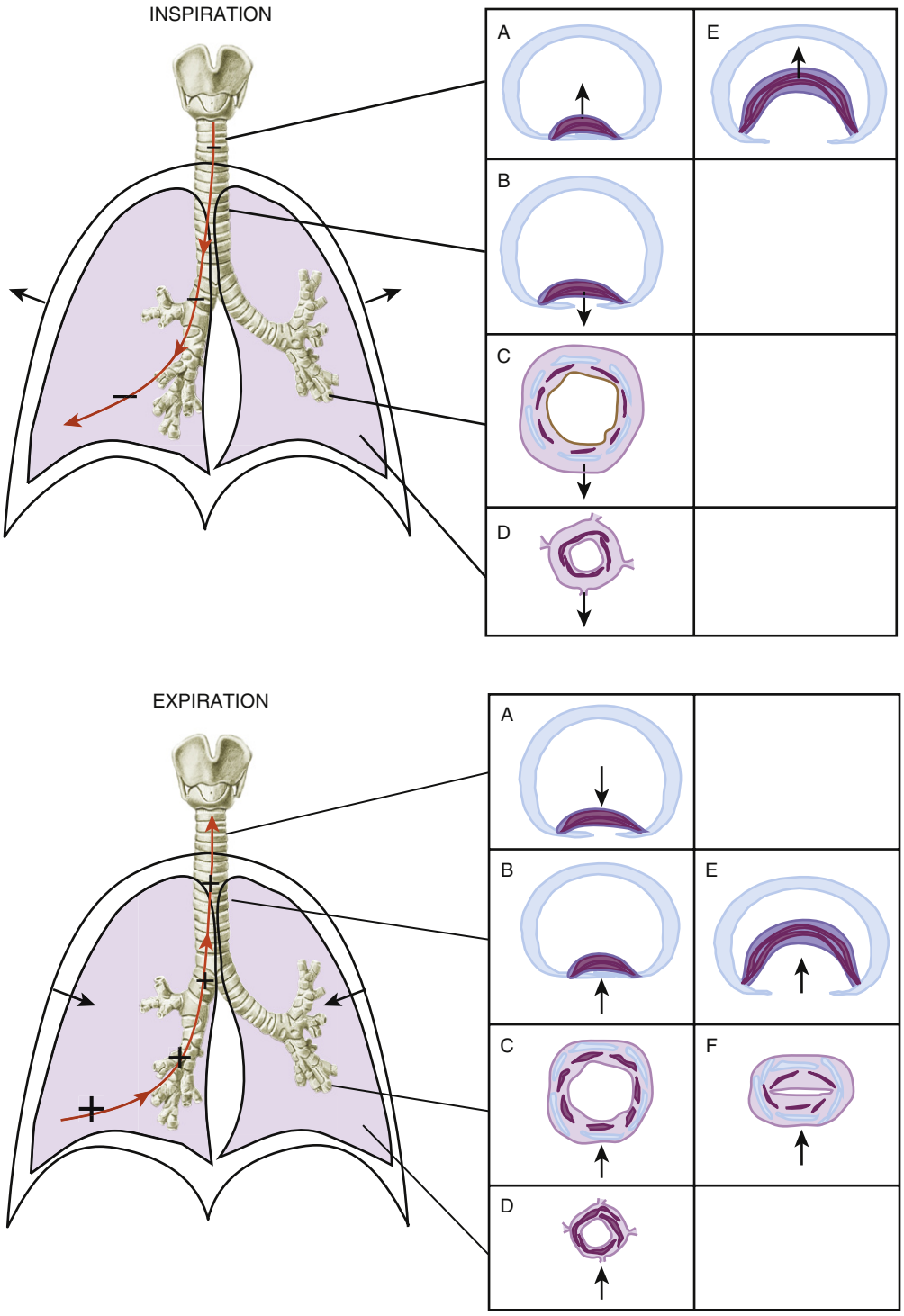

Figure 42–7. Schematic representation of the effects of inspiration and expiration on the dimensions of the extrathoracic and intrathoracic airways. During inspiration, the contraction of the respiratory muscles creates a negative pressure (relative to atmospheric) in the alveoli. This pressure drives inspiratory flow and, depending on the flow itself and the resistance of the airways, results in progressively less negative—but negative nonetheless—pressures in the direction of the mouth (as shown by the smaller size of the negative signs in the picture). During expiration, the recoil of the thorax (and, at times, the contraction of the expiratory muscles) reverses the situation, and pressures are more positive in the alveoli than in the more proximal airways. The caliber of the airways is determined by the difference between airway pressure and the pressure acting on the outside surface of their walls (airway transmural pressure). The latter approximates atmospheric pressure (zero reference) for the extrathoracic airways and pleural pressure for the intrathoracic airways. Thus, during inspiration, the transmural pressure acts to decrease the caliber of the extrathoracic airways (*A*) and to increase the caliber of the intrathoracic trachea (*B*), bronchi (*C*), and bronchioles (*D*). During expiration, transmural pressure has the opposite effect. Abnormalities in the tone of the airway muscle or the stiffness of the airway cartilage exaggerate these effects and promote collapse of the extrathoracic airways during inspiration (shown here for the trachea in *E*) and the intrathoracic airways during expiration (*E* and *F*).

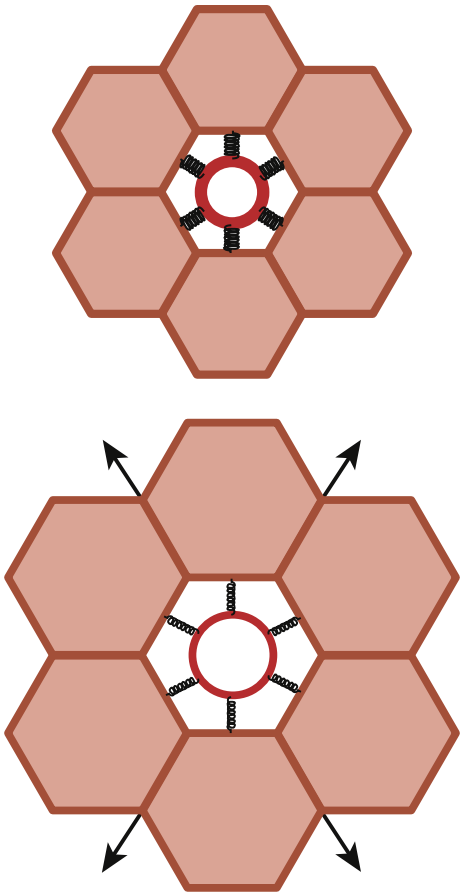

Figure 42–8. Schematic representation of the mechanical interdependence of airways and their surrounding structures. Airways and blood vessels (represented by the *red circle* in the middle of the figure) are tethered to their surrounding parenchyma by elastic elements (shown here as *small springs*). During inflation, these elements transmit the stress (or pressure) generated by the elastic recoil of the alveolar walls and pulmonary septa to the airway wall. As long as the airway changes volume proportionally to the rest of the lung, the normalized stress acting on the airway wall approximates pleural pressure. However, if the airway is stiffer than the rest of the lung (for instance, if the airway smooth muscle contracts vigorously), the tethering elements and the anchoring tissues can undergo considerable nonuniform strain (or deformation).

pressure inside the airways becomes equal to P_{pl}. Beyond this equal pressure point, airway transmural pressure becomes negative (i.e., the pressure outside exceeds the pressure inside the airway) and acts to collapse the airway. Depending on the airway's rigidity or compliance (see the following section) and diameter, the interplay between dissipative pressure loss, which increases with flow (Equation 10), and airway collapse, which depends on dissipative pressure loss, can lead to the development of a condition known as *flow limitation*,[20,21] whereby gas flow can no longer increase even if the subject makes a greater effort to raise alveolar pressure. Because the majority of the dissipative pressure losses are related to gas viscosity, this type of flow limitation is known as *viscous* flow limitation (Figure 42-9).

Flow limitation is an important concept that is pertinent to many clinical situations in which flow is both decreased and effort-independent. It occurs in persons with asthma and other forms of intrathoracic airway obstruction[22,23] when the increased effort to exhale does not accelerate lung emptying and is therefore wasted. It also occurs in persons with croup and other forms of extrathoracic airway obstruction when the increased effort to inhale only succeeds in creating more stridor and early respiratory muscle fatigue. However, it is important to point out that not all situations of flow limitation relate to dissipative pressure losses. For more than 30 years we have known that flow in a compliant tube, such as an airway, cannot exceed the minimum flow at which the velocity of a particle suspended in the flow equals the local wave-speed for the tube. The wave-speed is the velocity at which a disturbance travels through the tube, a concept that is familiar to clinicians because the wave-speed is the velocity at which the pulse waveform travels through arteries. Wave-speed flow limitation ultimately results from the coupling of airway compliance and convective acceleration (see Figure 42-9). As the respiratory gas moves through areas of decreasing cross-section, the kinetic energy of the gas increases at the expense of the total energy contained in the flow stream. As a result there is a decrease in the pressure acting on the inner surface of the airway (this decrease is the basis for the Venturi effect), and the transmural pressure of the airway decreases. Once again, if the airway is sufficiently compliant, there is a maximum flow beyond which the inside pressure would decrease faster than can be accommodated by the decrease in cross-sectional area, and flow becomes limited. Regardless of its causal mechanism (viscous or wave-speed), flow limitation occurs at lower flows in the presence of airway obstruction and at low lung volumes, when airway diameter is minimal.

Airway Muscle and Compliance of the Airways

The effect of transmural pressure on the caliber of an airway depends on the mechanical characteristics of the airway itself or, more specifically, on its ability to undergo collapse or distension, a property that is often described as airway wall compliance. The structure of each segment of the airway tree has evolved to minimize luminal distortion in response to the varying stresses that act on the airway wall during breathing. The pharynx and larynx, for example, contain skeletal muscle, which stiffens their walls or dilates the pharyngeal lumen and the glottis during inspiration under the control of cranial nerves IX and X.[24] Loss of pharyngeal or laryngeal tone during sleep or after pharmacologic inhibition or injury of the controlling neurons is the most important cause of upper airway obstruction during inspiration.

The smooth muscle of the trachea and bronchi has a similar function. For instance, the trachea is composed of a series of incomplete cartilaginous rings forming a relatively rigid arrangement that resists the collapsing effects of positive intrathoracic pressures during expiration. The rings leave a dorsal gap, where the wall of the trachea is soft. This weak point is bridged by the trachealis muscle, which, upon contracting, can approximate the edges of the cartilage rings and prevent the soft portion of the wall from bulging into the airway lumen (see Figure 42-7). Like the smooth muscle in other airway segments, the trachealis muscle is innervated by local parasympathetic ganglia. The ganglia in turn receive inputs from parasympathetic preganglionic neurons located in the medulla via nerve fibers carried by the vagus nerves.[25,26] The medullary preganglionic neurons are anatomically and functionally integrated in the control of breathing.[24] As a result,

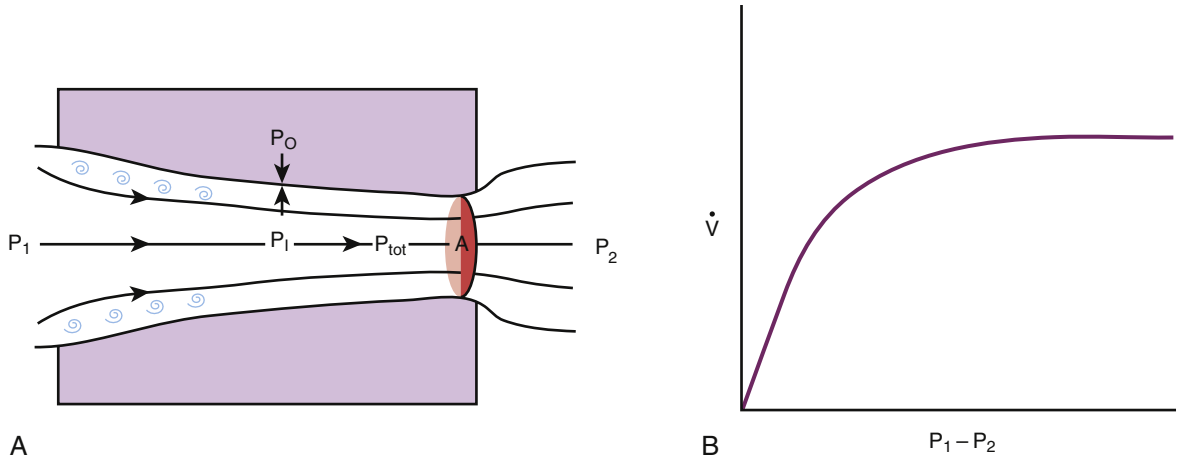

Figure 42–9. **A,** Flow limitation develops when the transmural pressure $(P_I - P_O)$ of a collapsible tube (such as an airway) and the flow in the tube interact in such a manner that the cross-section of the tube (*A*) cannot support an increase in the flow rate, independent of the pressure driving the flow ($P_1 - P_2$). Viscous flow limitation occurs when viscous friction (illustrated by the eddies at the edge of the flow stream) causes the pressure acting on the inner surface of the tube wall (P_I) to decrease faster than can be accommodated at any given flow. Wave-speed flow limitation takes place when the increase in the kinetic energy of the fluid or gas at a point of narrowing causes P_I to decrease relative to the head pressure (P_{tot} or the pressure that we would register with a probe facing the direction of flow) so that any further increase in flow cannot be supported by a further reduction in *A*. **B,** Regardless of the mechanism, when flow is limited, any increase in the driving pressure (or, in the case of the airways, the effort of the respiratory muscles) cannot increase flow ($\dot{V}$).

the traffic of impulses reaching the airway ganglia (and thus the tone of the muscle) varies with the phase of the breathing cycle and increases when the respiratory drive is increased, such as during exercise, hypercapnia, or hypoxemia.[24,27] Malformations or physical or pharmacologic interventions that disrupt the trachealis muscle or its nerve supply lead to tracheal obstruction when the intrathoracic pressure increases during expiration or when the child cries or exhales forcefully.[28] This form of tracheal obstruction often is attributed to tracheomalacia, even though no true softening of the tracheal cartilage occurs.

The bronchial smooth muscle also is innervated by the parasympathetic system.[26,29] In cartilaginous bronchi, the stiffening effect of the muscle contraction is augmented by the cartilage and prevents the bronchial lumen from collapsing when the transmural pressure decreases during expiration, coughing, or crying. In bronchioles, which in humans lack cartilage, contraction of the smooth muscle stiffens the airway walls as well. However, in these smaller airways, smooth muscle contraction may have a more important function of preventing excessive airway distension during inspiration, when the stressed transmitted to the airway wall may disrupt the delicate bronchiolar structure.

Airway Obstruction

Airway obstruction causes an exaggeration of the normal breathing changes in airway caliber. Thus the clinical manifestations of the obstruction depend on its location (extrathoracic or intrathoracic) and the direction of flow (inspiratory or expiratory). When the obstruction is extrathoracic (e.g., as occurs with croup, glossoptosis, and tonsil or adenoid hypertrophy), the subject must create a more negative pressure inside the airway segment downstream from the obstruction to overcome the increased resistance during inspiration. Therefore this segment of the airway tends to collapse, worsening the obstruction and producing a characteristic turbulent noise (inspiratory stridor) as gas accelerates through the narrowest point and induces vibrations in the airway mucosa, creating in the process a decrease in inside pressure that approximates the walls of the airway even further. The obstruction is relieved during expiration because the pressure inside the airway segment, now upstream from the obstruction, must become more positive with respect to atmospheric pressure to force gas flow through the obstruction.

When the obstruction is intrathoracic (e.g., as occurs with extrinsic compression of the trachea and bronchi, tracheobronchomalacia, and asthma), during inspiration the pressure inside the airways downstream from the obstruction has to become more negative than that inside the airways upstream. However, no matter how negative it is, the pressure inside the airways still must be less negative than the pleural pressure (Equations 3 and 4) because otherwise the lung recoil ($P_A - P_{pl}$) would be negative, which is unimaginable. Thus during inspiration the transmural pressure of intrathoracic airways remains always positive. In contrast, during expiration the pressure inside the airway segment located between the obstruction and the thoracic outlet may become lower than pleural pressure at some point (see the section on Airway Dynamics). This situation, coupled with the convective acceleration of flow at the obstructed segments, causes these airways to collapse and produce high-pitched vibrations (wheezing), expiratory delay, and dynamic hyperinflation.

A Specific Case Study in Airway Mechanics: Mechanical Ventilation

The application of positive pressure in the airways changes the balance of pressures that determines airway caliber. When positive end-expiratory pressure (PEEP) is used, pressure inside the airways is positive (relative to atmospheric pressure) during the entire respiratory cycle. As a result, any portion of the extrathoracic airway that is not bypassed by an endotracheal tube (or the entire extrathoracic airway when mask

ventilation is used) is exposed to transmural stresses that cannot have anything but a dilating effect during both inspiration and expiration. The pressure inside the intrathoracic airways also increases with respect to pleural pressure, with the difference between these two pressures varying as a function of the increase in elastic lung recoil produced by the inflation. For this reason, PEEP has been proposed as a therapy to decrease airway resistance and gas trapping in patients with intrathoracic airway obstruction.[30-33] Although PEEP is beneficial in some of these patients, in others, it increases lung volume,[34] interferes with cardiovascular function, and ultimately decreases oxygen delivery to the tissues.[35] The individual variations in the response to PEEP of patients with airway obstruction may simply reflect differences in the mechanisms of dynamic hyperinflation.[32] In patients who have gas trapping without expiratory flow limitation, proximal airway pressures (and thus also PEEP) are transmitted faithfully to the alveoli. As a result, their lung hyperinflation worsens. By contrast, in patients who have both gas trapping and expiratory flow limitation, PEEP may not affect the pressures upstream of the flow-limiting point; therefore, alveolar pressure and lung volume may not increase as much. The pressures inside the airways and downstream of the flow-limiting point increase, dilating the airway cross-section and thereby increasing the rate of lung emptying. Although PEEP is not recommended in every patient, its judicious use may be considered, under careful monitoring, to improve the mechanical function of the lungs of some selected infants and children with severe obstructive airway disease.

Determinants of Regional Gas Flow Distribution in the Lungs

From a mechanical perspective, the lungs form a parallel arrangement of acinary or multialveolar units, each supported by a conducting airway. The development of inequalities in the mechanical and gas-exchanging functions of these units is a fundamental factor in the manifestations of lung disease. To understand how mechanical inequality affects the distribution of ventilation in the lungs, it is essential to realize that the potential filling volume of any alveolar unit is determined by the unit's compliance. However, the actual filling volume during a breath depends on the rate at which the unit can fill relative to other units.[36] This rate is a function of the unit's compliance and resistance and often is defined by their product, a constant with the dimension of time known as the time constant (represented by the Greek letter τ).

The mathematical formulations that describe the distribution of flow among units with different time constants can be very complex. However, it is possible to make some basic predictions of how a certain flow pattern will influence the distribution of tidal volume among these units.[17,37] Imagine a simplified lung composed of three units (Figure 42-10), one with a normal compliance and resistance (normal τ), another with a low compliance and a normal resistance (short τ), and the third with a normal compliance and a high resistance (long τ). As long as the inspiratory time is sufficiently long to allow equilibration of alveolar pressures within the lungs, a decelerating inspiratory flow pattern (pressure-controlled ventilation) will inflate all three units proportionally to their compliances, thus favoring the two units with normal compliance. If the inspiratory time is shortened, however, gas is still flowing at the end of inspiration. This situation results in pressure and inflation inequalities among the units, with a disproportionate portion of the tidal volume being directed to units with a short time constant (once again proportionally to their compliance) and away from the unit supplied by an obstructed airway. The effect of such redistribution on gas exchange depends on the blood supply received by each type of unit and therefore is difficult to predict in diseased lungs. However, the astute clinician may derive some insight into the mechanism of a given patient's gas exchange abnormalities by observing carefully the changes induced by variations in the flow rate and duration of inspiration during mechanical ventilation.

Restrictive and Obstructive Respiratory Disease

As seen, inertial pressure losses are relatively insignificant at normal breathing frequencies in children, and viscoelastic pressure losses usually are small and lumped together with other dissipative pressure losses. Therefore the pressure that the respiratory muscles must generate to produce a certain volume excursion of the thorax can be simply considered the sum of elastic and resistive pressures that need to be overcome in the process (see Equations 6 and 7). Because work is calculated by integrating these pressures relative to the same volume change, it immediately follows that the total work done by the respiratory muscles is the sum of the works done to overcome elastic and resistive pressures.

When applying these formulations, it is important to realize that elastic and resistive forces do not always act in the same direction. During inspiration, the respiratory muscles must generate the force to overcome both elasticity and flow resistance. Thus both elastic and resistive works have the same sign and their effect on total work is additive. During expiration, however, the elastic recoil of the lungs normally provides the force needed to overcome resistance. Elastic and resistive works are of similar magnitude and opposite sign, and the total work done by the muscles is zero. When there is intrathoracic airway obstruction, however, the absolute value of resistive work often exceeds that of elastic work. Under these circumstances the expiratory value of total work is no longer negligible and the expiratory muscles must do the balance of the expiratory work.

The term *restrictive respiratory disease* encompasses all conditions in which elastic or nondissipative work is primarily increased. One could also say that restrictive disease is caused by a decrease in thoracic compliance. Whether originating in the lungs or the chest wall, a decrease in thoracic compliance has two important mechanical consequences. First, the work of breathing increases, but only during inspiration; expiration continues to be passive and, in fact, takes place at a faster rate as elastic recoil increases. Second, the relaxation volume of the thorax and the FRC decrease. The resultant decrease in lung volume, which may further reduce lung compliance, may be more pronounced in the infant, whose resting relaxation volume is already low. At low lung volumes, alveoli lack the support provided by the recoil of neighboring structures at higher volumes (mechanical interdependence[18]) and become inherently unstable, particularly if the surfactant system is affected by the disease and surface tension is increased. To prevent alveolar collapse, infants and small children with restrictive respiratory disease often close their glottis toward the end of

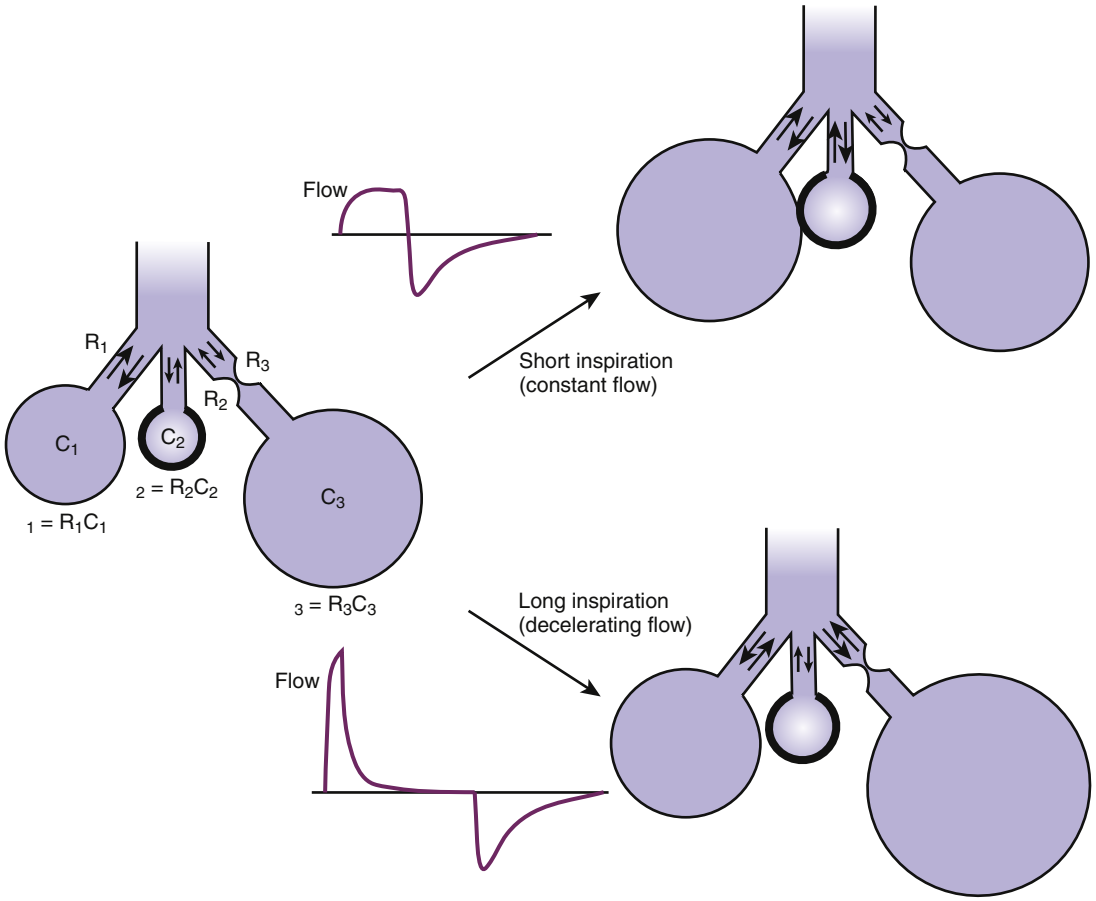

Figure 42–10. Schematic representation of the lung showing the effects of ventilatory pattern on the distribution of inspiratory gas flow. The rate of inflation or deflation of an airway-alveolar unit can be characterized by a time constant (τ) equal to the product of its resistance (*R*) and compliance (*C*). Three types of units are represented in the scheme (each identified by the corresponding numerical subscript): (1) a normal unit with normal compliance and resistance (normal τ); (2) a restrictive unit with decreased compliance and normal resistance (short τ); and (3) an obstructed unit with normal compliance and increased resistance (long τ). Inflation with a decelerating pattern of flow (typical of modern pressure-controlled ventilator modes) favors units with normal compliance (1 and 3). Inflation with a short inspiratory time and a constant flow (more typical of volume-controlled modes) directs flow away from the unit with a long time constant (3), causing the tidal volume of the other units (1 and 2) to be disproportionately larger relative to their compliance.

expiration, causing each breath to end in a grunt. PEEP and continuous positive airway pressure are effective therapeutic modalities to achieve the same objective of preserving the end-expiratory inflation volume.[38-41] Deep lung inflations during positive pressure ventilation (often described as recruitment maneuvers) also may maintain unstable alveoli open for a period. This effect of volume history on alveolar volume decreases the work needed for spontaneous breaths following the inflation and explains some of the beneficial effects of intermittent mandatory ventilation in patients with restrictive lung disease.

Obstructive respiratory disease includes all conditions in which resistive or dissipative work is predominantly increased. The small caliber and high wall compliance of the developing airways render the infant and child more vulnerable to the development of airway obstruction.[42,43] Under normal breathing conditions the small caliber of the airways represents no mechanical disadvantage because there is good correspondence between airway cross-sectional area and gas flow. When obstruction develops, however, airway resistance increases as an exponential function of the reduction in airway diameter (see Equation 11). Because the same absolute decrease in caliber causes a much greater proportional reduction in airway diameter in a small than in a large airway, obstructive lesions tend to have more severe consequences in children than in adults.

Determinants of Respiratory Efficiency

The respiratory system has a surprising ability to compensate for mechanical dysfunction. However, compensation does not come cheap. It raises the work of breathing in almost every instance, usually by combining increases in the force of contraction of the respiratory muscles with changes in ventilatory pattern. If the increase in work is sufficient to overcome the additional restrictive and obstructive loads applied on the respiratory system, minute alveolar ventilation and arterial P_{CO_2} are maintained within normal limits and respiratory failure is averted. In contrast, if the metabolic and contractile machinery of the respiratory muscles cannot meet the greater work demands, alveolar ventilation becomes insufficient to support gas exchange and respiratory failure ensues.

In the final analysis, the success or failure of the compensatory effort is a simple matter of balance between the energy resources available to the respiratory muscles and the energy demands imposed on these muscles. The energy resources are

relatively well defined and limited by the blood supply of the muscles, their ability to metabolize substrates, and the internal efficiency of the muscle's metabolic apparatus. The energy demands on the respiratory muscles are more variable, however, and depend on the workload these muscles must perform per unit of time (i.e., the power they must generate) and the overall efficiency with which the work is performed.

In thermodynamic terms, efficiency is defined as the proportion of the free energy available within a system that is transformed into external work (Equation 1). In the case of the respiratory system, this notion can be reshaped to define efficiency as the quotient of breathing power ($W \times t$) divided by respiratory muscle energy consumption.

In practice, the breathing power has to be calculated from the volume-pressure relationships of the lungs in spontaneously breathing subjects. The energy consumption of the respiratory muscles is in turn estimated from their oxygen consumption,[44] computed as the difference between the total body oxygen consumptions measured during spontaneous and supported ventilation. Some obvious sources of energy consumption, which are not included in the breathing power, reduce the respiratory system's efficiency. For example, the work of breathing does not account for isometric activity of the respiratory and postural muscles, which is not proper work in a physical sense (no volume change) but consumes energy. Other forms of volume-pressure work usually are not taken into account when calculating respiratory efficiency, so they also become sources of apparent inefficiency. The work performed to inflate the chest wall, for instance, cannot be determined during spontaneous breathing when contraction of the muscles changes the wall's passive properties (see the section on Volume-Pressure Relationships). Similarly, the work done to deform the rib cage is difficult to measure and often is ignored. Thus it is not surprising that the published efficiencies tend to be artifactually low.[45,46]

As defined here, the poor overall efficiency of the respiratory system implies that, during each breathing cycle, a substantial amount of energy derived from metabolic substrates is dissipated as heat and cannot be converted into volume-pressure work. Respiratory disease can increase this energy dissipation by various mechanisms, leading to efficiency values as low as 1% to 3%.[45,47,48] Disease-induced alterations in chest wall configuration, for example, can limit force generation by the muscles, thus interfering with the transformation of chemical energy into mechanical energy.[49] Changes in the geometry of the chest wall also modify the spatial relationships of the muscles and can interfere with the transformation of mechanical energy into work. Finally, disease-related anomalies in the contractile state of the muscles produced by fatigue or poor nutrition further decrease muscle force and the work of breathing without decreasing muscle energy demands.[50-52]

Power of Breathing and Breathing Frequency

Unlike work, which is a function of the volume-pressure characteristics of the thorax, respiratory power (work/time) is influenced by the pattern of breathing. It has been held for some time that, at any given time, each subject has an optimal breathing frequency at which minimum power, and thus a minimum energy consumption, is necessary to attain a certain minute alveolar ventilation (Figure 42-11).[46,53,54] Although this view has been challenged by those who believe that breathing frequency is adjusted to minimize average muscle force rather than power (after all, there are no known energy or power receptors anywhere in the body),[55] it is a common clinical observation that different types of mechanical derangement result in distinctive patterns of breathing. These patterns generally agree with the principle of minimal power expenditure. For instance, patients with restrictive lung disease breathe rapidly and shallowly. In contrast, patients with airway obstruction breathe more slowly and prolong their inspiration or expiration, depending on whether the obstruction is extrathoracic or intrathoracic. By simply inspecting the effort and frequency of the breathing movements, the clinician can therefore assess not only the severity but also the specific nature of a patient's respiratory dysfunction. It is important to remember, however, that the high ratio of dead space to minute ventilation in infants and small children mandates a relatively high breathing frequency at rest, even in the presence of airway obstruction. Nevertheless, severe tachypnea in a child with obstructive airway disease should always raise suspicions of an associated restrictive impairment. This distinction is best clarified by the following examples. A breathing frequency of 40 breaths/min can be considered low for a 3-month-old infant who has severe respiratory difficulty from bronchiolitis and is consistent with a predominantly obstructive dysfunction. On the contrary, a frequency of 100 breaths/min in the same infant would be indicative of a predominantly restrictive dysfunction, caused by either parenchymal involvement in the

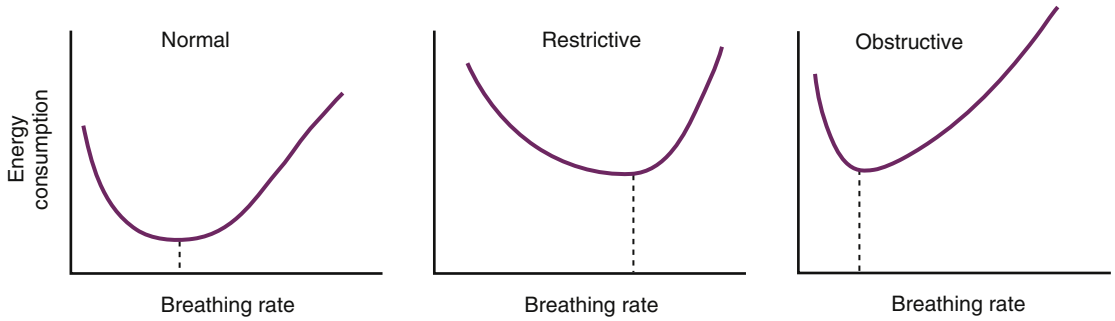

Figure 42–11. Each combination of mechanical conditions is associated with an optimal breathing rate for which the power (work × time) and thus the energy consumption of breathing are minimal. Restrictive disease increases the optimal rate, while obstructive disease decreases it. Actual breathing rates adhere remarkably to predictions based on minimal power. Consequently, it is safe to assume that, under most circumstances, the presence of tachypnea is indicative of a restrictive derangement and that a decrease in respiratory rate or, more precisely, a prolongation of inspiration or expiration indicates an obstructive derangement.

disease (e.g., pneumonitis or collapse) or severe distension of the lungs and chest wall caused by pulmonary hyperinflation.

Alterations in Chest Wall Configuration

Diaphragmatic Configuration

The amount of force developed by a muscle depends on its resting length. An optimal resting length for which maximal force is developed can be defined for each muscle. In the case of the diaphragm, the optimal length is attained at thoracic volumes close to the normal FRC. At these volumes, the muscle has the shape of a dome-capped cylinder, a configuration that has several advantages. First, diaphragmatic contraction shortens the cylinder in the axial direction,[56] producing a pistonlike motion that displaces more volume than if the diaphragmatic dome simply became flatter (assuming the same degree of fiber shortening). Second, the descent of the diaphragmatic dome increases the surface of contact between the rib cage and the lungs. Therefore the increase in lung surface produced by lung inflation can be accommodated without changing the shape of the lung or the chest wall. Finally, at normal breathing volumes, the sides of the diaphragmatic cylinder are apposed to the internal surface of the rib cage. This area of apposition establishes a mechanical link between intraabdominal pressure and lung volume.[52,57] As the diaphragm contracts during inspiration, intraabdominal pressure increases, pushing the lower portion of the rib cage forward and laterally. Thus diaphragmatic contraction has an additional contribution to lung inflation at low energy cost and may help to stabilize the lower rib cage against inspiratory distortion.[58]

The configuration of the chest in the infant and small child minimizes these advantages. At these ages, the lower portion of the infant's rib cage has large anteroposterior and lateral diameters. As a result, the insertions of the diaphragm are spread out, thereby reducing the axial shortening range of the muscle. Moreover, the lack of a substantial area of apposition of the diaphragm and rib cage abolishes the inspiratory and stabilizing effects of intraabdominal pressure on the rib cage.[52]

Thoracic hyperexpansion and abdominal distension exaggerate these limitations by widening the diameters of the lower portion, spreading out the diaphragmatic insertions. The length of the muscle fibers is diminished to a suboptimal length, and the force generated during inspiration is decreased. Abdominal distension has the additional disadvantage of raising intraabdominal pressure, which opposes diaphragmatic contraction and raises the work that the muscle has to do.

Rib Cage Distortion

Until now, we have assumed that the rib cage and abdomen have the same configuration during spontaneous breathing and passive inflation-deflation maneuvers. This assumption implies that all the various parts of the chest wall move with a single degree of freedom and that there are no volume shifts between parts. However, it has been known for quite some time that, under certain conditions, the rib cage and abdomen can change volume independently of one another and even in opposite directions.[59] In other words, the chest wall has multiple degrees of freedom and can undergo regional distortion.

Regional chest wall distortion results from the coupling of changes in pressure (pleural or intraabdominal) and the local compliances of the rib cage and abdominal wall. Rib cage distortion is more pronounced during inspiration, when pleural pressure decreases with respect to atmospheric pressure or the diaphragm pulls the rib cage by its costal insertions, forcing the thoracic wall inward in the expiratory direction. This inward movement of the rib cage causes visible retractions in areas where the chest wall has no bony support (intercostal, subcostal, or suprasternal spaces) or where the support has been abnormally weakened (e.g., costal fractures). Abdominal distortion, in contrast, usually involves alterations in the contractile state of the diaphragm or the abdominal wall muscles. When one hemidiaphragm becomes paralyzed, for example, the negative pleural pressure generated by other inspiratory muscles pulls the paralyzed muscle upward, into the rib cage, during inspiration. As a result, the abdominal wall of the affected side moves paradoxically in the inward direction, and the chest wall becomes distorted. As another example, contraction of the abdominal muscles stiffens the abdominal wall, raising intraabdominal pressure and shifting all volume changes to the rib cage during both inspiration and expiration.

The developing chest wall is particularly susceptible to distortion. As we have seen, the rib cage is very compliant in the newborn.[3,5,60] Although this high compliance facilitates passage through the birth canal, it also promotes distortion of the rib cage during inspiration. In addition, the intercostal muscles, whose main contribution to breathing is to stabilize the rib cage by contracting simultaneously with the diaphragm, appear to have decreased tone at early ages, especially during rapid eye movement sleep and in preterm infants.[61] Finally, the lack of a substantial area of apposition between the diaphragm and the rib cage removes the stabilizing effect of the intraabdominal pressure on the lower rib cage. Accordingly, in infants chest wall retractions tend to develop in the presence of minimal mechanical lung dysfunction.

Chest wall distortion represents a pressure-induced change in volume, and therefore it constitutes a form of work. Distortional work usually is not computed as part of the work of breathing. However, it has a measurable energy cost, and therefore it needs to be viewed as a source of respiratory inefficiency. Both the distortional work and its energy cost can be better understood if we analyze the volume-pressure relationships of the thorax in the particular case of rib cage retractions during inspiration. Regardless of whether such retractions are present, at any point in time, the volume change of the lungs (ΔV_L) must be equivalent to the sum of the volume changes of the rib cage (ΔV_{rc}) and abdomen (ΔV_{ab}):

$$\Delta V_L = \Delta V_{rc} + \Delta V_{ab} \tag{12}$$

Consequently, if ΔV_L is to remain constant, decreases in ΔV_{rc} caused by rib cage retractions during inspiration must be accompanied by a proportional increase in ΔV_{ab} (Figure 42-12). If, as often occurs, ΔV_{rc} is negative, then ΔV_{ab} becomes greater than ΔV_L. Because the volume displacement of the diaphragm approximates ΔV_{ab}, chest wall retractions inevitably result in an increase in the diaphragmatic excursion.

The amount of work done by the diaphragm is calculated by integrating the pressure developed by the muscle relative to the volume displacement produced by the diaphragmatic contraction. In practical terms, the pressure developed by the diaphragm or transdiaphragmatic pressure is defined as the

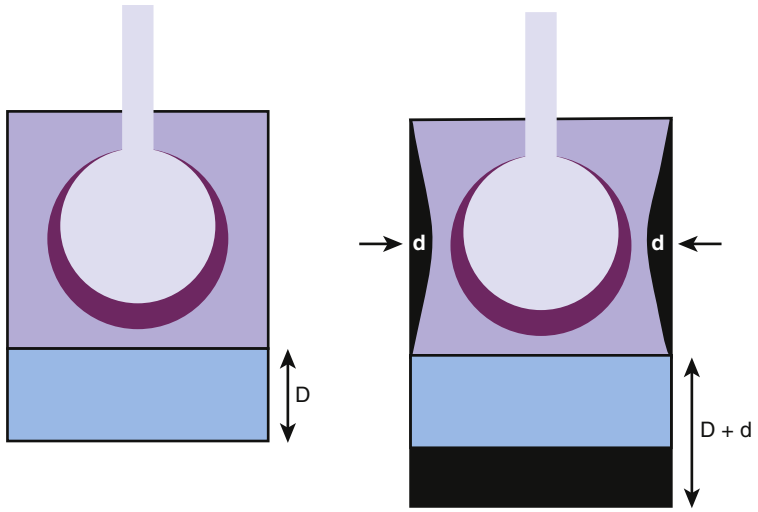

Figure 42–12. Effect of inspiratory rib cage distortion on the volume displacement of the diaphragm. When the rib cage caves inward during inspiration, to generate the same tidal volume in the lungs (shown in *red*), the diaphragm must increase its volume excursion above the non-distorted value (*D*) by an amount equivalent to the volume of the inward movement of the rib cage (*d*). Rib cage distortion usually relates to the combination of an increased rib cage compliance and increased respiratory effort, which translates into more negative pleural pressures acting on the inner surface of the rib cage. However, it can occur without apparent increase in effort, especially in premature infants, or as a result of disease- or trauma-induced chest wall distortion (e.g., rib fractures or unilateral phrenic palsy).

difference between the intraabdominal pressure (P_{ab}, often estimated from measurements of gastric pressure) and the pleural pressure (P_{pl}, estimated from the esophageal pressure). The volume displaced by the diaphragm is estimated as ΔV_{ab} in Equation 12.[62] Thus diaphragmatic work (W_{di}) can be computed as:

$$W_{di} = \int (P_{ab} - P_{pl}) \cdot dV_{ab} \qquad (13)$$

The work done on the airways and lungs to move gas in and out of the alveoli (see Equations 3 and 4) is:

$$W_L = \int (P_M - P_{pl}) \cdot dV_L \qquad (14)$$

P_{ab} is generally greater than P_M (which is 0 in the absence of positive airway pressure), particularly in a recumbent subject. In the presence of rib cage retractions, dV_{ab} greatly exceeds dV_L, and consequently W_{di} substantially exceeds W_L. The volume displacement of the diaphragm may be up to twice the tidal volume of the lungs in premature infants without apparent lung disease,[63] an increase that could be responsible for the poor weight gain and development of fatigue of infants recovering from the respiratory distress syndrome.

Alterations in Contractile State of the Respiratory Muscles

Respiratory efficiency is affected by the functional state of the respiratory muscles. Sustained increases in activity likely will eventually result in decreased contractile force and lower minute alveolar ventilation, a condition often classified as muscle fatigue. When muscle fatigue is present, the energy consumption of the muscle may be increased with respect to the actual work performed. Similar decreases in contractility without a decrease in energy consumption can be present in a variety of clinical situations. Some result from an imbalance between the energy demands of the muscle's contractile machinery and its substrate availability (e.g., shock[64,65]). Others are simply the expression of the inadequate coupling of the excitation-contraction processes inside the muscle cell, changes in the recruitment of specific fiber populations within the muscle,[66] or chronic depletion of the muscle's energetic resources as a result of malnutrition.[50-52]

Conclusion

Although the developing respiratory system has obvious mechanical disadvantages, the reader should not be left with the idea that infants and children are constantly on the brink of respiratory failure. Quite the contrary, they have a remarkable capability to tolerate respiratory disease. This capability is in great part based on a very proficient system of mechanical compensation. The information contained in this chapter is intended to provide an overview of the factors involved in both mechanical dysfunction and its compensation. Unfortunately, the physiological principles underlying the basic concepts presented here are receiving less and less attention in our training programs. The reader is encouraged to visit and study the many classical references contained in the bibliography. While many of them certainly show the signs of age, they provide the critical foundation for a more rational approach to the therapy of respiratory disease in the critically ill child.

References are available online at http://www.expertconsult.com.

III

Chapter 43

Noninvasive Monitoring in Children

Sally E. Rampersad, Kenneth A. Schenkman, and Lynn D. Martin

PEARLS

- Many patients in the pediatric intensive care unit are unusually sensitive to environmental temperature fluctuations. Temperature fluctuations in these patients may occur rapidly and may have important effects on physiology and metabolism.
- Most pulse oximeters measure only oxyhemoglobin and deoxyhemoglobin and ignore other forms of hemoglobin, such as methemoglobin and carboxyhemoglobin. However, blood cooximeters and recently developed noninvasive cooximeters account for these other species.
- The accuracy of the capnogram depends on the sampling site. If the tidal volume is small and the sample flow rate is large, the gas sample may be diluted by entrained fresh gas.
- Capnography can be a good global indicator of the patient's condition.
- The bispectral index monitor is a form of processed electroencephalogram that integrates various electroencephalographic descriptors into a single unitless number that gives an indication of the brain's response to hypnotic agents.

The purpose of monitoring is to obtain frequent, repetitive, or continuous measurement of vital functions that are displayed at the bedside to allow prompt recognition of clinical problems and early initiation of therapy. No single physiologic measurement or group of measures can completely convey the clinical condition of the patient. Monitoring provides objective criteria for the evaluation and treatment of physiologic deficiencies and is an invaluable supplement to clinical judgment, which is more subjective and less easily quantified.

Noninvasive monitoring in the form of vital signs (i.e., heart rate, respiratory rate, noninvasive blood pressure, fluid intake and output, and temperature) has been used routinely for all patients receiving care in the intensive care unit (ICU) since the birth of the specialty. Guidelines for equipment and monitoring and for levels of care for pediatric ICUs (PICUs) were specified by the American College of Critical Care Medicine in 2004.[1] It has become increasingly apparent that accurate and continuous core temperature management may significantly influence outcomes in pediatric critical care. Admission temperature is inversely related to both mortality and late-onset sepsis in low birth weight infants.[2] Cold stress may lead to or worsen hypoglycemia in late preterm infants.[3]

Pulse oximetry and capnometry have significantly affected the practice of critical care medicine and are now standards of care. New technologies currently under development to noninvasively monitor physiologic function may significantly decrease the need for more invasive monitoring and lessen the associated risks of such modalities.

Vital Signs

Heart and respiratory rate, noninvasive blood pressure, fluid balance, and temperature are the simplest, most easily measured, and most commonly monitored and recorded physiologic variables. Heart rate and respiratory rate are continuously recorded and displayed electronically. Changes in these variables alert the ICU team to cardiovascular and respiratory physiologic responses and to changes in clinical conditions and/or responses to pharmacologic interventions.

Electrocardiographic Monitoring

The electrocardiogram (ECG) evaluates the electrical events of cardiac contraction by sensing and recording voltage changes at the body surface. The body is assumed to be a homogeneous volume conductor with uniform geometry. The heart is represented by two charged electrodes: a dipole with one positive pole and one negative pole. This dipole is surrounded by a hypothetical equilateral triangle. The electrical activity of the heart (i.e., changes in magnitude and orientation) are measured throughout the cardiac cycle. The sides of the triangle, which represent the axes of the three standard limb leads, provide a triaxial frame of reference for spatial orientation of the cardiac electrical activity. When combined with the chest (V lead) recordings, the model provides frontal, sagittal, and horizontal components. Continuous ECG monitoring enables the ICU team to be aware of the rate and rhythm of the cardiac contractions. By tracking transthoracic impedence, the ECG leads also monitor respiratory rate and regularity.

Blood Pressure Measurement

Accurate, continuous measurement of noninvasive blood pressure (NIBP) in infants and children can be challenging. Current methods of measuring NIBP are limited to auscultation, oscillometry, ultrasound, and the flush or return to flow.[4] Because of technical difficulties, routine, reliable

measurements of NIBP in infants and children did not become possible until approximately 4 decades ago. Auscultatory determinations, even on an intermittent basis, can be difficult to obtain in infants. In the flush or return to flow technique, the distal extremity is compressed, facilitating blood drainage. An occluding cuff is inflated proximally on the limb and gradually deflated. The systolic pressure is the pressure at which flow returns to the compressed distal extremity.

Numerous subjective influences play a major role in accuracy. Sensitive sound amplification systems have been used, but not commonly in the ICU setting. The most popular method used is based on the principle of oscillometry (e.g., Dinamap, Critikon, Tampa, Fla.), which automatically inflates and deflates the cuff and uses crystal microphones and piezoelectric crystals and the Doppler principle to measure and display systolic, mean, and diastolic pressures. During oscillometry, blood flow through an artery during cuff deflation causes the arterial wall to oscillate.[5] The rapid increase in oscillation amplitude represents systolic pressure, whereas the sudden decrease in oscillation represents diastolic pressure. The period of maximum oscillation is used to estimate mean blood pressure.

The needle bounce technique is another oscillometric method commonly practiced by flight nurses/physicians. An inflated distal or proximal extremity circumferential cuff is slowly deflated, and the first visible bounce corresponds to systolic pressure. Automatically obtained blood pressures by the oscillometric method compare favorably with those obtained via arterial cannulas in infants and children.[6-8] Oscillometric devices do not perform well if there is significant limb movement or in the presence of dysrhythmias.[4] Occlusive systems using frequent measuring intervals can be associated with problems such as skin breakdown after prolonged use.[4,9]

Doppler devices are extremely useful for determining blood pressure in small babies, particularly when shock is present. First, a small Doppler probe is placed over an extremity artery. Blood movement causes changes in exquisitely sensitive ultrasound reflectance, and thus, as a cuff on the proximal extremity is slowly deflated, systolic pressure is signaled by the appearance of the first Doppler effect signal. Diastolic pressure is read when the strength and quality of the signal decrease. Correlation of these two pressures with arterial catheter pressures is good.[10] However, it is important to place the Doppler probe directly over an artery. When an arterial catheter is not available and the automatic oscillometric device is not able to provide pressure readings, the Doppler technique can be used to obtain intermittent blood pressure measurements in the ICU setting.

When measuring blood pressure in babies and children, it is important to select the appropriate-sized blood pressure cuff. Numerous cuff sizes are available, including neonatal sizes. For the upper extremity, the cuff should occupy at least two thirds of the upper arm.[11] The cuff bladder circumferential dimension should be 20% greater than that of the extremity.[11] A cuff that is too small will result in falsely increased readings.[7,11] In contrast, an oversized cuff will artificially decrease blood pressure readings, but the magnitude of this error is small.[7]

Temperature Monitoring and Routine Temperature Management

Body temperature can dramatically alter physiology and metabolism. Monitoring of temperature is a routine part of the practice in the ICU. The accepted normal range of rectal temperature in children is from 36.1° C to 37.8° C.[12] This range is closely guarded by an intact thermoregulatory system that controls heat production and loss. However, many ICU patients can be considered poikilothermic, meaning they are unusually sensitive to environmental temperature fluctuations. A number of factors may contribute to this poikilothermic tendency, including the presence of either endogenous or exogenous vasoactive influences, hypothalamic dysfunction, the administration of drugs that blunt the normal regulation of body temperature, and depression of the central nervous system (CNS), either endogenous or exogenous from administration of sedatives at moderate to high doses. Temperature fluctuations in such patients may occur rapidly. For this reason, the continuous monitoring of core temperature can be particularly useful in selected patients, including those with increased intracranial pressure or status epilepticus who are managed with high-dose CNS depressants and mechanical ventilation; those with unstable hemodynamics after open heart surgery; those experiencing respiratory failure and extreme mechanical ventilation support; and, of course, those being observed for the development of malignant hyperthermia.[13]

Temperature Monitoring Sites

Because core temperature is the principal thermoregulatory controller, monitoring core temperature is more useful than monitoring peripheral skin temperature. Commonly used core temperature monitoring sites include the distal esophagus, tympanic membrane, pulmonary artery, and nasopharynx. These sites detect core temperature changes rapidly, in contrast to urinary bladder or rectal measurements, which are good reflections of core temperature during steady-state conditions.[14] Cutaneous temperature monitoring is the least reliable indicator of rapid core temperature changes. However, monitoring peripheral temperatures can be useful in defining core peripheral gradients in temperature and assist in tracking vasoconstriction and vasodilation. Oral probes are used as thermometers, and some have been attached to pacifiers. A thermometer that scans the temporal artery is also available.[15]

The ideal spot for continuous core temperature monitoring is a pulmonary artery via a catheter, but because of the invasive nature of this monitor, it would never be placed for temperature monitoring alone. An esophageal temperature probe positioned in the lower third of the esophagus is a good alternative. In this position, the temperature sensor is immediately behind the left atrium and accurately tracks core temperature without significant time lag in the majority of situations. If a gastric tube with applied suction is present next to the temperature probe, it must be on the low intermittent setting or the temperature readings will be falsely lowered.

Nasopharyngeal and tympanic membrane temperatures are good indicators of cerebral temperature but can be inaccurate as a result of sensor positioning. Furthermore, trauma to the nasopharynx or tympanic membrane may result in troublesome bleeding, especially when coagulation and platelet function are abnormal.

Axillary and peripheral skin probably are the most convenient sites for monitoring temperatures, although they also provide the most inaccurate readings because of skin perfusion. These sites may be monitored through use of a

wearable continuous-read precision phase change thermometer, which is a dot matrix system of heat-responsive indentations that is secured to the patient via an adhesive backing. In a dot matrix thermometer color changes occur in the dots at specific temperatures related to the melting point of the specific chemical materials in each dot.[15] When continuous core temperature monitoring is desirable, the most reliable and convenient device is the lower esophageal temperature probe.

Pulse Oximetry

Pulse oximetry has become a standard monitoring modality for many aspects of medical care. In the ICU, pulse oximetry is routinely and continuously used to monitor most patients. Of all of the advances in medical monitoring during the past several decades, pulse oximetry has undoubtedly had the largest positive impact on the clinical care of hospitalized patients.

Takuo Aoyagi, working for the Nihon Kohden Corporation in Japan, first proposed the theory for pulse oximetry in 1972. His idea was developed into a working oximeter, which subsequently was patented in Japan in 1974 and marketed as the world's first commercial pulse oximeter. In 1977 a fiberoptic-based pulse oximeter with improved accuracy was marketed by Minolta, and in 1982 Nellcor began marketing a pulse oximeter that ultimately became an industry standard.[16] Since then numerous companies have produced and marketed pulse oximeters, and improvements in technology continue to improve the accuracy and reliability of these devices. Most recently, Masimo Corporation (Irvine, Calif.) introduced pulse oximeters with signal extraction technology[17] that minimizes motion artifact and interference from ambient light and is able to function in relatively low perfusion states. This approach has improved the accuracy of pulse oximetry readings and has decreased the frequency of false alarms in clinical settings.[18-22]

There is also a "blue" sensor that is particularly sensitive in patients with cyanotic congenital heart disease.[23] Standard pulse oximeters are not accurately calibrated for the low saturations seen with some congenital cardiac lesions. Accurate pulse oximetry is especially vital in the neonatal population, who benefit from tight control of oxygenation in order to minimize oxidative stress and to decrease the risk of retinopathy of prematurity.[24]

Principles of Pulse Oximetry

Pulse oximetry is based on the elegant observation that the attenuation of light passing through blood-perfused tissue changes with pulsation of blood and that the alternating component of the light attenuation results from the composition of arterial blood.[25] Figure 43-1 is a schematic diagram showing that the component of light attenuation as a result of pulsatility comes from arterial blood. This information can be analyzed to determine the hemoglobin saturation in the arterial blood. Absorption of light as a result of other tissue components and capillary and venous blood in the static portion of the signal is ignored in the analysis.

Light passing through a turbid media such as tissue is attenuated by absorption and scattering. If light scattering in tissue is assumed to be fairly constant, then measured changes in the attenuation of the transmitted light can be assumed to result from changes in absorption. Beer's law describes the theoretical absorption of light as follows:

$$\text{Absorbance (OD)} = -\log_{10}(I/I_O) = \varepsilon bc \qquad (1)$$

where I is light emerging from the sample, I_o is incident light illuminating the sample, ε is molar extinction coefficient of the specific absorbing species at a specific wavelength, b is path length (in centimeters) the light traverses, and c is molar concentration of the absorbing species. Thus changes in the concentration of an absorber, that is, oxyhemoglobin, results in changes in absorbance.

Hemoglobin has characteristic light-absorbing properties that change with oxygen binding. Figure 43-2 shows absorption spectra of oxyhemoglobin and deoxyhemoglobin in the visible and near-infrared spectral region. At any given wavelength there is a difference in absorption between oxyhemoglobin and deoxyhemoglobin except where the spectra cross at wavelengths called isosbestic wavelengths, where the absorption is the same for each state. At nonisosbestic wavelengths, the difference in absorption can be used to determine

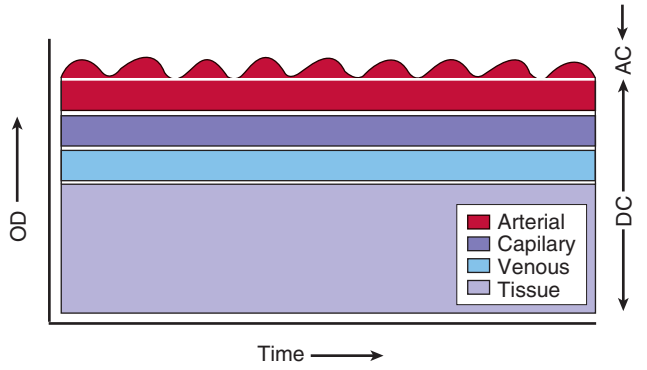

Figure 43–1. Light passing through a pulsating tissue will be absorbed by multiple components of tissue and blood. The alternating component (*AC*) is composed only of arterial blood.

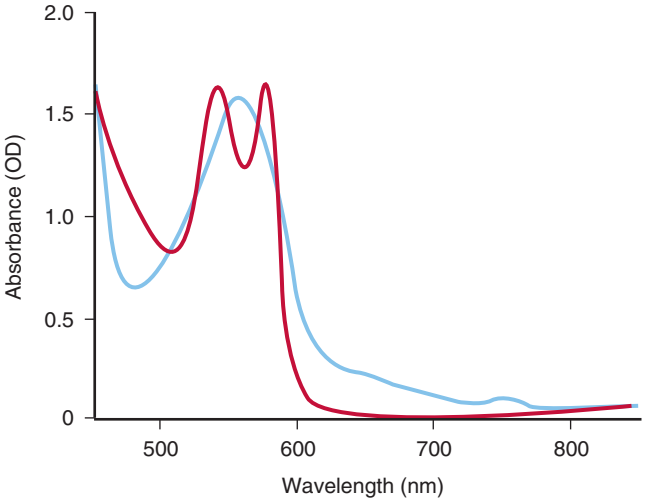

Figure 43–2. Absorption spectra of hemoglobin in the visible and near-infrared spectral region. The deoxy form of hemoglobin (*blue*) has a single peak in the visible and near-infrared region. Oxyhemoglobin (*red*) has two peaks in the visible region but no significant peak in the near-infrared region.

the fraction of oxyhemoglobin. Saturation of hemoglobin is defined as follows:

$$Hb_{sat} = [OxyHb] / ([OxyHb] + [DeoxyHb]) \quad (2)$$

where Hb_{sat} is fractional saturation of hemoglobin, [*oxyHb*] is concentration of oxyhemoglobin, and [*deoxyHb*] is concentration of deoxyhemoglobin. Hemoglobin percent saturation, as commonly reported, is determined by multiplying Hb_{sat} by 100.

Pulse oximeters typically use two wavelengths of light to determine the saturation of hemoglobin, usually one around 660 nm in the visible light region and one around 940 nm in the near-infrared region.[17] The absorption around 940 nm is relatively low and fairly constant over the range of saturations; thus a change in absorbance at 660 nm can be referenced to the absorption at the 940-nm wavelength and is used to determine the saturation. Each pulse oximeter uses a complex algorithm to convert the change in absorbance at the two wavelengths to an absolute saturation value. More wavelengths can be used to improve the accuracy of the measurement.

In the presence of other forms of hemoglobin, primarily carboxyhemoglobin or methemoglobin, the saturation of hemoglobin is correctly determined by the more complex relationship:

$$Hb_{sat} = [OxyHb] / ([OxyHb] + [DeoxyHb] + [MetHb] + [CarboxyHb]) \quad (3)$$

where [*metHb*] is concentration of methemoglobin and [*carboxyHb*] is concentration of carboxyhemoglobin. Most pulse oximeters usually cannot accurately account for the presence of these other forms of hemoglobin. Blood cooximeters, however, do account for these species, as do the newer Masimo pulse oximeters.

Validation

Numerous studies have been performed to validate existing pulse oximeters.[26,27] Pulse oximeters also must be subjected to extensive testing prior to obtaining U.S. Food and Drug Administration (FDA) approval for marketing in the United States. Despite all of the current testing, difficulties in both calibration and validation remain. One of the most significant issues surrounding calibration is the development of an appropriate universal test that will accurately test the pulse oximeter for a wide range of potential clinical applications. Pulse oximeters must be accurate for a wide range of skin thickness and color and over a wide range of saturations. In general, pulse oximeters are most accurate at higher saturations, usually above 75%.[28-30]

Sources of Error

Although pulse oximetry is widely accepted as a valid clinical monitor and provides valuable minute-to-minute clinical data, pulse oximeters are subject to multiple potential sources of error. The most clinically significant source of error usually results from movement or "motion artifact," which, as most clinicians recognize, results in frequent and annoying false alarms. Other sources of error include dyshemoglobinopathies, interfering dyes or other pigments in the blood, ambient light,[31] and poor tissue perfusion. The extent of ambient light interference has been questioned for some of the pulse oximeters studied,[32] but shielding of the probe from ambient light is often used clinically to improve performance. Hypoperfusion also may limit the ability of pulse oximeters to adequately detect a pulsatile signal and can adversely affect reported saturation values.[31]

The presence of interfering dyes or dyshemoglobinopathies is an infrequent clinical problem but can result in erroneous pulse oximetry readings. In methemoglobinemia, the iron in the heme groups in hemoglobin becomes oxidized from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state. The oxidized form of hemoglobin, called methemoglobin, cannot bind oxygen. Thus the presence of significant quantities of methemoglobin leads to tissue hypoxia because these molecules no longer participate in oxygen transport. However, light absorbance by methemoglobin more closely resembles oxyhemoglobin than deoxyhemoglobin at the measured wavelengths, erroneously leading the pulse oximeter to indicate a higher percentage of oxygen saturation than expected.[33,34] Similarly, the presence of carboxyhemoglobin may result in erroneous reading in pulse oximetry because carbon monoxide–bound hemoglobin also does not participate in oxygen transport.[35]

Masimo has recently introduced a pulse oximeter, known as the Masimo Rainbow SET, that uses eight wavelengths of light (Figure 43-3) and thus is able to determine carboxyhemoglobin and methemoglobin levels in addition to oxygenated and deoxygenated hemoglobin.[36] Because these other species of hemoglobin are recognized, it is also possible to have a continuous readout of total hemoglobin. The Rainbow oximeter will be useful not only for monitoring patients with dyshemoglobinemias but also in situations where occult blood loss may be occurring because of its ability to report total hemoglobin. Because the technology is relatively new, confirmation with laboratory samples may still be needed, but trends can then be followed with the oximeter, minimizing the need for blood sampling.[37]

Because cooximeters account for the presence of both carboxyhemoglobin and methemoglobin, blood gas samples sent for cooximetry should correctly measure hemoglobin saturation in cases where measurable levels of either methemoglobin or carboxyhemoglobin are present or suspected. Fetal hemoglobin has a sufficiently similar absorbance spectrum to adult hemoglobin, such that the presence of fetal hemoglobin does not significantly affect the determined saturation.[38] The presence of bilirubin also does not appear to significantly affect pulse oximetry readings.[39]

Probe Placement

Pulse oximetry probes typically are placed on fingers or toes, with the light-emitting diodes placed across the digit, opposite from the detector. For premature and small infants, the probe often is placed around the entire palm or foot with good results. Because of scattering of light in tissue, pulse oximeter probes also can be used in a reflectance mode. In this manner, both light-emitting diodes and detectors are on the same surface and can be placed, for example, on the forehead.[40,41] Transesophageal probes have been designed and are used for care of operative or critically ill patients with potentially poor peripheral perfusion.[42-44]

Cerebral Oximetry

The basic principles underlying pulse oximetry have been extended to determine hemoglobin saturation in the brain. Currently a small number of devices for determination of

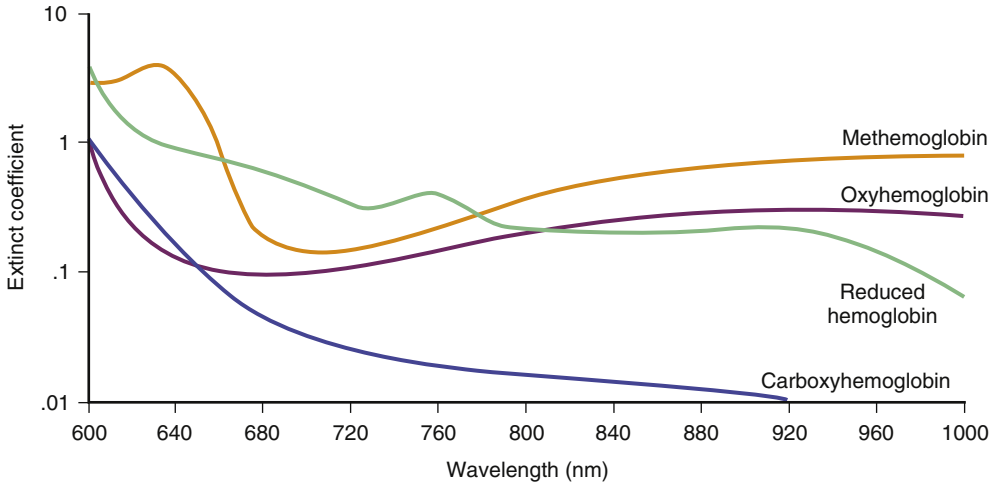

Figure 43–3. Absorption spectra for carboxyhemoglobin, deoxyhemoglobin, oxyhemoglobin, and methemoglobin used in the Masimo SET Rainbow pulse oximeter. *(Modified with permission from the Masimo Corporation.)*

cerebral oxygenation are commercially available. Somanetics and Casmed both have FDA-approved devices available for pediatric use. Hamamatsu also makes a device, the NIRO 300, but it currently has not been approved by the FDA.[45] These devices take advantage of the relative transparency of the skull and brain in the near-infrared spectral region. However, because these devices do not restrict analyses to a pulsatile component, the information provided comes from light absorption of hemoglobin in arterial, venous, and capillary blood and is contaminated to some extent by the presence of other light-absorbing molecules, primarily the cytochromes. Thus these devices provide a "relative" saturation value of cerebral oxygenation, which may have some correlation with clinical conditions,[46] but these devices currently do not report an absolute saturation value in the way that pulse oximeters do. Technical advances likely will improve the clinical utility of cerebral oximetry as the information provided becomes more reliable.

Somatic Regional Oximetry

Near infra-red spectroscopy (NIRS) also has been used to measure somatic regional oxygen saturation (rSO_2). In one resusucitation study of children with moderate dehydration, NIRS probes were placed on the forehead to reflect cerebral rSO_2 and on the flank to reflect somatic rSO_2. In children with moderate dehydration the cerebral rSO_2 was preserved but the somatic rSO_2 demonstrated regional hypoperfusion when the patients were dehydrated and showed an increase with rehydration.[47] Similarly, NIRS was used to provide cerebral and somatic oxyhemoglobin data for a group of neonates with hypoplastic left heart who were awaiting palliation, and it was found to simplify management, allowing more accurate assessment of systemic perfusion.[48]

Muscle Oximetry

Optical spectroscopy has been used to assess muscle oxygenation with increasing success. Earlier approaches for determining muscle oxygenation have been limited by the similarity between optical absorbance spectra from hemoglobin and myoglobin. Many reports of tissue oxygenation as a combined hemoglobin plus myoglobin saturation have been reported.[49] Because hemoglobin and myoglobin have vastly different oxygen dissociation relationships,[50] a combined saturation may have little clinical significance. Successful distinction of myoglobin saturation from hemoglobin saturation has been reported, using a complex multiwavelength spectra analytic approach.[51,52] Because myoglobin is an intracellular oxygen-binding molecule in cardiac and skeletal muscle, myoglobin saturation can be used to determine intracellular oxygen tension. This approach has led to the determination of intracellular oxygen tension measurements in both cardiac and skeletal muscle in laboratory studies.[53-55] Technical advances using this approach likely will have a significant impact on clinical monitoring of critically ill and injured patients.

Capnometry and Capnography

Another monitoring technology routinely used in the critical care unit is the measurement of carbon dioxide (CO_2). Capnometry is the measurement of the partial pressure (or concentration) of CO_2 in the patient's airway during the entire ventilatory cycle. A capnometer provides a numerical measurement of inspired and expired, end-tidal CO_2. Capnography is the graphic display of the partial pressure or concentration of CO_2 as a waveform (capnogram), usually plotted as P_{CO_2} versus time. When the waveform display is calibrated, capnography includes capnometry.

Physiologic Basis

When ventilation and perfusion are well matched throughout the lung, the arterial partial pressure of CO_2 ($Paco_2$) and the partial pressure of end-tidal CO_2 ($Petco_2$) are nearly equal, normally 40 mm Hg. If a discrepancy between ventilation and perfusion exists, a difference between the $Paco_2$ and $Petco_2$, also known as (a-et)ΔPco_2, occurs.

The capnogram displays the CO_2 concentration in the patient's airway over time (Figure 43-4). The essentials of a normal capnogram are (1) zero baseline during early exhalation, which reflects gas exhaled from the anatomic dead space;

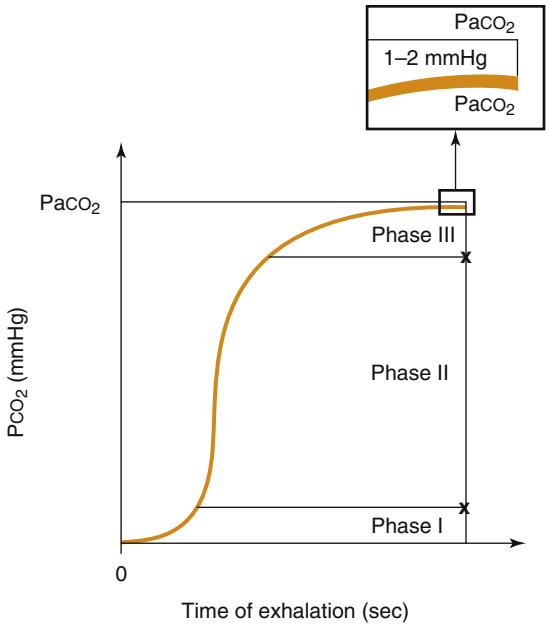

Figure 43–4. Normal capnogram.

(2) sharp upstroke during mid exhalation, which reflects the transition to alveolar gas; (3) relatively horizontal alveolar plateau (the final peak is also known as $Petco_2$ because it reflects the end of expiration; prolonged exhalation caused by obstructive lung disease causes a steeper plateau); and (4) sharp down stroke and return to a zero baseline at the start of inhalation. A capnogram without these normal attributes suggests an anomaly in the patient's cardiopulmonary system, a malfunction in the airway, or a malfunction in the gas delivery system.[56]

Operating Principles of Capnometry

To measure the partial pressure of CO_2 in the airway, respiratory gas must be sampled. In the most common sampling method, gas is diverted from the airway and aspirated through a tube (sidestream) to the CO_2 monitor. Diverting capnometers allow true zero-P_{CO_2} reference measurements, which tend to produce dependable, drift-free performance and thus accurate CO_2 measurements. An alternative to the diverting instrument is the nondiverting or "mainstream" capnometer in which a special flow-through adapter and CO_2 monitor are placed on the patient's airway.

In the majority of stand-alone capnometers, CO_2 concentration is measured by infrared spectroscopy. By comparing absorption by the sample gas with absorption by the reference gas, the capnometer determines the amount of CO_2 in the sample gas, which it then displays as the CO_2 concentration. Raman scattering and mass spectrometry are alternative methods of P_{CO_2} measurement.

Clinical and Technical Issues

Both physiologic anomalies and technical factors can result in $Petco_2$ values that do not approximate $Paco_2$. For $Petco_2$ to approximate $Paco_2$, two assumptions must be met: (1) the lung units must empty synchronously with uniform time constants, and (2) ventilation and perfusion must be well matched in the lung units. Additionally, technical variables can produce $Petco_2$ values that do not approximate $Paco_2$. These include the design of the gas sampling system, the distance the gas must be transported, and the instrument's calibration methods.

Gas Sampling Issues

The gas sampling method used by a capnometer affects the accuracy of the capnogram and $Petco_2$ measurements. Relevant factors include the location of the ventilatory circuit from which the gas is sampled, the distance over which the gas is transported before analysis, and the sample flow rate of the instrument. With a nondiverting or mainstream device, the CO_2 monitor is placed on the airway, so there is no need to divert gas from the airway. This sampling configuration typically is available only in infrared capnometers because only infrared CO_2 monitors can be designed small enough to fit on the airway. A study comparing mainstream proximal end-tidal CO_2 to a novel method that sampled distal end-tidal CO_2 via a special double lumen tube found that the distal end-tidal samples had the best correlation with $Paco_2$ and remained reliable even when severe lung disease was present.[57] Another sampling configuration is seen in the proximal-diverting device. A lightweight, low-profile airway adapter is placed on the patient's airway and gas is sampled from the airway and transported to the sensor, which is placed near the patient but not on the airway itself. A third sampling configuration is found in the distal-diverting device, the classic "sidestream" capnometer. In a distal-diverting system, gas is sampled from the airway and transported to the CO_2 monitor, which is located in the display unit distal to the patient.

The accuracy of the capnogram, the $Petco_2$ measurements, and the displayed values depends on the sampling site (Figure 43-5). In continuous gas flow circuits, sampling in or at the endotracheal tube results in the most accurate values because there is little contamination with fresh gas from the breathing circuit (point A). The Y-connector of the breathing circuit is the next best sampling site (point B). However, if the fresh gas flow is large compared with the expiratory flow rate of the patient (as may be the case in neonates and small children), the capnogram and the $Petco_2$ values may be distorted as a result of dilution with the fresh gas flowing through the Y-connector. If gas is sampled "downstream" from the patient, the waveform and $Petco_2$ are increasingly diluted by fresh gas from the circuit (points C and D). If gas is sampled "upstream" from the patient in the fresh gas supply, none of the exhaled CO_2 is detected and the measured $Petco_2$ is zero (point E). Therefore the best sampling site is within the patient's endotracheal tube or at the tube connector, as far as possible from the Y-connector of the breathing circuit.[58]

In breathing circuits with intermittent flow (demand-valve ventilators) and in larger children with large exhaled tidal volumes, the capnogram and $Petco_2$ values usually are unaffected by minor changes in sampling location. If the tidal volume is small (e.g., as in infants and children) and the sample flow rate is large (i.e., >150 mL/min), the capnogram and $Petco_2$ measurements may be significantly diluted by the entrainment of fresh gas. Using a capnometer system with a low sample flow rate, typically less than 75 mL/min, restores the waveform and $Petco_2$ readings to more accurate values.

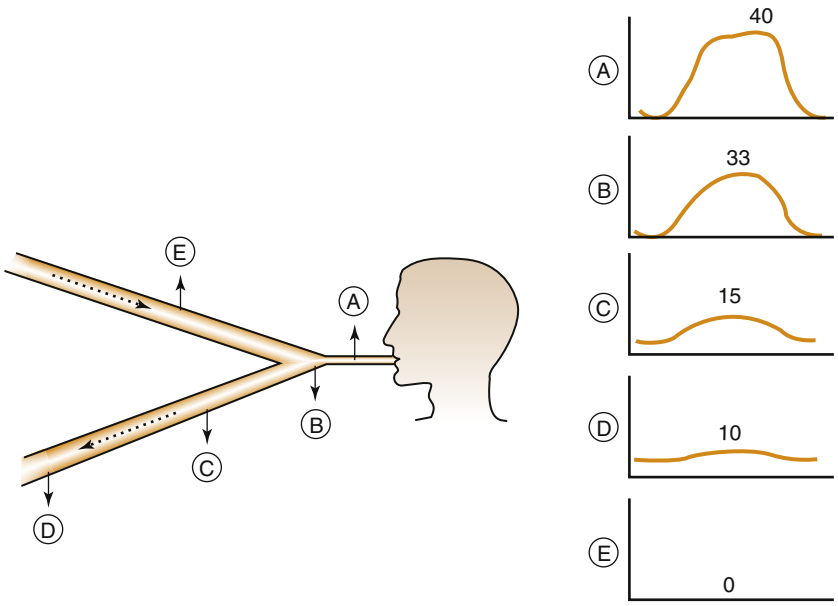

Figure 43–5. Accuracy of end-tidal CO_2 measurements is highly dependent on obtaining good samples of expiratory gas from the patient. If sampled gas is contaminated with fresh gas from the breathing circuit, the measured values will not be accurate. The best samples are obtained from a site nearest to the source of CO_2, the patient (*point A*).

Dead-Space Ventilation

Dead space is the volume of gas in the airways and lung that participates in tidal breathing but does not participate in gas exchange. Obvious examples are the volume of the endotracheal tube and ventilator circuit (apparatus dead space) and the volume of the tracheal lumen and central airways (anatomic dead space). A less obvious, but still important, source of error in critically ill patients is alveolar or physiologic dead space. This dead space is attributable to lung units in which ventilation greatly exceeds perfusion. Gas exchange in these overventilated, relatively underperfused lung units is less efficient than normal.

The fraction of the tidal volume that is delivered to all dead spaces taken together can be calculated using the Bohr equation. A sample of mixed expired air collected over numerous breaths is analyzed for mixed P_{CO_2} (PE_{CO_2}). The total fraction of dead space per tidal volume is given by:

$$V_D/V_T = (Pa_{CO_2} - PE_{CO_2}) / Pa_{CO_2} \quad (4)$$

Physiologic dead space (VD/VT) can be determined from a variant of the Bohr equation:

$$V_D/V_T = (Pa_{CO_2} - Pet_{CO_2}) / Pa_{CO_2} \quad (5)$$

or

$$V_D/V_T = 1 - (Pet_{CO_2} / Pa_{CO_2}) \quad (6)$$

where Pet_{CO_2} is used in place of a sample of mixed expired air.

In many clinical situations, dead-space ventilation is an appreciable fraction of tidal breathing, including severe respiratory dysfunction,[59] pulmonary hypoperfusion, pulmonary thromboembolism, and cardiac arrest (Box 43-1). In these conditions, the clinician using a capnometer may see a large arterial to end-tidal P_{CO_2} gradient (typically >10 mm Hg). This gradient can be used as an indicator of severity of disease, and Pet_{CO_2} can be used to evaluate trends rather than as a specific measure of alveolar P_{CO_2}.

Box 43–1 Clinical Conditions Associated with Abnormalities in ET_{CO_2}

Increases in ET_{CO_2}

Sudden
Sudden increase in cardiac output
Release of a tourniquet
Injection of sodium bicarbonate

Gradual
Hypoventilation
Increased metabolism (carbon dioxide production)

Decreases in ET_{CO_2}

Sudden
Sudden hyperventilation
Sudden decrease in cardiac output
Massive pulmonary embolism
Air embolism
Ventilator disconnection
Ventilator circuit leakage
Obstruction of the endotracheal tube

Gradual
Hyperventilation
Decrease in metabolism (carbon dioxide production)
Decreased pulmonary perfusion

Absent ET_{CO_2}

Esophageal intubation
Accidental extubation

Modified from Tobin M: Respiratory monitoring, *JAMA* 264:244-251, 1990.

Differential Diagnosis of Abnormal Capnograms

The capnogram probably is the single most reliable and effective monitor of pulmonary ventilation. The integrity and function of the patient's cardiopulmonary system and the

breathing circuit both affect the capnogram, and malfunctions often can be detected by changes in the capnogram.[57,60]

Gradually Decreasing End-Tidal CO_2 Concentration

When the capnogram retains its normal morphology but there is a slow, progressive drop in $ETco_2$ (Figure 43-6), the possible causes include falling body temperature, slowly decreasing systemic or pulmonary perfusion, and hyperventilation. Sedation and neuromuscular blockade attenuate the normal body mechanisms for generating heat to preserve body temperature. As body temperature falls, the patient's rate of metabolism and CO_2 production also fall. If ventilation is controlled and kept constant as body temperature decreases, alveolar CO_2 concentration and arterial Pco_2 decrease. This decrease is reflected in the capnogram as a slow decrease in $Petco_2$ over many minutes. Another cause of decreasing $Petco_2$ is a fall in total body perfusion associated with blood loss or cardiovascular depression. As systemic and pulmonary perfusion decrease, alveolar dead space increases with a resultant fall in $Petco_2$.

Sustained Low End-Tidal CO_2 Concentrations Without Plateaus

Occasionally, with no apparent malfunction in the breathing circuit or in the patient's cardiopulmonary status, the capnogram shows sustained low $Petco_2$ values without a good alveolar plateau. In this situation, $Petco_2$ is not a good estimate of alveolar Pco_2. The absence of a good alveolar plateau suggests that either full exhalation is not occurring before the beginning of the next breath or the patient's tidal volume is being diluted with fresh gas because of a small tidal volume, high aspirating sample rate, or high fresh gas dilution from the circuit. Several maneuvers are available to distinguish between these possibilities.

Incomplete emptying of the lungs may be suggested by adventitial sounds such as wheezing or large airway rhonchi with compromise of small airway patency caused by bronchospasm or secretions. If rhonchi are present, tracheal suctioning often corrects the partial obstruction and restores full exhalation. Bronchospasm may be treated with a variety of bronchodilators. An endotracheal tube that is kinked or partially obstructed by secretions may prevent full exhalation. Passing a suction catheter down the endotracheal tube usually confirms or eliminates this possibility. Gently squeezing the child's chest to assist with a forced exhalation often produces a waveform in which the CO_2 concentration continues to rise toward an alveolar plateau. If the plateau is present, the "squeeze end-tidal CO_2" value may be taken as a good estimate of alveolar CO_2 concentration.

When no signs of partial airway obstruction are present, another explanation for this type of capnographic waveform should be considered. In infants and other patients who have small tidal volumes, the aspirating sample rate may exceed the expiratory flow rate near the end of exhalation. When this occurs, the aspirating sample is diluted with fresh gas from the breathing circuit, resulting in a drop-off of the plateau and a fall in $Petco_2$ as a result of dilution. Reducing the flow rate of fresh gas or moving the sampling site closer to the endotracheal tube connector usually corrects the problem. In very small newborns, a sample rate of 100 to 250 mL per minute may be too high to result in good plateaus despite instituting the preceding corrective measures. Then either a capnographic system having a very low sampling rate (50 mL/min) can be used or the capnogram can be used as a gross monitor of the integrity of the ventilatory circuit and trends in cardiopulmonary function rather than as an accurate estimate of alveolar ventilation.

Sustained Low End-Tidal CO_2 Concentration with Good Plateaus

In some circumstances, the capnogram demonstrates a low $Petco_2$ with a widened (a-et)ΔPco_2 and preservation of a good alveolar plateau. This discrepancy may indicate that the capnograph is malfunctioning or miscalibrated. The clinician can evaluate this possibility by sampling his or her own exhaled CO_2 and verifying that the $Petco_2$ concentration is between 5% and 6% (equivalent to approximately 38 to 46 mm Hg). If the instrument is functioning properly and is well calibrated, a wide (a-et)ΔPco_2 is an indication of excessive dead-space ventilation in the patient.

Exponential Decrease in End-Tidal CO_2

An exponential drop in $Petco_2$ that occurs within a short time (e.g., a dozen or so breaths) almost always signals a sudden and probably catastrophic event in the patient's cardiopulmonary

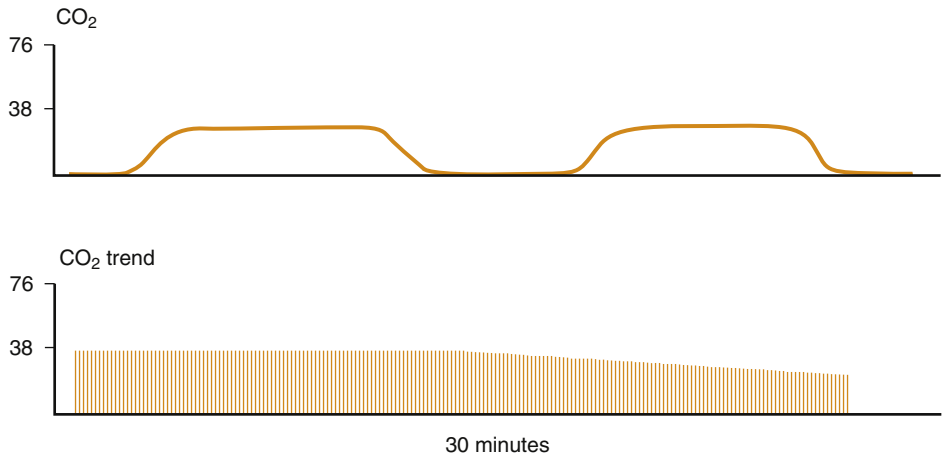

Figure 43–6. Slow, progressive fall in end-tidal CO_2 occurs when CO_2 elimination exceeds CO_2 production or wasted ventilation increases slowly.

system (Figure 43-7). The basis for this capnogram is a sudden and dramatic increase in alveolar dead-space ventilation. Possible causes include sudden hypovolemia, circulatory arrest with continued pulmonary ventilation, and pulmonary embolus with thrombus or air. Only after ruling out these catastrophic events and determining that the patient is hemodynamically stable should more mundane explanations for the exponential decay in $Petco_2$ be considered. The most common noncatastrophic cause is an accidental increase in ventilation attributable to an incorrect ventilator adjustment, resulting in a gradual decrease in $Petco_2$. However, it is important to note that even doubling the alveolar ventilation decreases the $Petco_2$ to only half of the preadjustment value, not to the near-zero values that may accompany catastrophic cardiopulmonary events.

Gradual Increase in both Baseline and End-Tidal CO_2

A gradual rise in both baseline and $ETco_2$ value indicates that previously exhaled CO_2 is being rebreathed from the circuit (Figure 43-8). In this situation, the inspiratory portion of the capnogram fails to reach the zero baseline, and there may actually be a premature rise in CO_2 concentration during the inspiratory phase of ventilation. $Petco_2$ usually increases until a new equilibrium alveolar CO_2 concentration is reached, when excretion once again equals production.

Transcutaneous Monitoring

The development of portable, miniaturized electrodes led to the use of this technology to continuously measure both oxygen and carbon dioxide tension transcutaneously. This technology works under the assumption that transcutaneous values reflect those from the arterial circulation. Heating the skin allows more rapid diffusion of both oxygen and carbon dioxide from the subcutaneous tissues to the surface of the electrode. However, the heating affects both tissue and blood by decreasing oxygen solubility, shifting the oxyhemoglobin dissociation curve to the right, and dilating local arterioles. Temperatures of 44° C to 45° C

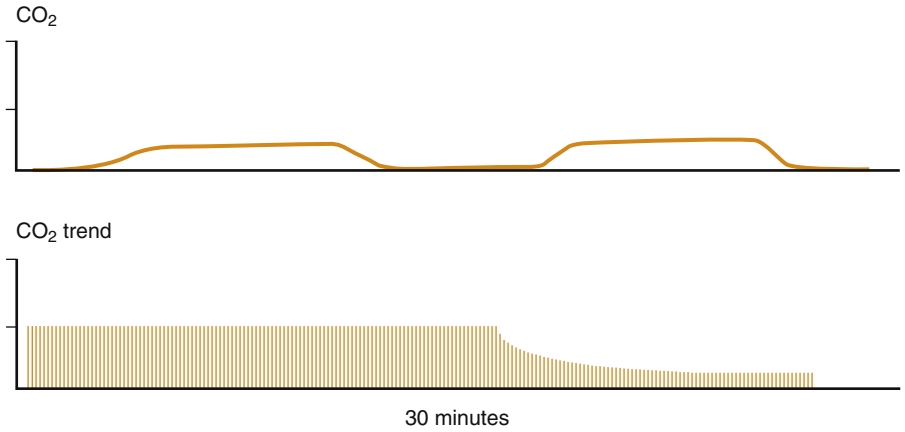

Figure 43–7. Sudden, exponential decay in end-tidal CO_2 values almost always signals a potential catastrophe in the cardiopulmonary function of the child. The causative factor is a dramatic increase in wasted ventilation or dead space. Possible causative events include sudden hypotension such as that resulting from massive blood loss, circulatory arrest with continued pulmonary ventilation, and pulmonary embolism with thrombus or air.

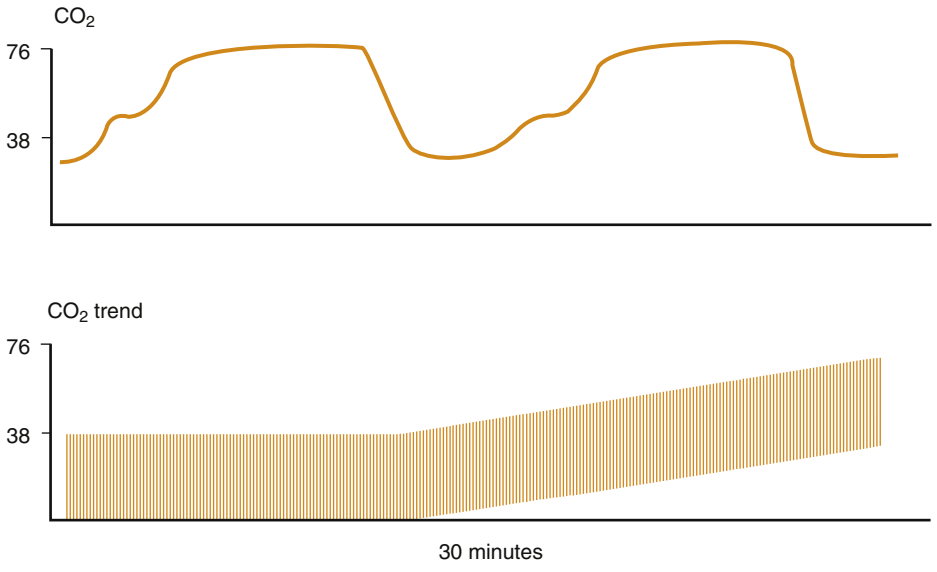

Figure 43–8. Persistent elevation of the inspired CO_2 baseline and a rising end-tidal CO_2 value suggest that the child is rebreathing previously exhaled CO_2. In the intensive care unit, this pattern is often seen when the fresh gas supply to a breathing circuit becomes disconnected from the source.

increase diffusion and prevent vasoconstriction in the local area of the skin.[61]

Oxygen Monitoring

Transcutaneous Clarke electrodes measure oxygen tension in a local segment of the heated skin. Because skin is the organ most responsive to adrenomedullary-induced vasoconstriction, local oxygen tension may not be the same in all skin segments or other tissues. In essence, transcutaneous oxygen tension ($TcPO_{2)}$ is only an indirect reflection of arterial oxygen tension; it is more directly related to local tissue perfusion and oxygenation.

This technology has several limitations. Electrode placement must be changed every 4 to 6 hours to prevent thermal injury to the site of measurement or when readings become unstable. A thermal neutral environment to limit peripheral vasoconstriction increases the correlation between transcutaneous and arterial tensions. Finally, the electrode membranes must be calibrated before each use and each change of measurement site. However, displaying the $TcPO_2$ was shown to result in less time spent hyperoxemic and less time spent hypoxemic than displaying the SpO_2.[62]

Carbon Dioxide Monitoring

Transcutaneous carbon dioxide tension using a Stowe-Severinghaus electrode has been widely used in the neonatal population to approximate $Paco_2$. Transcutaneous CO_2 values parallel but consistently overestimate $Paco_2$ values in hemodynamically stable neonates and adults.[63] The difference in arterial and transcutaneous values reflects accumulation of carbon dioxide in the tissues as a result of inadequate perfusion. Transcutaneous monitoring of CO_2 more closely approximates arterial CO_2 tension in infants and children who are experiencing respiratory failure than does end-tidal CO_2.[64] This technology also is useful in settings where nonconventional forms of ventilation (high-frequency ventilation) preclude the use of end-tidal monitoring.

Cerebral Function Monitoring

Clinical assessment of the level of consciousness is a sensitive indicator of cerebral function. Unfortunately, the assessment can be subjective, particularly in the pediatric population. Standardization of clinical methods, such as the Glasgow Coma Scale, with modifications for infants and children,[65] can decrease but not eliminate the subjective nature of the assessment of consciousness. During the past decade, efforts to use electroencephalographic signals as a more objective measure of cerebral function have been pursued.

Bispectral Index Monitoring

The bispectral index (BIS) monitor uses a processed electroencephalogram (EEG) that integrates various electroencephalographic descriptors, as an assessment of the brain response to hypnotic agents, into a single unitless number on a scale from 0 to 100. The technology processes and evaluates via fast Fourier transform analysis the common characteristic changes and waveform relationships that are seen on the EEG in response to the administration of sedative, hypnotic, and anesthetic agents.

Historical Perspective and Development of the Electroencephalogram

Attempts to monitor the brain have a long history. Dr. Richard Caton, an English physician, described the first recognition of the EEG while mapping brain waves in animals.[66] The physiologic basis for the origin of the EEG potentials comes from the extracellular current flows associated with postsynaptic activity in the upper layers of the cerebral cortex.[67] A psychiatrist, Dr. Hans Berger, went on to describe the human EEG in a series of reports in 1929.[68] In 1937, Gibbs et al.[69] reported that the EEG responded to administration of potent inhaled anesthetic agents.

The electrical signal from the brain is measured in microvolts and is easily acquired using technologically advanced sensors.[70] Advances in computer processing of electrical signals has led to the development of electroencephalographic technology that allows rapid processing of real-time complex waveforms in a small, inexpensive, compact, easy-to-use electroencephalographic monitor. The computer analyzes the complex waveforms using a technique called bispectral analysis, a mathematical procedure originally used for describing wave motion in the ocean. Barnett et al.[71] described the first clinical applications of bispectral analysis of the EEG waveform during natural sleep and waking. Kearse et al.[72] were the first to report that bispectral analysis may predict anesthetic depth.

Age-Related Maturation of the Electroencephalogram

Development of the normal EEG in infants and young children parallels brain maturation, with the most abrupt changes occurring between the last few weeks of gestation and the first 3 months of life. Synapse formation continues after birth up to age 5 years, with the majority occurring (with gradual loss of neonatal patterns) in the first 3 months of life.[73] Wide variations and developmental differences exist in the EEG of infants and children because of progressive development of the immature brain. Developmental maturation of the pediatric EEG, including changes in power and frequency, progresses to an adult pattern in late adolescence. Data on EEG changes produced by anesthetic drugs in the pediatric population are not available.[73,74] Bispectral index monitoring has yet to be validated for all pediatric patient age groups, particularly because age-related maturation differences in the EEG may affect the BIS algorithm.[75] Some evidence supports the validity of the algorithm in infants, but further studies in children younger than 1 year are needed.

Validation Studies

The BIS is a continuous form of complex processed EEG derived parameterthat has been validated in adults as a quantifiable, objective measure of the sedative, hypnotic drug effect on the CNS.[70,76] It has been shown to correlate with loss of consciousness, recall, and return to consciousness during general anesthesia. Glass et al.[77] established the strong correlation between the BIS value and level of sedation, as quantified

by the Observer's Assessment of Alertness/Sedation Scale. This same study also demonstrated the correlation between BIS values and measured plasma concentrations of propofol, alfentanil, midazolam, and isoflurane. The investigators also tested for responsiveness and memory recall at targeted plasma concentrations. Another study demonstrated a relationship between the pre-incision BIS value and the likelihood of purposeful movement with skin incision.[78]

Several studies have attempted to determine the clinical validity in infants and children; however, methods used to validate BIS performance in adults are difficult to replicate in children. The BIS range guidelines were developed based largely on responsiveness and recall data that were obtained from studies of adult volunteers who were maintained at various steady-state plasma concentrations of anesthetic, hypnotic agents. These studies cannot easily be conducted in children. The first report comparing the dose responses of sevoflurane to BIS values in infants and children scheduled for elective surgery showed that both pediatric and adult populations had awake BIS values between 90 and 100 that decreased precipitously after induction of anesthesia.[79] A second study found that the correlation between BIS and end-tidal sevoflurane concentration in children is very similar to that observed in adults.[80] No differences in BIS values between infants (0 to 2 years) and children (2 to 12 years) at similar clinical levels of anesthesia were seen. An end-tidal concentration-response difference between the two age groups is consistent with existing data regarding minimum alveolar concentration required to prevent movement with stimulus. The same age-related difference has been demonstrated for halothane minimum alveolar concentration.[81]

Utility Studies

The utility of the BIS as a clinical parameter to measure the depth of sedation or hypnosis has been well established through a multitude of adult clinical studies using inhalation anesthesia.[78,82] The titration of propofol to a specific BIS range during surgery resulted in a wide range of patient benefits compared with a standard practice (non–BIS-titrated) group. These benefits included a reduction in the amount of anesthetic agent used, faster emergence and shorter time to postanesthesia care unit discharge eligibility, and higher levels of patient orientation on arrival in the postanesthesia care unit as assessed by blinded observers. Similar results were achieved in a variety of studies conducted using all of the commonly administered anesthetic, hypnotic agents.[83-85]

A growing number of observational and clinical utility studies in the pediatric population have demonstrated promising results with use of the current BIS algorithm in both infants and children. Experience to date suggests that BIS monitoring in children and infants could provide similar benefits to those achieved in the adult population, with respect to improved sedative, hypnotic drug administration and recovery profiles.[86-88] However, not all persons agree. A subsequent study showed a weaker correlation between BIS and sevoflurane concentration in infants.[89] BIS values have been recorded at various clinical endpoints during cardiac surgery with cardiopulmonary bypass in children with results similar to those observed in adults.[90] A later study revealed large interpatient variability of BIS at different levels of anesthetic depth, which may limit the applicability of BIS to pediatric anesthesia.[91]

Summary of Bispectral Index–Related Studies in Critical Care

After the clinical introduction of BIS into operating rooms, this technology naturally found its way into the ICU. Numerous studies in both adults and children have been published. Initial reports in both populations suggested good correlation between objective sedation scores and BIS.[92,93] One such study in children showed that the BIS and COMFORT scale measurements were highly correlated ($R^2 = 0.89$).[94] Others demonstrated a strong correlation between the Ramsay Sedation Score and BIS in nonparalyzed children for sedation monitoring.[95] They also noted that, in the presence of chemical paralysis, the Ramsay Sedation Score and bedside nursing assessment were not able to accurately recognize adequate or inadequate sedation states. Other researchers found that the correlation between sedation scores and BIS was suboptimal and inconsistent in the heterogeneous ICU population.[96,97] Reliance on the BIS as the sole monitor of sedation may result in excessive sedation, primarily because of high levels of muscular activity.[98]

Although BIS monitoring is a well-established clinical parameter in the adult surgical population, its use and application in the critical care and pediatric arenas is still under investigation. Several preliminary clinical studies of BIS monitoring in both the operating room and the ICU have demonstrated possible clinical utility and efficacy for improved sedation titration, decreased drug usage, strong sedation score correlation, and greater accuracy and reliability in sedation assessment for paralyzed children.

Conclusion

Noninvasive monitors, such as pulse oximetry and capnometry, are standards of care in the pediatric critical care environment. It is therefore important to understand key clinical and technical issues that determine how these instruments can be used most effectively. These noninvasive technologies provide early warning of potential catastrophic events and facilitate early intervention, with potential for better outcomes. Concerns for complications related to invasive monitors will continue to drive the search for newer and better devices for noninvasive physiologic monitoring. Promising recent advances have been made in the technology of pulse oximeters, allowing measurements of all types of hemoglobin, including dyshemoglobins and total hemoglobin, with less artefact resulting from patient movement, which is a vital consideration in the PICU patient population. However, with all of the technological advances, we must remember the importance of basic vital sign monitoring and clinical observation, such as heart rate, respiratory rate, temperature, and fluid balance.

References are available online at http://www.expertconsult.com.

Specific Diseases of the Respiratory System: Upper Airway

David Jardine, Omar J. Bhutta, and Andrew Inglis

PEARLS

- Diseases leading to compromise of the airway are the most frequent cause of cardiac arrest in pediatric patients. A small reduction in the caliber of the child's airway may lead to a life-threatening reduction of airflow.
- Laryngomalacia is the most common congenital anomaly of the larynx. Infants tend to outgrow this problem during the first year of life; however, the condition may be of sufficient severity in some infants that activities such as feeding are compromised.
- The trachea may be compressed by the presence of an abnormal vascular structure. Children affected by this problem may have such diverse symptoms as stridor, wheezing, lobar atelectasis, or recurrent pulmonary infections.
- The practice of treating laryngotracheobronchitis with corticosteroids is standard of care, especially for hospitalized patients. A meta-analysis in which the efficacy of corticosteroids was evaluated suggests that corticosteroids may reduce the need for endotracheal intubation and hasten improvement when given in the first 24 hours of illness.
- Epiglottitis, a bacterial infection of the supraglottic tissues historically caused by *Haemophilus influenzae* type B, is now most frequently caused by group A β-hemolytic streptococcus.
- Patients with bacterial tracheitis usually do not respond to inhaled racemic epinephrine, have a high fever, and appear very ill.

Diseases leading to compromise of the airway are the most frequent cause of cardiac arrest in pediatric patients. Prompt recognition of these illnesses can lead to timely intervention and improve the outcome of these patients. The small size of the infant's trachea makes airway obstruction more likely and particularly dangerous. The normal anteroposterior diameter of the infant's glottis is 4.5 mm. One millimeter of circumferential tracheal edema reduces the glottic lumen to 30% of its normal size. Poiseuille's law stipulates that laminar flow of gas through a tube is inversely proportional to the fourth power of the radius of the lumen:

$$R = \frac{8ln}{\pi r^4}$$

where R is the resistance to gas flow, l is the length of the tube, n is the viscosity of the gas, and r is the radius. Unfortunately, airflow through a narrowed trachea is usually turbulent, which worsens the situation because resistance to turbulent flow of gas past an obstruction is inversely proportional to the fifth power of the radius of the lumen.[1,2] Gas exchange will be dramatically reduced by minor degrees of impingement on an infant's trachea. Consequently, a child will not tolerate lesions that would not even produce symptoms in an adult.

Initial Management

Once the diagnosis of upper airway obstruction is made, efforts should be undertaken to minimize disturbing the patient unless the respiratory embarrassment is severe enough to be life-threatening. Airway obstruction often worsens when infants and children are alarmed during a diagnostic evaluation. Humidified oxygen should be administered through a nasal cannula or facemask. These devices may frighten younger children who may more readily accept oxygen delivered through flexible tubing held by the parent. If the child will tolerate placement of a pulse oximeter probe, this provides a noninvasive way of evaluating oxygenation. If oxygen saturation by pulse oximeter measurement is within an acceptable range (>95%), arterial blood gas determination may be unnecessary. An arterial blood gas is useful to identify the patient who may be hypercapnic, but to obtain these data may further upset the child.

After upper airway obstruction has been diagnosed, a combination of physical and radiographic findings may help localize the lesion. With identification of the anatomic site of the lesion, the diagnostic possibilities are greatly narrowed. During the diagnostic evaluation, the child may sit in the parent's lap if this reduces anxiety. This position usually does not interfere with diagnostic evaluation, like lateral neck and chest radiography. The dose of radiation to a nonpregnant parent is small and should be of little concern.

If it is thought to be safe, examination of the patient's head and neck may reveal the cause of the illness. Depending on the patient's condition, the degree of respiratory embarrassment may be quantified with a rating scale (Table 44-1). One of the primary benefits of using such a scale is that signs of respiratory obstruction are systematically sought and objectively documented. This information may be valuable in helping

Table 44–1 Subjective Assessment of Clinical Severity of Laryngotracheobronchitis

	0	1	2	3
Stridor	None	Mild	Moderate at rest	Severe on inspiration and expiration or none with markedly decreased air entry
Retractions	None	Mild	Moderate	Severe, marked use of accessory muscles
Air entry	Normal	Mild decrease	Moderate decrease	Marked decrease
Color	Normal	Normal (0 score)	Normal (0 score)	Dusky or cyanotic
Level of consciousness	Normal	Restless when disturbed	Anxious, agitated; restless when undisturbed	Lethargic, depressed

From Davis HW, Gartner JC, Galvis AG, et al: Acute upper airway obstruction: croup and epiglottitis, Pediatr Clin North Am 28:859, 1981.

to define the course of the patient's illness and the response to treatment. During the initial evaluation, an assessment may be made regarding the likely location of the obstruction. Extrathoracic airway obstruction usually results in stridor (the obstruction is most severe during inspiratory phase), while intrathoracic airway obstruction usually results in wheezing (the obstruction is most severe during expiratory phase). Localizing the obstruction in this manner helps to narrow the diagnostic possibilities.

The initial evaluation should allow one to make important triage decisions about management and further evaluation of the patient with upper airway compromise. Depending on the severity of the illness, a decision must be made about which diagnostic tests will be undertaken. In the case of severe respiratory compromise, it may be necessary to plan for invasive procedures (endotracheal intubation or operative intervention) while the diagnostic evaluation is being performed. Finally, it should not be forgotten that pulmonary edema might follow relief of severe upper airway obstruction.[3] Postobstructive pulmonary edema may be severe enough to require vigorous therapy, including endotracheal intubation, mechanical ventilation, and positive end-expiratory pressure.

Congenital Malformations

A variety of congenital malformations can affect the pediatric airway. Many of these become evident in the delivery room. Some congenital malformations do not present until the child is older and somatic growth has made the airway impairment more evident.

Choanal Atresia

Choanal atresia is estimated to occur about once in every 5000 to 9000 live births.[4] Choanal atresia is seen commonly with other defects, especially CHARGE syndrome, which accounts for 25% of all patients with choanal stenosis.[5] Unilateral choanal atresia, the most common form, is often seen without accompanying congenital defects and may not be diagnosed at the time of delivery. Bilateral choanal atresia almost always occurs in the presence of other congenital defects.[5] For the first 5 months of life, many infants breathe only through their noses and do not open their mouths when the nasal passages are occluded; consequently, bilateral choanal atresia often results in respiratory distress shortly after birth. Bilateral choanal atresia (Figure 44-1) is diagnosed through examination of the naris with the mouth closed. If no airflow is present, a presumptive diagnosis of choanal atresia is established. Some authorities advocate passing a thin, flexible catheter through the naris. This will confirm the diagnosis of choanal atresia; however, if the symptoms are resulting from choanal stenosis, edema formation following even minor trauma of the nasal mucosa after catheter placement may lead to complete occlusion of the nasal airway and worsening of respiratory distress. Surgery is indicated for the correction of bilateral choanal atresia if the infant has symptoms[6] (Figure 44-2). Infants with bilateral choanal atresia generally have surgery within the first 3 months of life, while infants with unilateral choanal atresia typically have surgery after the second year of life.[7] Topical application of mitomycin to inhibit fibroblast proliferation has been shown to be an effective adjunct to surgical repair of choanal atresia.[8] Although choanal atresia is the most common cause of nasal airway obstruction, midline nasal masses such as meningoencephaloceles, gliomas, or dermoid tumors can also cause obstruction. Because these lesions may originate from within the cranial vault, computed tomography (CT) scanning or magnetic resonance imaging (MRI) should be performed before a biopsy or surgical correction of the abnormality is attempted.[9]

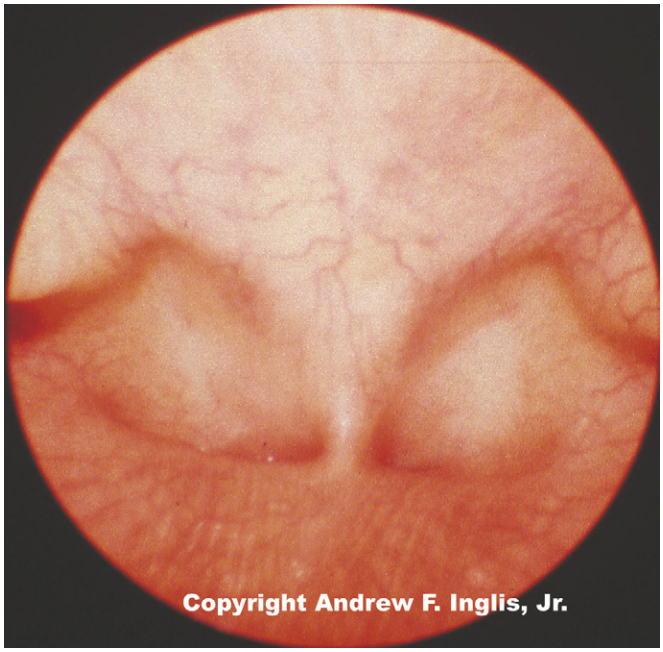

Figure 44–1. Choanal atresia before repair. View of choanal atresia from posterior nasopharynx. There is complete absence of choanae. *(Copyright Andrew F. Inglis Jr.)*

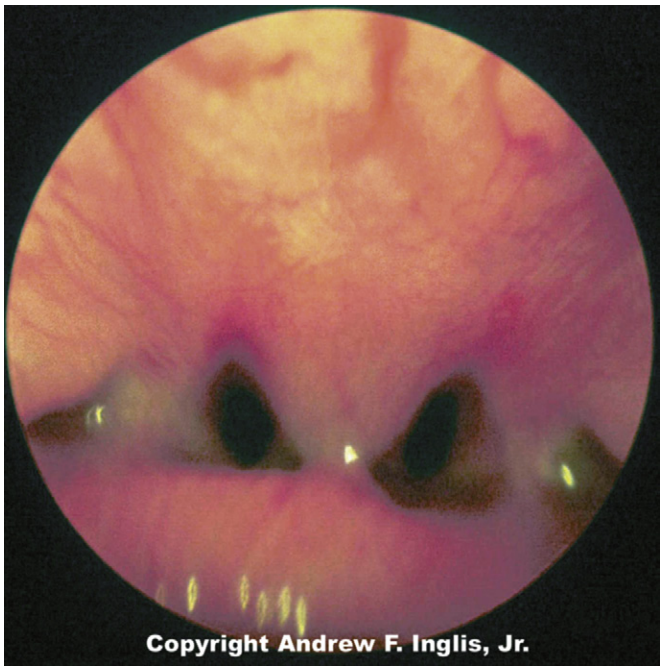

Figure 44–2. Choanal atresia after repair. View from the posterior of the nasopharynx demonstrating patency of choanae following surgery. *(Copyright Andrew F. Inglis Jr.)*

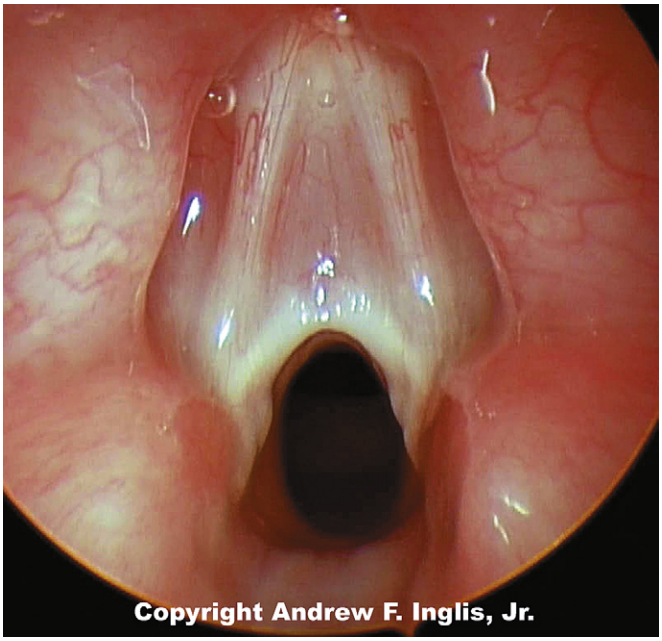

Figure 44–3. A laryngeal web occludes most of the tracheal lumen in this patient. This web, which is a thin membrane of soft tissue at the level of the glottis, has many of the features typical of this class of lesions. *(Copyright Andrew F. Inglis Jr.)*

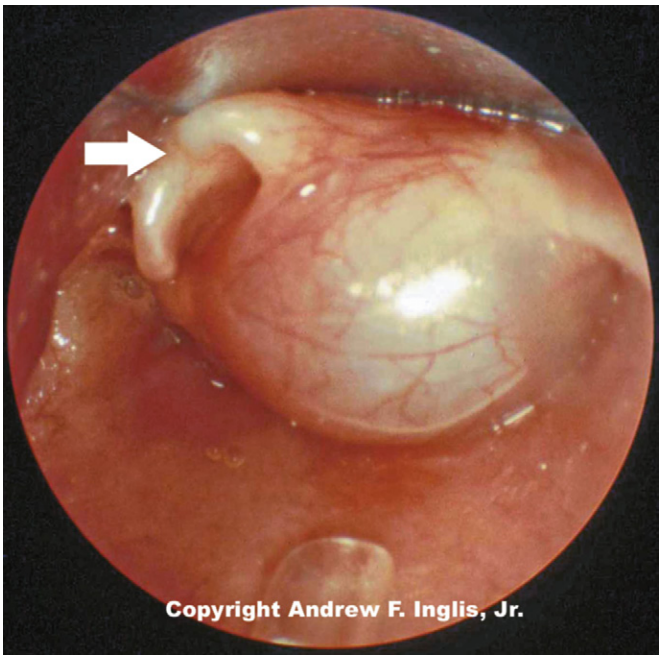

Figure 44–4. A large laryngeal cyst protrudes from the lateral wall of the trachea, just below the level of the glottis. *(Copyright Andrew F. Inglis Jr.)*

Laryngomalacia

Laryngomalacia is the most common congenital anomaly of the larynx. The infant has inspiratory stridor that is exacerbated by crying or distress. Although no gross anatomic abnormalities are present, the laryngeal cartilages lack their usual rigidity. When the larynx is observed during fiberoptic examination of the glottis, the arytenoid cartilages and supraglottic structures collapse inward (toward the glottis) during inspiration, leading to inspiratory stridor. The negative intrathoracic pressure generated during inspiration contributes to a high incidence of gastroesophageal reflux[10] and pulmonary aspiration.[11,12]

These abnormalities can be graphically observed with fiberoptic laryngoscopy, which shows the dynamic component, with obstruction during inspiration and full airflow during expiration. In some patients with laryngomalacia, gastroesophageal reflux may be the primary cause of the airway compromise, whereas in others it may be a significant cofactor exacerbating preexisting neurologic or anatomic abnormality.[13] The respiratory embarrassment associated with this problem is usually minor and self-limited, although hypoxia and hypercapnia have been documented.[14] Infants tend to outgrow this problem during the first year of life; however, the condition may be severe enough in some infants that activities such as feeding are compromised. In the most severe cases, surgical intervention may be necessary.[15] The goal is to relieve airway obstruction by excision of tissue that collapses into the glottis during inspiration.

Laryngeal Webs, Stenosis, and Tumors

Laryngeal webs usually occur at the level of the glottis and are usually located anteriorly. These may be congenital or acquired and are generally thin membranes of soft tissue that partially occlude the tracheal opening, producing symptoms of feeble cry and dyspnea shortly after birth (Figure 44-3).[16] Surgical lysis of these lesions corrects the problem. Laryngeal cysts and laryngoceles are soft tissue masses that protrude into the glottic lumen (Figure 44-4). The resulting respiratory compromise is usually recognized as inspiratory stridor. Treatment is surgical excision of the lesion.[17]

Another lesion presenting as inspiratory stridor is congenital laryngotracheal (subglottic) stenosis. This is the second most frequent cause of stridor in infants.[18] The infant with this

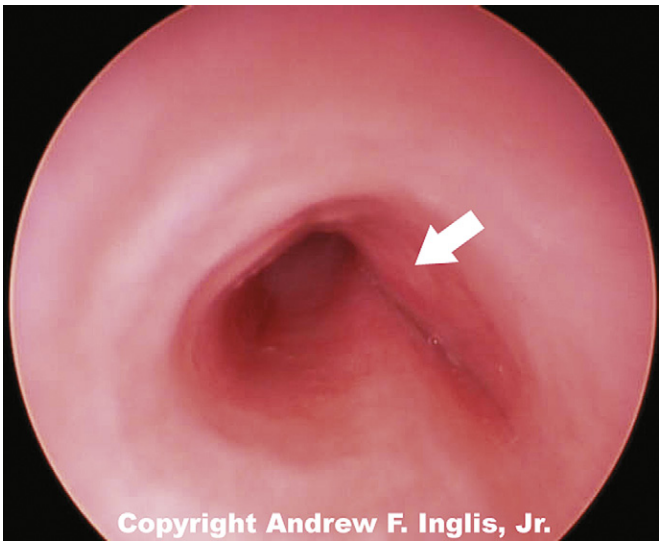

Figure 44–5. The lateral portion of the tracheal lumen is severely compressed by the impingement of the vascular ring. *(Copyright Andrew F. Inglis, Jr.)*

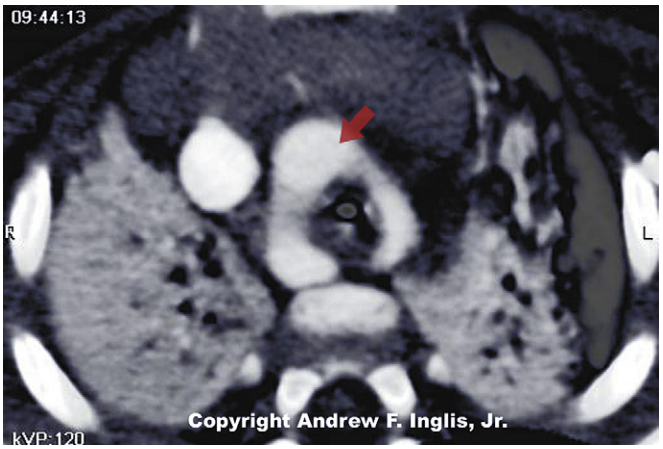

Figure 44–6. Contrast CT scan showing vascular ring encircling and compressing the trachea (arrow indicates vascular ring encircling trachea). *(Copyright Andrew F. Inglis Jr.)*

problem may have symptoms when newborn but often comes to medical attention later when the tracheal edema produced by a minor respiratory infection causes severe inspiratory stridor. This may be initially diagnosed as croup (laryngotracheobronchitis) but is noted to recur with each subsequent upper respiratory infection. Although the diagnosis of laryngotracheal stenosis may be made radiographically, it is usually established with bronchoscopy. If endotracheal intubation is necessary, a smaller than normal endotracheal tube should be used to reduce trauma and ischemia of the subglottic tissues. Depending on the severity of the lesion, surgical intervention may be necessary (see the discussion about acquired laryngotracheal [subglottic] stenosis for details of the surgical procedures).

Soft tissue masses may reduce the caliber of the tracheal lumen, either by extrinsic compression, as happens with a cystic hygroma, or by growth into the tracheal lumen from the tracheal wall, as happens with a hemangioma. Although these lesions may be present at birth, they often do not produce symptoms for the first few months until the growing

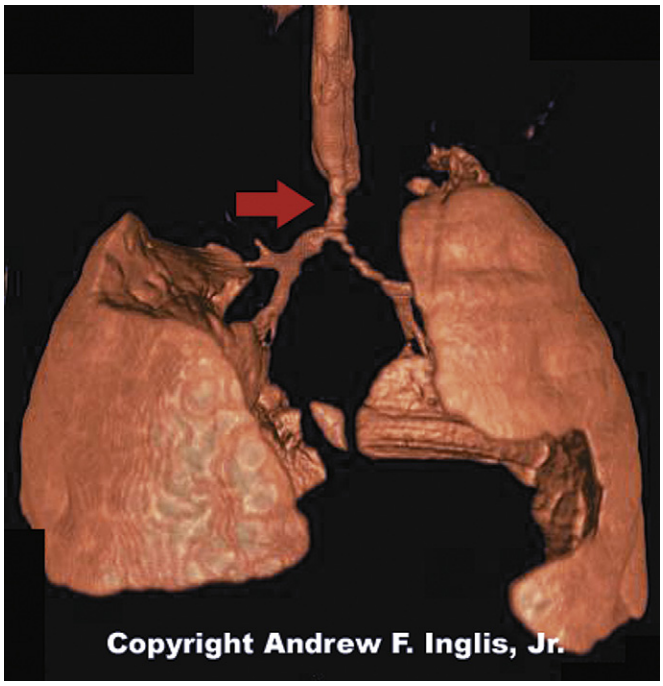

Figure 44–7. High-resolution three-dimensional reconstruction of CT scans clearly shows severe tracheal compression caused by vascular ring (arrow indicates tracheal narrowing caused by vascular ring). *(Copyright Andrew F. Inglis Jr.)*

lesion further impinges on the trachea. Although surgery is frequently used for treatment of tracheal hemangiomas,[19] pioneering work by Judah Folkman was instrumental in demonstrating that some of these lesions respond to steroid therapy.[20]

Vascular Impingement on the Trachea

The trachea may be compressed by the presence of an abnormal vascular structure (Figure 44-5). The innominate artery is the most common vessel causing tracheal compression. Vascular rings and enlarged pulmonary arteries are also known to cause tracheal compression, as are a variety of other vascular abnormalities.[21] These lesions may present with physical findings such as stridor or wheezing. Alternatively, the patient may be symptom-free, but may suffer respiratory problems such as recurrent lobar atelectasis or frequent pulmonary infections. Because of this, it is difficult to recognize a vascular ring as the underlying cause of illness.[22] Careful inspection of the chest radiograph may reveal indentation of the trachea, but often this sign is absent. Barium swallow has been the historic method of diagnosing vascular impingement of the trachea. CT scanning and MRI have become the diagnostic modalities of choice (Figures 44-6 and 44-7).[23,24] These noninvasive methods are effective at showing complex three-dimensional cardiovascular anatomy, especially the extracardiac morphology. Treatment involves surgical correction of the vascular anomaly, in severe cases. Respiratory distress may persist postoperatively because prolonged compression of the trachea has made the affected segment softer and collapsible. In severe cases, the tracheomalacia may severely compromise the patient and may be improved by surgical intervention to prevent tracheal collapse.[25]

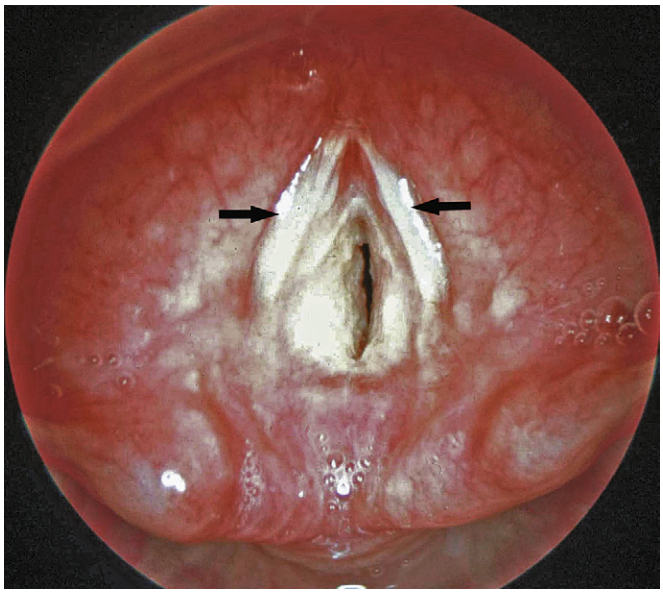

Figure 44–8. Laryngotracheobronchitis: below the level of the vocal cords the trachea appears swollen and the tracheal walls are covered with purulent material (vocal cords are indicated by *arrows*).

Bronchomalacia and Intrathoracic Tracheomalacia

During normal respiration, the upper airway is subject to cycles of positive and negative intraluminal pressure. The cartilaginous components of the upper airway are rigid ringlike structural elements that resist the tendency to collapse caused by the cycling of pressure within the airway lumen. When these structures lack their characteristic rigidity, the mechanics of breathing are altered.[26] The symptoms produced by these changes depend on the location of the damaged cartilages. Characteristically, intrathoracic cartilaginous lesions such as bronchomalacia or tracheomalacia impede exhalation. Diagnosis of this problem may be made through observation of collapse of the upper airways during active exhalation, such as occurs while crying. Collapse can be observed with several diagnostic modalities including fluoroscopy, flexible or rigid bronchoscopy, and ultrafast CT scanning.[27]

Although these lesions may be congenital, many of the cases of tracheomalacia and bronchomalacia seen in the pediatric intensive care unit (PICU) are the result of an infectious or mechanical insult to the trachea. Infants with bronchopulmonary dysplasia and persistent respiratory problems may be affected by bronchomalacia alone or in combination with tracheomalacia.[28] The obstructive symptoms produced by these lesions may be relieved by continuous positive airway pressure to maintain patency of the airway during exhalation.[29] The level of continuous positive airway pressure necessary to improve respiratory function may be assessed clinically (relief of obstructive symptoms), mechanically (measurement of flow-volume loops), or bronchoscopically (maintenance of airway patency throughout the respiratory cycle).[30] With sufficient time, many of these infants outgrow their respiratory difficulties. As an alternative to tracheostomy and positive airway pressure, some have advocated surgical intervention with pericardial flap aortopexy[31] or, in extreme situations, metallic airway stents.[32]

Infectious Processes

A variety of infectious processes may affect the pediatric airway. Poiseuille's law dictates that airway compromise from the swelling that accompanies an infectious process is greater in infants and young children than it is in adults. A small reduction in the caliber of the smaller child's airway may lead to a life-threatening reduction of airflow.

Laryngotracheobronchitis

Laryngotracheobronchitis (croup) is a common childhood infection. It is caused by a variety of infectious agents; parainfluenza virus, coronavirus, and rhinovirus are the most common.[33] This is a seasonal illness, occurring predominately during winter months, and most commonly affecting children from age 6 months to 3 years. There is frequently a history of prodromal infection accompanied by an unusual cough (described as sounding like the bark of a seal). Swelling of the tracheal mucosa in the subglottic region causes airway compromise (Figure 44-8). Medical attention is usually sought when the child develops inspiratory stridor and respiratory distress. Various scales have been devised to quantify the severity of the stridor to document the progression of the illness and the response to therapy. One of the most commonly employed scales is the Westley scale,[34] which has been validated (see Table 44-1).[35]

When a chest radiograph is obtained during an episode of laryngotracheobronchitis, the trachea is seen to have a gradual progressive narrowing of its lumen, reaching the narrowest point just below the vocal cords (the "steeple sign") (Figure 44-9). The upper glottis, as seen on a lateral neck radiograph, is normal.

Many care providers believe that exposing the child to cold or misty air often dramatically improves the symptoms; although evidence in support of this therapy is lacking.[36,37] When the illness is refractory to these measures, racemic epinephrine has been shown to produce dramatic reduction of airway obstruction. This probably is accomplished by stimulation of the α-adrenergic receptors, producing vasoconstriction and resulting in diminished tracheal edema. Rebound tracheal edema may occur several hours later as the effect of the racemic epinephrine dissipates. Because this problem is unpredictable, the child should be admitted to the hospital for observation after racemic epinephrine has been used.

The practice of treating laryngotracheobronchitis with corticosteroids is widespread, especially for hospitalized patients.[38] Oral, intramuscular, and nebulized corticosteroids have been shown to be beneficial in randomized, blinded trials.[39,40] Meta-analyses in which the efficacy of corticosteroids was evaluated suggest that corticosteroids reduced the need for endotracheal intubation or inhaled epinephrine, hasten improvement in the first 24 hours of illness, shorten the duration of hospitalization, and reduce the frequency of readmission.[41-44]

Mixtures of 70% helium and 30% oxygen (heliox) may be beneficial because the characteristics of this mixture permit greater gas flow past areas of airway narrowing. Some authors suggest that this therapy is as efficacious as racemic epinephrine[45]; however, this therapy has not been conclusively demonstrated to be superior to the administration of supplemental oxygen by itself.[46]

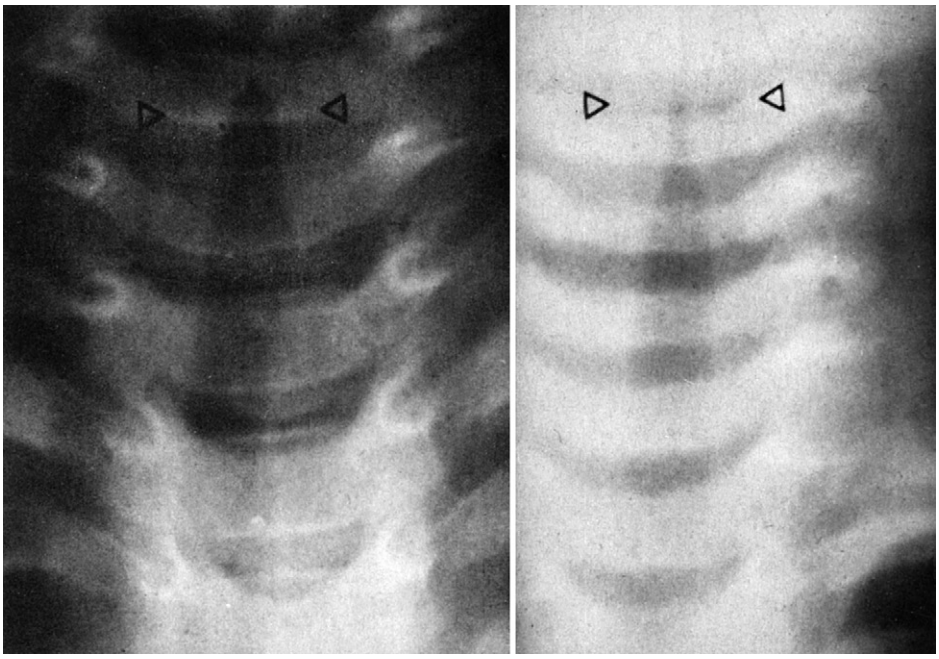

Figure 44–9. Anteroposterior radiograph of the neck. *Left,* A normal tracheal air column (between the *arrows*). *Right,* Trachea narrowed by laryngotracheobronchitis.

Table 44–2 Characteristics of Laryngotracheobronchitis, Bacterial Tracheitis, and Epiglottitis

	Laryngotracheobronchitis	Bacterial Tracheitis	Epiglottitis
Age	3 mo to 3 yr	6 mo to 12 yr	12 yr (average)
Onset	Gradual	Intermediate	<24 hr
Fever	Usually low	Usually high	High
Cough	Characteristic "barking"	Characteristic "barking"	None
Sore throat	None	Usually absent	Often severe
Drooling	No	No	Usually
Posture	Any position	Any position	Sitting forward, mouth open, drooling
Voice	Normal	Normal or hoarse	Muffled
Appearance	Nontoxic	Toxic	Toxic
Seasonal distribution	Usually winter, epidemic	Throughout the year	Throughout the year

Endotracheal intubation is occasionally necessary when laryngotracheobronchitis proves refractory to medical intervention. Unless merited by special circumstances, such as severe subglottic stenosis in association with laryngotracheobronchitis, tracheostomy offers no advantages over endotracheal intubation. The endotracheal tube should be of a smaller size than would normally be used, to avoid additional injury to the swollen tracheal mucosa. If the tracheal edema is severe, even a small tube may fit tightly in the trachea.

Later, when an audible leak around the endotracheal tube is present, the trachea may be extubated with a high probability that reintubation will not be necessary.[47] If a leak does not become audible after 2 to 4 days, it is our practice to extubate the trachea, because prolonged intubation may increase the risk for subglottic injury. Racemic epinephrine is commonly needed to treat stridor after extubation. If a patient should have especially severe or recurrent laryngotracheobronchitis, an anatomic lesion causing tracheal narrowing should be suspected.

Epiglottitis

Epiglottitis caused by *Haemophilus influenzae* type B was once a common cause of serious respiratory illness in pediatric patients, but the widespread use of *H. influenzae* type B vaccine has reduced the frequency of this problem by more than 90% in young children.[48] Patients who present with epiglottis are now older, with an average age of 11.6 years, as opposed to an average age of 5.8 years before the advent of Hib vaccination.[49] Although cases of *H. influenzae* epiglottis continue to occur, even among vaccinated patients,[50] other causes of epiglottitis have assumed greater importance in the postvaccination era. Group A β-hemolytic *Streptococcus* is now identified as the cause of epiglottitis in many patients and is clinically indistinguishable from epiglottitis caused by *H. influenzae* type B.[51] Thermal injury to the epiglottis from ingesting hot liquids can also cause epiglottitis.[52] Several points serve to distinguish epiglottitis from laryngotracheobronchitis (Table 44-2).

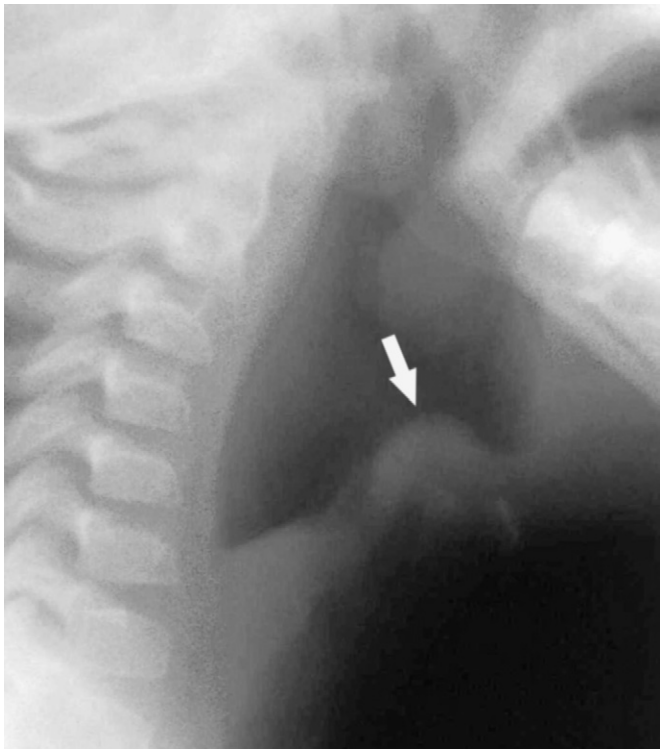

Figure 44–10. Lateral radiograph of the neck of a patient with epiglottitis. Note the large, swollen epiglottis.

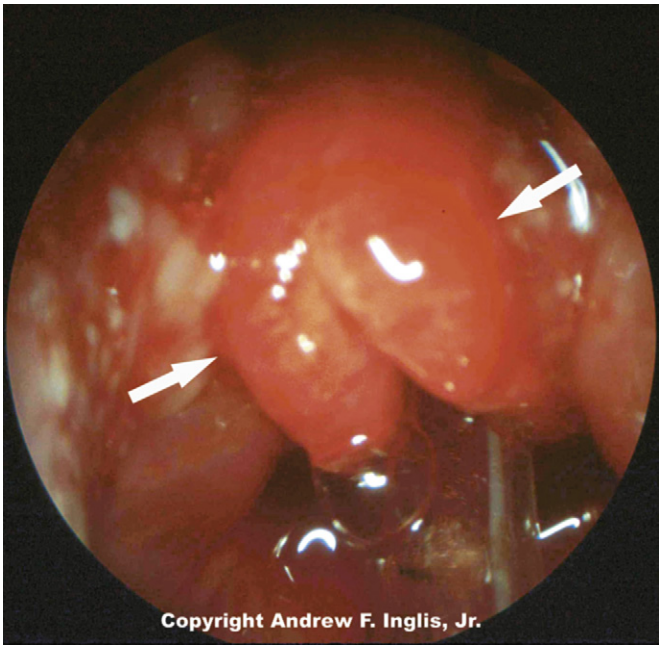

Figure 44–11. Epiglottitis causing a severely swollen epiglottis (between the *arrows*). In the lower portion of the picture, the endotracheal tube can be seen. *(Copyright Andrew F. Inglis Jr.)*

Management of epiglottitis in young children is a multidisciplinary undertaking, involving pediatric intensive care specialists, anesthesiologists, and otolaryngologists. When a child with presumed epiglottitis is admitted to the emergency department, this team should be notified in anticipation of taking the child to the operating room to secure his or her airway. As the team members are being notified, lateral radiographs of the neck may be obtained if tolerated by the patient. This may be done with the child sitting on the parent's lap to minimize the child's anxiety. In epiglottitis, the anteroposterior view of the trachea appears normal, but a lateral neck radiograph shows a markedly swollen and edematous epiglottis (Figure 44-10). The diagnostic evaluation of the patient should proceed expeditiously, while care is taken to disturb the patient as little as possible. For this reason, fiberoptic examination of the epiglottis in the awake patient is usually not advisable. Attempts to examine the oropharynx directly or to start an intravenous line should be discouraged. The apprehension caused by these events may lead to tracheal obstruction by the enlarged epiglottis. If the patient will tolerate it, humidified oxygen should be administered, preferably through a plastic hose held by the parent.

If the diagnosis of epiglottitis is strongly suspected or confirmed on the lateral neck x-ray film, the child should go to the operating room as quickly as possible. In the operating room, the patient is anesthetized with an inhaled anesthetic (sevoflurane) and oxygen while the patient is spontaneously breathing. Once the patient has been anesthetized, an intravenous catheter is inserted. Laryngoscopy is then performed (Figure 44-11). It may be exceedingly difficult to obtain a direct view of the glottis and trachea because of the large swollen epiglottis. Nevertheless, it is almost always possible to pass an endotracheal tube through the edematous tissues and into the trachea. Nasotracheal intubation is preferred to orotracheal intubation because the tube is more readily secured to the face, the patient cannot bite the tube, and salivation is decreased. An otolaryngologist should be in the operating room and ready to do an emergency tracheostomy if an airway cannot be secured by endotracheal intubation, although this is rarely necessary. As with laryngotracheobronchitis, endotracheal intubation is preferred to tracheostomy because it has been shown that complications are more common when a tracheostomy has been routinely used to treat epiglottitis. After the airway is secured, blood cultures and cultures of the epiglottis are obtained, and antibiotic therapy is initiated with a penicillinase-resistant antibiotic because of the high incidence of *H. influenzae* resistance to ampicillin.[53]

In the PICU, patients usually require endotracheal intubation for 24 to 72 hours while the swollen epiglottis returns to normal size. The patient may be allowed to breathe spontaneously through the endotracheal tube or may undergo mechanical ventilation. Variable amounts of sedation are usually necessary. Extraepiglottic sites of *H. influenzae* infection are common. In one series, pneumonia occurred in 25% of patients with epiglottitis.[54]

The management of epiglottitis depends upon the patient's age. Adults and teenagers with epiglottitis usually present with severe pharyngitis, but usually have mild or absent airway obstruction. In contrast to younger unsedated children, teenagers and adults may tolerate examination of the airway with a small fiberoptic bronchoscope. This procedure may have superior diagnostic sensitivity compared to lateral neck radiographs. Although the management of epiglottitis in young children is almost always accomplished with placement of an endotracheal tube, teenagers and adult patients may be admitted to the hospital for close observation and expectant airway management. Endotracheal intubation is reserved for those patients who develop respiratory compromise.[55,56]

Peritonsillar Abscess

The initial presentation of peritonsillar abscess may resemble that of epiglottitis. The child usually has a severe sore throat and may also have a muffled voice and drooling. If the abscess is of sufficient size, the child may also experience respiratory distress. Unlike epiglottitis, children with peritonsillar abscess often experience trismus and usually do not have respiratory embarrassment. If the abscess is fluctuant, surgical incision and drainage may be indicated. Although trismus may be of concern in evaluation of the patient for anesthesia, there is usually no anatomic restriction of jaw movement. Once the patient has been anesthetized, the mouth may be easily opened. Extubation is almost always possible after the abscess has been drained, unless there is severe inflammation and swelling extending well beyond the tonsillar bed. Intraoral ultrasound examination has been suggested to be a useful test to differentiate abscess from cellulitis.[57] The most commonly encountered microorganism is Group A *Streptococcus*.[58]

Retropharyngeal Abscess

Almost 90% of children with retropharyngeal abscess are younger than 6 years.[59] Patients may have fever, stiff neck, sore throat and, in severe cases , respiratory distress. During examination of the oropharynx, the posterior pharyngeal wall may be observed to bulge, but most commonly, the findings are unremarkable. Palpation of the posterior pharyngeal wall should be avoided because it may cause rupture of the abscess with possible spillage of the contents into the tracheobronchial tree. An inspiratory radiograph of the lateral neck may show thickening of the prevertebral soft tissue, and occasionally an air-fluid level may be present (Figure 44-12). A chest radiograph should be obtained to evaluate possible mediastinal extension of the infection. CT scanning is commonly employed to evaluate these infections; however, evidence of abscess on CT scan does not reliably predict the quantity of purulent material obtained at the time of surgical drainage.[60]

A trial of antibiotic therapy is often indicated before any decision is made to proceed with surgical drainage of the abscess,[61] as between 30% and 90% of patients treated with antibiotic therapy can be cured without surgical intervention.[62,63] Surgical treatment of this lesion is drainage of the abscess, after the patient has been anesthetized and an endotracheal tube has been inserted to protect the patient from pulmonary aspiration of the purulent fluid. The organisms most often isolated are group A β-hemolytic *Streptococci* and *Staphylococcus aureus*.[59,64]

Bacterial Tracheitis

The peak incidence of this infection occurs in the fall and winter and tends to affect children between 6 months and 8 years of age. Bacterial tracheitis is a secondary infection that begins during a viral upper respiratory infection.[65-67] Frequently, but not always, bacterial tracheitis will resemble viral laryngotracheobronchitis (croup). Children will frequently complain of a severe sore throat or pain during coughing. In contrast to viral laryngotracheobronchitis, patients with bacterial tracheitis usually have a high fever and may appear very ill at the time of presentation (see Table 44-2). Because of the clinical similarity between bacterial tracheitis and viral

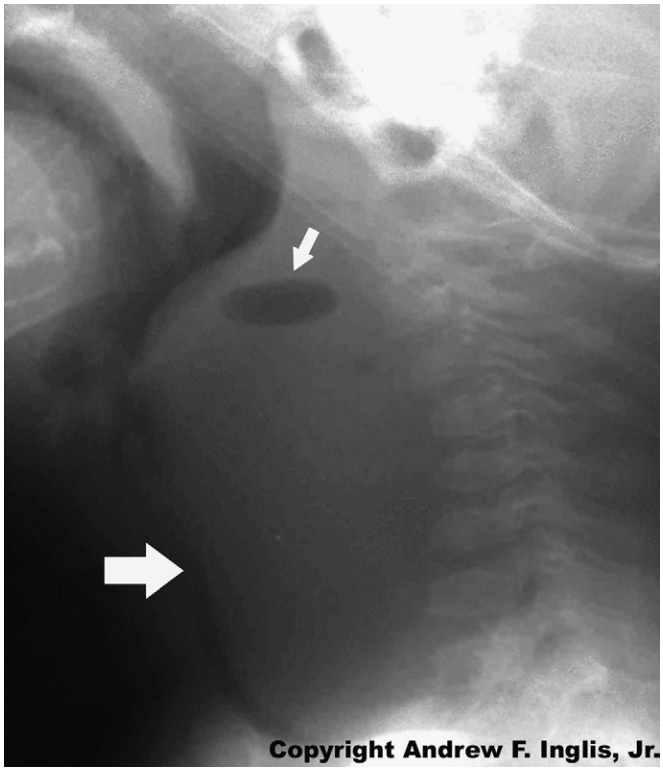

Figure 44–12. Lateral radiograph of the neck of a patient with retropharyngeal abscess. Note the thickening of the prevertebral soft tissue and the radiolucent area caused by the presence of air in the tissue. *(Copyright Andrew F. Inglis Jr.)*

laryngotracheobronchitis, these patients are treated with racemic epinephrine but fail to respond. If bronchoscopy is performed, it shows normal supraglottic structures, and diffuse inflammation of the larynx, trachea and bronchi,[68] with adherent or semiadherent purulent membranes in the trachea.[69] Endotracheal intubation is often necessary because of severe, progressive respiratory distress. Following endotracheal intubation, aggressive tracheobronchial toilet may be necessary because thick, tenacious purulent debris may rapidly occlude the endotracheal tube.

A variety of bacterial agents have been reported in association with this illness, including *Moraxella catarrhalis*, *Staphylococcus aureus*, *Haemophilus influenzae* type B, and *Pneumococcus*.[70,71] The injury to the respiratory epithelium caused by the virus may predispose the patients to bacterial superinfection. The most common complication of bacterial tracheitis is pneumonia, which is observed in approximately 60% of patients with this illness. Antibiotics are an important aspect of therapy and should be directed by the results of bacterial cultures obtained during bronchoscopy or immediately after endotracheal intubation.

Laryngeal Papillomatosis

The laryngeal papilloma is the most common benign tumor of the larynx during childhood. The agent causing this disease is human papilloma virus, with types 6 and 11 causing the vast majority of cases.[72] Despite its nonmalignant structure, the propensity of this tumor to cause respiratory obstruction may result in injury to the patient or death. The onset of symptoms occurs between infancy and 4 years of age. New onset of

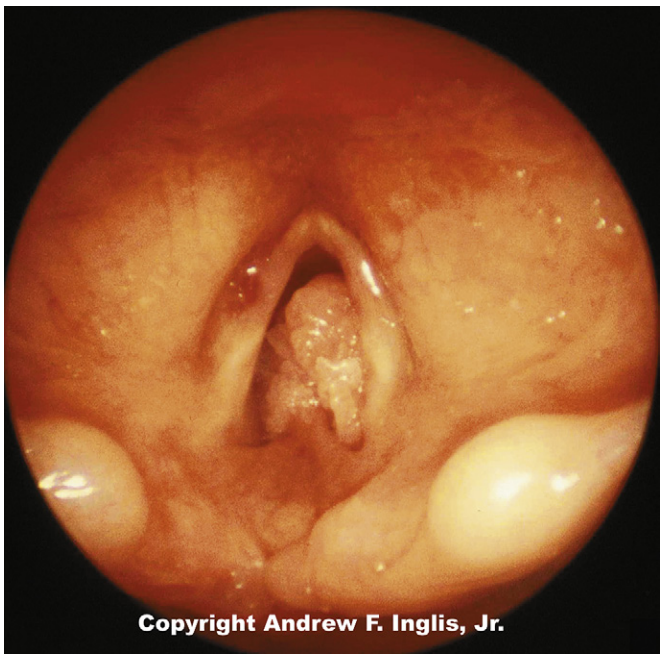

Figure 44–13. Large, pedunculated papilloma is seen just below the vocal cords. These papillomae almost completely occluded the tracheal lumen and produced marked respiratory distress. *(Copyright Andrew F. Inglis Jr.)*

infection is less frequent after age 5 years. The most common medical complaint in these children is voice change, which occurs in more than 90% of the patients. Airway obstruction is present in almost half of the patients, although it is mild in many of these. The presence of inspiratory stridor may misdirect the diagnostician to think that the child has laryngotracheobronchitis. The diagnosis is typically made with laryngoscopy (Figure 44-13).

Little is known about the immunological mechanisms involved in laryngeal papillomavirus infection, but cellular immunity is considered a more important mechanism than humoral immunity.[73] Better understanding of human papillomavirus infection is hampered by the lack of a good experimental model in which the entire viral life cycle can take place.

The treatment for this illness is surgical excision of the polyps. Induction of anesthesia in the child with severe airway obstruction may be hazardous, because it may be difficult or impossible to ventilate the child's lungs after loss of consciousness. Although patients characteristically require multiple surgical resections of these lesions (an average of 11 resections over the course of the disease), the mortality with this illness is low. Carbon dioxide laser vaporization of the papillomata is widely used. During laser excision of lesions caused by a similar viral agent, anogenital condylomas, medical personnel have become infected with the virus, presumably from viable virus particles carried in the smoke plume.[74] Although this has caused concerns about the spread of infection after excision of laryngeal papillomatosis, test results of the smoke plume have been negative for viral DNA.[75] Despite this, careful scavenging of the plume is routine in most centers where this operation is performed.

Despite modern surgical treatments, recurrence of laryngeal papillomata is relatively common and has prompted the search for other treatment options. Adjunctive treatment with interferon-α has been shown to reduce the relapse rate in both children and adults.[76] Molecular analysis has shown that patients infected with human papillomavirus-11 were sensitive to interferon treatment as opposed to those with human papillomavirus-6.[77]

Vocal Cord Paralysis

The bulk of the motor innervation to the larynx is supplied by the recurrent laryngeal nerves. These nerves originate in the nucleus ambiguous in the brainstem, travel to the chest with the vagus nerve, and then loop back up to the larynx in the tracheoesophageal groove. The left recurrent laryngeal nerve loops under the ductus arteriosus in the chest, and thus is vulnerable to injury during ligation of this vessel, and with other thoracic vascular procedures.[78]

Symptoms associated with even complete unilateral vocal cord paralysis vary greatly in severity. In infants, they may range from merely a mildly diminished cry up to a severely disabled larynx with significant stridor, feeding difficulties from aspiration, and loss of voice.[79] Bilateral vocal cord paralysis almost always produces significant stridor with varying degrees of airway distress. Stridor in these instances is typically inspiratory, and may be confused with laryngomalacia, a much more common entity. Diagnosis can usually be made at the bedside by fiberoptic laryngoscopy.[80]

Congenital vocal cord paralysis is usually idiopathic, and often resolves spontaneously over several months. This is the most common cause of bilateral vocal cord paralysis in children.[81] Other neurological causes, such as Arnold-Chiari malformation, are occasionally seen, and workup usually includes an MRI. The cause of acquired vocal cord paralysis is usually obvious, with most cases coming after thoracic or cervical surgery.[82]

The treatment of vocal cord paralysis in the critical care setting is primarily supportive. Airway support may include temporizing with high-flow nasal oxygen or continuous positive airway pressure/biphasic positive airway pressure (CPAP/BiPAP). Longer-term interventions include tracheotomy, or various procedures aimed at enlarging the glottic airway, including vocal cordotomy, arytenoidectomy, vocal cord lateralization, and posterior cricoid split and cartilage grafting.[80] If a specific lesion may be addressed medically or surgically (such as decompression of the brainstem in Arnold-Chiari malformation), such therapy should be undertaken.

Intrathoracic Mass Lesions Causing Respiratory Obstruction

The intrathoracic trachea may be compressed by a variety of anterior mediastinal masses. Because the symptoms produced by a malignant mass impinging on the trachea can worsen dramatically over several days, the child with respiratory compromise resulting from a mediastinal mass deserves rapid evaluation and aggressive medical therapy.

Before caring for a child with this problem, the parents should be asked if the child refuses to lie in certain positions. The child's reluctance to recline in a given position may be caused by airway compromise from the mass. Forcing the child to lie down may result in airway obstruction or even cardiac arrest.[83] Endotracheal intubation is indicated only if respiratory function becomes severely compromised. Unfortunately,

this measure may be of little benefit, because the lesion may compress the bronchi distal to the tip of the endotracheal tube requiring advancing the endotracheal tube into the mainstem bronchi.[84] In addition, it may be impossible to ventilate the child's lungs after muscle relaxants have been administered to facilitate placement of the endotracheal tube. Mechanical support with ECMO has been used to support patients with large mediastinal masses; however, the mass may distort the great vessels and pose unusual challenges for the ECMO team.[85] Obtaining tissue for a pathologic diagnosis can be a challenge, as these patients are at significant risk for anesthetic complications.[86] Factors associated with airway compromise are (1) anterior location of the mediastinal mass, (2) histological diagnosis of lymphoma, (3) symptoms and signs of superior vena cava syndrome, (4) radiological evidence of vessel compression or displacement, (5) pericardial effusion, and (6) pleural effusion.[87]

Trauma

Postextubation Stridor

After endotracheal intubation that lasts more than a few hours, postextubation stridor is a relatively common problem in small children and is most frequently caused by laryngeal edema. Estimates of the frequency of postextubation stridor in children vary widely. Most authors cite figures of less than 2% to 9%,[88,89] although the incidence may be as high as 37% in patients with trauma or burns.[90]

In addition to audible stridor, patients with this problem show decreased air movement; flaring of the alae nasi; and in more severe cases, decreased arterial oxygen saturation and mental status changes. The severity of these signs reliably indicates the severity of airway obstruction.[91]

Several risks are associated with the development of postextubation stridor. Endotracheal tube size plays an important role, because too large an endotracheal tube may compress the tracheal mucosa, causing submucosal ischemia. When the endotracheal tube is removed, the injured tissue may swell and partially obstruct the larynx. Endotracheal tube movement within the trachea may produce trauma to the tracheal mucosa, resulting in tissue injury and swelling. Whether stridor occurs depends on the extent of the swelling and the diameter of the child's airway. Small patients are more likely to have postextubation stridor because a larger proportion of their airway is obstructed with a given degree of swelling and because of the unfavorable characteristics of turbulent flow through small passages. Lack of an audible leak of air around the endotracheal tube is frequently used as a predictor of postextubation stridor in children; however, one study suggests that this measure may be valid only in children ages 7 years and older.[92]

Uncuffed endotracheal tubes are often recommended for children younger than 8 years because of concern that the presence of an endotracheal tube cuff may contribute to the risk of postextubation stridor. The subglottic region is the narrowest portion of the airway in this age group and will often provide an adequate seal around the endotracheal tube. Although historically, cuffed endotracheal tubes were not frequently used in children younger than 8 years, there are increasing data suggesting the safety of such endotracheal tubes. Data regarding the harmful effects of cuffed endotracheal tubes were derived from tubes with high-pressure, low-volume cuffs, which are likely to cause submucosal tracheal ischemia. These endotracheal tubes have been replaced by low-pressure, high-volume cuffs that seal the trachea by providing a larger area of contact with the mucosa at a lower pressure, resulting in less submucosal ischemia. When such endotracheal tubes are used, the risk of postextubation stridor appears no greater than when uncuffed endotracheal tubes are used.[88,89,93] Because cuffed endotracheal tubes may provide a better seal than uncuffed endotracheal tubes, they can be useful in delivering higher pressures needed in patients with noncompliant lungs who require mechanical ventilation. A large multicenter randomized control trial also suggests there is a significant reduction in endotracheal tube exchanges when cuffed tubes are used.[88]

Postextubation stridor has a greater risk of developing in children with trisomy 21; as many as one third of these patients have stridor after extubation. There appear to be several causes for this problem, including hypotonia and facial abnormalities, such as a large tongue.

Although most cases of postextubation stridor are caused by laryngeal edema, when this problem persists, other causes should be sought. Anatomical airway anomalies, which may not be visible during endotracheal intubation (such as tracheal hemangioma), may cause persistent postextubation stridor. Vocal cord paralysis is one of the more common causes of persistent postextubation stridor and may be caused by increased intracranial pressure, brainstem compression,[94] trauma to the brainstem after neurosurgery, or recurrent laryngeal nerve during thoracic surgery.[95]

The therapy of postextubation stridor is aimed at reducing airway edema. Racemic epinephrine and dexamethasone are the most widely used therapeutic agents. Racemic epinephrine, delivered by aerosol nebulizer, probably works by stimulation of α-adrenergic receptors; this stimulation causes vasoconstriction, which, in turn, reduces tracheal edema. Racemic epinephrine works rapidly, so improvement, when it occurs, should be observed within a few minutes of completion of therapy. Mixtures of helium and oxygen have also proven helpful in the treatment of postextubation stridor.[96]

The practice of using dexamethasone to treat postextubation stridor is widespread,[97] although the efficacy of this therapy remains controversial. Although data from animal studies suggest that corticosteroid use at the time of extubation may reduce tracheal edema, inflammation, and capillary dilation, a recent meta-analysis of prior studies has failed to show reduction of postextubation stridor after corticosteroid use.[98] Nevertheless, many practitioners think that dexamethasone (or an equivalent dose of another steroid) will ameliorate postextubation stridor, especially if the medication is administered several hours before extubation.

In most cases, postextubation stridor is self-limited, but occasionally, endotracheal intubation may be necessary. If the degree of airway obstruction before reintubation was severe, postobstructive pulmonary edema may be observed and should be treated with positive end-expiratory pressure. When reintubation is contemplated, the size of the previous endotracheal tube should be determined, and a smaller endotracheal tube should be selected in the hope of preventing additional tracheal injury. Ideally, the trachea should remain intubated until a leak around the endotracheal tube is observed, indicating resolution of the laryngeal edema.

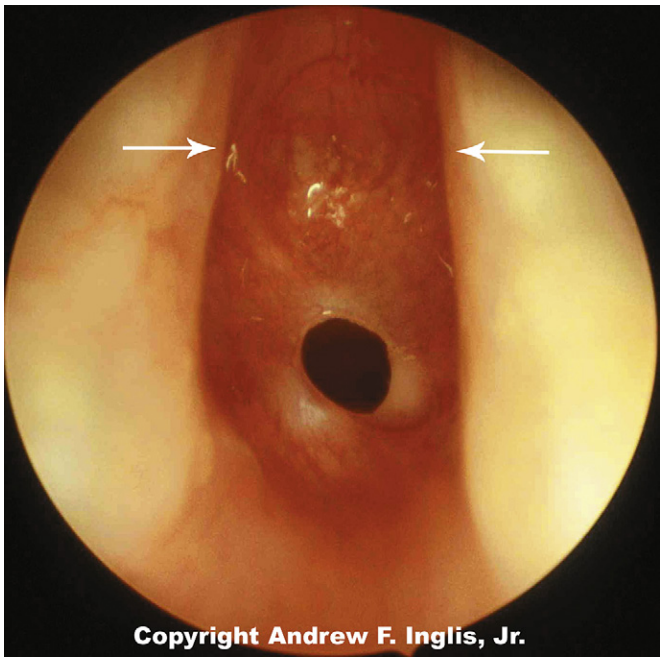

Figure 44–14. A cicatricial ring is demonstrated just below the glottis. This was caused by trauma from prolonged endotracheal intubation. *(Copyright Andrew F. Inglis Jr.)*

Laryngotracheal (Subglottic) Stenosis

Laryngotracheal stenosis is most commonly seen as a complication of prolonged endotracheal intubation, and as such is of special interest to the critical care practitioner (Figure 44-14). Injury most commonly occurs in the larynx at the level of the cricoid cartilage, just below the vocal cords, the only part of the airway below the nose that is surrounded by a complete circumferential ring of cartilage. This region cannot expand under pressure and is thus more susceptible to pressure necrosis and scarring (subglottic stenosis). Airway stenosis also can occur at the level of the vocal cords (glottic stenosis) when scarring occurs within the cricoarytenoid joints (cricoarytenoid ankylosis) or between the arytenoid cartilages (interarytenoid fibrosis). Glottic stenosis prevents vocal cord abduction and occasionally may be confused with bilateral vocal cord paralysis. Rarely, tracheal stenosis may be seen as a result of endotracheal tube (ETT) cuff injury, often in the setting of infection requiring high pressure ventilation.

Laryngeal intubation injury appears to result from an interaction of several elements, including individual susceptibility, movement of the endotracheal tube, size of the ETT, presence of infection, and duration of intubation. Fortunately, the incidence of this complication in neonates appears to be decreasing.[99] The odds of prevention will be enhanced by choosing the smallest tube that allows adequate ventilation and pulmonary care; this reduces the risk of subglottic stenosis. It is also thought that nasotracheal intubation may reduce movement of the ETT within the airway and thus diminish trauma, although this benefit comes with an increased risk of sinusitis secondary to obstruction of drainage from the sinus cavities. Gastroesophageal reflux is frequently present, and perhaps plays a significant role in the development of laryngotracheal stenosis.[99] The role of early intervention with a tracheotomy for the prevention of laryngeal stenosis is controversial.[100]

Clinically, laryngeal stenosis presents initially as postextubation stridor. It may be successfully managed with steroids or racemic epinephrine. Some patients may benefit from noninvasive positive-pressure breathing therapies such as BiPAP or CPAP. If reintubation is necessary, the larynx may heal successfully if a smaller endotracheal tube is used. Multiple failed attempts at extubation may require treatment with either an anterior cricoid split and cartilage graft, or tracheotomy.

Chronic laryngeal stenosis can be managed a variety of ways.[101] The obstruction may be bypassed with a tracheotomy, or may be managed with endoscopic excision of scar, cricoid expansion via cricoid split and cartilage grafts, and excision of the stenotic segment and reanastomosis via partial cricotracheal resection. Postoperative management of these patients is frequently complicated by the need to allow the larynx to heal for 5 to 14 days while maintaining a patent airway with an endotracheal tube. Management of the patient during this critical period is controversial. Some favor heavy sedation including the use of neuromuscular blocking agents to minimize the chance of movement of the ETT and accidental extubation. Others favor the opposite, actually allowing the patient to be alert and active with the ETT in place.[102] Fortunately, improvements in postoperative care have resulted in improved outcomes after laryngotracheal reconstruction.[103]

Ideally, reconstruction will be performed at a young age (younger than 25 months) to minimize the time period the child is exposed to the hazards of being dependent on the tracheotomy airway, and so that the child's speech and language development is not impaired.[104] Earlier laryngotracheal reconstruction may, however, be more prone to failure and requirement for revision procedures.

Foreign Body Aspiration

Airway obstruction may be produced by aspiration of a variety of foreign bodies, with nuts being one of the most frequent offenders in children.[105] Most of the patients aspirating foreign bodies are aged 1 to 3 years, with more than 95% being younger than 10 years. Fewer than 30% of patients aspirating foreign bodies receive medical attention within the first 24 hours, with many patients experiencing a significant delay before seeking medical attention. A clear history of foreign body aspiration may be elicited from 40% to 80% of the patients.[106] Patients with an aspirated foreign body may initially be symptom-free or may have a cough, wheezing, and evidence of respiratory embarrassment. Patients without symptoms who do not seek medical attention may have a persistent cough and may develop pneumonia distal to the obstructed bronchus. Recurrent bouts of pneumonia may lead to bronchiectasis if the foreign body is not removed.

Foreign bodies may become lodged in the airway anywhere from the posterior pharynx to the bronchi. The symptoms produced by foreign body aspiration vary according to the site of the foreign body and the degree of obstruction it produces. Foreign bodies of the extrathoracic airway characteristically produce inspiratory stridor. Foreign bodies lodged in the intrathoracic trachea and bronchi tend to produce expiratory stridor and wheezing.

Radiographic evaluation should include inspiratory and expiratory radiographs because a single anteroposterior radiograph will be unremarkable in 18% of children with an aspirated foreign body (Figure 44-15).[106] If the foreign body

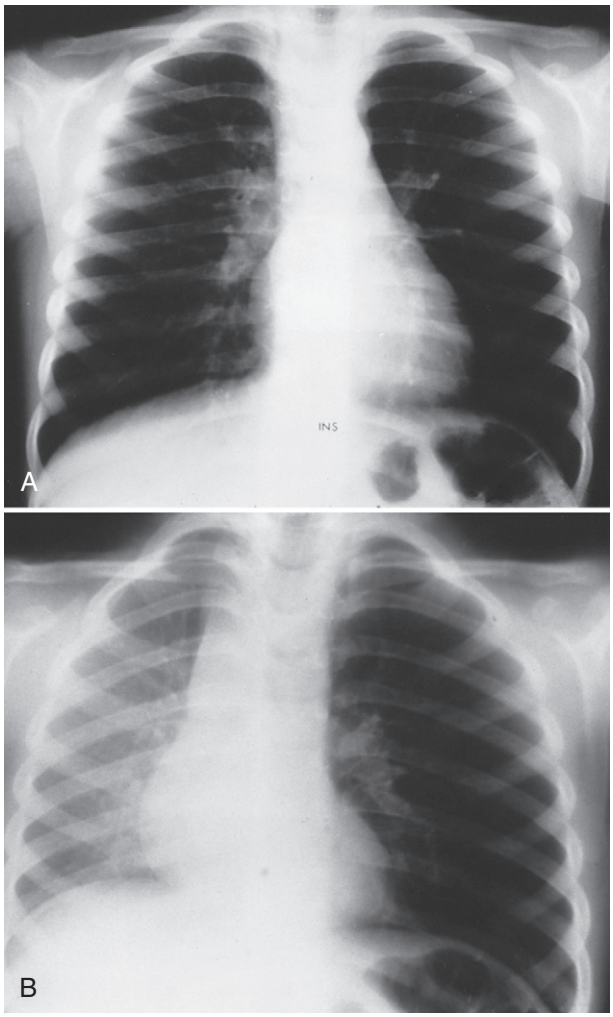

Figure 44–15. **A,** Inspiratory chest radiograph with foreign body present in left mainstem bronchus. The left lung is slightly hyperinflated but could be considered normal. **B,** Expiratory chest radiograph with foreign body present in left mainstem bronchus. The left lung is clearly hyperinflated because of air trapping by the foreign body. *(**A** and **B**, Courtesy Eric Effmann, MD.)*

is producing ball-valve bronchial obstruction, hyperinflation of the involved lung will be seen during the expiratory radiogram. Many foreign bodies are not radiopaque,[107] so failure to see a foreign body on the chest radiograph cannot exclude this diagnosis. If a suspicion of an aspiration is high, a bronchoscopy is warranted (Figure 44-16).

Foreign bodies are removed from the tracheobronchial tree with a bronchoscope.[108] Depending on the material, this may be a difficult procedure, although improvement in bronchoscopes in recent years has greatly facilitated this undertaking. Cardiopulmonary bypass has been successfully used to support a patient who had extensive foreign body aspiration. Occasionally, bronchoscopic extraction is unsuccessful, and a pulmonary lobectomy is required.

Traumatic Injury to the Airway

Traumatic injury to the upper airway may be divided into two broad categories: oral facial trauma and laryngeal/tracheal trauma. Patients with obvious oral facial trauma may be at

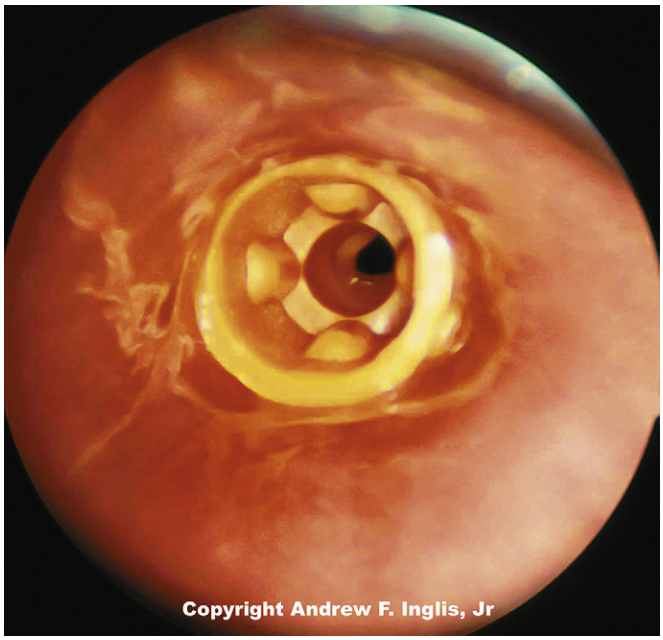

Figure 44–16. Hollow plastic foreign body in patient's trachea. Because the lumen of the foreign body was aligned with the tracheal lumen, severe respiratory embarrassment did not occur. *(Copyright Andrew F. Inglis Jr.)*

risk for upper airway obstruction. Even if the patients have no sign of respiratory distress at the time of presentation, swelling of soft tissues and hemorrhaging to the airway may lead to airway compromise.

Patients who must undergo operative intervention to treat their traumatic injuries need careful evaluation of their airway, including radiographs and CT scan examination. Traumatic injuries may make intubations in the trachea difficult in these patients. For this reason, sedation is to be avoided and endotracheal intubation with the patient awake should be considered. This may be accomplished with direct laryngoscopy after local anesthesia has been applied to the patient's oropharynx. In more difficult cases, it may be necessary to use a fiberoptic bronchoscope to guide the ETT into the trachea.

Postoperatively, patients undergoing repair of facial trauma may have their jaw wired shut and the ETT sutured in place to prevent accidental extubation. These patients should undergo extubation only when fully awake, and after resolution of their airway and facial edema. Instruments to open the wires should always be kept at the patient's bedside. Emesis may present a grave hazard in these patients.

Injury to the larynx and trachea may occur after blunt trauma such as automobile accidents, after penetrating trauma, or with crush injuries such as hanging. Blunt trauma to the neck may lead to fracture of the cartilaginous rings supporting the trachea or to disruption of the tracheal mucosa. In the latter case, attempted endotracheal intubation may worsen a partial tracheal transection and create an airway emergency.[109] Signs of laryngeal injury include dyspnea, altered phonation, pain on swallowing, hoarseness, swelling, and subcutaneous emphysema of the neck. The development of subcutaneous emphysema after blunt trauma to the neck suggests that a laryngeal fracture or tracheal tear has occurred. The quantity of air in the subcutaneous tissues does not correlate with the severity of the injury. Establishment of an adequate airway is

an essential consideration. Acute trauma of the larynx is often treated with placement of a tracheostomy before surgical repair of the larynx.

Blunt thoracic trauma can cause tracheal or bronchial disruption. Most commonly, these are "blowout" injuries that result in tracheobronchial disruption. These injuries usually occur near the carina, and most involve mainstem bronchi.[110] Because children have flexible ribs, severe intrathoracic injuries can occur without rib fractures. The signs of tracheobronchial disruption include persistent air leak, failure to expand the lung with thoracostomy tube drainage, and massive atelectasis (from failure to conduct gas through an injured bronchus). Diagnosis of these injuries is usually made with bronchoscopy. Although small tracheobronchial disruptions may be managed conservatively, most of these lesions require surgical repair.[110]

Burn Injury to the Upper Airway

Thermal injury to the upper airway may complicate the management of a patient with burns. The presence of facial burns and singed nasal hairs, hoarseness, or inspiratory stridor should suggest the possibility of burn injury to the upper airway. Although respiratory compromise may not be present at the time of admission, it may develop later as swelling of the injured airway becomes more severe. Because of the efficient cooling capacity of the upper air passages, thermal injury to the airway below the vocal cords is uncommon, occurring in less than 5% of all hospitalized patients with burns.

Evidence of respiratory embarrassment in a patient with burns should be rapidly evaluated. Neck radiographs and fiberoptic examination of the larynx may show swelling of the soft tissues of the airway. If these findings are present, endotracheal intubation should be expeditiously performed to secure the airway before obstruction occurs. Because of the risk of infection, attempts are made to avoid tracheostomy placement in the patient with burns, and data suggest this is a safe practice.[111] Upper airway embarrassment is often accompanied by smoke inhalation injury to the lower airway, resulting in hypoxemia and hypercapnia. The products of combustion result in severe carbon monoxide intoxication or cyanide poisoning, both of which have nonspecific symptoms but require prompt medical therapy.[112]

Angioedema

Angioedema is a well-demarcated localized edema involving the deep layers of skin, including the subcutaneous tissue. Angioedema may occur in response to a variety of systemic disorders, including allergic reactions that are mediated with immunoglobulin E, anaphylactic and anaphylactoid reactions, and other illnesses. Angioedema may lead to swelling of the soft tissue of the face, particularly the eyes and lips. If this should involve the soft tissues of the upper respiratory tract, laryngeal obstruction may result. Administration of subcutaneous epinephrine may dramatically reduce swelling caused by this condition. Compared to adults, children often have a rapid response to antihistamines and steroids.[113] Occasionally, respiratory embarrassment caused by this condition is so severe that endotracheal intubation is warranted. The evaluation of patients with this disorder should be directed at (1) the identification of the causative agents so that the patients can avoid these in the future and (2) the anatomic site of presentation to allow stratification of airway risk and planning of appropriate triage for airway intervention.[114]

Tracheostomy

Indications for the placement of a tracheostomy fall into three broad, frequently overlapping categories: airway obstruction, assisted ventilation, and pulmonary toilet. Pediatric anatomical anomalies that may necessitate tracheostomy are most often manifested in the neonatal period or in infancy, although some may not appear until childhood. The most common abnormalities include vocal cord paralysis (congenital and postbirth injury), subglottic stenosis, tracheal stenosis, cystic hygroma, tracheal hemangioma, and laryngeal cyst. The accurate diagnosis of these problems is frequently made during bronchoscopic examination of the larynx and trachea while the patient is anesthetized. If the obstruction is of sufficient magnitude, consideration should be given to doing a tracheostomy at the time of bronchoscopy.

Infants may require a tracheostomy because of the need for prolonged periods of assisted ventilation. The advent of neonatal intensive care has enabled small preterm infants to survive despite severe respiratory illness. Many of these patients will need lengthy periods of mechanical ventilation to treat infant respiratory distress syndrome and bronchopulmonary dysplasia. Prolonged intubation may lead to subglottic stenosis.[115] For a reduction in the frequency of this complication, a tracheostomy may be performed. The optimal timing of tracheostomy for children who need long-term intubation is controversial. In many neonatal ICUs, infants needing mechanical ventilatory support for more than 30 to 45 days will undergo a tracheostomy. Placement of a tracheostomy is not a trivial matter, with several large studies showing a tracheostomy-related mortality rate of 0.5% to 0.7%.[116,117] One recent study provided evidence that long-term tracheostomy is associated with airway inflammation (number of cells, neutrophils), more frequent bacteria, and reduced concentration of surfactant protein-D.[118] The decline of polio in the United States during the decade following 1950 dramatically decreased the number of tracheostomies performed to facilitate mechanical ventilation and pulmonary toilet. Nevertheless, several pediatric diseases predictably lead to prolonged neuromuscular failure. Infants with infant botulism may have prolonged neuromuscular weakness and may undergo a tracheostomy to simplify management of mechanical ventilation. Similarly, older children with Guillain-Barré syndrome and respiratory failure may need a tracheostomy if a lengthy course of mechanical ventilation is expected. The use of tracheostomy has been advocated to promote pulmonary toilet and improve ventilation during the treatment of flail chest.

The timing of the tracheostomy will depend on several issues, including the patient's underlying illness and the severity of the condition that makes tracheostomy necessary. If possible, emergency tracheostomy under unfavorable conditions should be avoided because the complications are more common in this setting. Percutaneous placement of a tracheostomy has been widely used in the adult population; however, experience in children remains limited. One small retrospective series suggests that placement in the ICU can be done safely with adherence to sound techniques and prudent patient selection.[119]

Postoperative Nursing Care

Care from attentive, trained nurses is essential for the well-being of the patient with a tracheostomy. Until a tract of granulation tissue has formed in the stoma between the cervical and tracheal epithelium, precautions should be taken to prevent the accidental displacement of the tracheostomy tube. Although stay sutures simplify replacement of the tracheostomy tube, this procedure may be difficult, especially in an emergency situation with a struggling patient. A hastily replaced tube may be incorrectly located in the pretracheal soft tissue, resulting in asphyxiation. If positive-pressure ventilation is attempted with the tube in this position, subcutaneous and mediastinal emphysema may be followed by a life-threatening tension pneumothorax. Because of these risks, patients routinely stay in the ICU for 5 to 7 days postoperatively. Smaller children have arm restraints placed to prevent them from pulling at the tracheostomy tube. If necessary, sedation is given until the child grows accustomed to the tracheostomy and the tract matures with the formation of granulation tissue. If accidental displacement of the tracheostomy tube does occur, replacement may be facilitated with a gentle insertion of a 0 Miller laryngoscope blade into the stoma and the identification of the tracheal lumen before the tube is passed.

Besides avoiding accidental displacement of the tracheostomy, the nurse must constantly monitor the patient for obstruction of the tracheostomy tube. The tube may be obstructed by dried tracheal mucus. Sometimes the patient's chin may obstruct the tube. Humidified gas may be administered to prevent drying and inspissation of secretions.

Complications

Any operation on the airway involves risk. The complication rate after tracheostomy has been reported to be 10% to 30%, with a death rate of 3%. Early postoperative complications include air leak, hemorrhage, and aspiration. Air leak is seen more often in children than in adults and may be life-threatening. The risk of complications declines as the patient ages. Some life-threatening complications, such as accidental decannulation or tracheostomy tube obstruction, may occur anytime after the placement of a tracheostomy. The safety and well-being of patients with a tracheostomy require constant vigilance to prevent these mishaps.

Swallowing dysfunction after tracheostomy may lead to aspiration of saliva and food. This may be due in part to anchoring of the trachea to the skin of the neck, preventing the cephalad movement of the trachea during swallowing. Children who have a tracheostomy often have difficulty learning to eat. The high frequency of pneumonia observed after tracheostomy may be in part due to the problem of recurrent aspiration. Aerophagia, another form of swallowing dysfunction, occurs with modest frequency in pediatric patients after tracheostomy.

Late complications include granulation tissue formation, tracheal stenosis, infection of the stoma, pneumonia, fused vocal cords, and distal tracheomalacia. Although infection of the stoma and distal tracheomalacia may be evident before decannulation, granulation formation and fused vocal cords may not be apparent until decannulation is attempted. An uncommon, but particularly dangerous late complication is erosion of the tracheostomy tube into the innominate artery.

Decannulation

Problems at the time of decannulation occur in up to 36% of children. These difficulties are most frequent in patients younger than 1 year. Structural abnormalities that result in decannulation problems include subglottic stenosis, tracheomalacia at the tracheostomy site, granuloma tissue obstructing the trachea, and fused vocal cords. If respiratory distress is encountered during decannulation, it should not be attributed to the patient's psychological dependence on the tracheostomy tube. Evaluation of the airway with bronchoscopy or a lateral neck radiograph is important. Psychological factors should not be considered until structural causes of respiratory embarrassment have been eliminated.

References are available online at http://www.expertconsult.com.

Asthma

Alexandre T. Rotta, Veda L. Ackerman, and Howard Eigen

PEARLS

- Patients with severe acute asthma exacerbations should be aggressively managed in the emergency department with inhaled β-agonist agents, ipratropium bromide, and systemic corticosteroid drugs. Patients who fail to improve or who further deteriorate should be admitted to the intensive care unit for a higher level of monitoring and escalation of therapy. Standard treatments include administration of fluids, oxygen, β-agonist agents by intermittent or continuous nebulization, ipratropium bromide, parenteral corticosteroid drugs, and intravenous infusion of a β_2-agonist agent. Other therapies available in the intensive care unit include intravenous infusions of magnesium sulfate and methylxanthine agents, and breathing helium-oxygen mixtures.
- Failure to respond to treatment can lead to further deterioration and the development of respiratory insufficiency, necessitating intubation and mechanical ventilatory support. Ventilation should be initiated with a strategy that avoids dynamic hyperinflation. Select patients may benefit from inhalational anesthetic agents for bronchodilatation or from bronchoscopy to relieve airway obstruction or atelectasis resulting from mucous plugging.
- Aggressive medical treatment and a mechanical ventilation strategy that minimizes dynamic hyperinflation result in low morbidity and near-zero mortality rates in patients with severe acute asthma.

Asthma is a highly prevalent chronic disease that affects both children and adults and is the most common medical emergency in the pediatric population. Despite adequate treatment and access to medical care, patients with asthma are at risk for episodic acute deteriorations in pulmonary function, commonly known as reactive airway disease exacerbations or asthma attacks. These attacks vary greatly in severity, ranging from mild episodes that are easily managed in the outpatient setting with intensification of corticosteroid and bronchodilator therapy to severe episodes with intense airway obstruction that rapidly evolve to respiratory failure.

The term *status asthmaticus* has been used to denote a more severe form of asthma attack, but its definition varies widely among different authors. To some authors, status asthmaticus is an asthma attack that does not respond to initial treatments with bronchodilators,[1,2] whereas to others it indicates severe asthma that leads to respiratory failure and requires mechanical ventilatory support.[3] For the purposes of this text, status asthmaticus is defined as an asthma attack that fails to respond to initial doses of nebulized β_2-adrenergic and anticholinergic agents and systemic corticosteroid drugs and that requires admission to the hospital for continuation of treatment. Patients who experience relentless progression of respiratory signs and symptoms and require admission to the intensive care unit (ICU) are reported as having near-fatal asthma.[4]

Epidemiology and Risk Factors

Asthma is the most common chronic illness in childhood, affecting approximately 6.7 million children and adolescents in the United States, or 9.1% of persons younger than 18 years.[5] Asthma is also a very common discharge diagnosis in children's hospitals, accounting for approximately 5.6% of all hospital admissions and more than 150,000 admissions each year in the United States alone.[5] The prevalence of asthma worldwide is highly variable, with greater than twentyfold differences in prevalence of symptoms encountered among centers located in various parts of the world.[6] The highest prevalence rates for asthma are found in the United Kingdom, Australia, New Zealand, and the Republic of Ireland; very low prevalence rates occur in eastern Europe, the Indian subcontinent, and China.[6] Race is a significant factor in determining prevalence and severity of asthma in children and young adults. African Americans are 4.1 times more likely to require treatment for asthma in the emergency department, two times more likely to be hospitalized for asthma, and 7.6 times more likely to die compared with white persons.[5] Socioeconomic status also has been shown to negatively correlate with asthma prevalence, morbidity, and mortality in the United States.[7]

Asthma prevalence has increased steadily during the past 27 years in the United States.[5] However, while the rate of nonurgent asthma-related outpatient visits continues to increase, emergency department visits and death rates have steadily declined during the past decade.[5]

The incidence of asthma-related respiratory failure requiring mechanical ventilation is difficult to determine because of variability in diagnostic criteria and reporting practices. Nonetheless, up to 36% of adult patients admitted to an inner-city medical ICU with near-fatal asthma require invasive mechanical ventilation.[8] This figure appears to be significantly lower for children, considering that only 22 (10.2%) of 237 patients treated for near-fatal asthma underwent mechanical ventilation during a 2-year period in the pediatric ICU (PICU) of a tertiary

children's hospital (A.T. Rotta, unpublished data), and that only 14 (8.6%) of 163 patients required intubation in another study.[9]

The majority of patients with asthma who experience respiratory failure or arrest do so during the first stages of therapy or prior to arrival in the emergency department.[9] Therefore early identification and close monitoring of patients at high risk for near-fatal asthma could be advantageous. High-risk patients often have a history of ICU admissions,[10] mechanical ventilation,[2,10] seizures or syncope during an attack,[11] $Paco_2$ greater than 45 torr,[2,10] attacks precipitated by food,[10] or a history of rapidly progressive and sudden respiratory deterioration.[1] These patients are likely to use more than two canisters of β-agonist metered-dose inhalers per month[12] and often are poorly compliant or are receiving insufficient steroid therapy.[13,14] Denial or failure to perceive the severity of an attack are factors frequently associated with near-fatal asthma.[15,16] Although unquestionably some patients at risk for near-fatal asthma simply ignore early warning signs and do not seek adequate therapy, a subgroup of patients actually lacks normal perception of disease severity. Some patients with near-fatal asthma exhibit reduced chemosensitivity to hypoxia and blunted perception of dyspnea.[17] Other patients have a decreased perceptual sensitivity of inspiratory muscle loads and display abnormal respiratory-related evoked potentials.[18]

Although many of these high-risk factors are commonly present in patients with near-fatal asthma, they fail to identify a significant number of cases. In one study, 33% of patients who died of asthma were judged to have a history of trivial or mild asthma, whereas 32% had never been admitted to the hospital with an asthma exacerbation.[1] Some of these patients may in fact have what likely represents a distinct clinical entity known as sudden asphyxial asthma, a condition marked by acute onset of severe airway obstruction and hypoxia that rapidly leads to cardiorespiratory arrest in patients known to have only mild asthma or no asthma history at all.[19,20]

Pathophysiology

Asthma is primarily an inflammatory disease and, as such, it is marked by highly redundant pathways and complex interactions among inflammatory cells, mediators, and the airway epithelium[21] (Figure 45-1). Functionally, asthma is characterized by variable airflow obstruction and airway hyperresponsiveness associated with airway inflammation. Pathologically, it is marked by mast cell degranulation, accumulation of eosinophils and CD4 lymphocytes, hypersecretion of mucus, thickening of the subepithelial collagen layer, and smooth muscle hypertrophy and hyperplasia.[22]

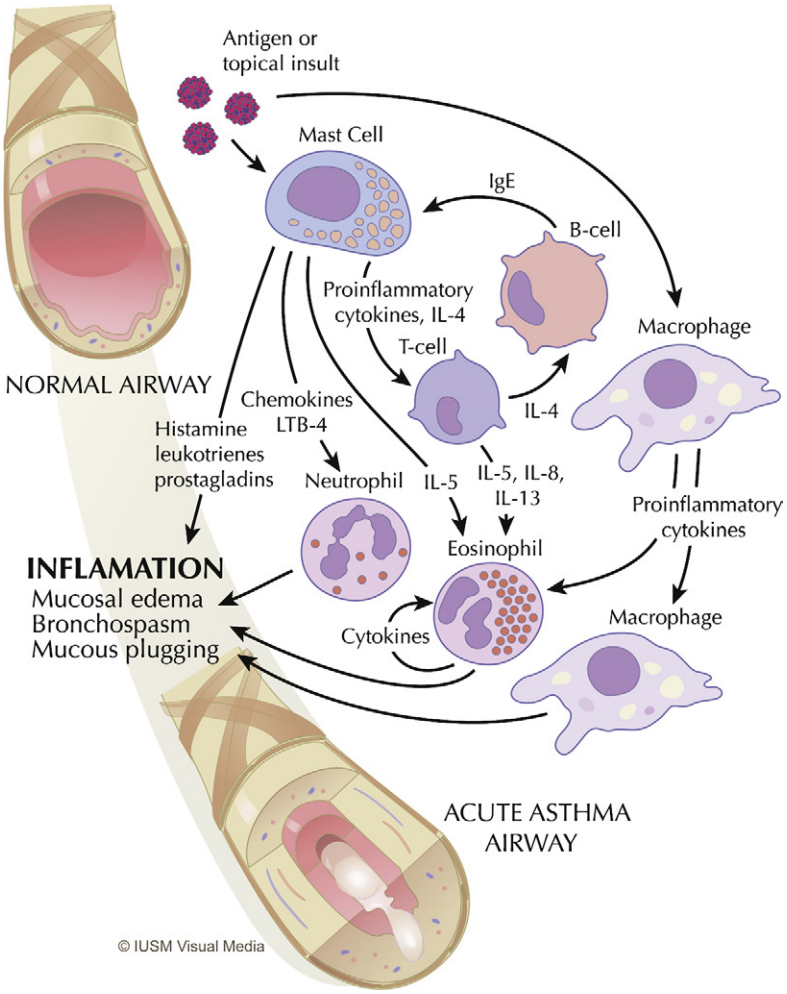

Figure 45–1. Cellular and humoral mediators that lead to mucosal edema, bronchospasm, and mucous plugging in patients with acute asthma. *IL*, Interleukin; *LTB-4*, leukotriene B-4. *(Modified with permission from Indiana University School of Medicine Visual Arts Media.)*

Mast cells, eosinophils, macrophages, and T lymphocytes are central to the derangements that occur during an acute attack (see Figure 45-1). The usual cascade begins with the activation and degranulation of mast cells in response to allergens or topical insults. The mast cells in turn promote activation of T lymphocytes by presenting these cells to the allergenic particles. The inflammatory process is then amplified by T-lymphocyte release of cytokines and chemokines. Increasing evidence exists that airway inflammation in asthma is the result of T-lymphocyte activation with the production of T_H2 cytokines, such as interleukin (IL)-4, IL-5, IL-8, and IL-13.[23] The presence of these T_H2 cytokines leads to further augmentation of the inflammatory process through overexuberant production of immunoglobulin E (IgE) by B cells, stimulation of airway epithelial cells, and eosinophil chemotaxis. IgE stimulates mast cells to release leukotrienes, whereas interleukins (particularly IL-5) promote maturation and migration of activated eosinophils into the airway.[24] This highly inflammatory milieu results in stimulation of airway epithelial cells and continued augmentation of the inflammatory process by further release of leukotrienes, prostaglandins, nitric oxide, adhesion molecules, and platelet-activating factor. This process results in overproduction of mucus and epithelial cell destruction that lead to airway plugging and denudation of the airway surface. Epithelial denudation is known to expose nerve endings, resulting in hyperirritable airways[25] that become more susceptible to spasm and obstruction when challenged by subsequent exposure to allergens,[26] inhaled irritants such as cigarette smoke and pollution,[27] respiratory tract infections,[28] psychological stress,[29] and exercise,[30] among other insults. Mucus itself is pathological in content,[31,32] and mucus hypersecretion has been underappreciated as a cause of respiratory failure in persons with severe asthma, when in fact strong evidence exists that it may be a principal cause.[31-33]

Inflammation-mediated edema, mucus hypersecretion, airway plugging, and bronchospasm lead to the severe airway obstruction seen in patients with status asthmaticus and near-fatal asthma. The resulting obstruction and increased airway resistance create an impediment for inspiratory and expiratory gas flow, which leads to deranged pulmonary mechanics and increased lung volumes.[32]

Airway plugging can result in ventilation/perfusion mismatching and increased oxygen requirements. Hypoxemia is common in patients with a severe asthma attack, but it is generally easily corrected with supplemental oxygen[34] and is only weakly correlated with pulmonary function abnormalities.[35] More frequently, airway plugging and obstruction lead to regional alveolar hyperinflation associated with reduced perfusion, resulting in a significantly increased pulmonary dead space. Most patients with this condition exhibit an increased respiratory rate in attempt to achieve a higher minute volume and compensate for the ventilation abnormality. Unfortunately, in patients with more severe disease, airway obstruction also results in significant prolongation of expiratory time, which, coupled with initiation of inspiration prior to completion of the previous exhalation, leads to dynamic hyperinflation, gas trapping, and the development of abnormally high lung volumes[36] (Figure 45-2).

The higher lung volumes that result from incomplete alveolar emptying and dynamic hyperinflation serve as an adaptation mechanism to allow for higher expiratory flows than would have been possible at lower, more physiologic lung volumes. This higher expiratory flow is accomplished, however, at a high energy cost. Expiration becomes an active process, and the use of accessory muscles is required to overcome the high resistances to airflow both during inspiration and exhalation.[37] During a severe attack, inspiratory transpulmonary pressures in excess of 50 cm H_2O may be generated, compared with approximately 5 cm H_2O during normal breathing.[38] The increased muscle work is accompanied by an increase in blood flow to the diaphragm, but this flow often is insufficient to meet the much greater metabolic demands.[39] Failure to promptly relieve the airway obstruction and reduce the work of breathing eventually leads to respiratory muscle fatigue, inadequate ventilation, and respiratory failure.

States of advanced airway obstruction and dynamic hyperinflation typical of severe asthma attacks have a significant impact on the circulatory system. The highly negative intrapleural pressures generated by spontaneously breathing patients during inspiration favor transcapillary edema fluid movement into the air spaces.[37] They also cause a phasic increase in left ventricular afterload and a decrease in cardiac output[40] that is clinically manifested as pulsus paradoxus.[41] Right ventricular afterload may be increased during severe asthma as a result of pulmonary vasoconstriction related to hypoxia and acidosis. A state of increased pulmonary vascular resistance resulting from dynamic hyperinflation also can increase right ventricular afterload, further affecting cardiac output.[41-43]

Clinical Assessment

History

The child with an asthma exacerbation usually presents with complaints of difficulty breathing and shortness of breath. The presence of these complaints in a child known to have had previous asthma exacerbations is highly suggestive of the diagnosis. A significant percentage of children have a history of a coexisting viral upper respiratory infection, whereas some describe exposure to known allergic triggers. Circumstances permitting, time should be taken to inquire about the presence of high-risk factors (Box 45-1) for near-fatal asthma and the adequacy of maintenance intercrisis therapy.

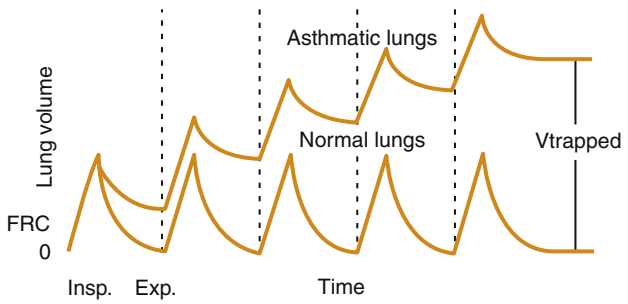

Figure 45–2. Mechanics of dynamic pulmonary hyperinflation in the setting of severe airflow obstruction. The next inspiration begins before complete exhalation, leading to gas trapping and increased end-expiratory lung volume. *Exp.,* Expiration; *FRC,* functional residual capacity; *Insp.,* inspiration; *Vtrapped,* volume of trapped gas above FRC. *(From Levy BD, Kitch B, Fanta CH: Medical and ventilatory management of status asthmaticus,* Intensive Care Med *24:105-117, 1998.)*

Box 45–1 Risk Factors for Near-Fatal Asthma.

Medical Factors

Previous asthma attack with:

- Admission to intensive care unit
- Respiratory failure and mechanical ventilation
- Seizures or syncope
- $Paco_2$ >45 torr
- High consumption (>2 canisters per month) of β-agonist metered-dose inhalers
- Underuse of corticosteroid therapy

Psychosocial Factors

- Denial of or failure to perceive severity of illness
- Associated depression or other psychiatric disorder
- Noncompliance
- Dysfunctional family unit
- Inner-city residents

Ethnic Factors

- Nonwhite children (black, Hispanic, other)

Data from Werner HA: Status asthmaticus in children: a review, *Chest* 119:1913-1929, 2001.

Table 45–1 Clinical Asthma Evaluation Score*

	0	1	2
Pao_2 (torr) *or*	70–100 in 21% O_2	<70 in 21% O_2	<70 in 40% O_2
Cyanosis	None	In 21% O_2	In 40% O_2
Inspiratory breath sounds	Normal	Unequal	Decreased to absent
Accessory muscles used	None	Moderate	Maximal
Expiratory wheezing	None	Moderate	Marked
Cerebral function	Normal	Depressed or agitated	Coma

*A score of 5 or more is thought to be indicative of impending respiratory failure. A score of 7 or more with $Paco_2$ >65 torr indicates existing respiratory failure.

Data from Wood DW, Downes JJ, Lecks HI: A clinical scoring system for the diagnosis of respiratory failure. Preliminary report on childhood status asthmaticus, *Am J Dis Child* 123:227-228, 1972.

Physical Examination

Children with severe forms of acute asthma commonly present with tachypnea, diaphoresis, increased use of accessory muscles, and nasal flaring. Sick nonverbal children may appear anxious, agitated, or simply unable to be distracted from the task of breathing. Older children often assume a tripod sitting position and may voice a sensation of impending doom. Speech flow is truncated by the need to inspire. The presence of intercostal, subcostal, and suprasternal retractions, nasal flaring, inability to speak in sentences, and agitation are signs of impending respiratory failure. Evolution or persistence of these signs is followed by slower labored breathing, confusion or obtundation, and respiratory arrest.

Wheezing, which is a common clinical finding in patients with acute asthma exacerbations, is the audible manifestation of the transmitted turbulence to airflow in the intrathoracic intrapulmonary airways. Wheezing may be predominantly expiratory as a result of the dynamic phasic compression of conducting airways, but it also can be biphasic. Wheezing in persons with severe asthma usually is symmetrical. An asymmetrical distribution suggests regional mucous plugging, atelectasis, pneumothorax, or the presence of a foreign body. The degree of wheezing correlates poorly with disease severity,[44] because wheezes are heard only in the presence of airflow. As such, a patient with severe airway obstruction and very limited airflow may have a silent chest upon arrival at the emergency department, but loud wheezes may develop after effective therapy is instituted. Likewise, in a patient with loud wheezes that continue to worsen, a silent chest may develop as a prelude to respiratory failure.

An objective assessment of disease severity is important in evaluating a patient's response to therapy. Wood and colleagues[45] developed a practical clinical asthma score composed of five variables with three different grades that allows for semiquantitative assessment of disease severity (Table 45-1). This clinical asthma score has been shown to correlate well with the need for prolonged bronchodilator therapy and hospitalization.[46] However, although clinical asthma scores seem to be useful for assessing the severity of an attack, they are not as effective in prospectively identifying patients who require prolonged hospitalization or in whom complications and subsequent disability develop.[47,48]

A less frequently used but more objective method of assessing disease severity and progression in patients with severe asthma is measurement of the pulsus paradoxus. Originally described by Adolf Kussmaul[49] in a patient with constrictive pericarditis, pulsus paradoxus also is observed in conditions in which pleural pressure swings are exaggerated, such as status asthmaticus and near-fatal asthma. The simplest definition of pulsus paradoxus is an exaggeration of the physiologic inspiratory decrease in systolic blood pressure[50] (Figure 45-3). It has been suggested that the term pulsus paradoxus is inappropriate to describe this phenomenon,[51] because an accentuated inspiratory decrease in systolic pressure in the same direction as the normally occurring change cannot be described as a paradox. However, the true paradox described by Kussmaul[49] was "the presence of a pulse slight and irregular, disappearing during inspiration and returning upon expiration despite the continued presence of the cardiac impulse during both respiratory phases."[50] Several mechanisms have been implicated in the occurrence of pulsus paradoxus in persons with asthma, and it is likely that various mechanisms contribute differently depending on the adequacy of intravascular volume, the magnitude of pleural pressure swings, the degree of pulmonary hyperinflation, and the state of cardiac contractility. These mechanisms include increased left ventricular afterload from highly negative intrapleural pressure[52]; decreased left ventricular preload as a result of inspiratory blood pooling in the pulmonary vasculature[53]; impaired left ventricular diastolic filling caused by a leftward shift of the interventricular septum resulting from increased venous return to the right heart[54]; constraint of cardiac filling because of longitudinal inspiratory deformation of the pericardium[41]; and increased right ventricular afterload with decreased filling of the left ventricle as a result of hyperinflation, acidosis, and hypoxia.[55] The pulsus paradoxus can be measured easily in a patient who is spontaneously breathing by transducing pressure signals from an indwelling arterial catheter or by using a manual sphygmomanometer. In the

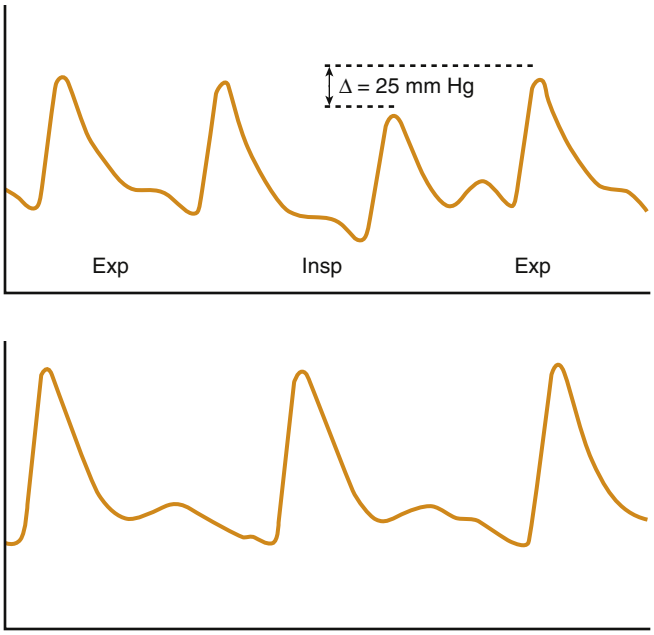

Figure 45–3. Pressure recording from a radial artery catheter of a spontaneously breathing patient with airway obstruction. *Upper panel:* Abnormally high pulsus paradoxus of 25 mm Hg is measured as the difference (Δ) in systolic blood pressure between expiration (Exp) and inspiration (Insp). *Lower panel:* Normal slight physiologic variation of the systolic blood pressure as a function of the respiratory cycle 12 hours after onset of treatment. *(Modified with permission from Indiana University School of Medicine Visual Arts Media.)*

latter technique, the cuff is inflated 20 mm Hg above the systolic pressure and then deflated until the first Korotkoff sounds are heard (systolic blood pressure). Initially, Korotkoff sounds are heard only during expiration. The cuff is then carefully deflated until the point where the sounds are heard equally during both inspiration and expiration. The difference between the highest systolic pressure and the pressure at which all Korotkoff sounds are heard is the magnitude of the pulsus paradoxus. During normal breathing, this difference is less than 5 mm Hg, but it is generally greater than 10 mm Hg during acute asthma exacerbations and greater than 20 mm Hg in patients with more severe disease.[56] Changes in the magnitude of pulsus paradoxus during the course of therapy are good indicators of disease severity and clinical response to treatment.[41,56]

Patients with status asthmaticus frequently have a palpable liver with normal liver span on physical examination. This sign is more pronounced in patients with significant hyperinflation and is explained by caudal displacement of the liver by the flattened diaphragm.

Radiography

Chest radiography is not routinely indicated in spontaneously breathing patients known to have asthma. However, it is a valuable diagnostic tool in patients suspected of having a pneumothorax or pneumomediastinum, pneumonia, or clinically important atelectasis and in children presenting with a first episode of wheezing in whom anatomic abnormalities (such as vascular rings or a right-sided aortic arch) or foreign bodies are suspected. One should consider obtaining a chest radiograph in patients who are sick enough to require monitoring and treatment in the ICU to exclude the possibility of unsuspected extrapulmonary air and airspace disease.

Laboratory Data

Arterial Blood Gas Analysis

Arterial blood gas measurements provide objective information on the adequacy of ventilation and oxygenation of the patient with asthma. The typical blood gas abnormality encountered in the early phase of asthma is relative hypoxemia with hypocapnia ($Paco_2$ <35 torr), reflecting hyperventilation.[57] With worsening of airway obstruction, $Paco_2$ measurements return to the normal range of approximately 40 torr. However, this "normal" $Paco_2$ should not be viewed as reassuring when taken in the context of prolonged expiratory time, tachypnea, and accessory muscle use.[58] In fact, $Paco_2$ greater than 40 torr in a patient with status asthmaticus should be interpreted as a sign of evolving respiratory muscle fatigue and warrants close clinical observation. Sicker patients often exhibit a mixed respiratory and metabolic acidosis.[59] Lactic acidosis is frequently encountered in these patients and is thought to represent exaggerated lactate production by the respiratory muscles and tissue hypoxia.[60]

The decision of whether to intubate a child with asthma should not be made on the basis of arterial blood gas measurements but on the basis of the overall clinical status. As such, routine arterial blood gas determinations are not a critical component of the evaluation of a spontaneously breathing child with status asthmaticus. In contrast, children with asthma undergoing mechanical ventilation require frequent blood gas measurements to monitor disease progression and the adequacy of ventilatory support.

Electrolytes and Complete Blood Cell Count

Routine chemistry results and blood cell counts generally are not revealing in patients with status asthmaticus. Children who present with a protracted asthma attack may have evidence of dehydration with elevated blood urea nitrogen as a result of decreased oral fluid intake and increased insensible water losses. Patients undergoing repeated treatments with nebulized or intravenous (IV) β-agonist agents might show evidence of hypokalemia from the potassium shift to the intracellular space. The blood cell count usually is normal, although some patients who are atopic may exhibit elevated eosinophil counts. The presence of leukocytosis in some patients does not necessarily indicate infection and likely is related to adaptive stress or the administration of exogenous corticosteroid agents.

Muscle Enzymes

At least one third of patients with acute severe asthma exhibit an elevated plasma creatine kinase (CK) level.[61] Although such elevations seem to be more pronounced in patients with marked acidemia or in those presenting with more severe respiratory insufficiency, a convincing correlation between disease severity and CK elevation has not been established.[61] Myoglobin, a heme protein present in skeletal and cardiac muscle, is often also elevated in patients with near-fatal asthma.[61] Elevations of CK-myocardial bound (CK-MB) isoenzyme develop in some patients with near-fatal asthma, suggesting a possible

myocardial injury. This scenario certainly is plausible, considering that many patients are hypoxemic, acidotic, have high myocardial energy demand, and are receiving medications with adverse cardiac effects. However, plasma myoglobin and CK-MB elevations cannot be solely attributed to myocardial injury because the lungs and respiratory muscles are also known sources of these substances.[62] Cardiospecific troponin T is a very sensitive and specific marker of myocardial cell damage[63] and should be used preferentially to address the question of cardiomyocyte involvement in patients with severe asthma.

Electrocardiography

Patients with status asthmaticus or near-fatal asthma with significant airway obstruction and hyperinflation may exhibit a change in the mean frontal P-wave vector. A P-wave axis greater than 60 degrees has been associated with hyperinflation in both pediatric and adult patients with airway obstruction and is thought to represent positional atrial changes caused by inferior displacement of the diaphragm.[64]

Twelve-lead electrocardiography and continuous cardiac monitoring are valuable tools in the care of patients with near-fatal asthma in the ICU environment. These patients usually receive high doses of β-agonist drugs and may show evidence of hypokalemia (low-voltage T waves) or cardiac arrhythmias.[65,66] The already increased myocardial energy demand resulting from airway obstruction is compounded by the chronotropic and vasodilatory effects inherent to β-agonist drugs and may lead to myocardial ischemia, particularly in adult patients with restricted coronary perfusion. Pediatric patients also may exhibit electrocardiographic (ECG) and enzymatic evidence of myocardial ischemia, particularly during treatment with intravenously administered isoproterenol.[67] However, despite the fact that a study reported that a high percentage (66%) of patients exhibited nonspecific ST segment changes or other criteria suggestive of ischemia, these changes were not well correlated with initiation of terbutaline therapy or elevations in cardiac troponin T.[68]

Spirometry

Measurement of peak expiratory flow rates can be used to estimate the degree of airway obstruction and response to therapy in patients presenting to the emergency department with an acute asthma attack. Use of this simple technique is less ubiquitous to the pediatric ICU environment because sick patients with severe respiratory distress simply may be unable to perform an adequate forced expiratory maneuver. Measurements also may not be reliable in younger patients who are incapable of coordinating a rapid forced expiratory effort.

Treatment

Initial Management in the Emergency Department

Pediatric patients with mild acute asthma exacerbations generally are treated in the emergency department with one or more doses of an inhaled β-agonist, such as albuterol (salbutamol). Most of these patients also should receive a systemic-acting corticosteroid, such as prednisone, and generally are sent home to complete a 3- to 5-day course of therapy. Patients with mild disease generally respond well to initial treatment and do not require the attention of a pediatric intensivist.

Patients with moderate or severe acute asthma attacks require aggressive treatment from the outset, including the prehospital setting. Because most patients with moderate or severe attacks have enough intrapulmonary shunt to result in clinically measurable hypoxemia, supplemental oxygen therapy should be initiated in patients with an oxygen saturation measured by pulse oximetry (Spo_2) of lower than 91%. It should be obvious that use of supplemental oxygen will cause an increase in Spo_2 but will have no impact on ventilation. Therefore one must not incorrectly assume that ventilation is adequate in a patient with normal Spo_2 during administration of supplemental oxygen therapy.

Nebulized β-agonist agents, such as albuterol (salbutamol), are the most commonly used first-line therapy in the emergency department. The usual albuterol dose ranges between 0.05 and 0.15 mg/kg, diluted with 1 or 2 mL of normal saline solution. However, from a practical standpoint, patients weighing 20 kg or more usually are administered 5-mg doses, whereas patients weighing less than 20 kg receive 2.5-mg doses. Albuterol doses are repeated every 20 minutes during the first hour, with the need for additional doses dictated by clinical response.

Patients with moderate or severe acute asthma also should receive a dose of systemic corticosteroid in the emergency department, which usually is administered prior to the second dose of albuterol. Prednisone (2 mg/kg) can be administered orally and is generally well tolerated. Oral prednisone is superior to inhaled fluticasone in children with severe asthma as evidenced by greater improvement in pulmonary function and lower hospitalization rates.[69] The role of corticosteroid drugs in reversing an acute asthma attack in the emergency department has been the subject of debate, considering that these drugs require at least 4 to 6 hours for peak effects to be manifested.[70] However, regardless of considerations about onset of action, acute suppression of inflammation is a cornerstone of acute asthma treatment and should be initiated as early as possible. Sicker patients with severe asthma exacerbations, those unable to tolerate oral medication because of respiratory distress or emesis, or those with a history of nausea during intensive β-agonist therapy should be given parenteral corticosteroid drugs such as methylprednisolone (2 mg/kg administered intravenously, followed by 0.5 to 1 mg/kg/dose administered intravenously every 6 hours).

Inhaled or nebulized anticholinergic agents such as ipratropium bromide are now considered an important adjunct in the treatment of persons with moderate and severe asthma exacerbations in the emergency department. In patients treated with one dose of a corticosteroid, use of ipratropium bromide (500 μg/2.5 mL) in conjunction with the second and third albuterol (salbutamol) doses has been associated with greater clinical improvement[71] and reduced hospitalization rates compared with corticosteroid and albuterol (salbutamol) alone.[72]

Admission Criteria

The majority of patients with an acute asthma exacerbation respond to treatment in the emergency department and are discharged home. Among patients whose symptoms persist despite initial treatment, most can be safely managed in the

general pediatric inpatient ward. Indications for hospitalization after treatment in the emergency department are loosely defined but may include (1) an inadequate response to three or four aerosol treatments; (2) relapse within 1 hour of receiving treatment with aerosols and steroids; (3) persistent Spo_2 measurements of less than 91% in room air; (4) the need for oxygen therapy; (5) a significant reduction in peak expiratory flow rate; (6) having unreliable family support or being unable to comply with outpatient treatment; and (7) multiple visits for the same episode.[73,74] Patients who require higher levels of monitoring or more invasive and aggressive treatment or who deteriorate during hospitalization in the general pediatric ward should be admitted to the PICU.

Management in the Intensive Care Unit

General

Patients with near-fatal asthma who are admitted to the ICU represent a heterogeneous group and, as such, require different levels of monitoring, technology, and treatments. However, all patients who are sick enough to warrant admission to the ICU should be attached to a monitor capable of displaying continuous ECG tracing, respiratory rate, noninvasive blood pressures, and Spo_2. Sicker patients who require blood samples to be obtained frequently or who require monitoring of pulsus paradoxus will benefit from an indwelling arterial catheter. Patients in respiratory failure requiring mechanical ventilation should have adequate central venous access and a Foley catheter in addition to the more basic instrumentation.

Oxygen

Sick patients with asthma are likely to exhibit hypoxemia as a result of intrapulmonary shunts caused by mucus plugging and atelectasis. Treatment with β-agonist agents also can contribute to hypoxemia by abolishing regional pulmonary hypoxic vasoconstriction and increasing intrapulmonary shunt.[75,76] Therefore humidified oxygen should be offered both as a carrier gas for nebulizations and continuously between treatments.[77] Supplemental oxygen can be safely incorporated into the treatment algorithm because, unlike in some adult patients with severe chronic obstructive pulmonary disease[78] or asthma,[79] no evidence exists to suggest that supplemental oxygen suppresses the respiratory drive in children with near-fatal asthma.

Fluids

Patients with near-fatal asthma usually present in a state of decreased total body water because of decreased oral fluid intake and increased insensible water losses. Therefore most patients require some degree of volume expansion. This need should be carefully balanced with the need to avoid overhydration because of the propensity for transcapillary fluid migration and alveolar flooding that is exhibited by some patients with large swings in intrathoracic pressures. The need for rapid fluid expansion often becomes obvious shortly after intubation of patients with low intravascular volumes who are receiving IV β-agonist agents.

Corticosteroids

Corticosteroid drugs play a central role in the treatment of patients with status asthmaticus and near-fatal asthma, considering that these conditions are predominantly inflammatory in nature. Glucocorticosteroid agents modulate airway inflammation by a number of mechanisms, including direct interaction with cytosolic receptors and glucocorticosteroid response elements in gene promoters and indirect effects on binding of transcription factors, such as nuclear factor–κB, and on other cell signaling processes, such as posttranscriptional events.[80] Gene products suppressed by glucocorticosteroid agents include a wide range of cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-11, IL-12, IL-13, tumor necrosis factor-α, and granulocyte-macrophage colony-stimulating factor), adhesion molecules (intracellular adhesion molecule-1 and vascular cell adhesion molecule-1), and inducible enzymes, including NO synthase and cyclooxygenase-2.[81] Transcription of other genes, such as lipocortin-1 and the β_2-adrenergic receptor, may be enhanced.[81] Glucocorticosteroid agents also decrease airway mucus production, reduce inflammatory cell infiltration and activation, and attenuate capillary permeability.[82-85]

In children with status asthmaticus or near-fatal asthma, glucocorticosteroid drugs should be administered by the IV route. The oral route can be used in selected cases, but inhaled glucocorticosteroid drugs play no role in the treatment of the sick hospitalized patient.[21,69] The most common agent used in the United States is methylprednisolone because of its wide availability as an IV preparation and lack of mineralocorticoid effects. The usual dose of methylprednisolone is 0.5 to 1 mg/kg/dose, administered intravenously every 6 hours. Hydrocortisone, an agent with both glucocorticoid and mineralocorticoid activity, can be used as an alternative at doses of 2 to 4 mg/kg/dose, administered intravenously every 6 hours. Short courses of steroids usually are well tolerated without significant adverse effects.[84] However, hypertension, hyperglycemia, mood disorders, and serious viral infections, such as fatal varicella, have been reported in previously well patients with asthma who have received glucocorticosteroid drugs.[84,86,87] Duration of corticosteroid therapy is dictated by the severity of illness and the clinical response. Once initiated, treatment in patients with status asthmaticus or near-fatal asthma is generally continued for 5 to 7 days. Longer treatment courses necessitate gradual weaning of the drug to decrease the chances of symptomatic adrenal insufficiency or relapse. Prophylaxis with an H_2 blocker should be considered because of the possibility of steroid-associated gastritis and gastric perforation.[88]

β-Agonists

The β-agonist properties of the sympathomimetic agents cause bronchial smooth muscle relaxation and hence bronchodilatation. These agents also can increase diaphragmatic contractility, enhance mucociliary clearance, and inhibit bronchospastic mediators from mast cells.[89] Therefore β-agonists, along with systemic corticosteroids, are the mainstay of pharmacotherapy in persons with near-fatal asthma. β_2-receptor selectivity is desirable to avoid adverse effects of nonselective α- and β_1-adrenergic receptor stimulation. However, despite β_2 selectivity, cardiovascular adverse effects remain a dose-limiting factor. The relative potency of various agents

for the β_2 receptor is as follows: isoproterenol > fenoterol > albuterol > terbutaline > isoetharine > metaproterenol.[90] Of these agents, only albuterol and terbutaline are widely used in clinical practice, with some centers still using isoproterenol in selected occasions.

Once bound to the β-adrenergic receptor, β-agonists activate adenyl cyclase, resulting in increased intracellular cyclic adenosine monophosphate (cAMP) levels, which leads to bronchial and vascular smooth muscle relaxation. Dose-response curves demonstrate that large dose increases fail to enhance bronchodilation significantly; however, as the degree of bronchial constriction increases, the bronchodilation dose-response curve shifts to the right, indicating the need for a higher dose to achieve the desired response.[90]

In persons with near-fatal asthma, parenteral and aerosol routes of administration are used exclusively. Traditional therapy for persons with acute asthma previously included subcutaneous doses of epinephrine, but epinephrine is no longer widely used because of the development of newer, more selective β-agonist agents with longer duration of action and fewer adverse effects.

The most frequent untoward adverse effects of β-agonist agents are skeletal muscle tremor, nausea, and tachycardia. These adverse effects are common to both nonselective and selective β-agonist drugs administered by IV and inhalational routes. Other cardiovascular adverse effects include blood pressure instability (predominantly diastolic hypotension) and cardiac dysrhythmias.[91,92] Myocardial ischemia has been well documented as a complication of IV isoproterenol administration to children with near-fatal asthma.[67,93] However, continuous IV infusions of terbutaline appear to be safe and are not associated with significant cardiotoxicity.[68] Prolongations of the QTc interval and hypokalemia have been observed during IV infusions of β-agonist drugs.[94] Hypokalemia occurs in the setting of relatively stable total body potassium and is the result of intracellular potassium shifting that results, at least in part, from an increased number of sodium-potassium pumps and not from augmented potassium elimination.[95] Therefore supraphysiologic potassium supplementation is rarely necessary. A less frequently recognized adverse effect of β-agonist agents is hypoxemia, which is likely related to decreased regional hypoxic pulmonary vasoconstriction in areas of atelectasis and the resultant increased intrapulmonary shunt.[75,76]

Albuterol (Salbutamol)

Albuterol is the most β_2-specific aerosol agent available in the United States. It usually is administered every 20 minutes during the initial phase of treatment at a dose of 0.05 to 0.15 mg/kg. The optimal dose and frequency of albuterol are controversial because less than 1% of the nebulized drug is deposited in the lung.[96] Moreover, spontaneous tidal volume, breathing pattern, and technique are unpredictable yet major determinants of drug delivery. After the initial series of three albuterol treatments, continuous albuterol nebulization should be started for patients who require nebulization treatments more frequently than every 1 hour.

Continuous albuterol nebulization appears to be superior to repeated intermittent dosing and has not been shown to cause significant cardiotoxicity.[97-99] A small prospective randomized study in children with near-fatal asthma and impending respiratory failure indicated that children treated with continuous albuterol nebulization had more rapid clinical improvement and shorter hospitalizations compared with children treated with intermittent albuterol doses.[98] Continuous administration of albuterol also was associated with more efficient allocation of respiratory therapists' time[98] and could offer the added advantage of more hours of uninterrupted sleep to patients who often are already exhausted.[100] The usual dose of continuously administered albuterol ranges between 0.15 and 0.45 mg/kg/h, with a maximum dose of 20 mg/h. Higher doses of albuterol have been used in patients who are unresponsive to standard treatment.[51] However, we do not support this practice, because the intensification of adverse effects can outweigh any small incremental gain in bronchodilatation.

The availability of levalbuterol has generated some controversy. Albuterol is a 50:50 mixture of R-albuterol (levalbuterol), the active enantiomer that causes bronchodilation, and S-albuterol, which was thought to be inactive in humans. The U.S. Food and Drug Administration has approved levalbuterol, the pure R-isomer, as a preservative-free nebulizer solution.[101] The purported advantage of using levalbuterol over albuterol stems from the fact that S-albuterol may not be completely inert and has a longer elimination half-life than R-albuterol.[102,103] However, the notion that S-albuterol is not inert and that it is capable of clinically significant adverse effects is not universally accepted.[104-106] A large randomized controlled trial of levalbuterol versus racemic albuterol in children with asthma demonstrated a decreased rate of hospitalization in patients treated with levalbuterol. However, this study had methodological problems, as the primary outcome variable (rate of hospital admission) was left to the discretion of the treating physicians and none of the secondary outcome variables were significantly different between treatment groups once the patients had been admitted to the hospital.[107] More recent randomized clinical studies in children with asthma failed to show definitive evidence that levalbuterol is superior to a regular racemic albuterol.[108,109] Furthermore, although the cost of levalbuterol has decreased significantly in the past few years, this drug continues to be more expensive than albuterol (C. A. Thomas, PharmD, Riley Hospital for Children, personal communication, 2011). Considering the lower cost of albuterol and the paucity of clinical evidence supporting the superiority of levalbuterol, we continue to favor albuterol as the routine bronchodilator of choice in children with near-fatal asthma.

Intravenously administered albuterol is not available in the United States. However, the efficacy of albuterol infusions in patients with severe asthma has been well established in countries where the IV preparation is available.[110-112]

Terbutaline

Terbutaline is a relatively selective β_2-agonist with a mechanism of action that is similar to that of albuterol. It is the most commonly used parenteral β-agonist in the United States and is available for nebulization, subcutaneous injection, and IV use. Because of its lower β_1-receptor affinity, subcutaneous administration of terbutaline has largely supplanted the use of epinephrine in persons with severe acute asthma. The use of subcutaneous terbutaline is limited in the PICU environment; it is reserved for patients with acute worsening of the respiratory status who do not have vascular access and in whom access cannot be easily obtained. Subcutaneous terbutaline is more commonly used in the acute management of sick patients in the emergency department and in the prehospital

setting. The usual subcutaneous terbutaline dose is 0.01 mg/kg/dose (maximum 0.25 mg) subcutaneously every 20 minutes for three doses, as necessary.

Terbutaline is more commonly used in the ICU environment through the IV route. This therapy is indicated for patients with near-fatal asthma who fail to improve or show signs of deterioration during treatment with nebulized β_2-agonists, ipratropium bromide, and steroids. The usual IV terbutaline doses are 0.1 to 10 μg/kg/min as a continuous infusion,[91] prepared in 0.9% normal saline solution or D_5W. In our clinical experience, however, most patients are started on a dose of 1 μg/kg/min and the dose is titrated to effect, with doses higher than 4 μg/kg/min rarely necessary. Patients receiving doses lower than 1 μg/kg/min can be given a loading dose of 10 μg/kg over 10 minutes to accelerate the onset of action.

Anticholinergic Agents

Anticholinergic agents have become an important part of the treatment of children with severe acute asthma. The prototypical anticholinergic agent used in treating patients with asthma is ipratropium bromide, a quaternary ammonium compound formed by the introduction of an isopropyl group to the N atom of atropine. Unlike atropine (a tertiary ammonium compound), ipratropium bromide does not cross the blood-brain barrier, thus preventing the occurrence of central anticholinergic adverse effects. Considering that bronchial smooth muscle tone is influenced by the parasympathetic tone, ipratropium bromide can produce bronchodilation by inhibition of cholinergic-mediated bronchospasm.[113] An unexpected but important property of ipratropium bromide is the lack of negative effect on ciliary bronchial epithelium, unlike the marked inhibition of ciliary beating and mucociliary clearance produced by atropine.[113]

Nebulized ipratropium bromide (250- to 500-μg doses) can be used every 20 minutes during the first hour in the emergency department. The recommended dose for continuation therapy is 250 to 500 μg, given every 6 hours. After inhalation, peak responses usually develop over 30 to 90 minutes, and clinical effects may persist for more than 4 hours.[113] Systemic effects are minimal because less than 1% of an inhaled dose of ipratropium bromide is absorbed into the circulation. However, extrapulmonary effects such as mydriasis and blurred vision have been reported as a result of topical ocular absorption of the drug.[114,115]

The addition of ipratropium bromide to nebulized albuterol in the treatment of bronchospasm makes pharmacological sense, because albuterol causes bronchodilatation by increasing cAMP levels, while the effect of ipratropium bromide is mediated by a decrease in cyclic guanosine monophosphate. The combined use of ipratropium bromide and nebulized albuterol in treating children with asthma who present to the emergency department has proved to be cost effective and reduces the rate of admission to the hospital.[71,72] However, the routine addition of repeated doses of nebulized ipratropium bromide to a standard regimen of β_2-agonist agents and systemic steroid drugs in hospitalized children with status asthmaticus does not appear to confer a significant benefit.[116,117] Considering the high safety profile of inhaled ipratropium bromide treatments, the benefits of its use in the emergency department, and the lack of data specific to the PICU population, we find it reasonable to administer ipratropium bromide along with standard therapy for critically ill patients with status asthmaticus until definitive evidence becomes available.

Magnesium Sulfate

Magnesium is a physiologic calcium antagonist that causes smooth muscle relaxation as a result of inhibition of calcium uptake. It has been known for more than 60 years that magnesium causes bronchorelaxation in patients with asthma,[118] but its incorporation as an adjunct in the treatment of patients with severe asthma has occurred only recently. Numerous reports, case series, and randomized controlled trials have suggested clinical improvement when asthmatic patients with severe airway obstruction receive IV magnesium sulfate infusions in the emergency department or ICU.[119,120] Magnesium appears to be as effective as albuterol when delivered by nebulization[121] and has been used successfully by some practitioners as a liquid vehicle for albuterol nebulization.[122]

The indication for IV magnesium sulfate in children with status asthmaticus or near-fatal asthma is still controversial because of the paucity of randomized controlled trials. Some studies suggest that magnesium sulfate infusions are associated with significant improvements in short-term pulmonary function,[123-126] whereas another study failed to show improvement in disease severity or a reduction in hospitalization rates.[127] The usual dose of magnesium sulfate in children with status asthmaticus or near-fatal asthma is 25 to 40 mg/kg/dose, intravenously, infused over 20 to 30 minutes.[126] The onset of clinical response is rapid (occurring in minutes) and is generally observed during the initial infusion. During the infusion patients should be carefully monitored for adverse effects, which include hypotension, nausea, and flushing. Serious toxicity involving cardiac arrhythmias, muscle weakness, areflexia, and respiratory depression has not been reported with the use of magnesium sulfate in persons with acute asthma, when used as directed. The IV infusion of magnesium sulfate under controlled conditions appears to be safe, and a subset of patients with status asthmaticus and near-fatal asthma clearly responds to this mode of therapy.[123-126] A systematic review of the published randomized controlled trials supports the use of magnesium sulfate in addition to β_2-agonist agents and systemic steroid drugs in the treatment of persons with severe acute asthma.[128]

Methylxanthine Agents

Methylxanthine agents, as the name implies, are substances formed by the methylation of xanthine, such as caffeine, theobromine, and theophylline. The water solubility of methylxanthine agents is very low but can be greatly enhanced by formation of complexes with a variety of compounds. Most notably, the combination of theophylline and ethylenediamine yields aminophylline, a water-soluble salt. A large number of methylxanthine derivatives have been developed, but only theophylline and aminophylline are relevant to the treatment of patients with asthma.

The exact molecular mechanism of theophylline-mediated bronchodilation is unclear but is thought to involve, at least in part, its action as a phosphodiesterase-4 inhibitor, reducing the degradation of cAMP, which in turn mediates

cellular responses that result in bronchial smooth muscle relaxation.[129] Other mechanisms of action have been proposed, including inhibition of phosphoinositide 3-kinase activity,[130] adenosine receptor antagonism,[131] increasing histone deacetylase activity,[132] stimulation of endogenous catecholamine release,[133] prostaglandin antagonism,[134] and alterations in intracellular calcium mobilization.[135] Theophylline is also known to cause inhibition of afferent neuronal activity,[136] thereby leading to inhibition of bronchospasm mediated by reflex activation of cholinergic pathways. Theophylline has antiinflammatory and immunomodulatory actions[137] and is known to augment diaphragmatic contractility and increase respiratory drive.[138]

The bronchodilator effects of theophylline in isolated human bronchial preparations in vitro occur at concentrations greater than 70 μmol/L, which is capable of inducing a 50% reversal of bronchoconstriction.[139] Such high local concentrations presumably would be achieved with plasma levels greater than 10 to 20 μg/mL.[140] In clinical practice, however, this range poses a difficult problem because of the narrow window between therapeutic levels and toxicity, which often overlap. The half-life of theophylline ranges from 3 to 7 hours.[141] Therefore theophylline is generally administered as a continuous IV infusion to avoid significant fluctuations in serum concentrations. Aminophylline is equivalent to 80% theophylline and also is administered by continuous IV infusion. When a decision is made to initiate therapy with theophylline or aminophylline, a loading dose is given to achieve serum levels between 10 and 20 μg/mL. Assuming a normal average volume of distribution, a 1 mg/kg dose of theophylline (1.25 mg/kg of aminophylline) raises the serum concentration by 2 μg/mL. The loading dose should be administered over 20 minutes and should be followed immediately by the continuous infusion of the drug. Empiric doses can be started for patients with normal hepatic and cardiac function as follows: infants younger than 6 months: 0.5 mg/kg/h; infants aged 6 months to 1 year: 0.85 to 1 mg/kg/h; children aged 1 to 9 years: 1 mg/kg/h; and children older than 9 years: 0.75 mg/kg/h. Patients with compromised hepatic and cardiovascular function should be started at a dose of 0.25 mg/kg/h. Obese patients should have doses calculated by ideal body weight to prevent toxicity. Serum drug levels should be monitored 30 to 60 minutes after the loading dose and frequently during the continuous infusion, considering that steady-state concentrations are not achieved until approximately five half-lives, which corresponds to 24 to 36 hours of infusion.

A number of studies in adults and children with acute asthma indicate that therapy with theophylline or aminophylline is of no clinical benefit.[142-144] More recently, randomized, placebo-controlled trials tested the efficacy of aminophylline[9] and theophylline[145] in children with near-fatal asthma in the ICU environment. Aminophylline treatment resulted in significantly improved physiologic outcomes, such as oxygenation and pulmonary function testing, but did not decrease ICU length of stay and was associated with adverse effects such as nausea and vomiting.[9] Theophylline was associated with faster clinical improvement, but it had no effect on PICU length of stay and led to a significantly higher frequency of vomiting compared with control subjects.[145]

Considering that the narrow therapeutic window (10 to 20 μg/mL) often overlaps the toxicity (>15 μg/mL), that there is questionable evidence of clinical efficacy, and that methylxanthine agents have been associated with serious adverse effects ranging from nausea, vomiting, and fever to dyskinesias, seizures, and death, enthusiasm for these agents has decreased significantly in the past decade. Although methylxanthine agents are still used as first-line agents in many parts of the world, in North America they have been reserved for occasional selected patients who fail to respond to maximal therapy with β-agonist agents, steroids, anticholinergic drugs, and other adjuncts.

Helium-Oxygen Mixtures

Helium is a biologically inert gas that is less dense than any other known gas except hydrogen and is about one seventh as dense as air. The medicinal application of helium and oxygen mixtures (heliox) in the treatment of asthma and extrathoracic airway obstruction has been known for approximately 7 decades.[146] Because of its low density, heliox reduces the Reynolds number. This effect is associated with a reduced likelihood of turbulent gas flow while facilitating laminar gas flow in the airways, thus decreasing the work of breathing in situations associated with high airway resistance.[147] Heliox provides a theoretical benefit to patients with obstructive lesions of the extrathoracic and intrathoracic airways. Several reports advocate the benefit of heliox in the management of children with extrathoracic airway obstruction.[147,148] The role of heliox in patients with asthma is less clear.

Research using heliox mixtures has demonstrated a greater percentage of lung particle retention and a greater delivery of albuterol from both metered-dose inhalers and nebulizers,[149,150] suggesting that one of the beneficial effects of heliox use in patients with asthma is improved deposition of aerosolized drugs. A recent study in children with moderate to severe asthma exacerbations showed that 70%/30% heliox-driven continuous nebulized albuterol treatments were associated with a greater degree of clinical improvement compared with oxygen-driven continuous nebulized albuterol.[149]

Heliox has been recommended by some persons as a useful adjunct in adult patients with severe asthma, both during spontaneous breathing and during mechanical ventilation.[151-154] Anecdotal reports suggest that heliox is associated with improvement in pulmonary function in children with acute asthma.[155,156] However, a small randomized crossover trial of heliox in spontaneously breathing patients with severe asthma failed to show improvement in pulmonary function or dyspnea scores.[157] Additionally, a systematic review of seven prospective, controlled trials in children and adults failed to provide support for the use of heliox in patients with moderate or severe acute asthma.[158] The paucity of well-executed, randomized, controlled studies makes it impossible to assess the therapeutic effect of heliox in children with asthma at this time. In addition, should heliox be beneficial in some patients, the duration of administration and optimal helium-oxygen mixture remain undetermined. Until more sound information emerges, heliox remains an unproved therapy for pediatric asthma, and its use should be restricted to individual attempts in selected patients with severe refractory near-fatal asthma who did not respond to more conventional treatments.[159] The need to use 80:20 or 70:30 helium-oxygen mixtures to take full advantage of the lower gas density properties may further thwart the use of heliox in sicker patients who exhibit significant hypoxemia.

Ketamine

Ketamine hydrochloride is a dissociative anesthetic agent available in a solution for IV or intramuscular administration. The term *dissociative anesthetic* is derived from the strong feeling of dissociation from the environment that is experienced by the subject to whom it is administered. After IV administration, a sensation of dissociation is generally experienced within 15 seconds, and unconsciousness becomes apparent after another 30 seconds. This reaction is followed by intense analgesia that lasts approximately 40 to 60 minutes and amnesia that may persist for up to 2 hours. Some patients, particularly older children, may experience a postanesthesia emergence reaction with confusion, agitation, and hallucinations. Usual ketamine doses do not significantly affect hypoxic or hypercarbic respiratory drive.[160] Pharyngeal and laryngeal reflexes are maintained, and although the cough reflex is somewhat depressed, airway obstruction does not normally occur. Aside from its anesthetic properties, ketamine exerts a number of other effects, including sialorrhea. It increases airway secretions, cardiac output, heart rate, blood pressure, metabolic rate, cerebral blood flow, and intracranial pressure.[161] Pulmonary vascular resistance is not altered, and hypoxic pulmonary vasoconstriction is preserved. Ketamine inhibits bronchospasm and lowers airway resistance, presumably through blockage of *N*-methyl-D-aspartate receptors in airway smooth muscle.[162] The bronchodilatory effect of ketamine makes it an attractive agent in patients with asthma who require sedation and anesthesia for intubation or mechanical ventilation.[163,164] However, the bronchodilatory effects of ketamine are often obliterated by the significant observed increase in airway secretions and sialorrhea.

Some controversy exists regarding the use of ketamine in nonintubated patients with near-fatal asthma, with the goal of avoiding the need for mechanical ventilation. Limited evidence suggests that this strategy may be viable in selected patients.[165] In our experience, the administration of ketamine to nonintubated children with severe refractory asthma frequently precedes the need to intubate and is rarely associated with significant and noticeable clinical improvement. For this reason, attempts at administering ketamine to nonintubated children with severe refractory asthma should always take place in the ICU under strictly monitored conditions and with personnel capable of rapidly establishing an airway for initiation of ventilatory support.

Ketamine usually is administered as an IV bolus of 2 mg/kg, followed by a continuous infusion of 1 to 2 mg/kg/h. The resulting sialorrhea and increased airway secretions can be attenuated by administration of glycopyrrolate or atropine. The concurrent use of benzodiazepines may attenuate the agitation and hallucinations in patients who experience emergence reactions following ketamine anesthesia.

Mechanical Ventilation

Indications

Only a small minority of patients with near-fatal asthma admitted to the PICU (approximately 8% to 10%) require endotracheal intubation. The indications for intubation are not precisely defined, and the decision to proceed with intubation is largely based on clinical judgment. Absolute indications are obvious and include cardiac or respiratory arrest, profound hypoxemia refractory to supplemental oxygen administration, and respiratory failure. The decision to intubate should not be based solely on blood gas results. However, the presence of a mixed respiratory and metabolic acidosis, persistent hypoxemia, and agitation or obtundation, despite adequate therapeutic efforts, indicate impending respiratory arrest and signal the urgent need to proceed with intubation and mechanical ventilation.

Some patients may benefit from attempts to attenuate respiratory muscle fatigue with a trial of noninvasive ventilation.[132] However, the use of bilevel positive airway pressure requires patient cooperation and a well-fitted and sealed mask, which may prove difficult, if not impossible, to achieve in an anxious and agitated child with impending respiratory failure.

Intubation

The intubation of patients with severe near-fatal asthma is complicated by the fact that these patients are, by definition, fatigued, acidotic, and often also hypoxemic or agitated. Once the decision to intubate is reached, the procedure should be performed promptly by someone skilled and experienced in rapid sequence intubation. Intubation should be preceded by the administration of an anesthetic, such as an opiate, propofol, or ketamine; a benzodiazepine; and a neuromuscular blocker. Ketamine is the preferred anesthetic because of its bronchodilatory properties. Our preference is to use ketamine with a benzodiazepine, such as midazolam or lorazepam, to ensure adequate sedation and reduce the risk of hallucinations during emergence from anesthesia. Propofol may cause bronchodilatation and could be used as an alternative to ketamine, although this drug currently is not approved in the United States for continued use for anesthesia in the PICU after induction. Among the opiates, fentanyl is a widely available choice; morphine should be avoided because it is associated with histamine release and could, at least in theory, contribute to the allergic and inflammatory process. A rapid-acting neuromuscular blocker such as succinylcholine can be used to induce chemical paralysis. More commonly, a nondepolarizing neuromuscular blocker such as vecuronium, rocuronium, or cisatracurium can be used. The patient should be preoxygenated with 100% oxygen by face mask during spontaneous breathing. Assisted breathing with a bag-mask apparatus should be avoided, and cricoid pressure should be maintained throughout the procedure to reduce the risk of aspiration. Whenever possible, a nasogastric tube should be placed in advance to decompress the stomach.

A cuffed endotracheal tube should be introduced and its placement confirmed by a colorimetric method or capnography, auscultation, and chest radiograph. Special attention to the manual ventilation technique is needed to avoid fast rates that often are inadvertently applied immediately following intubation. Rapid respiratory rates applied to intubated children with severe airway obstruction lead to a state of high lung volume, significant dynamic hyperinflation, hypoxemia, and hemodynamic instability (hypotension). These patients require slow respiratory rates with very prolonged expiratory times to allow for adequate gas exchange and lung volumes. A helpful maneuver is to establish the timing of the next inspiration by using a stethoscope to auscultate for the disappearance of expiratory wheezes, thus marking the end of the previous exhalation. The occurrence of desaturation and hypotension

following intubation should prompt an equipment check and confirmation of tube placement. A tension pneumothorax must be considered in patients with hypoxemia and hypotension who fail to improve rapidly after administration of fluids and optimization of ventilation (or brief endotracheal tube disconnection), particularly when unequal breath sounds are present.

Ventilator Settings

The goal of mechanical ventilation in patients with acute asthma should be to reverse hypoxemia (if present), relieve respiratory muscle fatigue, and maintain a level of alveolar ventilation compatible with an acceptable pH, while avoiding iatrogenic hyperinflation and levels of intrathoracic pressure that could adversely affect cardiac output. Therefore the choice of mechanical ventilator settings must take into consideration the significant derangements of lung mechanics and function that are inherent to persons with severe acute asthma. Ill-advised attempts to achieve a normal $Paco_2$ would require fast respiratory rates, high minute volumes, and very high airway pressures, which are associated with the development of barotrauma (pneumothorax and pneumomediastinum) and high mortality rates.[166-168]

A paradigm shift in the ventilatory management of patients with asthma occurred with the introduction of a strategy of controlled hypoventilation reported by Darioli and Perret.[169] Their strategy resulted in no mortality in 34 episodes of mechanical ventilation in 26 patients and significantly lower complication rates in comparison with historical controls.[169] This approach used tidal volumes between 8 and 12 mL/kg and targeted peak airway pressures up to 50 cm H_2O. Tidal volumes were further reduced if the peak pressure limit could not be respected and higher $Paco_2$ measurements were tolerated.[169] A similar approach using respiratory rates lower than 12 breaths/min, tidal volumes between 8 and 12 mL/kg, peak inspiratory pressures of 40 to 45 cm H_2O, and permissive hypercapnia also resulted in very few complications and no mortality or long-term morbidity in 19 mechanically ventilated children with near-fatal asthma.[170]

From a simplified perspective, the modes of ventilatory support for patients with severe acute asthma can be divided between pressure and volume preset. No definitive evidence exists to suggest that one particular mode of ventilation is superior to the other. However, to safely ventilate a patient with asthma, the characteristics of each mode must be understood. Pressure control modes use a decelerating gas flow and have the advantage of ensuring that a particular inspiratory pressure limit is respected. The main disadvantage of pressure control modes is that tidal volumes can vary greatly with changes in airway resistance and the state of hyperinflation. Volume control modes deliver a constant tidal volume, provided there is no significant air leak. An added advantage of volume control is that it allows for comparison of peak inspiratory pressure and plateau pressure measurements (peak-to-plateau pressure), which can serve as a longitudinal indicator of airway resistance and response to therapy. For these measurements, the plateau pressure is obtained by performing an inspiratory hold (a feature ubiquitous to most ventilators) and is then compared with the peak inspiratory pressure (Figure 45-4). An increasing peak-to-plateau pressure indicates increasing airway resistance, whereas a decreasing peak-to-plateau pressure suggests response to therapy. A disadvantage of volume control ventilation is that very high lung volumes can develop if exhalation is incomplete, because tidal volumes remain constant breath to breath. The option of using pressure-regulated volume control, a mode available in some ventilators, offers some of the advantages of pressure control and of volume control, including optimal inspiratory gas flow, assured tidal volumes, and minimized airway pressures.

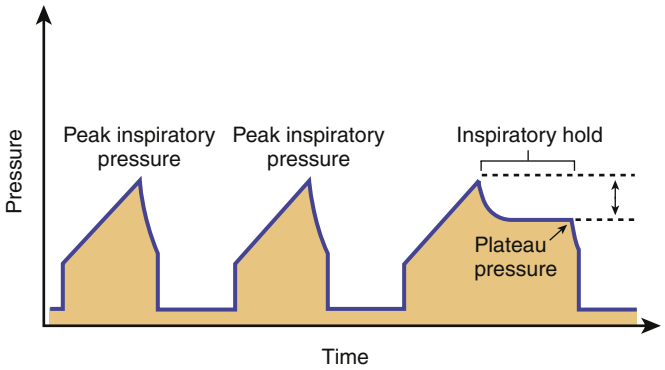

Figure 45–4. Schematic representation of the airway pressure waveform over time during volume control ventilation. The peak-to-plateau pressure difference (*double-headed arrow*) is obtained after an inspiratory hold by comparing the peak pressure and the measured plateau pressure. *(Modified with permission from Indiana University School of Medicine Visual Arts Media.)*

Use of positive end-expiratory pressure (PEEP) in intubated patients with asthma has been the focus of controversy. Externally applied PEEP may benefit patients with expiratory flow limitation resulting from dynamic compression of small airways by moving the equal pressure point, stenting collapsed or severely narrowed airways, and enabling decompression of upstream alveoli.[171] The application of low levels of PEEP that are, by definition, lower than the level of auto-PEEP also may relieve dyspnea by facilitating ventilator triggering and synchronization for intubated patients capable of drawing spontaneous breaths.[171,172] However, as elegantly demonstrated by Tuxen,[173] use of PEEP in chemically paralyzed patients with severe airflow obstruction was uniformly associated with higher lung volumes, increased airway and intrathoracic pressures, and circulatory compromise (Figure 45-5).

Our personal preference is to use the volume control synchronized mandatory ventilation mode or the pressure regulated volume control mode, with tidal volumes of 8 to 12 mL/kg, which can be reduced as needed to generate peak inspiratory pressures of 45 cm H_2O or less and plateau pressures 30 cm H_2O or less. The initial tidal volume target of 8 to 12 mL/kg might seem high, particularly in the era of lung protective ventilation with reduced tidal volumes for patients with acute respiratory distress syndrome. However, it is important to note that the prototypical patient with near-fatal asthma does not have significant parenchymal lung injury or the heterogeneously decreased lung compliance typical of patients with acute respiratory distress syndrome and that tidal volumes are often reduced as needed to target conservative peak and plateau pressure goals, as previously discussed. Respiratory rate is initially set between 6 and 12 breaths/min, and inspiratory time is set between 1 and 1.5 seconds, allowing for expiratory times between 4 and 9 seconds. PEEP is set at zero for the patient under neuromuscular blockade. With intensification of therapy and clinical improvement, neuromuscular blockade

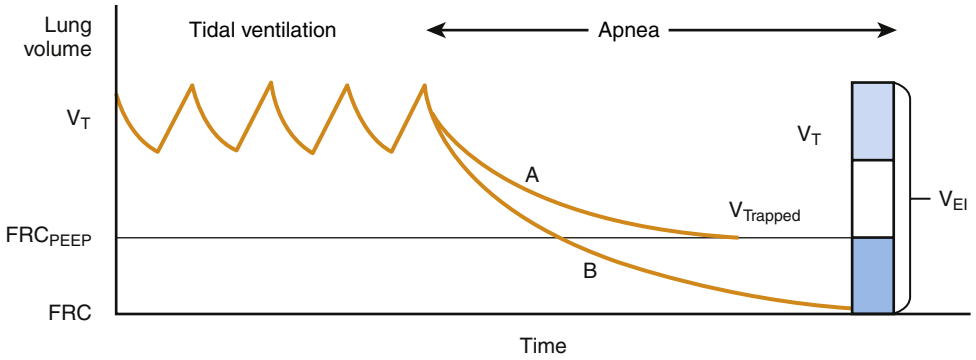

Figure 45–5. Schematic representation of the measurement of V_{EI} both on and off PEEP by a period of apnea during steady-state ventilation. *A,* V_{EI} measured with PEEP left on; *B,* V_{EI} measured with PEEP turned off. *FRC,* Functional residual capacity; FRC_{PEEP}, functional residual capacity resulting from PEEP; *PEEP,* positive end-expiratory pressure; V_{EI}, end-inspiratory lung volume above FRC; V_T, tidal volume; $V_{Trapped}$, volume of trapped gas above FRC. *(From Tuxen DV: Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction,* Am Rev Respir Dis *140:5-9, 1989.)*

is stopped and trigger sensitivity for spontaneous breaths is optimized. A low level of PEEP (lower than the measured auto-PEEP and never in excess of 8 cm H_2O) is applied to facilitate synchronization between patient and machine, and spontaneous breaths are aided by the application of pressure support.

Use of high-level pressure support in the management of spontaneously breathing intubated patients with asthma with the goal of reducing inspiratory work while allowing the patient to actively assist with exhalation is an intriguing strategy that warrants further study.[174]

Ventilatory Monitoring

Regardless of the chosen mode of ventilation, patients with near-fatal asthma undergoing mechanical ventilation require very close monitoring. Frequent auscultation can provide valuable information regarding symmetry of breath sounds (e.g., pneumothorax or mucus plugging) and optimal length of exhalation. Monitoring modules capable of analyzing and displaying permutations of important variables, such as pressure, volume, flow, and time, can provide important information that assists in the optimization of ventilatory settings (Figure 45-6). Monitoring peak-to-plateau pressure differences allows for inferences regarding airway resistance and response to treatment. The shape of the capnography curve also may provide insights regarding adequacy of lung emptying (Figure 45-7), while integrated volumetric capnography can track changes in alveolar dead space over time.

Analgesia, Sedation, and Muscle Relaxation

Patients with near-fatal asthma who are undergoing mechanical ventilation require adequate analgesia and sedation to avoid tachypnea, breath stacking, and ventilator dyssynchrony, particularly in the setting of hypercapnia. Ketamine is the anesthetic agent of choice because of its bronchodilatory properties. Its use with continuous infusions of midazolam or lorazepam can provide deep sedation while decreasing the chance of postanesthetic emergence hallucinatory reactions. Despite its bronchodilatory effects, the use of ketamine may not be favored by many practitioners because of concerns about the negative impact of increased secretions on an already hypersecretory and narrowed airway. When opiates

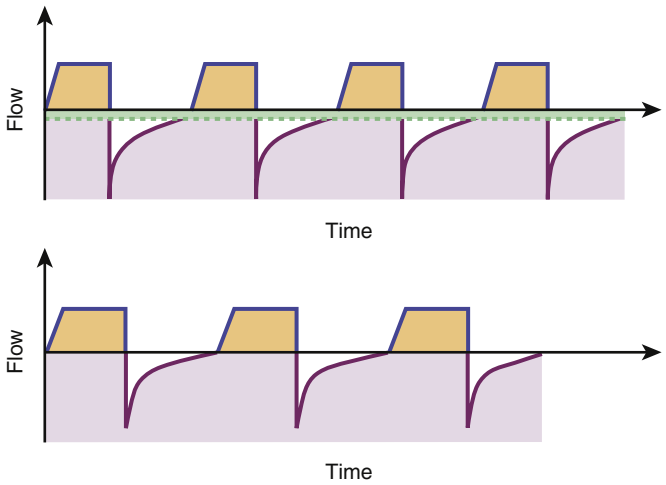

Figure 45–6. Schematic representation of the airway flow tracing over time during volume control ventilation. *Upper panel:* Expiratory flow does not return to zero prior to the initiation of the following breath, resulting in auto-PEEP. *Lower panel:* Expiratory flow returns to baseline prior to initiation of the following breath after optimization of ventilator settings (lower respiratory rate and longer expiratory time). *(Modified with permission from Indiana University School of Medicine Visual Arts Media.)*

are used instead, fentanyl is the preferred agent because morphine can cause histamine release and theoretically aggravate an acute attack.

Muscle relaxation with neuromuscular blockers should be maintained following initiation of mechanical ventilation until satisfactory gas exchange and clinical stability are achieved. Patients who exhibit hypercapnia during mechanical ventilation require continuation of neuromuscular blockers to abolish spontaneous respiratory movements that could worsen dynamic hyperinflation. However, use of neuromuscular blockers should be discontinued as soon as feasible to reduce the likelihood of serious neurologic complications, such as prolonged muscle weakness or paralysis, from the association of these agents and corticosteroid drugs.[175,176] Reports of prolonged paralysis and myopathy after the concomitant use of corticosteroid drugs and aminosteroid-based agents, such as vecuronium and pancuronium, led to the preferential use of benzylisoquinolinium compounds, such as cisatracurium, in patients with asthma. However, this combination may not be completely safe, because prolonged muscle weakness has

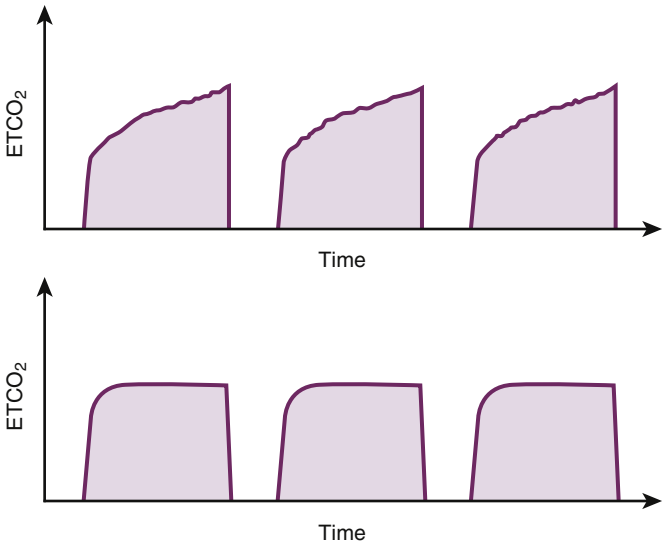

Figure 45–7. Schematic representation of a capnogram in near-fatal asthma (*upper panel*) and under normal conditions (*lower panel*). Severe airflow obstruction in persons with near-fatal asthma is manifested by sloping of the expiratory phase tracing and absence of a plateau, suggesting incomplete exhalation prior to the following inspiration. $ETCO_2$, End-tidal carbon dioxide. *(Modified with permission from Indiana University School of Medicine Visual Arts Media.)*

been observed in a patient treated with cisatracurium and corticosteroids.[177]

Inhalational Anesthetic Agents

Inhalational anesthetic agents have been used for their bronchodilatory effects in the treatment of mechanically ventilated patients with near-fatal asthma that is refractory to more conventional treatment modalities.[178] The exact mechanism responsible for bronchodilatation during inhalational anesthesia is unknown but may involve direct inhibition of vagal tone.[179] Various agents have been used successfully in both adult and pediatric patients with refractory near-fatal asthma, including halothane,[180] isoflurane,[181] enflurane,[182] and sevoflurane.[182,183] Although halothane is often recommended as an agent of choice, little evidence exists in humans to suggest that it is more effective than other agents.[184] Sevoflurane compares favorably with halothane and appears to be less noxious to human airways than isoflurane or enflurane.[185]

Inhalational anesthetic agents can be delivered by means of an anesthesia machine that feeds into the low-pressure gas port of a conventional mechanical ventilator or via a dedicated anesthesia ventilator with its own vaporizer. Attention should be taken to ensure proper disposal of exhaled gases into a scavenger system to prevent release of the anesthetic agent into the ICU environment. A monitor capable of continuously analyzing inspiratory and expiratory drug concentrations is helpful in ascertaining the actual amount delivered and signaling interruptions in therapy, such as those caused by an empty vaporizer reservoir or inadvertent failure to resume therapy after a refill. Usual doses range from 0.5% to 2% (isoflurane) and should be titrated for effect. Clinical response usually can be observed within 15 to 30 minutes of initiation of treatment.

Therapy for persons with refractory near-fatal asthma with an inhaled anesthetic agent should be performed only in a well-monitored ICU environment, under the direction of personnel experienced in the administration of these agents and their adverse effects. Patients treated with halothane can experience significant hypotension as a result of myocardial depression and require rapid fluid expansion and inotropic support.[186,187] Halothane is associated with cardiac arrhythmias, particularly during concurrent administration of epinephrine,[188] which explains why many physicians prefer a nonarrhythmogenic alternative such as isoflurane. Isoflurane does not have negative inotropic effects but may still cause hypotension because of vasodilatation.[159] Considering that halothane and isoflurane result in equivalent bronchodilation, isoflurane is preferred for use in children because of its less significant adverse effects. The use of subanesthetic doses of inhalational anesthetic agents in attempts to avoid mechanical ventilation in spontaneously breathing patients with severe asthma during maximal medical treatment is an intriguing strategy that warrants further study.[189]

Antibiotics

In children, acute asthma exacerbations frequently are triggered by a concurrent viral infection. As such, antibiotic agents are not indicated as part of the standard treatment strategy. A subset of school-aged children may present to the hospital with shortness of breath, accessory muscle use, hypoxemia, and expiratory wheezing caused by *Mycoplasma pneumoniae* pneumonia that simulates an acute asthma exacerbation. These patients usually are shown to have bilateral interstitial disease on a chest radiograph and should be treated with appropriate antibiotic agents such as a macrolide.

Patients with near-fatal asthma who require intubation and prolonged mechanical ventilation should be monitored for the development of nosocomial infections. The presence of fever and abundant thick white or purulent tracheal secretions should warrant a protected Gram stain and cultures to guide appropriate antibiotic coverage.

Bronchoscopy

Increased bronchial secretions and mucus plugging play a major role in the continued deterioration observed in some patients with severe acute asthma who fail to respond to maximal therapy.[31-33] Mucous plugging and casts can cause atelectasis of large segments and worsen the heterogeneity of ventilation and dynamic hyperinflation (Figure 45-8). Thus a small percentage of mechanically ventilated patients with severe near-fatal asthma may require selective suction of mucus plugs, casts, or thick secretions by bronchoscopy.[190] The combination of bronchial lavage with mucolytic agents such as *N*-acetylcysteine[191] or recombinant human deoxyribonuclease[192] and aggressive selective suction through a bronchoscope may be beneficial in patients with clinically significant mucous plugging who fail to respond to maximal therapy and traditional tracheal suction.

Extracorporeal Life Support

The use of extracorporeal life support (ECLS) has been reported in the management of the very few patients with near-fatal asthma who continue to exhibit a profound degree of clinical instability despite maximal therapy.[193,194] Such cases

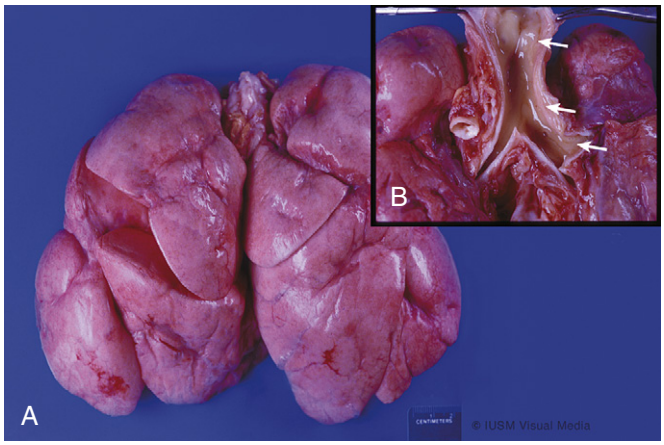

Figure 45–8. Excised lung block obtained from autopsy of a patient with fatal asthma. Despite equilibration with atmospheric pressure, the lungs retain their severely hyperinflated appearance (**A**) because of widespread airway plugging from viscous and tenacious secretions, which are also evident (*white arrows*) in the more proximal airways (**B**). *(Reprinted with permission from Indiana University School of Medicine Visual Arts Media.)*

are most unusual, as indicated by the very small number of patients with acute asthma as the primary diagnosis in the Extracorporeal Life Support Organization registry (1.36%, i.e., 173 of 12,763 pediatric and adult ECLS runs).[195] Interestingly, the survival rate for persons with near-fatal asthma supported by ECLS is approximately 78%,[195] which is remarkable considering that the vast majority of these patients were extraordinarily sick and had not responded to all forms of aggressive treatment.

Prognosis

The prognosis of patients with status asthmaticus or near-fatal asthma who receive proper medical therapy is excellent. Better understanding of the pathophysiology of airway obstruction and dynamic hyperinflation, coupled with improved mechanical ventilation strategies and aggressive pharmacologic treatment, has reduced the ICU mortality rate to nearly zero in these patients.[196,197] Asthma fatalities still occur in patients with sudden onset of severe airway obstruction who do not come to medical attention prior to the development of respiratory failure or cardiorespiratory arrest.[198,199] The treatment plan for patients admitted to the hospital with status asthmaticus or near-fatal asthma should be carefully reviewed prior to discharge to ensure adequate outpatient therapy, education, and follow-up in an attempt to reduce the likelihood of a preventable recurrence.

References are available online at http://www.expertconsult.com.

III

Chapter 46

Neonatal Respiratory Disease

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PEARLS

- Pulmonary or nonpulmonary disorders can lead to respiratory distress or failure.
- Respiratory distress presenting in the first hours of life is a common reason, second only to low birth weight, for admission to the intensive care nursery.
- The following factors are important in reducing complications and improving the outcome of neonates with respiratory distress: early recognition of respiratory distress, the ability to distinguish respiratory disorders from normal neonatal transition, and prompt intervention as indicated.
- Fetal lung fluid must be cleared from the airways to allow normal breathing after birth.
- As a group, pulmonary air leaks are more common during the neonatal period than at any other time of life. The two most common leaks are pneumothorax and pneumomediastinum.
- In most cases, what is called pulmonary hemorrhage is actually the most severe manifestation of pulmonary edema rather than vascular disruption. True pulmonary hemorrhage in a neonate is rare and is almost always terminal.
- In addition to respiratory distress syndrome, many other clinical disorders may be associated with "functional" surfactant deficiency.
- Infants with "classic" bronchopulmonary dysplasia typically require a high degree of ventilatory and oxygen support beyond age 1 week, are slow to wean, and have episodes of bronchospasm or desaturation. The goal of treatment is to promote growth while simultaneously supporting respiratory needs and minimizing further injury to the lungs.
- In the neonate, significant congenital heart disease typically presents in one of two ways: (1) cyanosis with minimal or no respiratory distress or (2) cardiorespiratory failure.

Effective gas exchange within the lung requires both adequate ventilation and perfusion. Determinants of ventilation include the ventilatory "pump" (e.g., central drive, muscle strength, and chest wall recoil),[1] compliance of the lung and chest wall, and resistance to airflow within the airways. Determinants of perfusion include the circulatory pump (right ventricular output) and pulmonary vascular resistance. A disorder in any one or a combination of these determinants can lead to respiratory insufficiency. Clearly then, a variety of disorders, either pulmonary or nonpulmonary, can lead to respiratory insufficiency.

Acute or Early-Onset Respiratory Disorders

Respiratory distress presenting in the first hours of life is a common reason, second only to low birth weight, for admission to the intensive care nursery. Even in the current era of surfactant replacement, high-frequency ventilation (HFV), extracorporeal membrane oxygenation (ECMO), and nitric oxide inhalation, morbidity and mortality resulting from acute respiratory disorders can be high. Early recognition of respiratory distress in the neonate, the ability to distinguish respiratory disorders from normal neonatal transition (addressed later in this chapter), and prompt intervention when indicated are all important in reducing complications and improving the outcome of neonates with respiratory distress.

Delayed Clearance of Fetal Lung Liquid

Fetal lung fluid, which is actively produced by the lung and is critical for normal fetal lung development,[2] must be readily cleared from the airways to allow normal breathing after birth. On the basis of results from animal studies, the relative volume of liquid within potential airspaces, which remains constant in utero, is approximately 20 to 30 mL/kg near term and is the result of a balance between net accumulation within the lung (production minus reabsorption) and efflux out the trachea into the amniotic cavity.[3] In the hours to days before delivery, net accumulation diminishes, and during labor, reabsorption predominates.[4] As a result, extravascular lung liquid (i.e., liquid within the airspaces and interstitium) decreases. Any excess fluid remaining within the airspaces at the time of delivery is further removed as air entry into the lung displaces liquid from the airways into the interstitium. Residual liquid within the interstitium is then taken up into the circulation during the next several hours. Excessive extravascular liquid will lead to impairment of gas exchange, interstitial liquid pressure can compress small airways leading to atelectasis and gas trapping, and excess liquid within airspaces will impair alveolar gas exchange.[5]

Fetal lung liquid production and reabsorption are the result of active ion transport[6] and are presumably hormonally regulated (Figure 46-1). Chloride ions enter the lung epithelial cell across the basolateral membrane via a Na/K/2CL cotransporter (the transporter on which furosemide acts). The mechanism of transepithelial movement of lung fluid at the time of birth is passive movement of sodium through epithelial

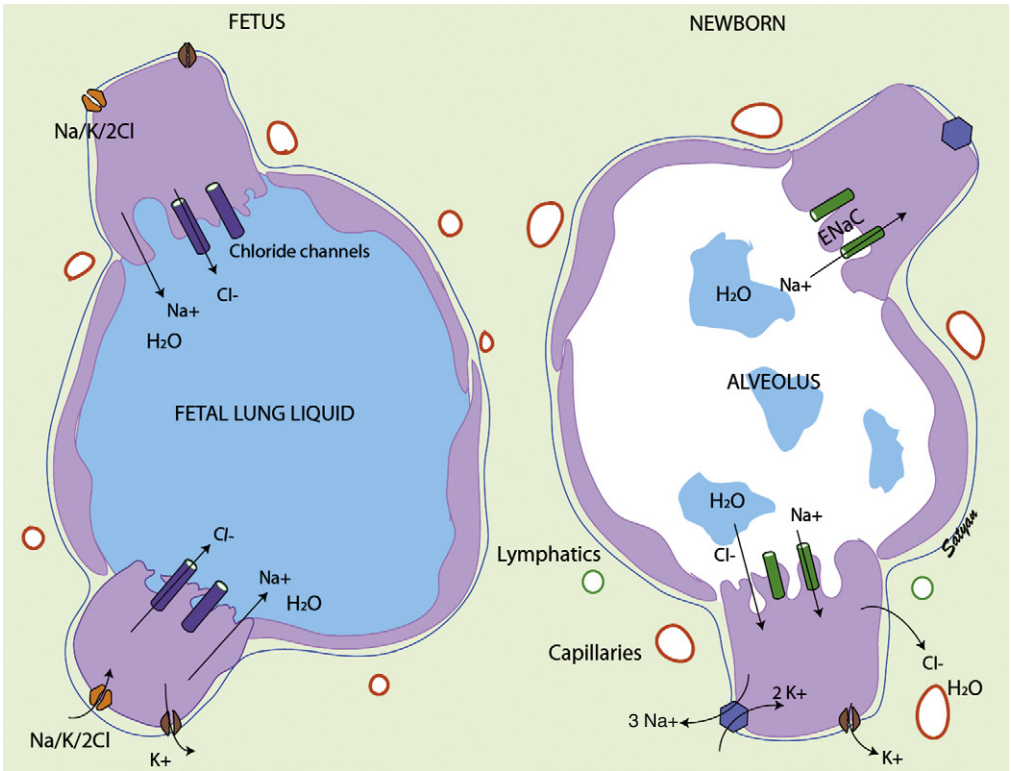

Figure 46–1. Mechanism of fetal and neonatal lung fluid transport. *(Modified from Guglani L, Lakshminrusimha S, Ryan RM: Transient tachypnea of the newborn,* Pediatr Rev *29:e59-e65, 2008. Copyright Satyan Lakshminrusimha.)*

sodium channels (ENaC), which are closed during fetal life; adrenergic stimulation during parturition activates these channels.[7] Although β-adrenergic agents such as terbutaline and epinephrine enhance Na ions and thus liquid reabsorption,[7,8] β-adrenergic blockade does not inhibit the reabsorption of lung liquid during spontaneous labor and delivery in animal studies.[9,10] Other hormones of parturition, such as vasopressin, may be important as well.[11,12]

The pulmonary circulation is also a key factor in fetal lung fluid clearance; not only does interstitial liquid drain directly into the circulation,[13,14] but the dramatic increases in pulmonary blood flow seen after birth may enhance reabsorption of liquid from fetal airspaces.[15] The onset of breathing not only increases the surface area for liquid reabsorption but also is associated with the opening of pores through which liquid can readily enter the interstitium.[16] Drainage of interstitial liquid is generally complete by the end of neonatal transition (4 to 6 hours). Interstitial liquid appears to be directly absorbed into the microcirculation, and this process is governed by Starling forces; the contribution of lymphatic drainage is negligible.[3]

Interference with this process of liquid removal from the airspaces and interstitium leads to impaired gas exchange and respiratory distress with a variable clinical presentation. Excess liquid within the airspaces reduces compliance and increases intrapulmonary shunting, which results in tachypnea and mild to moderate hypoxemia. The chest radiograph may show opaque areas similar to neonatal pneumonia or surfactant-deficient respiratory distress syndrome (RDS). This picture is often described as "prolonged neonatal transition" or "delayed extrauterine adaptation." Excess interstitial liquid reduces compliance and compresses small airways, which leads to the clinical signs of tachypnea and air trapping. The chest radiograph may show streaky densities within the lung, fluid collection within interlobar fissures, or even small pleural effusions; the lungs will also appear hyperinflated because of gas trapping. This clinical picture is often labeled retained fetal lung liquid or transient tachypnea of the newborn.[5,17]

Taken together, these clinical entities resulting from delayed fetal lung liquid clearance represent the most common type of respiratory disorder in the neonate and occur in 5% to 10% of all neonates. Typically, affected infants are term or near term and have persistent tachypnea beyond the immediate perinatal period. Infants born precipitously, or by cesarean delivery, are at highest risk for this disorder. With the increasing incidence of cesarean section deliveries worldwide, a record number of term and near-term newborns are now being admitted to neonatal intensive care units (NICUs) for transient respiratory difficulty.

Several additional points are worth noting. Infants who have been stressed in utero or whose mothers have been receiving β-mimetic agents are less likely to have retained lung liquid. Preterm infants with this condition may be mistakenly assumed to have surfactant-deficient RDS; supportive treatment is similar, although surfactant therapy has not been studied in infants with this condition. Because neonatal pneumonia also can present with tachypnea, an oxygen requirement, and a "wet" chest radiograph, infants with retained lung liquid who have symptoms often are treated with antibiotics. The clinical severity of this disorder can vary widely, and although most infants need only supplemental oxygen, others may require intubation and mechanical ventilation for 12 to 24 hours. Supplemental oxygen should be required for

no more than 24 to 48 hours, but tachypnea may persist for several days.

It is of interest to note that infants born to mothers who have asthma are at increased risk of transient respiratory difficulty immediately after birth.[18,19] In addition, reactive airway disease is more likely to develop later in life in newborns who present with transient respiratory distress.[20,21]

Pulmonary Air Leak Syndromes

Pulmonary air leak syndrome encompasses a spectrum of disease including pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, pneumoperitoneum, and pulmonary interstitial emphysema (PIE). As a group, pulmonary air leaks are more common during the neonatal period than at any other time of life. The two most common types of air leaks—pneumothorax and pneumomediastinum—occur spontaneously in 1% to 2% of term neonates.[22] Preterm infants with surfactant-deficient respiratory distress had previously reported rates of air leaks in excess of 30%[23]; these rates fell rapidly with the advent of surfactant therapy in the 1980s but still remain around 5%.[24] Infants with meconium aspiration or hypoplastic lungs have much higher rates of air leaks. Although techniques such as HFV and ECMO have markedly reduced the incidence of air leaks associated with these disorders, the rates still remain high, at 25% to 30%.[25,26]

The pathophysiologic cause of pulmonary air leaks has been hypothesized for many years as the uneven filling and redistribution of air in the lung; overdistension of more compliant air spaces leads to rupture. The alveoli most susceptible to this injury are those that border on arterioles and other structural elements of the lung; uniform protection by surrounding alveoli is lacking. After rupture of the alveolus or terminal airspace, air escapes into the lung interstitium and tracks along the vascular sheaths toward the hilum. For reasons that remain unclear, in the preterm infant the air may dissect within the interstitium (PIE).[27] More commonly, the air breaks through the pleural reflections at the hilum (pneumomediastinum) and from there gains access to various potential compartments: the pleural cavity (pneumothorax), the pericardial reflection (pneumopericardium), and the soft tissue planes of the neck (subcutaneous emphysema), or across the diaphragmatic apertures and into the peritoneal space (pneumoperitoneum).

In the past, pulmonary air leaks most commonly occurred as a result of excessive ventilatory pressures due to either aggressive mechanical ventilation (barotrauma) or air trapping caused by partial airway obstruction with meconium or other debris (ball valving). Now, air leaks are more commonly seen during the recovery phase of acute respiratory disease, when lung compliance dramatically improves and pressure-limited ventilation leads to excessive tidal volumes (volutrauma). This phenomenon explains the clinical observations that air leaks tend to occur during the recovery phase of RDS[28] and that the incidence of air leaks actually increased during early trials of surfactant therapy.[29] Both observations underscore the need to closely monitor ventilatory volumes and wean pressure aggressively as compliance improves; these observations also suggest that volume-limited ventilation may be safer during the recovery phase of acute neonatal respiratory disease, although this theory has not been studied.

Pneumomediastinum is one of the most common air leaks and, considering the pathways by which air will track, is often the harbinger of further air leaks. Infants with isolated pneumomediastinum generally have few or no symptoms other than low-density widening of the mediastinum, which is visible on chest x-ray film. Distention of the mediastinum has the potential to compress the great vessels and compromise circulation. This situation rarely occurs in clinical practice because air will usually track into the soft tissues of the neck or rupture into the pleural spaces before reaching the pressure needed for circulatory compromise.

Pneumothorax is a clinically common and more worrisome form of pulmonary air leak. The initial signs of pneumothorax reflect compression of the lung and diminished lung compliance. If compromise is minimal, the infant will maintain minute ventilation by simply increasing ventilatory rate (tachypnea); if that is insufficient, the infant will increase the use of accessory muscles (retractions) in an effort to improve tidal volume. If positive pressure within the pleural space builds to the point of vascular compromise (i.e., tension pneumothorax), cardiac return will decrease, and the heart rate will rise in an attempt to compensate for diminished stroke volume. Eventually, blood pressure may fall, and if oxygen delivery cannot be maintained, bradycardia and arrest will ensue.

Pneumopericardium is a rare but often life-threatening form of pulmonary air leak. The clinical signs closely resemble those of tension pneumothorax, but diminished heart sounds are invariably present. Clinical deterioration is often sudden and severe, and differentiation from pneumothorax is often difficult because usually no time is available to obtain a chest radiograph. The incidence of mortality may be as high 80%.

Pneumoperitoneum occurs when air dissects from the chest through a foramen of the diaphragm. This condition generally results in few if any symptoms or problems, other than possible confusion with a perforated viscus. Pneumoperitoneum is usually distinguished from bowel perforation by the clinical history of a prior pneumomediastinum or pneumothorax, especially with a lack of gastrointestinal symptoms. Although it usually requires no treatment, pneumoperitoneum can compromise ventilation. In that case, aspiration of air from the pneumoperitoneum is not only therapeutic but also diagnostic; oxygen tension in ventilatory gas is markedly higher than that in bowel gas.

PIE is a more severe manifestation of the same pathophysiologic process that leads to the rest of the air leak syndromes. In this case, the air accumulates in the interstitial space instead of tracking toward the hilum. This accumulation produces compression of the airways and vasculature, making ventilation more difficult. This situation creates a need for higher airway pressures to maintain open airways, which increases the air leak, and therefore the PIE. Avoiding this escalation of therapy has become the primary principle in the treatment of PIE.

The approach to management of air leaks in infants is similar to that in older children. Pneumothorax, pneumopericardium, and occasionally pneumoperitoneum are acute, life-threatening emergencies because they can seriously impair cardiac output by decreasing venous return. A high degree of suspicion for air leaks in a patient who has a sudden cardiovascular deterioration for no apparent reason is critical for prompt diagnosis. Transillumination of the relatively translucent neonatal chest wall with an intensely focused light source is a quick and useful tool for diagnosing a large pneumothorax.

Immediate aspiration of the air, preferentially with a large-bore angiocatheter, should be done without radiographic confirmation if the infant is severely compromised. Clinical signs of compromise, not the radiographic interpretation of percent size or extent, should dictate treatment, and many cases can be managed expectantly.[30] An unstable or recurrent pneumothorax may require a thoracostomy tube; however, tube thoracostomy may have significant complications, including parenchymal lung injury, phrenic nerve paralysis, chylothorax, and hemorrhagic pericardial effusion.[30] Penetration of the chest tube into the pulmonary parenchyma is a complication that often is not appreciated by chest radiographs; one study of autopsies of infants with pneumothorax reported a lung perforation rate of 25%.[31] Cardiac tamponade resulting from a pneumopericardium may be suggested by distant heart tones and hypotensive shock with a normal-appearing electrocardiogram tracing (so-called *electromechanical dissociation*). Pneumomediastinum often is asymptomatic and rarely benefits from drainage, even in the presence of symptoms. PIE occurs predominantly in preterm infants and often leads to a vicious cycle of increasing ventilator delivery pressures to open alveoli compressed by extrinsic air, which in turn leads to more extravasation of air and further collapse. Conventional treatment of PIE, including positioning, selective mainstem intubation, and steroids, has been unsatisfactory.[27,32] HFV, which may maintain alveolar patency while reducing inspiratory airway pressure, appears to be the ventilatory mode of choice in managing infants with PIE[33] and refractory pneumothoraces.[34]

Pulmonary Hemorrhage

The term *pulmonary hemorrhage* is often misapplied in the neonatal intensive care setting. True pulmonary hemorrhage in a neonate is rare and almost alwaysresults in death. In most cases, what is called pulmonary hemorrhage is actually the most severe manifestation of pulmonary edema rather than vascular disruption.[35] This distinction has been drawn by measuring the hematocrit of hemorrhagic fluid suctioned from the airway.[36] The airway fluid generally will be 15 to 20 points lower than whole blood in the same patient at that time. Finding whole blood in the airway is rare and is usually a result of trauma from suctioning.

Similar to older children and adults, factors that alter Starling forces within the pulmonary microcirculation will predispose the lung to hemorrhagic pulmonary edema. These factors include increased perfusion pressure (e.g., left ventricular failure), increased blood flow (e.g., from a left-to-right shunt across a patent ductus arteriosus [PDA]), increased microvascular permeability (e.g., associated with sepsis or oxygen toxicity), and decreased oncotic pressure (e.g., protein malnutrition or water overload). Most infants who have pulmonary hemorrhage will have more than one risk factor present. In the neonate, the factors most commonly associated with hemorrhagic pulmonary edema are those that increase pulmonary blood flow, such as a left-to-right shunt or treatment with surfactants.[35,37] Clinical features that increase the risk of hemorrhagic pulmonary edema or even frank pulmonary hemorrhage in neonates include extreme preterm gestation, asphyxia, hypothermia, certain types of congenital heart disease, and underlying coagulopathies.[38] Pulmonary hemorrhage also has been associated with neurologic disorders, including seizures, stroke, subarachnoid hemorrhage, and massive intraventricular hemorrhage. This association has led some researchers to suggest that pulmonary hemorrhage may have a neurogenic origin and that neonates with known or suspected neurologic injury represent a particularly high risk group.[39]

The diagnosis of hemorrhagic pulmonary edema is presumptively made when the appearance of bloody secretions within the endotracheal tube coincides with acute respiratory deterioration that requires increased oxygen and ventilatory support. The chest radiograph is the key to diagnosis; homogeneous, diffuse haziness, or fluffy infiltrates are signs that best indicate hemorrhagic pulmonary edema. Focal opacities on a radiograph require an alternative explanation such as pneumonia or upper airway trauma with subsequent aspiration of blood.

Although the diagnosis of hemorrhagic pulmonary edema is relatively straightforward, management can be challenging. The most important approach to managing hemorrhagic pulmonary edema is to establish high positive end-expiratory pressure (PEEP); this not only effectively reduces alveolar flooding but also improves oxygenation and left ventricular function. Although the airway must be kept clear, frequent suctioning not only may be traumatic but also can aggravate the condition by reducing PEEP. High mean airway pressures, which can be safely achieved with HFV, can be effective in massive pulmonary hemorrhage with rapid improvement in oxygenation.[40]

Some persons have advocated administration of epinephrine or iced saline solution via the endotracheal tube, but the efficacy of this method is questionable, and epinephrine may worsen the condition by elevating pulmonary vascular pressures. Aggressive volume resuscitation also should be avoided for the same reason. Antibiotics should be considered if sepsis is clinically suspected, but the efficacy of prophylactic antibiotics to prevent bacterial contamination of the airways is unproven. If an underlying cause such as a PDA or coagulopathy is suspected, it should be treated accordingly. Additional therapies under investigation include surfactant[41] and recombinant activated factor VII.[42] Prevention also may be possible in some cases; in preterm infants at high risk of the development of hemodynamically significant PDA, indomethacin prophylaxis appears to reduce the incidence of severe hemorrhagic pulmonary edema.[43] In a recent randomized trial of hemocoagulase given to preterm newborns requiring mechanical ventilation, the incidence of pulmonary hemorrhage (suspected or proven) was reduced by 70%[44]; however, in that study, the definition of "pulmonary hemorrhage" was rather broad and occurred in more than 40% of control infants, a much higher rate than is typically reported for this condition.

Even with aggressive management, the incidence of mortality from hemorrhagic pulmonary edema can exceed 25%, and surviving infants are at increased risk for neurodevelopmental impairment (e.g., cerebral palsy or cognitive delay) and neurosensory impairment (e.g., hearing loss requiring amplification or bilateral blindness).[43]

Pneumonia

The lungs represent the most commonly affected organ in neonates with sepsis. Bacterial or viral infection of the neonate may begin in utero, either by transplacental passage

or, more commonly, ascending infection from the maternal genital tract. A delay from the time of rupture of the amniotic membranes until delivery increases the risk of an ascending infection, although some organisms may invade through intact membranes. Cervical bacterial colonization with group B streptococci or primary herpesviral cervical infection during pregnancy increases the risk of transmitting those diseases; however, routine cervical cultures taken during pregnancy often do not reliably predict the actual flora at the time of delivery. Also, infants born vaginally are invariably colonized with organisms from the vaginal canal and typically swallow organisms during vaginal passage. Cesarean delivery is not necessarily protective because fetuses may swallow contaminated amniotic fluid or aspirate organisms in utero. Infection occurring during the perinatal period may not present clinically for several days; thus infections congenitally acquired may be indistinguishable from infections postnatally acquired (i.e., nosocomial).

Organisms that cause perinatal pneumonias, then, typically are those found in the genital tract of the mother and include streptococci (groups A, B, and D), gram-negative rods (e.g., *Escherichia coli* and Klebsiella species), *Listeria monocytogenes*, Ureaplasma, genital hemophilus, and herpesvirus. Less commonly, maternal viral infections due to adenovirus, enteroviruses, or varicella can be vertically transmitted to the fetus. Although perinatal tuberculosis is rare compared with other causes of neonatal pneumonia, the increasing prevalence of this disease in women of child-bearing age increases the likelihood of new cases[45]; in congenitally acquired cases, the mother may be symptom free.[46] Perinatal infection with other organisms, most typically chlamydia, may not present for several weeks.

Pneumonia as a nosocomial infection may develop in neonates, particularly those who require mechanical ventilation for other critical illness. Although reported rates vary widely, in part because of the lack of a diagnostic gold standard in this population, some authors have suggested that the incidence of ventilator-associated pneumonia may be as high as 30% in selected NICU populations.[47,48] In addition to the presence of an endotracheal tube, risk factors for ventilator-associated pneumonias include low birth weight, prolonged mechanical ventilation, sedation with opiates, frequent endotracheal tube suctioning, and the crowding that is typical in some units.[47,49] If a ventilator-associated pneumonia is suspected, typical nosocomial pathogens such as staphylococcus, Klebsiella and Pseudomonas species, and the pathogens previously listed for congenital pneumonias should be considered as possible causes.

Congenital pneumonia can be difficult to diagnose because clinical symptoms and radiographic signs may be nonspecific. Although congenital infections are generally introduced through the respiratory tract, symptoms are rarely limited to those of pneumonia; the neonate is particularly prone to rapid dissemination of either bacterial or viral infections and typically has signs of sepsis or meningitis in addition to respiratory distress. The chest radiograph initially may appear normal, except for some slight streakiness or hyperinflation, or may be so opaque as to be confused with surfactant-deficient RDS. Meconium aspiration with resultant severe chemical pneumonitis may be indistinguishable radiographically from bacterial pneumonia. Heart failure, or obstructed anomalous pulmonary venous drainage, also can present with a clinical and radiographic picture similar to pneumonia/sepsis.

Congenitally acquired pneumonia/sepsis can be a rapidly fatal disease, especially in the case of group B streptococcal or herpesviral infections, for which mortality rates as high as 50% have been reported.[50,51] A high degree of suspicion is therefore important because prompt treatment may be lifesaving. Although antibiotics are routinely used in neonates with suspected pneumonia or sepsis, antiviral therapy should be considered if the infant has systemic signs such as shock or disseminated intravascular coagulation or is not responding to initial therapy.

In regard to group B streptococcus (GBS) infection, guidelines for antenatal screening and antepartum prophylaxis published by the Centers for Disease Control and Prevention in 1996, and revised in 2002, have been followed by a significant decrease in GBS-related neonatal morbidity and mortality in the United States.[52] However, because of the inability of current microbiologic screening to identify all carriers, the failure in some cases to administer adequate intrapartum prophylaxis, and the need to deliver some infants prior to scheduled screening, GBS continues to be an important cause of early onset sepsis.[53] Given the complications and potential limitations associated with maternal screening and intrapartum prophylaxis, vaccines may be the most effective means of preventing neonatal GBS disease and are currently under development.[53]

Meconium Aspiration Syndrome

Passage of meconium in utero is generally considered a sign of fetal distress. The stress can be acute, as in the case of cord compression during labor, or chronic, as in the case of preeclampsia. Moderate distress occurring during labor results in passage of meconium during the final stages of delivery (terminal meconium), whereas more severe or chronic distress results in passage in utero, with resultant staining of the amniotic fluid and fetus. The incidence of meconium staining as a more significant marker of fetal distress occurs in 10% to 20% of all deliveries and is most common in postmature infants.[54] There also appears to be a maturational aspect to the ability to pass meconium because it is rarely observed in fetuses younger than 36 weeks' gestation.[54]

Not only is meconium-stained amniotic fluid a sign of antenatal distress, but it also can cause subsequent difficulties in the neonate. The contaminated amniotic fluid may be aspirated by the fetus, either in utero or during passage through the birth canal, and lead to subsequent respiratory distress. Meconium is a lipid and protein-rich substance that is highly irritating to mucous membranes of the distal airways, resulting in a chemical pneumonitis.[55] Dissolved meconium may travel down the respiratory tree and inactivate pulmonary surfactant; this inactivation leads to a functional surfactant deficiency.[56,57] In addition, meconium induces a potent inflammatory response, further impairing lung function.[58,59] As inflammatory markers improve, so too does pulmonary function.[60] More particulate meconium will remain trapped in small airways, and this leads to a ball-valve type of gas trapping. In most cases the meconium is gradually removed from the respiratory tract through phagocytosis, and normal pulmonary function returns in 5 to 7 days. In more severe cases, meconium aspiration syndrome may lead to respiratory failure, and even death, despite aggressive intervention.

Infants with meconium aspiration are typically postmature, with elongated nails, peeling skin, and staining of the umbilical cord, skin, and nails. Respiratory distress develops soon after birth, although the infant's respirations initially may be depressed if meconium passage occurred in response to a recent asphyxial episode in utero. Gas trapping may lead to a barrel-shaped appearance to the chest, and signs of respiratory distress may be severe. Chest radiographs often show characteristic patchy densities, hyperinflation, and areas of collapse. Air leaks are especially common. Aspiration of blood during delivery results in a similar clinical and radiographic picture; however, blood aspiration usually has a much milder course.[61]

An important step in the treatment of meconium aspiration syndrome is prevention. This has led to the routine practice of aggressive suctioning, beginning with clearing of the infant's nose and mouth while still at the perineum and before delivery of the infant's chest, followed by endotracheal intubation once the infant is delivered. A couple of large, randomized clinical trials have brought these practices into question and have even raised concerns that such interventions may produce harm, particularly in the vigorous infant.[62,63] On the basis of these trials, current recommendations are that suctioning should be limited to infants who are not vigorous at delivery.[64] Another intervention aimed at reducing disease as a result of meconium aspiration has been amnioinfusion, that is, the introduction of fluid transcervically during labor. The theoretical benefits of this approach include dilution of thick meconium and reducing cord compression by providing support to the umbilical cord. However, a recent large, randomized clinical trial has put this practice into question.[65] As with tracheal suctioning, it can be argued that distressed fetuses may aspirate in utero, long before delivery, and that severe complications such as persistent pulmonary hypertension are more likely the result of the antecedent stress and are not due to meconium aspiration per se.

The treatment of meconium aspiration syndrome is to provide supportive care; infants are recognized as being at increased risk for having persistent pulmonary hypertension (see section on "Persistent Pulmonary Hypertension of the Neonate"). Supplemental oxygen support to maintain arterial oxygen saturation, endotracheal suctioning to clear remaining meconium, and ventilatory techniques to minimize gas trapping are techniques that are commonly used. HFV may be helpful in preventing subsequent air leaks. Antibiotics are commonly used because distinguishing the clinical and radiographic picture from sepsis may be difficult and because damage to the airways may predispose to subsequent bacterial infection. Surfactant therapy has been recently explored as an adjunctive therapy, following promising results from two small pilot studies.[66,67] A recent systematic review of four clinical trials in term and near-term infants concluded that surfactant administration significantly reduced the need for extracorporeal life support, although the overall incidence of mortality was not affected[68]; in many centers, surfactant replacement has been added to other therapies routinely use in this condition, including high-frequency ventilation and inhaled nitric oxide.

A recent modification of surfactant replacement has been to lavage the lung with relatively large volumes of diluted surfactant to facilitate removal of meconium and improve surfactant function.[69,70] While this approach has merit, more clinical work needs to be done to determine the optimal approach, because some infants do not tolerate the procedure.[70]

Despite the intense inflammatory nature of meconium aspiration, the utility of steroid administration remains unclear[54]; although a recent small, randomized, controlled trial showed some clinical improvements, the mortality rate remained high.[71]

Because meconium passage in utero and meconium aspiration syndrome per se often are associated with an hypoxic event, long-term outcome remains guarded, particularly with regard to neurodevelopment.[72] In addition, a recent study has suggested that meconium aspiration during the perinatal period may be associated with increased risk of reactive airway disease in early childhood.[73]

Surfactant-Deficient Respiratory Distress Syndrome

For years, infants born preterm were recognized as being at increased risk for severe, occasionally lethal respiratory distress that presented within minutes to hours of age. In the past, the term commonly used to describe acute neonatal lung disease was hyaline membrane disease, a pathologic description of abnormal protein deposition in the alveolar linings of preterm infants who died after the onset of this disease. Today this disorder is commonly referred to as RDS; this term emphasizes the clinical instead of the pathologic presentation because hyaline membranes generally develop only in those now rare infants who eventually succumb to the disease. Recognizing that this disorder is primarily due to inadequate surfactant production, some authors prefer the term surfactant-deficient RDS to differentiate the pathophysiologic origins of this disorder from other types of neonatal respiratory distress such as transient tachypnea or retained fetal lung liquid.

Pulmonary surfactant disperses at the air-liquid interface on the inner surface of the alveolus, reduces surface tension at that interface, and prevents alveolar collapse at end-expiration. Surfactant is produced by type II alveolar epithelial cells and is a phospholipid and glycoprotein composite with phospholipid as the surface-active agent and glycoproteins aiding in surface adsorption, spreading, and metabolism of surfactant.[74] Maturation of the pulmonary surfactant system is generally not complete until the latter part of the third trimester of fetal life, but it can be induced by intrauterine stress, by maternal steroid therapy, and after preterm delivery. The incidence of surfactant deficiency at birth is inversely related to gestational age; approximately 50% of infants born between 30 and 36 weeks' gestation will be surfactant deficient, and virtually all infants born before 28 weeks' gestation will be affected to some degree.[75]

Surfactant-deficient alveoli are more prone to collapse, and this leads to diffuse atelectasis, reduced ventilatory compliance, and intrapulmonary shunting. Infants with surfactant deficiency have stiff, noncompliant lungs and require significant distending pressure for the lungs to be ventilated. Neonates will have tachypnea, retractions, and expiratory grunting; these symptoms indicate RDS. Preterm infants with RDS have significant morbidity, although some complications may primarily be a result of prematurity per se. Short-term complications can be life-threatening and include pulmonary air leaks, pulmonary hemorrhage, and intracranial hemorrhage. Infants with RDS are at risk for later complications including necrotizing enterocolitis and chronic lung disease. Infants who require prolonged intubation and mechanical ventilation also

are at risk for subglottic injury including subglottic stenosis and tracheomalacia. Before surfactant therapy, the mortality rate from RDS exceeded 20%[76]; now infants rarely succumb to RDS unless severe complications develop.[77-79]

Assessment of fetal lung maturity using phospholipid analysis of amniotic fluid and maternal steroid therapy, both introduced in the mid 1970s, have reduced the incidence of RDS in infants born before term. Treatment with surfactants in neonates with symptoms during the first few days of life has significantly reduced the clinical severity of RDS and improved survival.[24]

Unfortunately, although surfactant therapy has reduced some short-term complications such as pulmonary air leaks, the incidence of long-term morbidity remains unchanged, in part because of the increased survival rate of preterm infants with extremely low birth weight (<1000 g).[78,79]

Surfactant Protein B Deficiency

Pulmonary surfactant consists of surface-active phospholipid and a small amount (approximately 10% by weight) of protein.[74] Various surfactant-associated proteins (SPs) have been identified. SP-A and SP-D are large molecular weight, hydrophilic glycoproteins. Although these larger proteins have no surface tension–lowering ability per se, SP-A regulates surfactant phospholipid synthesis, secretion, and recycling and blocks the inhibition of native surfactant by plasma proteins that may leak into the alveolus during lung injury. SP-D does not appear to be involved in surfactant function but does play a key role in host defense of the lung. Despite having little to do with surfactant function, a recent study found that certain SP haplotypes for SP-A and SP-D conferred protection against newborn RDS.[80] In contrast to SP-A and SP-D, SP-B and SP-C are small, hydrophobic glycoproteins that promote spreading of surfactant across an air-liquid interface, which is an essential prerequisite for surfactant to function. A deficiency of either SP-B or SP-C markedly interferes with natural surfactant function in animal models.[74]

Congenital alveolar proteinosis is a rare disease entity with histopathologic similarities to alveolar proteinosis in older children and adults.[81] The clinical course of congenital alveolar proteinosis, however, is markedly different, characterized by rapid progression to death within several hours to days. A clustering of cases within families has suggested a genetic basis for this disorder; the condition in older children and adults is thought to result from a nonspecific alveolar injury. Pulmonary lavage has been helpful in adults and some children with alveolar proteinosis, but it has not been studied in infants with congenital disease.[82] Extracorporeal support has not altered the long-term prognosis of infants with this condition.[83]

In the early 1990s, several cases of congenital alveolar proteinosis were described in which SP-B and its messenger protein have been shown to be totally absent.[84,85] Since then, more than 25 loss of function mutations have been identified in patients with SP-B deficiency, the most common being a single gene mutation (121 ins2).[86] Adult humans heterozygous for this mutation have normal pulmonary function,[87] whereas homozygous cases are uniformly lethal within days of life. Affected infants respond only transiently to exogenous surfactants that contain SP-B[88]; to date, the only survivors are those who have undergone a lung transplant. Molecular techniques can identify affected infants and even predict fetal outcome, allowing us to provide specific counseling for parents whose infants have this fatal disorder.[89]

Congenital Malformations of the Lung

In utero, the organ of gas exchange is the placenta. As such, fetal viability does not depend on a functioning lung. Not surprisingly, substantial abnormalities of the lung can exist antenatally with little or no clinical indication until delivery of the neonate, when the lung must assume the placental function of gas exchange.

Pulmonary Hypoplasia

Both static and dynamic expansion of the fetal lung appears to be an important determinant of normal fetal lung development.[90] Static lung expansion occurs as a result of fetal lung liquid production. Epithelial cells within the lung actively secrete fluid into the lung lumen, distending the future airspaces. An intraluminal pressure gradient above amniotic fluid pressure is maintained by glottic regulation of fluid efflux from the trachea into the amniotic cavity, thus keeping the lungs expanded at a fluid volume that approximates postnatal functional residual capacity.[91] Failure to maintain this distention, either by inadequate production or excessive drainage of fetal lung liquid, leads to developmental hypoplasia. Dynamic lung expansion occurs during fetal breathing movements, which are rhythmic in nature and occur with increasing frequency during the latter part of gestation.[92] Absent or abnormal fetal breathing also appears to result in pulmonary hypoplasia.[90]

Pulmonary hypoplasia, unlike pulmonary agenesis or aplasia (discussed later in this chapter), can occur any time during gestation. Hypoplastic lungs are small in volume, and DNA content relative to body size have reduced numbers of alveoli, bronchioles, and arterioles per unit mass.[90] Although the pathophysiologic origin is not well understood, pulmonary hypoplasia is thought to result from impairment of normal fetal lung expansion and generally occurs in conjunction with one of the following conditions: (1) space-occupying lesions within the hemithorax, such as a diaphragmatic hernia, or massive pleural effusions associated with fetal hydrops; (2) an inadequate thoracic cage, as in asphyxiating thoracic dystrophy or achondrogenesis; (3) a deficiency of amniotic fluid (oligohydramnios), either because of leakage (e.g., preterm rupture of fetal membranes) or underproduction (e.g., renal dysplasia) [25]; (4) inadequate vascular supply to the developing lung, as may be seen with pulmonary artery atresia, hypoplastic right heart, or tetralogy of Fallot; (5) lack of the fetal breathing movements that normally occur throughout the latter part of gestation; and (6) chromosomal anomalies such as trisomy 13 or 18. Pulmonary hypoplasia may occur in the absence of any of these conditions, but such cases of primary isolated pulmonary hypoplasia are rare.[90]

Infants with pulmonary hypoplasia generally have signs of respiratory failure in the immediate newborn period. Reduced lung volumes impair ventilation and lead to hypercarbia, and decreased surface area for gas exchange (due to decreased alveoli) leads to hypoxemia. A decreased cross-sectional area of the vasculature makes these infants particularly susceptible to pulmonary hypertension, which further exacerbates the hypoxemia. The chest radiograph in infants with pulmonary

hypoplasia should show low lung volumes but may otherwise be unremarkable. The severity of the respiratory distress depends on the degree of hypoplasia and the presence of associated problems such as fetal hydrops or cyanotic heart disease. The most common association is renal dysplasia or agenesis; in these cases infants have a history of moderate to severe oligohydramnios and have severe respiratory distress and compression deformities of the face and extremities (Potter's syndrome).[93]

Treatment of infants with pulmonary hypoplasia is supportive, and outcome depends on the severity of the hypoplasia and the presence of any associated lethal anomalies such as renal agenesis or achondrogenesis. The lungs of infants with severe pulmonary hypoplasia may be extremely difficult to ventilate, and pneumothoraces are common because of the need for high distending pressures. HFV may be an effective means of ventilating these infants' lungs through a combination of high ventilatory rates with extremely low tidal volumes.

Congenital Diaphragmatic Hernia

Failure of the pleuroperitoneal canal to close at 6 to 8 weeks' gestation results in a diaphragmatic defect that allows gastrointestinal structures to travel into the thoracic cavity as the intestines return from outside the fetus to the abdominal cavity.[94] The resulting mass effect in the chest exerts a negative influence on ipsilateral lung growth, characterized by a quantitative reduction in airways and their associated preacinar arteries. Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 3000 births and is the most common cause of pulmonary hypoplasia in the neonate.[95] The defect occurs on the left side in 80% to 85% of cases; the reason is that closure of the right pleuroperitoneal membrane normally precedes the left during fetal development. Because herniation often occurs before the tenth week of gestation when normal gut rotation occurs, malrotation is common. Nongastrointestinal anomalies are found in approximately 25% of cases; the most common involve the cardiovascular system, where virtually any kind of defect has been reported.[94-96] Other associated anomalies include esophageal atresia, trisomies (13, 18, and 21), Turner's syndrome, neural tube defects, and renal anomalies. While it has been assumed the pulmonary hypoplasia seen with CDH is secondary to mechanical forces, studies in newborns and animals have found that CDH may be associated with nutritional deficiencies.[97,98] In the rat model of nitrofen-induced CDH, prenatal retinoic acid improves alveologenesis[99]; the experimental data regarding vitamin E supplementation has yielded conflicting results.[100-102]

Clinical presentation of CDH depends on the degree of pulmonary hypoplasia present (see section on "Pulmonary Hypoplasia"). In addition, the abdomen is often scaphoid because of a paucity of abdominal contents. As the infant cries and swallows air, the degree of lung compression may worsen, and an infant who appears healthy at delivery may undergo decompensation within minutes. The chest radiograph will show a cystic lesion in the lower lung field, often extending upward along the lateral chest wall. Initially, while the intestines remain fluid filled, the radiograph may be similar to that seen with pulmonary sequestrations or fluid-filled cysts (discussed later in this chapter); as the infant swallows more air, the radiographic findings can be confused with congenital emphysema or even a pneumothorax. Small or right-sided defects in infants may not present for weeks or even months; indeed, occasional cases have been diagnosed incidentally during childhood when chest radiographs are obtained for other reasons. Today, with the widespread use of antenatal sonography, most cases are diagnosed before birth, and significant confusion is avoided in the delivery room. In cases where sonographic findings are equivocal, prenatal magnetic resonance imaging may be particularly useful.[103]

Initial management focuses on stabilization, including immediate intubation and gastrointestinal decompression. Ventilation by bag and mask should be avoided because this intervention will only introduce more gas into the gastrointestinal tract. As with pulmonary hypoplasia, the clinical course is usually complicated by persistent pulmonary hypertension, which has accounted for mortality rates as high as 80%.[104] With the advent of ECMO this number has dropped somewhat but is still significant.[105] High-frequency ventilation appears to have particular merit for this condition and may improve mortality rates independent of bypass technology.[96,106] In a lamb model of CDH the contralateral nonhypoplastic lung is functionally immature, leading some investigators to suggest that surfactant therapy may be beneficial,[107] but this suggestion has not been borne out in a recent review of a large, national CDH registry.[108] Attempts at intrauterine intervention, either to close the defect or to encourage lung growth through temporary blocking of the fetal lung liquid egress at the trachea, have been disappointing; fetal surgery is associated with an unacceptably high incidence of complications, including recurrence of the defect, preterm delivery, and miscarriage.[96,109] In infants with significant pulmonary hypoplasia who require ECMO, distending the lung with perfluorochemical can promote lung growth, but further study is needed.[110]

Although early corrective surgery had been advocated in the past, recently a paradigm shift toward delayed repair has occurred, in large part because of the observation that respiratory function often worsens in the immediate postoperative period.[95,96,111,112] Thus early, aggressive cardiorespiratory stabilization followed by surgery has become the recommended approach and is associated with improved outcome.[95,113] An alternative to an initial period of attempted stabilization has been an ex-utero intrapartum therapy procedure, in which the delivering fetus is orally intubated and placed on a mechanical ventilator prior to umbilical cord ligation. In this approach, a brief trial of ventilation may be given; if oxygen saturation does not improve during the trial, the fetus is cannulated and ECMO is begun, followed by delivery of the infant. This approach may be helpful in selecting infants who are least likely to respond to initial stabilization in the NICU, and reported outcomes with this approach have been favorable, although the mortality rate for infants with this condition remains quite high.[114]

Cystic Adenomatoid Malformation

Cystic adenomatoid malformation (CAM) is a relatively infrequent lesion, estimated at 1 in 30,000 pregnancies.[115] It results from abnormal mesenchymal proliferation and failure of maturation of bronchiolar structures early in gestation.[116,117] The resultant adenomatous overgrowth leads to the development of cysts and suppression of alveolar growth. The cysts are almost always multiple, and in more than 95% of cases the cystic malformations lie within a single lobe. No lobar

predilection exists. Histologically, the lesions are notable for the preponderance of elastic tissue and for a lack of cartilage. The cysts communicate directly with the tracheobronchial tree and with each other.

CAMs have been divided into three types, which vary both in anatomic and clinical characteristics. According to the traditional Stocker classification scheme, Type 1 CAM, which accounts for about half the cases, occurs as a few large (>2 cm) cysts, usually one to four in number, or a single large cyst surrounded by much smaller "satellite" cysts. Type 2 CAM, which accounts for about 40% to 45% of the cases, consists of multiple, small (<2 cm), evenly spaced cysts scattered throughout the affected area. Compared with type 1 CAM, type 2 cysts are associated with a much higher incidence (about 25%) of anomalies in other organs, particularly within the genitourinary tract (e.g., renal dysgenesis). Type 3 CAM, which accounts for less than 10% of cases, occurs as large collections of numerous tiny cysts; the affected area can be large, and this type often leads to early cardiovascular compromise, resulting in fetal hydrops or immediate postnatal complications. The Stocker classification scheme is based primarily on postnatal lung examinations; recent studies of fetal lung specimens suggests that a different classification scheme may be needed, particularly as this condition is now detected antenatally in most cases.[118,119]

Depending on the type, CAM presents during the neonatal period in 50% to 85% of infants, but presentation can be delayed for up to several years. Occasionally cases are discovered on chest radiographs taken for other reasons; many lesions are now detected prenatally during routine sonography. The most common presentation is respiratory distress that results from obstruction, although infection of the cyst leading to recurrent lobar pneumonias can occur as well. The elastic walls of the cyst allow easy expansion on inspiration, but the lack of cartilaginous support results in premature closure during exhalation, leading to a ball-valve type of respiratory compromise.

Chest radiograph findings are variable and depend somewhat on the type of CAM. In the neonate a solid, space-occupying mass will appear, becoming air-filled over the next several hours or days. In types 1 and 2, multiple air-filled cysts may become apparent. This appearance can be confused easily with diaphragmatic hernia; placement of a nasogastric tube to determine the location of the stomach and intestines and absence of a scaphoid abdomen will help rule this out. The multiple small cysts of type 3 CAM cannot be delineated on a chest radiograph; in this case a computed tomography (CT) scan of the chest can be helpful.

Treatment of infants with symptoms may require positive pressure ventilation; in some infants PEEP may facilitate emptying of the cysts. Definitive treatment is surgical removal of the affected lobe, which can be done thoracoscopically in many cases.[120] Even if an infant is asymptomatic, surgical resection is recommended by 3 to 6 months of age because of the high risk of expansion or infection if the cysts are left untreated.[115,121]

Prognosis depends on the type and extent of the CAM. The large type 3 lesions are more likely to cause immediate distress and carry a higher incidence of mortality, especially if associated with pulmonary hypoplasia or fetal hydrops.[115,121] The prognosis in type 2 CAM depends on the presence and nature of associated anomalies. In addition, malignant transformation of CAM has been reported.[94,116,121] Most cases of CAM, however, carry a good prognosis.[115,117,121]

Bronchogenic Cysts

Bronchogenic cysts occur as a result of anomalous budding of the ventral or tracheal diverticulum of the foregut during the sixth week of gestation, with subsequent separation from the normally developing bronchi by the sixteenth week of gestation.[116,117] If separation occurs early (<12 weeks), the bronchogenic cyst tends to be located in the mediastinum (which is the most common type); if separation occurs later, it is more likely to occur in the peripheral pulmonary parenchyma. The cyst walls are cartilaginous and receive either systemic or pulmonary blood supply depending on their location. Bronchogenic cysts are more common in male infants, are usually singular, are more commonly right sided, and are generally less than 10 cm in diameter. They generally do not communicate with the airway and remain fluid filled, which differentiates them from pulmonary parenchymal cysts.

Bronchogenic cysts generally do not present in the neonatal period unless they are large, expand rapidly, or are located near major airways; in these cases infants may have moderate to severe respiratory distress. More commonly the young child will have recurring episodes of wheezing or infection. Occasionally, asymptomatic bronchogenic cysts are visualized on chest radiographs taken for other reasons.

Chest radiographs can readily disclose most bronchogenic cysts.[122] The cyst typically appears as a round or oval water-density mass, commonly in the mediastinal or perihilar area; if the cyst has been infected, an air-fluid level may be present. Mediastinal bronchogenic cysts usually appear just beneath the carina and extend to the right. Pulmonary bronchogenic cysts are usually sharply circumscribed and appear toward the periphery; two thirds of these cysts will be located in the lower lobes, with no right or left predilection. About 25% of bronchogenic cysts may be difficult to visualize with a chest radiograph; in these cases CT scans cannot only delineate the lesion but can also discern associated anomalies, such as a pulmonary sequestration (see later).[116,122]

Treatment may require ventilatory support for infants with symptoms. In all cases, surgical resection is indicated. Prognosis for infants with bronchogenic cysts, whether mediastinal or pulmonary, is good.[123]

Pulmonary Parenchymal Cysts

Pulmonary parenchymal cysts are thought to represent a disorder of bronchial growth,[116,117] although they also may be acquired.[124] Like adenomatoid malformations and bronchogenic cysts, congenital cysts arise early in fetal life; pulmonary parenchymal cysts are thought to develop at a time when completion of the terminal bronchioles and development of the alveoli are occurring. Pulmonary cysts are typically thin walled, singular, multilocular, and located in the periphery. Unlike bronchogenic cysts, some communication usually exists between the pulmonary cyst and the tracheobronchial tree, and thus approximately 75% will become filled with air. Like adenomatoid malformations, pulmonary cysts contain mostly elastic tissue and little or no cartilage.

Although pulmonary cysts are generally small (1 to 2 cm in diameter), they can expand dramatically and thus are much

more likely to be symptomatic than are bronchogenic cysts. As with adenomatoid malformations, the lack of cartilaginous support leads to trapping of air. Unlike adenomatoid malformations, pulmonary cysts are rarely associated with other anomalies. Rupture of a peripheral cyst can result in a pneumothorax. Rarely, multiple cysts can occur and involve both lungs in an extensive fashion; these cases are generally fatal within the perinatal period.

Chest radiographs typically reveal thin-walled, round cysts with an air density. Often faint strands of lung tissue can be seen within the cysts. A large pulmonary cyst may be confused with congenital lobar emphysema; in this case a CT scan should easily distinguish the cystic nature of the former condition.[122]

Reports of spontaneous resolution of pulmonary cysts have been infrequent. As with other cystic lesions of the lung, however, surgical resection of the affected lobe is usually indicated.[116,124]

Pulmonary Sequestrations

Like bronchogenic cysts, pulmonary sequestrations are thought to result from an abnormal budding of the foregut, which retains its embryonic systemic arterial connections.[116,117] Thus a sequestration is a mass of nonfunctioning, ectopic pulmonary tissue with its own blood supply. Pulmonary sequestrations are divided into two types, which are histologically similar. Extralobar sequestrations are surrounded by their own separate pleura, and intralobar sequestrations have no separate pleural covering.

Extralobar sequestrations account for about 25% of cases, are more common (90%) on the left side, are more common in males (80%), and are usually located in a subpulmonic location. Extralobar sequestrations have a high (50% to 60%) association with other anomalies, including direct esophageal communication, bronchial atresia, colonic duplication, cystic adenomatoid malformation, pulmonary hypoplasia, and diaphragmatic hernia. Most cases of extralobar sequestration become evident in infancy; presentation ranges from fetal hydrops with massive pleural effusions and pulmonary hypoplasia to recurrent lower respiratory infections (particularly if there is a gastrointestinal communication).

Intralobar sequestrations are the more common type (75%); they are usually left sided (65% to 70%) and typically occur in the lower lobes. Unlike extralobar sequestrations, they are rarely associated with other anomalies.[125] Most cases are asymptomatic and are found on chest radiographs obtained for other reasons. Symptomatic cases typically present in late childhood with recurrent infections.

Distinguishing between extralobar and intralobar sequestrations on chest radiographs may be difficult. Both can appear as either solid or cystic structures, although extralobar lesions are more often solid and intralobar lesions are more often cystic.[122] Delineation of the vascular supply to the sequestration is important, not only to differentiate extralobar sequestrations from adenomatoid malformations, but to guide surgical management; in the past few years, magnetic resonance imaging has replaced arteriography for obtaining this information.[122] Some authors recommend a study of the gastrointestinal tract, particularly if communication with the sequestration is suspected.

As with other cystic lesions of the lung, surgical removal is indicated and may be done thoracoscopically.[126-128] Whereas extralobar sequestrations can be removed en bloc because of their separate pleural covering, intralobar sequestrations require lobectomy.[94] Recently, success with a nonsurgical approach using transumbilical artery embolization during the newborn period has been reported.[129]

Congenital Lobar Emphysema

Congenital lobar emphysema is an unusual disorder characterized by overdistension of a pulmonary lobe caused by air trapping. The term *emphysema* is misapplied because usually no emphysematous destruction of the alveoli occurs; thus many authors favor the term *congenital lobar overinflation*.[94,116,117] Although clinical and radiographic findings are typical of a ball-valve type of obstruction, evidence for this is found in less than 25% of cases. In most cases the cause for the air-trapping is unknown. Intrinsic bronchial obstruction may be the result of a deficiency of cartilaginous support or an intraluminal mass such as a mucous plug. Extrinsic bronchial obstruction usually results from an underlying cardiovascular abnormality, such as a vascular sling or, rarely, a PDA. Intrathoracic masses, such as an enlarged lymph node or a bronchogenic cyst, can lead to extrinsic obstruction as well.

Congenital lobar emphysema is more common in male infants and typically occurs in the upper lobes or the right middle lobe; fewer than 1% of cases occur in the lower lobes. Up to 20% of the cases have bilateral involvement. Associated cardiovascular anomalies are common; rib cage anomalies and aplasia/dysplasia of the kidneys have been reported in a small percentage of cases. In most infants with congenital lobar emphysema, the condition presents within the first month of life, and about one third of infants have symptoms within hours of birth. Symptoms relate directly to the degree of overinflation. Typically, infants have mild to moderate tachypnea, asymmetric inflation of the chest, and cyanosis. A chest radiograph reveals the overinflated lobe with ipsilateral atelectasis and flattening of the hemidiaphragm; also, a mediastinal shift away from the affected side may be observed. A CT scan may be helpful in identifying the cause of obstruction, if one is present. Lobectomy is the definitive treatment and may be done thoracoscopically.[130] Surgery should be limited to symptomatic cases; favorable outcomes reported in asymptomatic or minimally symptomatic cases in which surgery was not conducted suggests that a less aggressive approach may be warranted.[131]

Pulmonary Agenesis and Aplasia

Pulmonary agenesis and aplasia, which are both rare and highly lethal disorders, have similar underlying causes that differ from those of pulmonary hypoplasia.[117] Pulmonary agenesis and aplasia result from an arrest of development of the primitive lung during embryonic life. Obviously, the earlier in development that the arrest occurs, the more severe the defect. In pulmonary agenesis, the bronchial tree, pulmonary parenchyma, or pulmonary vasculature does not develop. In pulmonary aplasia there is a rudimentary bronchial pouch. The resulting lesion may involve one lobe or the entire lung; focal or bilateral defects are rare. Pulmonary agenesis or aplasia may be associated with other nonpulmonary anomalies including microphthalmia/anophthalmia, cleft palate, cardiac

defects, congenital diaphragmatic hernia/eventration, and limb abnormalities.[132]

The clinical presentation is variable. If the defect is focal and isolated, the infant may not have any symptoms, but usually some mild respiratory distress is present. A chest radiograph reveals unilateral lung or lobar collapse with a shift of mediastinal structures, which leads to a suspicion of bronchial or bronchiolar obstruction. Misdiagnosis may subject the infant to the unnecessary risks of bronchoscopy when CT is readily diagnostic.[133] Associated anomalies in the cardiovascular, gastrointestinal, genitourinary, central nervous, and musculoskeletal systems have all been described.[117]

If the defect is isolated to a single lobe, surgical resection will reduce symptoms and lessen the chance for infection.[134] If the defect is extensive but the fetus is considered salvageable, an ex-utero intrapartum therapy procedure may be performed.

Prognosis depends on the degree of pulmonary involvement, a history of recurrent pulmonary infections, and the presence of associated anomalies.[117] Bilateral defects are invariably lethal. If the defect is focal, the remaining normal lung tends to hypertrophy to compensate. Still, mortality rates exceed 50%, generally because of the presence of associated malformations, which are common. Right-sided defects have a poorer prognosis than left-sided lesions, partly because of a higher association with other anomalies and partly because of an increased risk for disseminating infection. It also has been suggested that right-sided lesions produce a greater mediastinal shift, distorting the trachea and great vessels.[135,136] Repeated lower respiratory infections result in progressive pulmonary debilitation and also increase the risk for death.

Special Treatment Considerations for Acute Respiratory Failure

Surfactant Replacement

Exogenous surfactant therapy has significantly decreased the incidence, severity, and morbidity of RDS and improved the survival of low-birth-weight infants.[137] Exogenous surfactants in current clinical use are considered "natural" because they are derived from either bovine or porcine lungs. Because of concerns for animal protein sensitization and for ease of standardization, newer surfactants under development and not yet commercially available contain no animal proteins but consist of surface active phospholipids and recombinant proteins that exhibit properties similar to the natural surfactant proteins, either B or C. While these surfactants may prove to have advantages over surfactants derived from animals, the earlier concerns regarding sensitization to foreign animal proteins have not been substantiated in more than two decades of clinical use. Human surfactant, purified and concentrated from pooled amniotic fluid, also has been studied clinically and is effective, but it is too expensive and sparse in supply to allow general use.

The three animal-derived surfactants are compositionally different from each other, even though two of them come from the same animal source. These differences are in large part due to the way in which the surface-active components are either extracted, or supplemented, in the different preparations. While most compositional differences are of little biophysical or clinical importance, differences in SP-B content appear to translate into clinical differences such as onset and duration of activity and resistance to inhibition.[138] This difference is important because many other clinical disorders besides RDS can be associated with "functional" surfactant deficiency. Increasing evidence exists that conditions such as meconium aspiration, persistent pulmonary hypertension, hemorrhagic pulmonary edema, congenital diaphragmatic hernia, pulmonary hypoplasia, acute respiratory distress syndrome (ARDS), pneumonia, bronchiolitis, and asthma are associated with surfactant dysfunction and inactivation and that persons with these conditions might theoretically benefit from exogenous surfactant therapy [67,139-145] Treatment of these conditions may prove to be an appropriate niche for synthetic products that contain protein analogues.[146]

High-Frequency Ventilation

Two types of HFV are commonly used in neonates.[34,147-150] The first type uses a highly pressurized intermittent jet of gas that is delivered at rates of 120 to 600 Hz and is called high-frequency jet ventilation. The second type uses an oscillating diaphragm or piston to provide active instillation and withdrawal of gas and is called high-frequency oscillatory ventilation (HFOV).

Although the effects of ventilator settings have been well studied in HFV, the actual mechanics of gas exchange during HFV are less well understood. Similar to conventional ventilation, oxygenation is affected primarily by inspired oxygen concentration and mean airway pressure. Although ventilation is affected by volume and frequency, the effect of volume is much more pronounced than with conventional ventilation, and the effect of frequency is contrary to what would be expected because it inversely affects tidal volume.[34,147,150] In general practice, frequency is not a critical variable within the ranges afforded by the high-frequency ventilator and is not further adjusted during HFV use.

One key advantage to HFV of particular use in the neonate is the ability for high-end expiratory pressures to be used without the need for high-inspiratory pressures to maintain normal tidal volumes, allowing adjustment of mean airway pressure more or less independently of volume. This ability is particularly desirable when a significant V/Q mismatch exists, such as with the neonate who has idiopathic persistent pulmonary hypertension and whose lungs may be easy to ventilate but who is marginally oxygenated with 100% oxygen. Another advantage of HFV is the ability to use low, usually subphysiologic tidal volumes. The use of low volumes prevents overdistension and rupture of more compliant alveoli, thereby reducing the risk of pneumothorax. Furthermore, HFV reduces airflow across existing air leaks, not only promoting their closure but also enabling more effective ventilation in situations such as severe PIE or a bronchopleural fistula.[34,147,148] Still, a specific advantage of HFV over conventional pressure ventilation in preterm infants with RDS, other than managing air leaks, has yet to be demonstrated.[34,147,148] Rehospitalized NICU graduates with chronic lung disease frequently require mechanical ventilation following upper airway infection, particularly with organisms such as respiratory syncytial virus (RSV). The use of HFV may attenuate additional lung injury by allowing higher PEEP while minimizing volutrauma in these babies; however, this advantage is theoretical and not well studied to date.

Complications that have been reported with HFV use include hypotension, pulmonary hypertension, tracheobronchitis, and in preterm infants, intraventricular hemorrhage.[34,147-150] Because the use of excessive airway pressures may impede cardiac return and increase pulmonary vascular resistance, hyperinflation must be avoided. Reports of necrotizing, sometimes lethal tracheobronchitis, a complication recognized during the early years of HFV use, are now rare, presumably because of better attention to humidification and avoidance of excessive mean airway pressures. While some studies have suggested that infants of very low birth weight (less than 1500 g) treated early with HFOV have a lower incidence of chronic lung disease,[151] others have suggested that HFOV increases the risk of intracranial hemorrhage in preterm infants, perhaps because of alterations in cerebral blood flow and drainage.[152-154] Researchers in several other clinical studies have found no such association,[106,151,155-160] and researchers in two studies in animals found no differences in the effects of HFV and conventional ventilation on the cerebral circulation.[161,162]

Extracorporeal Membrane Oxygenation

ECMO evolved from classic bypass technology with the advent of membrane oxygenators that could operate for days without significantly disrupting blood cells and plasma proteins. However, when applied to premature neonates with RDS, ECMO initially was disappointing.[163] ECMO did not reduce mortality rates in patients with ARDS and was associated with a high risk of intracranial hemorrhage in preterm infants. Nevertheless, subsequent use in term infants with cardiorespiratory failure, particularly those with persistent pulmonary hypertension and congenital diaphragmatic hernia for whom conventional therapies had failed, has led to its increasing application in this area, despite the absence of controlled clinical trials.[164] In neonates with respiratory failure, compared with other indications for ECMO, RSV/lower airway disease has a far higher survival rate (96%) and very low rate of neurologic sequelae.[165,166] Most causes of neonatal respiratory failure in the newborn are self-limited, and ECMO allows time for the lung to recover from the underlying disease process and for reversal of pulmonary hypertension, which frequently accompanies respiratory failure in the newborn.[167] In addition, the use of ECMO in older children and adults also has received a resurgence of interest see Chapter 53. The technical description, aspects of clinical management, and potential complications of ECMO are covered elsewhere in this book and are not detailed here.

Nitric Oxide Inhalation

In mammals, vascular smooth muscle relaxation is in large part induced by nitric oxide, which is released by adjacent endothelial cells in response to flow and shear stimuli and stimulates guanylate cyclase to produce cyclic guanosine monophosphate, a potent vasodilator. Inhaled nitric oxide causes significant pulmonary vascular vasorelaxation without a significant systemic effect because it is rapidly scavenged by hemoglobin as it enters the pulmonary microvascular circulation. In addition, inhaled nitric oxide selectively vasodilates the lung units that are better ventilated, optimizing ventilation-perfusion matching. Inhaled nitric oxide is approved for use in term and near-term (≥34 weeks' gestation) infants with persistent pulmonary hypertension; although it does not alter the long-term outcome in patients with this condition, it significantly reduces the need for rescue treatment with ECMO.

While nitric oxide inhalation has received much interest in the management of term infants with persistent pulmonary hypertension, other applications continue to be evaluated. Animal studies suggest that nitric oxide may have a significant role in the successful perinatal transition to breathing of air.[168,169] Clinical studies suggest that inhaled nitric oxide may be beneficial in infants with surfactant-deficient RDS, particularly those who do not respond to exogenous surfactant therapy.[170,171] The basis for these studies lies in the observation that pulmonary hypertension is not confined to term neonates but has been reported in preterm infants with RDS as well.[172,173] In addition, recent work has shown that nitric oxide production modulates basal pulmonary vascular tone in preterm animals.[174]

Many questions regarding nitric oxide use remain to be answered before it can be approved for clinical use in preterm infants with RDS. Recognized clinical complications include methemoglobinemia (because of its high affinity for hemoglobin) and prolonged bleeding times[175];the toxicity of nitric oxide metabolites includes the potential for injury to the pulmonary epithelium and surfactant system as well.[176] In time, the intense amount of ongoing basic research in nitric oxide biochemistry and clinical trials in both adults and children will begin to answer important questions about dosing, safety, and efficacy.[177,178]

Liquid Ventilation

Liquid ventilation with perfluorochemicals, a complete departure from traditional ventilation with gases, is one of the latest advances in ventilatory management for the neonate. Specific advantages of liquid instead of gas expansion of the lungs were first demonstrated in the 1920s, but application to the clinical setting was hampered by the poor solubility of most liquids for oxygen and carbon dioxide and technical difficulties in achieving liquid tidal volume exchange. The introduction of perfluorochemicals, which have high solubility for respiratory gases, and the development of specific liquid ventilators enabled researchers to study liquid ventilation in animals in the 1970s.[179] The demonstration that complete tidal liquid movement was not necessary to capitalize on the advantages of liquid ventilation[180] made liquid ventilation a clinical reality in the 1990s. Partial liquid ventilation is the term applied to conventional gas tidal volume ventilation superimposed on liquid-filled alveoli (i.e., alveoli filled to functional residual capacity).

Though gas exchange can be impaired by too rapid liquid ventilation in the healthy lung in animal studies,[181,182] it is clearly improved in many injured lung models. Possible mechanisms for this improvement includes reducing surface tension and maintaining alveolar stability, thus eliminating the need for alveolar surfactant by filling the alveoi with liquid and thereby removing the air-liquid interface normally present. Perfluorochemicals also may act as a mechanical PEEP, holding the alveoli open because of the higher density of the liquid. Therefore partial liquid ventilation offers the potential

to manage infants with respiratory distress resulting from surfactant deficiency or dysfunction, in which exogenous surfactant replacement has failed or becomes impractical (e.g., heterogeneous lung disease such as ARDS). In animal models, perfluorochemicals also reduce neutrophil accumulation and inflammatory responses to lung injury[183-186] and inhibit hydrogen peroxide and free radical production by macrophages.[187] Studies in animals also show that partial liquid ventilation leads to marked improvements in respiratory mechanics compared with conventional ventilation strategies.[188-192] In 13 premature infants with severe RDS for whom conventional mechanical ventilation had failed and who had a high predicted risk of mortality, 10 of 13 received partial liquid ventilation for 24 to 72 hours,[193,194] resulting in dramatically improved oxygenation and compliance; 8 of 10 survived to 36 weeks gestational age without significant complications. Large randomized human trials have been limited by the dose-dependent risk of hypoxia and barotrauma associated with perfluorocarbon.[195] No studies of perfluorochemical liquid ventilation have been conducted in term neonates with respiratory disease; however, other limited clinical trials and individual case reports have been encouraging.[194,196-200]

Chronic Pulmonary Disease

Chronic Lung Disease (Bronchopulmonary Dysplasia)

The first description of a chronic respiratory disease in neonates was in 1967 by Northway et al.,[201] who reported long-term radiographic and clinical outcomes of 32 low-birth-weight infants with acute respiratory disease. The infants described by Northway and colleagues progressed from acute respiratory disease (typically, hyaline membrane disease) requiring mechanical ventilation to a chronic phase with persistent oxygen requirement and respiratory distress, often resulting in right ventricular failure and death. Northway et al. coined the term bronchopulmonary dysplasia (BPD) to describe the patho logic findings in these infants at autopsy.

Over the years, this term has been loosely applied to include a wider variety of infants with chronic lung disease, most of whom survive.[202,203] Because of improvements in the management of severe RDS, pulmonary hypertension, and pulmonary hypoplasia and because of increased survival rates of infants born between 23 and 26 weeks' gestation, the BPD characterized in the original description by Northway and colleagues is relatively rare. The pathophysiology of BPD has evolved to encompass a new population of infants with chronic lung disease: extremely-low-birth-weight infants (weighing less than 1000 g) who without today's advancements in medicine and technology could not have survived at the time of the investigations by Northway et al. These infants typically have a relatively mild course of acute respiratory disease and usually wean to minimal ventilatory support, oxygen support, or both within the first 72 hours of life. The oxygen requirement, however, tends to persist for weeks, months, or even years, and these infants are at extreme risk for respiratory exacerbations. Although the incidence of mortality is rare, those with this "new" type of BPD who die typically do not show severe lung injury with marked fibrosis and cellular proliferation, as seen in infants with classic BPD. Instead, one finds arrested lung development, with evidence of both impaired vascular and alveolar growth.[204-207]

The pathophysiologic cause of chronic lung disease after relatively mild acute respiratory disease in these extremely-low-birth-weight infants may, in part, relate to an increased sensitivity and abnormal responsiveness of the immature airways to injury.[205,206,208-219] It has been suggested that preterm birth during the late canalicular stage (24 to 27 weeks' gestation) leads to an arrest of normal lung development[213]; this suggestion is consistent with the observation that "normal" preterm infants (i.e., those without clinical evidence of lung disease) have dysfunction of terminal respiratory units and higher elastic recoil than do term infants at comparable postmenstrual ages.[212] This arrested development sets the stage for disordered repair when the immature lung is subjected to postnatal injury, perhaps by oxidants, infection, or ventilatory trauma.[209] Inflammation clearly plays a role in the development of BPD[210]; indeed, evidence exists that it may begin in utero.[213] Mediators of epithelial lung injury include a variety of cytokines, including interleukin-1β (IL-1β), IL-6, and IL-8[218]; in addition, impaired signaling of growth factors such as vascular endothelial growth factor has been implicated.[208,215] Given these considerations, it is likely that the pathogenesis of BPD, particularly in the extremely-low-birth-weight infant, is multifactorial in nature.

Generally, the incidence of BPD increases with decreasing gestational age: at less than 28 weeks' gestation the incidence is approximately 40%, and it approaches 90% for infants at less than 26 weeks' gestation.[202,203] Additional risk factors include maternal infection, neonatal sepsis, and PDA.[219] Although better monitoring, improved ventilation strategies, and new technologies have all had a positive impact on reducing the incidence and severity of BPD in the more mature neonate, increased survival of extremely-low-birth-weight infants has increased the overall prevalence of this condition in NICU graduates.

The clinical presentation of BPD depends on the severity and extent of the acute lung injury. In cases of classic BPD, infants typically require a high degree of ventilatory and oxygen support beyond the age of 1 week. These infants are slow to wean, require supplemental oxygen for weeks to months, and have episodes of bronchospasm or desaturation. Infants with severe BPD can have varying degrees of right ventricular failure or, in less severe cases, simply display fluid intolerance. Findings of chest radiographs for these infants will be abnormal, showing areas of increased density interspersed with areas of hyperinflation or even cystic development.

In the new type of BPD, onset is much more insidious. For the first 2 to 3 weeks of life, these extremely-low-birth-weight infants appear stable on minimal ventilatory and oxygen support, but then their need for increased ventilatory and oxygen support slowly develops. These infants often have episodes of apnea, desaturation, or carbon dioxide retention. Increased secretions from the endotracheal tube may occur as well. The chest radiograph may show areas of atelectasis, but more commonly it is clear in the early stages or simply shows a minimal, homogeneous increase in density in both lung fields. Depending on clinical signs, confounding conditions such as a PDA, pneumonia, or aspiration must be considered and ruled out.

Treatment of infants with BPD is generally supportive. The goal of treatment is to promote lung growth while simultaneously supporting respiratory needs and minimizing further injury to the lungs. Supplemental oxygen should be used for infants with oxygen saturations below 93% in room air.

Bronchodilators may be helpful particularly during exacerbations because often there is a large airway component to BPD. Fluid restriction or diuretics may be helpful in infants with evidence of cor pulmonale or fluid intolerance. At initial presentation infants often receive a few days of antibiotics until infection is ruled out. Infants with pulmonary insufficiency have increased energy needs,[211] making nutritional support particularly important, although it is often overlooked.[220]

An approach aimed at reducing the inflammation and ongoing fibrotic injury is the use of steroids. However, although earlier study results have shown that intravenous dexamethasone reduces the severity of BPD and improves respiratory outcome in older premature infants,[221,222] concerns have been raised regarding long-term safety, particularly from studies that included younger and more immature infants.[223-225] Because of these observations and a growing body of data that questions the safety of high-dose steroids in extremely premature animals, the Academy of Pediatrics Committee on the Fetus and Newborn has recommended that steroid use for infants with BPD be within the context of well-designed, randomized trials until issues of long-term efficacy and safety are more clear.[226] Given the rapid and sustained response that many infants with BPD have to steroids, significant controversy exists regarding this recommendation, particularly as it applies to older or less premature infants with significant pulmonary disability.

What is clear is that infants who receive long courses of steroids for BPD usually show chemical evidence of adrenal suppression, which may last for several months;[221] infants who receive steroids for more than several days also should receive supplementation at times of increased stress (e.g., surgery and infection). It also is apparent that the inhaled method of administering steroids offers no particular advantage over the intravenous route, except for ease of administration.[227] Potential new therapies to prevent or reduce the severity of BPD include synchronous mode ventilation, HFV, antioxidants, nitric oxide, antiproteases, vitamin A, and antenatal therapy with steroids and thyrotropin-releasing hormone; however, to date, study results have been inconclusive.[151,155,157,217,228-231]

The long-term outcome for infants with classic BPD has improved over the years, although these infants remain at risk for significant morbidity and mortality.[219,232] Infants typically require supplemental oxygen for the first several months of life, and some may require chronic diuretic and bronchodilator use. High-caloric formulas should be considered for infants who cannot tolerate fluid loading. Rehospitalizations as a result of respiratory exacerbations, which often are brought on by infection, are common during the first 2 years of life.[233] Persons with relatively uncomplicated courses will gradually improve and by school age often have normal lung function.[219]

The long-term outcome for extremely-low-birth-weight infants with new BPD is less clear. Although these infants often require little or no respiratory support at the time of discharge from the NICU, fewer data exist on long-term outcome because extremely-low-birth-weight infants rarely survived to discharge from the hospital before the advent of surfactant replacement therapy in the 1980s. If these infants indeed have an arrest of lung epithelial and vascular development as a result of preterm birth, long-term cardiorespiratory function remains unclear. As with infants with classic BPD, these infants are at increased risk for rehospitalization as a result of pulmonary infection and reactive airway disease,[234] but they also may be at increased risk for long-term pulmonary dysfunction.[235-237]

Mortality as a result of BPD has markedly improved during the past decade but remains high in infants with complicating conditions (such as cardiovascular disease) or in those with intercurrent respiratory infections, particularly RSV or adenovirus. Passive immunization against RSV is now possible and is recommended for high-risk premature neonates[238]; however, it is costly and is not uniformly protective.[239,240] Minimizing exposure to environmental hazards, whether infectious or irritant (e.g., from kerosene burners or cigarette smoke), cannot be overemphasized.[230]

Congenital Defects of the Lymphatics

Chylothorax is not an uncommon entity encountered in the pediatric ICU because it can be a complication of cardiothoracic surgery; however, postoperative chylothorax has a different natural history and prognosis than does congenital chylothorax, which is thought to be due to a failure of peripheral and central lymphatic channels to fuse, or perhaps a rupture of inadequately fused channels at birth.[241] Most affected infants have symptoms within hours of birth and require mechanical ventilation. Congenital chylothorax, in contrast to the postoperative variety, can be associated with chromosomal abnormalities and other malformations, as described by a recent case series of 11 newborns. Familial cases are especially common in babies with associated congenital pulmonary lymphangiectasis with bilateral chylothoraces.[242] Progressive respiratory compromise develops as fluid accumulates in the hemithorax. Drainage is both diagnostic and therapeutic; initially the lymphocyte-rich fluid is clear, but it becomes opaque when milk feedings are introduced. Nutritional support is critical because of the tremendous loss of protein in the chylous drainage. Most cases self-resolve in 2 to 3 weeks; occasionally, a several-day course of a somatostatin-analog, which reduces chyle flow, or an attempt at surgical closure of the thoracic duct is indicated. Whether congenital or postoperative, common complications include nosocomial infection, hemodynamic disturbance, and protein loss.[243] In the congenital variety, length of time to resolution is significantly affected by additional underlying problems.[242]

Pulmonary lymphangiectasia is a very rare condition that can be a primary condition or a secondary dilation of pulmonary lymphatics resulting from obstructed pulmonary venous flow.[241,244] A primary lymphangiectasia can be isolated, which is termed congenital pulmonary lymphangiectasia, or it can be part of a generalized condition that includes intestinal lymphangiectasia, in which pulmonary involvement is less severe. Congenital pulmonary lymphangiectasia is thought to result from failure of connective tissue elements to normally regress during fetal lung development. In some cases, a hereditary pattern has been suggested. Affected infants usually have symptoms soon after birth; however, some infants may remain symptom free for several weeks. Affected infants are usually born at term and may appear normal except for mild tachypnea, or they may be more severely affected with cyanosis or be frankly hydropic[245]; infants born preterm may be mistaken as having surfactant-deficient RDS. Radiographs generally reveal streaky reticular densities as a result of engorged lymphatics, and occasionally a finer, "ground-glass" appearance

may be confused with surfactant deficiency. Pleural effusions have been reported but are unusual. The condition is progressive and untreatable; most infants die within days, but an occasional survivor beyond infancy has been reported.

Nonpulmonary Conditions that Result in Respiratory Disease

Many nonpulmonary disorders may present with respiratory distress in the neonate (Box 46-1). Conditions that affect the control or mechanics of breathing, the patency or integrity of the upper airway, perfusion to and from the lung, or acid-base balance can present with increased respiratory effort or signs of respiratory insufficiency (i.e., respiratory acidosis or hypoxemia). The clinical and radiographic picture may be consistent with an underlying pulmonary pathologic condition, but nonpulmonary causes must be considered, particularly if an infant is gravely ill or not responding to conventional treatments. In many of these nonpulmonary conditions, a delay in diagnosis can lead to irreversible injury and death.

Apnea of Prematurity

Apnea is one of the most common respiratory problems encountered in the neonatal population. The incidence of apnea is inversely proportional to the gestational age at birth, and more than 75% of infants born before 27 weeks will have apnea at some point in their NICU stay. Apnea can be broadly classified as physiologic (i.e., apnea of prematurity) or pathologic (i.e., resulting from an underlying disorder such as sepsis).

Three main types of apnea exist. The first is central apnea, which results from decreased central responsiveness to respiratory stimuli, such as hypoxia and hypercarbia. This responsiveness improves as the infant matures and approaches term. This type of apnea is characterized by cessation of respiratory effort, which usually occurs at the end of exhalation. The second type of apnea is called obstructive apnea because of an anatomical or physiologic restriction of the airway. Common examples include tracheomalacia or Pierre Robin syndrome. The respiratory pattern of obstructive apnea demonstrates increasing respiratory effort with little to no air movement. Mixed apnea represents the third type of apnea. Initially the infant has what appears to be a central apnea, but when a respiratory effort is made, an obstructive pattern is revealed. The obstructive pattern is thought to result from gradual airway collapse during the initial central apneic portion of the episode. Most apneic episodes lasting longer than 20 seconds fall into this category.

Although apneic spells are a common cause of rehospitalization following NICU discharge, apnea of prematurity is a diagnosis of exclusion. Most infants with apnea of prematurity achieve complete resolution of symptoms by 34 to 36 weeks after conceptual age. Once apnea of prematurity has resolved, it does not come back,[246] and pathologic causes such as hypoglycemia, hypoxemia, hypothermia or hyperthermia, infection, left-to-right shunt, and intracranial hemorrhage should be ruled out. Of particular concern is new-onset apnea in a previously symptom-free infant. Apnea also increases in response to less stressful stimuli, such as immunizations or an ophthalmoscopic examination. Apnea in a term or near-term infant is almost always pathologic.

Isolated apnea may be treated with simple tactile stimulation in many cases. Infants who remain apneic after stimulation may require blow-by oxygen, nasal cannula therapy, nasal continuous positive airway pressure, nasal intermittent mechanical ventilation, or even re-intubation and mechanical ventilation depending on the severity, recurrence, and presence of underlying pathology. Caffeine is the pharmacologic agent of choice to treat apnea because of a long plasma half-life and low toxicity. It is interesting to note that whereas high neonatal serum levels of magnesium resulting from maternal magnesium therapy have been associated with apnea, magnesium deficiency can also cause apnea. In one retrospective study of premature infants receiving supplemental magnesium because of low serum levels, reduction in apneic episodes was noted[247]; however, because of a narrow therapeutic index, using magnesium to treat preterm neonatal apnea would require frequent serum levels that are not necessary when using caffeine.

Box 46–1 Nonpulmonary Conditions that Cause Respiratory Distress in the Newborn

Disorders of Respiratory Control
- Central hypoventilation disorder
- Apnea

Airway Obstruction/Patency
- Choanal stenosis/atresia
- Mandibular hypoplasia/micrognathia
- Laryngomalacia
- Laryngeal web/stenosis
- Vocal cord injury
- Subglottic hemangioma
- Tracheobronchomalacia
- Tracheoesophageal fistula
- Vascular compression

Interference with Respiratory Mechanics
- Neuromuscular disorders
- Phrenic nerve injury
- Eventration of the diaphragm
- Pleural effusion
- Chest wall anomalies

Perfusion Abnormalities
- Persistent pulmonary hypertension of the newborn
- Hyperviscosity
- Congenital heart disease

Disorders of Acid-Base Balance
- Metabolic disorders (e.g., organic acidemias)
- Intestinal bicarbonate wasting
- Renal bicarbonate wasting
- Sepsis
- Iatrogenic metabolic acidosis/alkalosis

Choanal Atresia/Stenosis

Choanal obstruction resulting from failure of bony or membranous regression is the most common supralaryngeal congenital defect. It occurs in approximately 1 in 4000 live births. Choanal atresia is often associated with defects in other organs or with syndromes that include other craniofacial anomalies, especially CHARGE syndrome (i.e., coloboma of the eye, heart anomaly, choanal atresia, retardation, and

genital and ear anomalies). Choanal atresia is usually unilateral, typically on the right side; a 2:1 excess of choanal atresia has been reported in girls, though a recent review suggests equal sex predilection.[248] Unilateral choanal atresia occurs more frequently in isolated cases, whereas bilateral choanal atresia is an indication for further evaluation for other congenital anomalies. This phenomenon may be partly explained by the idea that genetic factors are more likely to result in symmetric errors of embryogenesis.[249] Associated findings include a high-arched palate, thickening of the vomer, and medial bowing of the lateral wall of the nose. Clinical presentation depends on the degree of obstruction; bilateral choanal atresia or severe bilateral stenosis will present in the newborn period, whereas unilateral cases or mild stenosis may not present for weeks, months, or years. Infants with symptoms are typically distressed during times of sleep or feeding, when nasal breathing is preferential. Clinical presentation in infants with unilateral obstruction or mild stenosis may occur only when the nares become obstructed, as with the passage of a nasogastric tube or inflammation during an upper respiratory infection. With occlusion of the patent nares, an infant can suddenly decompensate, with signs of severe respiratory distress.

Infants in severe distress may require elective intubation if an oral airway is insufficient or cannot be easily maintained. Direct visualization of the obstruction is best performed by an otolaryngologist using a fiberoptic scope. A cranial CT scan can determine the presence and thickness of the bony plate within the nasal cavity, which is an important surgical consideration. Definitive treatment generally involves drilling through the bony plate and stenting the nasal passage with tubes for 6 weeks to allow proper healing. A high degree of suspicion is key to diagnosing and properly treating this disorder, and if true bilateral choanal atresia is present, associated anomalies must be ruled out.

Laryngomalacia

Laryngomalacia is the most common cause of stridor in the neonate. It is thought to result from redundant soft tissue or delayed development of neuromuscular control. Similar to infants with mandibular hypoplasia, infants with laryngomalacia tend to have more symptoms in the supine position because this allows relatively unsupported anterior tissue to drop into hypopharynx, causing obstruction. Affected infants may be stridulous, however, only during periods of crying or distress. Treatment includes prone positioning, and resolution is common by age 1 to 2 years.

Vocal Cord Paralysis

Vocal cord paralysis can be unilateral or bilateral. Unilateral cord paralysis usually presents with a weak or sometimes hoarse cry. Obstructive symptoms, such as stridor or retractions, are less severe and less common. The infant may also cough or choke while feeding because of an inability to prevent aspiration while swallowing. The most common causes are stretch injury during delivery or recurrent laryngeal nerve injury during ductus ligation; thus left-sided paralysis or paresis is most common. Symptoms from unilateral cord paralysis usually improve over a few weeks or months with no intervention.

Bilateral cord paralysis represents a more serious problem and is usually the result of an intracranial pathologic condition, such as Chiari malformation, intracranial hemorrhage, or hypoxic-ischemic encephalopathy. These infants may have near total airway obstruction and will have moderate to severe stridor. Most will require tracheostomy to maintain a patent and reliable airway.

Subglottic Hemangioma

Congenital hemangiomas just below the level of the vocal cords are another relatively uncommon cause of stridor, with or without expiratory wheeze, in the neonate. As they enlarge they can threaten the airway. Positional changes tend to have little effect on the severity of the symptoms. Superficial, capillary hemangiomas on the skin of the neck are often present, suggesting the diagnosis. For acute exacerbations, systemic steroids may be used to reduce tissue swelling and improve airway patency; however, symptomatic infants eventually require surgical removal of the lesions. The availability of laser surgery has markedly reduced the need for tracheostomy in children with subglottic hemangioma.

Tracheobronchomalacia

Tracheobronchomalacia is characterized by abnormally compliant airway cartilage, leading to intermittent collapse of the airways during normal respiration. Specific classification depends on the area(s) involved (e.g., tracheomalacia, tracheobronchomalacia, and bronchomalacia). Infants can be mildly or severely affected, depending on the extent of involvement and the ability of surrounding supporting tissues to maintain airway patency. Affected infants generally have symptoms in the newborn period, but presentation may be delayed for many days or weeks if the defect is mild. In these milder cases, infants may remain symptom free until an intercurrent infection leads to increased airway secretions and increased work of breathing. Symptoms include expiratory wheezing and respiratory distress including tachypnea and retractions, and the infant may receive a mistaken diagnosis of reactive airway disease; however, the use of bronchodilators may actually worsen the condition. A chest radiograph may show hyperinflation. Definitive diagnosis is made by direct visualization, typically with flexible bronchoscopy. Treatment is supportive because airway compromise generally lessens as the infant grows; however, more severe cases may require stenting with continuous positive airway pressure or even surgical plication. Tracheostomy alone may not be helpful if the affected area extends beyond the proximal trachea. A high association with other congenital anomalies, including vascular rings or tracheoesophageal fistula (discussed later in this chapter) also must be kept in mind; a history of recurrent coughing or choking requires further investigation.

Tracheoesophageal Fistula

Tracheoesophageal fistula (TEF) occurs in approximately 1 in 4500 live births, making it one of the most common congenital malformations. Usually isolated, it can be associated with other anomalies including complex syndromes like VATER (vertebral defects, anal atresia, TEF, esophageal atresia, and renal anomalies), VACTERL (VATER plus cardiac and upper

limb defects), and CHARGE (coloboma, heart defect, choanal atresia, mental retardation, genital hypoplasia, ear anomalies, and deafness). In the absence of a more generalized syndrome, TEF is also associated with isolated cardiac defects, which may present in up to 50% of cases. Whether as part of a syndrome or an isolated anomaly, TEF usually is associated with esophageal atresia; however, in 5% to 7% of cases there is no associated esophageal atresia (H-type TEF).

TEF and an associated esophageal atresia and TEF as part of a more general disorder invariably present in the immediate newborn period; infants with an isolated H-type fistula can remain clinically silent for many weeks or even months. Although relatively rare (approximately 1 in 100,000 live births), an H-type fistula must be suspected in any infant who coughs during feedings and has recurrent pneumonitis. In preterm infants it can present as apnea spells with no other signs. The diagnosis of an H-type fistula can be difficult but is best found by a cine esophagram; in cases in which this study is inconclusive, bronchoscopy may be necessary. Successful repair and preservation of pulmonary function depends on early diagnosis.

Vascular Compression

Vascular compression of the trachea or mainstem bronchus can result from improper regression of the embryonic branchial arch arteries during fetal development. The most common anomaly is a vascular "ring" consisting of a double aortic arch, in which the vessel completely encircles the trachea and esophagus. Other variants include an ectopic aortic arch (passing behind the esophagus) or an aberrant origin of the right brachiocephalic artery.

Vascular rings will cause inspiratory stridor and expiratory wheezing, neither of which change appreciably with the infant's position. Intermittent worsening of symptoms is sometimes seen when feeding as boluses passing down the esophagus, further compressing the trachea. Feeding difficulty also may be present because of esophageal compression. When a previously undiagnosed child first presents with these symptoms, the child may be misdiagnosed as having tracheomalacia, bronchomalacia, or tracheobronchomalacia, until further imaging confirms the cardiovascular abnormality. This condition also can be detected antenatally.

The presence of an abnormally shaped mediastinum on a chest film often provides a clue to this diagnosis. Endoscopy may identify tracheal or esophageal compression. An echocardiogram may define the nature of the vascular anomaly; cardiac catheterization is sometimes necessary. Decisions regarding surgical correction of this defect depend on the relative compromise of the trachea and esophagus; however, the degree of compression may actually worsen as the infant grows.

Phrenic Nerve Paralysis

Stretch injury to the cervical nerve roots C3 to C5 during delivery can lead to temporary paralysis of the hemidiaphragm, and avulsion of the nerve roots will lead to a permanent injury. Most commonly on the right, this type of injury is associated with birth trauma; brachial plexus injury or Horner's syndrome is present in 70% to 80% of cases, and clavicular fracture is common. Infants at highest risk are those with estimated birth weights of more than 4 kg, shoulder dystocia, or difficult breech presentations. Diminished ventilation is present on the affected side, and the infant may have tachypnea or even be cyanotic if severely compromised. The chest radiograph will show a varying degree of atelectasis with a raised hemidiaphragm on the affected side and the heart and mediastinum shifted toward the contralateral side. Fluoroscopy will show that the paralyzed diaphragm elevates during inspiration and descends on expiration (paradoxical movement). Treatment is supportive in most cases because function usually returns spontaneously in several weeks; in cases of avulsion or permanent dysfunction, surgical plication may be necessary.

Eventration of the Diaphragm

The normal diaphragm consists of three layers: a muscular layer sandwiched between the pleural and peritoneal layers. Congenital dysplasia or absence of the muscular layer is a rare disorder that results in a nonfunctioning diaphragm that is highly stretchable. Partial defects are more common and appear most often on the right side; complete defects are more common on the left side and often are associated with anomalies of other organs. Under normal abdominal pressure, viscera easily push the affected diaphragm upward into the hemithorax. In utero this phenomenon may lead to pulmonary hypoplasia (although this is usually mild), whereas after birth it will cause respiratory compromise by affecting lung expansion. Radiographic and fluoroscopic findings are similar to those of a paralyzed diaphragm, but the clinical history of birth trauma or associated injuries is usually absent. With large defects the appearance of bowel apparently in the thoracic cavity on a chest radiograph may be mistaken for a diaphragmatic hernia; however, close inspection will reveal the thin, overlying diaphragmatic pleura. Treatment is supportive; defects that remain symptomatic beyond the neonatal period may require plication.

Pleural Effusion

Collection of fluid within the pleural cavity, if excessive, can result in significant respiratory embarrassment. Pleural effusions in the neonate can result from inflammation, transudation, or frank leakage from disrupted vessels (either vascular or lymphatic). Small pleural effusions are normal during the first hours of life, as fetal lung liquid is cleared from the airspaces, but large effusions or persistence beyond the first day of life is abnormal. Large effusions can result in significant respiratory compromise; although initial management is similar regardless of the cause, successful long-term management depends on accurately identifying the source of the pleural effusion.

Congenital Anomalies of the Chest Wall

Thoracic cage abnormalities represent a group of uncommon but often overlooked causes of respiratory distress in the neonate and can be classified as either structural or functional. Structural abnormalities may be limited to the sternum or involve the entire thoracic cage. Sternal deformities include pectus excavatum, a relatively common but usually benign condition, and complete separation of the sternum, which usually leads to ectopia cordis and usually is lethal. Generalized

structural abnormalities invariably involve some degree of thoracic restriction and pulmonary hypoplasia; many of these abnormalities are intrinsically lethal or are part of a more generalized lethal disorder. Some conditions, however, such as achondroplasia and Ellis-van Creveld syndrome, are compatible with normal life. Functional anomalies result from dysfunction of the chest wall musculature. Like structural defects, they can be isolated to the thoracic cage, but more often they are part of a systemic disorder, such as congenital muscular dystrophy, glycogen storage disease, or myasthenia gravis.

The condition of most infants with thoracic cage abnormalities is recognized in the immediate newborn period, although a relatively protuberant abdomen may distract the clinician from the primary problem. Infants with restricted thoracic cages (either structural or functional) will have tachypnea and retractions; the radiograph will show a narrow, elongated thoracic cage with high clavicles and low hemidiaphragms. Treatment is supportive, and in the absence of severe pulmonary hypoplasia or an underlying lethal disorder, infants may do relatively well, although they often require mechanical ventilation for a limited duration.

Persistent Pulmonary Hypertension of the Neonate

In the fetus, the organ of gas exchange is the placenta, not the lung. Thus placental blood flow is high, whereas pulmonary blood flow is minimal. To achieve this gas exchange, blood returning to the right side of the heart must be directed to the systemic (and thus placental) circulation. This blood flow is accomplished by two principal right-to-left shunts in the fetus: the foramen ovale, which shunts blood from the right to left atrium, and the ductus arteriosus, which shunts blood from the pulmonary artery to the descending aorta. These shunts result in less than 10% of the combined fetal ventricular output going to the lungs.

At birth, dramatic changes must occur within the lung if the fetus is to make a successful transition from placental to pulmonary gas exchange. Not only must liquid be removed from potential airspaces (see the section on Delayed Clearance of Fetal Lung Liquid in this chapter), but blood flow also must be redirected. After inflation of the lungs with air and dramatic increases in oxygen tension within the lungs, a marked increase in cyclic nucleotides occurs within the pulmonary vascular smooth muscle, leading to vasodilatation.[250,251] The resultant drop in pulmonary vascular resistance leads to a tenfold increase in pulmonary blood flow,[252] which causes left atrial pressure to exceed right atrial pressure, allowing the one-way flap across the foramen ovale to close. Flow across the ductus arteriosus reverses, and this, combined with the increase in oxygen tension in the blood, leads to gradual closure of the ductus over the first few hours of life.

In the syndrome of persistent pulmonary hypertension of the newborn (PPHN), this transition of the pulmonary circulation fails to occur normally (see Chapter 48). Pulmonary vascular resistance and pulmonary arterial pressure remain high and blood flow continues to bypass the lungs as in fetal life. (This is why the term persistent fetal circulation has been used, although it is not strictly correct because there is no longer any placental/umbilical circulation as in the fetus.) PPHN is associated with many neonatal disorders, including RDS, meconium aspiration, air leak syndromes, perinatal asphyxia, congenital sepsis, and structural lung disease such as pulmonary hypoplasia or alveolar-capillary dysplasia. PPHN can also be idiopathic. Infants with PPHN can be moderately or severely affected, depending on the degree of shunting. PPHN is often a self-limited disease, but this process may take several days; meanwhile, severe hypoxemia can lead to significant morbidity. The incidence of mortality can be as high as 50% to 60%; it has improved significantly with the advent of new treatment modalities such as HFV, inhaled nitric oxide, and extracorporeal bypass, which allow the infant more time to spontaneously recover.[105,106,149,163,164,253-256] Because nitric oxide works by increasing cyclic guanosine monophosphate levels, there has been recent interest in using selective phosphodiesterase inhibitors such as sildenafil, particularly in infants with a prolonged course of PPHN, or in whom PPHN develops beyond the newborn period, either idiopathic or as a result of underlying cardiorespiratory disease. However, the long-term benefits and risks of sildenafil are unknown, and its use should still be considered experimental.

Hyperviscosity Syndrome

Neonates with polycythemia (i.e., a central hematocrit greater than 65%) are at risk for abnormally high blood viscosity, which interferes with perfusion to vital tissues. Polycythemia can occur in several situations, including twin-twin transfusion, maternal-fetal transfusion, delayed cord-clamping, home delivery, maternal diabetes, small-for-gestational-age infants, postmature infants, and infants with Down syndrome or Beckwith-Wiedemann syndrome. Symptoms generally relate to the degree of hyperviscosity and can range from tachypnea to apnea, listlessness to irritability, and jitteriness to seizures. Hyperviscosity syndrome presents in the first few hours of infants' lives, and the presentation can mimic that in infants with congenital pneumonia, meconium aspiration, persistent pulmonary hypertension, or congenital heart disease. Affected infants are at risk for ongoing thrombotic injury unless the condition is reversed by partial blood volume exchange.

Congenital Heart Disease

In the neonate, significant congenital heart disease typically presents in one of two ways: (1) cyanosis with minimal or no respiratory distress or (2) cardiorespiratory failure. Cyanotic lesions, such as transposition of the great vessels or tetralogy of Fallot, usually present in an infant who is blue but comfortable. Characteristically, congenital cyanotic heart disease is suspected in such an infant, even if a murmur is absent, particularly if the infant remains desaturated or hypoxemic in 100% oxygen. Less common in the neonate are those conditions that lead to early failure, such as an atrioventricular canal defect or a large ventricular septal defect. These infants are generally not cyanotic but are pale with marked respiratory distress and often a loud murmur; chest radiographs may show the classic signs of cardiomegaly and pulmonary vascular congestion.

In some types of congenital heart disease there is an overlap in presentation, and infants will appear cyanotic and have signs of respiratory distress such as tachypnea and perhaps even retractions. This type of presentation, which is common with hypoplastic left heart syndrome and total obstructed anomalous pulmonary venous return, may initially be confused with

sepsis, pneumonia, meconium aspiration, or even RDS. Total anomalous pulmonary venous return (TAPVR) deserves particular mention because it cannot be detected in utero; it is often missed postnatally, even on repeated echocardiograms. In fact, this condition is the most common potentially correctable cardiac lesion for which neonates are mistakenly placed on ECMO. To diagnose TAPVR, one must keep a high index of suspicion, particularly in a term or near-term infant who has a clinical and radiographic picture of surfactant-deficient respiratory distress or group B streptococcal sepsis. If TAPVR is suspected and echocardiograms are not confirmatory, these infants must have a cardiac catheterization to make the diagnosis.

Metabolic Disorders

Several hundred inborn errors of metabolism (IEM) have been identified. Because they are a heterogeneous group, variable in presentation and relatively rare, they are frequently overlooked. Even with expanded newborn screening in many states, covering anywhere from 4 to 36 disease entities, results can be unavailable or difficult to interpret. An infant with an IEM may present with deep, labored respirations (Kussmaul breathing), if the underlying condition is associated with metabolic acidosis or increased intracranial pressure from cerebral edema. In many cases, this situation will rapidly progress to respiratory failure and apnea. Other manifestations of IEM result from either accumulation of a toxic product or deficiency of a necessary substrate. Although often present in the later course of the illness, many times these infants will not present with dysmorphic features, seizures, or vomiting. Rather, they display a pattern of worsening but nonspecific symptomatology that may not respond to routine intervention. It is important to maintain a high index of suspicion for IEMs, especially if there is no identified risk factor for respiratory distress, because a delay in diagnosis and treatment can be catastrophic.[257]

Intestinal and/or Renal Bicarbonate Wasting

Low plasma bicarbonate represents a metabolic acidosis that may present as tachypnea and respiratory distress in the neonate, although usually not in isolation. It is worth noting that metabolic acidosis with a normal anion gap may be a feature of neonatal diabetes or may be indicative of bicarbonate loss through the kidneys or intestines; gastroenteritis, renal tubular acidosis, and mineralocorticoid insufficiency are common causes.[258] Differentiating the source of the acidosis is important because bicarbonate therapy may actually be harmful depending on the underlying problem.

References are available online at http://www.expertconsult.com.

Pneumonitis and Interstitial Disease

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PEARLS

- Most pediatric pulmonary parenchymal disease occurs as the result of an infectious agent.
- Clinical evaluation for parenchymal lung disease in the pediatric patient should include a search for symptoms and signs associated with pulmonary disease, such as difficulty with feeding, exercise intolerance, chest pain, cough, tachypnea, dyspnea, cyanosis, orthopnea, clubbing of the nail beds, weight loss, and lethargy.
- Factors predisposing a child to bacterial pneumonia include having numerous siblings, having parents who smoke, preterm delivery, living in an urban environment, poor socioeconomic status, presence of an airway foreign body, impaired immune response, congenital and anatomic lung defects, abnormalities of the tracheobronchial tree, cystic fibrosis, and congestive heart failure.
- Viral agents are the leading cause of lower respiratory tract infection in infants and children.
- Three major clinical syndromes are associated with lower respiratory tract viral illness are (1) bronchitis, (2) bronchiolitis, and (3) pneumonia.
- Fungal infections are important in the differential diagnosis of pulmonary infections, particularly in children whose immunity is compromised and in healthy children who are exposed to pathogens in a particular geographic or environmental setting.
- Three forms of disease patterns in pneumocystosis are (1) childhood/adult, (2) infantile, and (3) chronic fibrosing observed in some patients infected with the human immunodeficiency virus.
- Chemical pneumonitis and/or pneumonia may be acquired by (1) aspiration, (2) inhalation, (3) ingestion, or (4) injection.
- Pulmonary hemorrhage is a potentially life-threatening event that can occur at any age. Clinical presentation varies from massive fatal hemoptysis to silent bleeding with respiratory distress and anemia.

Pneumonitis, or inflammation of the lung parenchyma, is perhaps the most common cause of life-threatening lower respiratory tract disease in pediatric patients. Although pneumonitis may result from noninfectious processes (Box 47-1), most pediatric pulmonary parenchymal disease occurs as the result of an infectious agent. Pneumonitis may involve the pleura, interstitium, and airways; pneumonia by definition must include alveolar consolidation. Whereas early parenchymal lung injury is associated with increased cellularity with minimal fibrosis, advanced disease is characterized by extensive fibrosis and destruction of gas exchange units. Physiologic changes may include the following: low lung volumes, diminished lung compliance, impaired gas exchange, and airflow limitation. This chapter addresses the principal potential causes of pediatric pulmonary parenchymal disease, including alveolar and interstitial disorders.

Pathogenesis

Regardless of the cause, pneumonitis often follows a common pathogenesis. The initial parenchymal injury can result from mechanisms that directly damage the endothelium or epithelial cells. Other agents may injure the lung indirectly by one or more of the following processes:

1. Generation of toxic radicals
2. Recruitment of inflammatory cells (e.g., neutrophils)
3. Activation of complement and/or release of chemotactic factors

If these processes go unchecked, alterations may occur in the lung parenchyma and connective tissues leading to end-stage fibrosis. This condition is characterized by severe destruction of gas exchange units and airways and the development of parenchymal cystic lesions.

Pathophysiology

Changes in lung volumes in pulmonary parenchymal disease depend primarily on the intensity of the alveolitis and stage of the disease process. Acute severe pneumonitis with an intense alveolitis is characterized by moderate to severe reduction in both vital capacity (VC) and total lung capacity. It also is associated with a reduction in pulmonary compliance. In the early stages, patients with chronic interstitial diseases involving the lung parenchyma often have normal VC and total lung capacity. Subsequent reduction in lung volumes and pulmonary compliance occurs as the disease progresses and pulmonary fibrosis ensues.[1] Expiratory flow rates usually are preserved in persons with pneumonitis involving the lung parenchyma, and major obstructive

Box 47–1 Etiology of Pediatric Interstitial Lung Disease

Infectious
- Bacteria
- Virus
- Mycoplasma
- Chlamydia
- Rickettsia
- Protozoa
- Fungus

Noninfectious
- Acute lung injury
  - Chemical agents
  - Physical agents
- Radiation
- Drugs
- Congenital lymphangiectasia
- Metabolic disorders
- Bronchopulmonary dysplasia
- Hypersensitivity pneumonitis
- Cardiovascular causes
- Collagen/vascular disorders
- Mixed connective tissue disorders
- Idiopathic pulmonary fibrosis
- Pulmonary hemorrhage syndromes
- Pulmonary hemosiderosis
- Pulmonary venoocclusive disease
- Desquamative interstitial pneumonia
- Lymphocytic infiltrative disorders
  - Lymphocytic interstitial pneumonitis
  - Familial erythrophagocytic lymphohistiocytosis
  - Angioimmunoblastic lymphadenopathy
- Sarcoidosis
- Inherited diseases
- Malignancy
  - Leukemia
  - Hodgkin disease
  - Non-Hodgkin lymphoma
- Histiocytosis X

defects, although reported, are rare. The carbon monoxide diffusing capacity, one of the earliest and most sensitive tests of parenchymal inflammation, is diminished in persons with interstitial lung disease (ILD). A reduction in the carbon monoxide diffusing capacity is not specific and may be found with other parenchymal disorders. Early in the course of parenchymal disease, resting arterial oxygen tension may be normal, but there is often mild alveolar hyperventilation with reduction in alveolar carbon dioxide tension and widening of the alveolar-arterial oxygen gradients ($P_{AO_2} - Pa_{O_2}$). With exercise, hypoxemia and an increased $P_{AO_2} - Pa_{O_2}$ become exaggerated because of ventilation/perfusion (V/Q) imbalance. V/Q mismatch is attributed to regional alterations of flow, altered parenchymal compliance, and increased obstruction to pulmonary airflow. Progressive alveolitis and subsequent derangement of gas exchange lead to deterioration of ventilatory efficiency and markedly increased work of breathing. Adequate oxygenation may become impossible even with the use of high-flow supplemental oxygen. Resting hypercapnia, pulmonary hypertension, and eventual right ventricular dysfunction with heart failure are common sequelae.[2-4]

Diagnosis

Diagnosing parenchymal lung disease in the pediatric patient may be quite challenging because of extreme variability in the presentation of disease. Clinical evaluation of the child should include a search for symptoms and signs associated with pulmonary disease, such as difficulty with feeding, exercise intolerance, chest pain, cough, tachypnea, dyspnea, cyanosis, orthopnea, clubbing of the nail beds, weight loss, and lethargy. In the child with diffuse alveolar disease, auscultative findings may be normal unless significant consolidation or small airway involvement is present. Fine crackles that may be heard throughout the chest late in inspiration are a characteristic finding of small airway disease. These rales are produced by the opening of occluded small peripheral airways.

Laboratory Diagnosis

The chest radiograph is critical in the diagnosis and management of pulmonary parenchymal disease. In children with ILD the classic radiographic features that are present in adults may be absent. Computed tomography scanning,[5-7] gallium lung scanning, and bronchoalveolar lavage (BAL)[8-10] are useful techniques in the diagnosis and management of diseases involving the lung parenchyma. Pulmonary function testing is important and usually can be performed reliably in children who are older than 4 years.[1,11]

Bacterial Pneumonitis

Bacterial infections of the lower respiratory tract continue to account for a significant number of hospital admissions. The frequency of bacteria as etiologic agents of lower respiratory tract infection varies from 10% to 50%, depending on the study population and the methods of evaluation used.[12,13] In a large study of pediatric patients with lower respiratory tract infection, an etiologic agent was identified in nearly 50% of the patients. Bacteria accounted for 10% to 15% of the causative agents identified.

Factors predisposing to bacterial pneumonia include having numerous siblings, having parents who smoke, preterm delivery, living in an urban environment, and poor socioeconomic status. Hospitalization also increases the risk of contracting bacterial pneumonia because of the clustering of ill patients in confined areas, administration of immunosuppressive therapy, and various medical and surgical interventions that enhance the opportunity for colonization and infection. Additional factors that increase susceptibility to bacterial pneumonia include the presence of an airway foreign body,[14] impaired immune response,[15-19] congenital and anatomic lung defects, abnormalities of the tracheobronchial tree, cystic fibrosis,[20] and congestive heart failure.

Definition

Bacterial pneumonia is an inflammatory process of the lungs that may involve interstitial tissue and pleura in its evolution but always progresses to alveolar consolidation.

Pathophysiology

Pneumonia occurs when pulmonary defense mechanisms are disrupted and bacteria invade the respiratory system by aspiration or hematogenous spread. In most instances pneumonia

appears to be a consequence of aspiration of a high inoculum of pathogenic bacteria. Viruses often are responsible for enhancing the susceptibility of the respiratory tract to bacterial infection. Less frequently, bacterial pneumonia may be the result of defects in host immunity because of young age, underlying immune dysfunction, or immunosuppressive therapy. Pneumonia also may occur when host defenses are mechanically disrupted because of tracheostomy or endotracheal intubation. The presence of respiratory pathogens in the terminal bronchioles and alveoli induces an outpouring of edema fluid and large numbers of leukocytes into the alveoli.[2,21] Macrophages subsequently remove cellular and bacterial debris. The infectious process may extend further within the lung segment, or it may disseminate through infected bronchial fluid to other areas of the lung. The pulmonary lymphatic system enables bacteria to reach the bloodstream or visceral pleura.

With consolidation of lung tissue, VC and lung compliance markedly decrease and intrapulmonary right-to-left shunt and V/Q mismatch occur, resulting in hypoxia. Subsequently, pulmonary hypertension may occur because of significant oxygen desaturation and hypercapnia, often leading to cardiac overload.

Clinical Features

Signs and symptoms of bacterial pneumonia vary with the individual pathogen, the age and immunologic condition of the patient, and the severity of the illness. Clinical manifestations, especially in newborns and infants, may be absent. General or nonspecific complaints include fever, chills, headache, irritability, and restlessness. Individual patients may have gastrointestinal complaints including nausea, vomiting, diarrhea, abdominal distension, or pain. Specific pulmonary signs include nasal flaring, retractions, tachypnea, dyspnea, and occasionally apnea.

Tachypnea is the most sensitive index of disease severity. The sleeping respiratory rate is often a valuable guide to diagnosis. On auscultation, diminished breath sounds are frequently noted. Fine crackles that may be heard in children and older patients are commonly absent in infants. Because of the relatively small size of the child's thorax and the thin chest wall, broad transmission of the breath sounds occurs, and the classic findings of consolidation are often obscured. Pleural inflammation may be accompanied by chest pain at the site of inflammation. This pleuritic pain may cause "splinting," which restricts chest wall movement during inspiration and reduces lung volume.

Extrapulmonary infections that may be present in some children include abscesses of the skin or soft tissue (*Staphylococcus aureus*); conjunctivitis, sinusitis, otitis media, and meningitis (*Streptococcus pneumoniae* or *Haemophilus influenzae*); and epiglottitis (*H. influenzae*).

Radiographic Features

Bacterial pneumonia typically is characterized by defined areas of consolidation with either segmental or lobar involvement. Lobar consolidation is the most characteristic, but multilobed disease is not unusual. The findings of pleural effusion, pneumatocele, or abscess are also strongly indicative of a bacterial infection. Staphylococcal pneumonia is suggested by rapid clinical and radiographic progression of disease, particularly in a young infant. Evidence of an abscess or pneumatocele further suggests a diagnosis of staphylococcal or gram-negative pneumonia such as Klebsiella. Group A streptococcal pneumonia may initially present with a diffuse interstitial pattern prior to the development of consolidation. Except for *Pseudomonas*, which may have a diffuse nodular appearance in the lower lobes, pneumonias caused by gram-negative organisms have no specific radiographic pattern. Anaerobic pulmonary infection is also associated with lung abscesses or air fluid levels.

Diagnosis

Bacterial pneumonia is suggested by fever, leukocytosis (>15,000 white blood cells), and increased band forms on the peripheral blood smear. Examination of the sputum may be helpful in establishing the diagnosis of bacterial pneumonia; however, it often is difficult to obtain a satisfactory sputum sample in pediatric patients unless transtracheal aspiration or bronchoscopy is used. Transtracheal aspiration, although useful in adolescents and adults, is associated with significant complications in infants and young children. If a sputum sample is obtained (an adequate specimen must have >25 polymorpho-nuclear cells and <25 epithelial cells per high-power field), the Gram stain should be examined for a predominant bacterial pathogen, and cultures should be performed with the appropriate antibiotic susceptibility studies. Counterimmune electrophoresis (CIE) performed on sputum specimens has proved helpful in establishing the diagnosis in both adults and children. Bacterial pneumonia is accompanied by bacteremia in a significant number of cases; hence blood cultures should be obtained prior to initiation of antibiotic therapy. Circulating antigens in *S. pneumoniae* and *H. influenzae* may be detected in the blood with CIE,[22] polymerase chain reaction (PCR),[23-25] or latex agglutination.[26,27]

If a significant pleural effusion is present, a diagnostic thoracentesis should be performed for the purposes of Gram stain and culture. Culturing pleural fluid has a relatively high yield in patients who have not received previous antibiotic therapy. If the Gram stain of pleural fluid is negative, CIE or latex agglutination should be performed because bacterial antigen may be detected in the fluid even after the initiation of antibiotics.

BAL should be considered in the management of a severely ill child in order to make a prompt diagnosis.[9,10] Making a prompt diagnosis is essential for the patient with progressive disease that has responded poorly to initial therapy or for the child with underlying immunodeficiency for whom empirical antibiotic treatment may be hazardous. In such instances, if the BAL is nondiagnostic, then lung aspiration or biopsy should be considered.[28] Material may be obtained through closed-needle biopsy, percutaneous needle aspiration, or an open lung biopsy. Positive results for such procedures in carefully selected cases identify an etiologic agent in 30% to 75% of cases, with open lung biopsy having the highest yield.[18,29]

Specific Pathogens

Group B Streptococci

Group B streptococci can cause infection in people of any age; however, these organisms are common pathogens in infants younger than 3 months.[30] Early-onset illness often is associated

with maternal fever at the time of delivery, prolonged rupture of membranes, amnionitis, prematurity, and low birth weight.

Infected neonates usually manifest clinical symptoms within the first 6 to 12 hours of life. Symptoms include fever, respiratory distress, apnea, tachypnea, and hypoxemia. By 12 to 24 hours of age, signs of cardiovascular collapse often are apparent. Frequently, the syndrome of pulmonary hypertension of the newborn is present, and pulmonary or intracranial hemorrhage may become the terminal event.

Isolation of the organism establishes the diagnosis. Cultures from blood and cerebrospinal fluids must be obtained in all instances of suspected group B streptococcal pneumonia. Rapid diagnostic techniques have been helpful in providing early diagnoses. The radiographic findings in neonates with group B streptococcal pneumonia can be either a lobar (40%) or a diffuse reticulonodular pattern with bronchograms similar to findings of respiratory distress syndrome.

Aggressive cardiovascular and ventilatory support is usually required, particularly in the early stages of the disease. Antibiotic therapy should include a combination of ampicillin or penicillin and an aminoglycoside agent.

Although in the past the mortality rate of patients with group B streptococcal pneumonia could be as high as 50% to 60%, recent studies suggest improvement with prompt initiation of therapy and even better outcomes with maternal prophylaxis.[31] Some infants experience a second episode of infection 1 to 2 weeks after discontinuation of antibiotic therapy. Infants with group B streptococcal pneumonia and meningeal involvement (30%) may demonstrate significant neurologic deficits (20% to 50%).

Streptococcus Pneumoniae

S. pneumoniae is a gram-positive diplococcus with at least 84 sera types; however, 80% of the serious infections are caused by only 12 sera types. Streptococci are a major cause of pneumonia in the United States. Victims are usually infants younger than 2 years, with a peak age between 3 and 5 months. Patients with asplenia, functional hyposplenia, or malignancy or those receiving immunosuppressive drugs are at special risk of the development of invasive disease.[32]

The radiographic finding in infants often is a patchy bronchopneumonia. Lobar consolidation is not uncommon. Penicillin is the drug of choice in the treatment of persons with streptococcal pneumonia. However, organisms relatively resistant to penicillin occur in 3% to 40% of culture-positive patients recorded in studies from different parts of the United States.[33] In such instances, pneumonias have been effectively treated with vancomycin or high-dose β-lactam cephalosporin agents such as cefuroxime, ceftriaxone, or cefotaxime. Disease resulting from penicillin-resistant pneumococci should be considered in patients who received therapy with β-lactam antibiotics.[33-35]

The heptavalent pneumococcal conjugate vaccine is recommended for all children aged 2 to 23 months. It also is recommended for certain children aged 24 to 59 months. Pneumococcal polysaccharide vaccine is recommended in addition to pneumococcal conjugate vaccine for certain high-risk groups.[36]

Haemophilus Influenzae

Haemophilus organisms are small, nonmotile, gram-negative rods that occur in both encapsulated and nonencapsulated forms. Approximately 90% to 95% of invasive disease is caused by the encapsulated sera type B. A pleural effusion or empyema is detected in nearly 40% of patients with *H. influenzae* pneumonia. There is an extremely high incidence of bacteremia in this disease. Serious complications such as epiglottitis, meningitis, and pericarditis can be diagnosed in 15% to 20% of patients. Cellulitis, anemia, and septic arthritis occur infrequently.

In a hospitalized patient, administration of the combination of ampicillin and chloramphenicol or a single cephalosporin such as cefuroxime, cefotaxime, or ceftriaxone generally is effective therapy.[33,37] The mortality rate in appropriately treated patients is generally considered less than 5% and often is related to associated meningitis, epiglottitis, or pericarditis rather than the pneumonic process itself. Hib conjugate vaccine is an important measure in reducing the incidence of *Haemophilus*-related disease and should be administered to all children.[33,38,39]

Staphylococcal Pneumonia

Primary *S. aureus* pneumonia has decreased in frequency in recent years but still accounts for approximately 25% of cases in young infants. The incidence of secondary or metastatic dissemination has increased since 1972. Patients with primary pneumonia present with fever and respiratory symptoms, whereas those with metastatic disease often present with fever, generalized toxicity, and musculoskeletal symptoms. In patients presenting with primary staphylococcal pneumonia, the disease often is preceded by an upper respiratory tract infection.[40,41] Pleural effusion or empyema develops in nearly 80% of the patients with primary staphylococcal pneumonia and is extremely common in patients with metastatic disease. It is not unusual for patients with staphylococcal pneumonia to remain bacteremic long after the initiation of appropriate antibiotic therapy.

Radiographic findings of *S. aureus* pneumonia differ according to the stage of disease. They vary from minimal changes to consolidation (most common) and are associated with pleural effusion (50% to 60%) or pneumothorax (21%). Pneumatoceles usually appear during the convalescent stage and may persist for prolonged periods in asymptomatic patients. Antibiotic therapy should be administered intravenously and include a drug that is resistant to inactivation. Strong consideration should be given to providing antibiotic coverage for methicillin-resistant *S. aureus*, which can account for 1% to 30% of isolates, depending on the prevalence in the area.[42] The duration of therapy usually is lengthier in patients with staphylococcal disease than for patients with other bacterial pneumonias and consists of 21 days or more of treatment. The mortality rate of staphylococcal pneumonia varies from 23% to 33%. An increased incidence of mortality usually is associated with younger age, inappropriate initial antimicrobial therapy, or failure to drain an empyema appropriately.

Mycoplasma Pneumonia

Mycoplasma organisms are the smallest free-living microorganisms. They lack a cell wall and are pleomorphic. Mycoplasma is an uncommon cause of pneumonia in children younger than 5 years but is the leading cause of pneumonia in school-aged children and young adults. Illness can range from a mild upper respiratory tract infection to tracheobronchitis to pneumonia. Symptoms include malaise, low-grade fevers, and headache. In 10% of children a rash develops that usually

is maculopapular. Cough, if it develops, usually occurs within a few days and may continue for 3 to 4 weeks. Initially the cough is nonproductive but then it may become productive and usually is associated with widespread rales on physical examination. Roentgenographic abnormalities vary but usually are bilateral and diffuse.[33]

Isolation of *Mycoplasma* by culture is complicated by the requirement for special enriched broth or agar media, which are not widely available; it is successful in only 40% to 90% of cases and requires 7 to 21 days. A fourfold increase in antibody titer between acute and convalescent sera is diagnostic but the time involved is lengthy, providing only a retrospective diagnosis. Complement fixation and immunofluorescent and several enzyme immunoassay antibody tests have been developed but have been of limited diagnostic value.[33] Serum cold agglutinins with titers of 1:32 or greater are present in more than 50% of patients with pneumonia by the beginning of the second week of illness. A PCR test has been developed but is not widely available. Where available, the PCR test has become an important means of diagnosing *M. pneumoniae* infections in clinical practice and allows for institution of therapy directed at the causative pathogen.[43] Treatment of upper respiratory tract infections or acute bronchitis is rarely indicated, but treatment with erythromycin or another macrolide such as azithromycin is indicated for persons with pneumonia or otitis media.

Miscellaneous Etiologic Agents

Pneumonia resulting from group A streptococcus accounts for less than 1% of all bacterial pneumonias. This disease is found in older children (median age 5 to 6 years), and nearly all patients are bacteremic and toxic at the time of diagnosis. Associated findings may include anemia, hyponatremia, and respiratory distress often accompanied by pleural effusion or empyema. Often a positive history of a preceding viral infection is noted.

Gram-Negative Bacteria

Pneumonia caused by gram-negative enteric bacteria, especially *Pseudomonas,* almost always is found in patients with underlying pulmonary disease, compromised immune status, or those receiving prolonged respiratory therapy.[44,45] Gram-negative enteric bacteria are a frequent cause of nosocomial infection in critical care units. These organisms can produce a severe necrotizing pneumonia that is associated with an increase in morbidity.[46]

Legionella Pneumophila

Pneumonia that occurs as a result of *Legionella pneumophila* has been reported infrequently in the pediatric age group.[47-50] The onset of this disease is characterized by high unremitting fever, chills, and a nonproductive cough.[48] Extrapulmonary manifestations include gastrointestinal symptoms such as diarrhea, liver involvement, and confusion. Chest radiographs typically consist of peripheral nodular infiltrates and pleural effusions. Cavitation occurs only in immunosuppressed individuals. Death in the normal host is unusual if prompt therapy with azithromycin or erythromycin is initiated.

Anaerobic Bacteria

Pneumonia resulting from anaerobic upper respiratory flora is uncommon in healthy children. When it does occur, it is frequently associated with risk factors such as underlying pulmonary disease, a central nervous system disorder (including seizures), a postanesthetic state, and aspiration of a foreign body. Lung abscess and empyema are frequent complications in persons with anaerobic bacterial pneumonias.

Complications

The mortality rate in persons with uncomplicated bacterial pneumonia is less than 1%. Death is more common in children with complicated disease or an underlying disorder. The most frequent complications of bacterial pneumonia are pleural effusion and empyema (Table 47-1). Thoracentesis should always be performed if fluid is present to facilitate an etiologic diagnosis and to establish the character of the fluid. Tube thoracostomy is indicated if a large amount of fluid is present and is producing respiratory compromise or if purulent fluid is obtained by thoracentesis. Empyema may extend locally to involve the pericardium, mediastinum, or chest wall. Evidence of empyema extension should be considered in the child who is unresponsive to antibiotic therapy.[28]

When tube thoracostomy/surgical drainage is required, it should be discontinued as soon as drainage has substantially decreased. For patients with staphylococcal empyema, streptococcal pneumonia, or *H. influenzae* empyema, 3 to 7 days of drainage usually is sufficient. Patients with empyema require prolonged antimicrobial therapy and careful follow-up.

Pneumothorax and pneumatoceles can be seen with almost any bacterial pneumonia but are especially common with staphylococcal disease.[40] Such pneumatoceles require no special therapy and usually resolve. Lung abscess is an infrequent complication of *H. influenzae* and pneumococcal pneumonia and is most often encountered with staphylococcal disease or anaerobic bacteria.

Table 47–1 Major Sequelae/Life-Threatening Complications Associated with Bacterial Infections

Complication/Sequelae	Organism
Necrotizing pneumonia	Anaerobic, GNB
Respiratory failure	GBS
Shock	GBS, SP, H. flu, GNB
Apnea	GBS
Pneumothorax	H. flu
Pneumatoceles	H. flu, anaerobic, staph, SP, GAS
Abscess (lung)	Staph, SP, anaerobic
Pleural effusion	H. flu, GAS, SP, staph
Empyema	H. flu, staph, SP
Epiglottitis	H. flu, GAS
Meningitis	H. flu, GBS, SP
Encephalopathy	*Legionella*
Pericarditis	H. flu
Bone/joint	H. flu, staph
Kidneys	Staph

GAS, Group A streptococcus; *GBS,* group B streptococcus; *GNB,* gram-negative bacteria; *H. flu, Haemophilus influenzae; SP, Streptococcus pneumoniae; Staph, Staphylococcus aureus.*

Prognosis usually is excellent even in persons with severe bacterial pneumonia complicated by empyema. Long-term follow-up of children with empyema has demonstrated remarkably few, if any, residual pulmonary function abnormalities and remarkable clearing of chest roentgenograms. In contrast to adults with empyema, children seldom require surgical procedures such as decortication. However, follow-up chest radiographs should be obtained on all patients with bacterial pneumonia to document complete resolution. Such radiographic follow-up studies probably are not indicated until at least 6 to 8 weeks following the initiation of antibiotic therapy.

Therapy

Therapy for persons with bacterial pneumonia should include appropriate intravenous antibiotic treatment directed toward the specific pathogen, if it is known (Table 47-2). Localized or compartmental complications such as empyema, lung abscess, pericarditis, or septic joints require appropriate surgical drainage and antibiotic therapy. Prevention via immunization or chemoprophylaxis has changed the incidence and epidemiology of pneumonitides significantly. Options for immunization, active or passive, and chemoprophylaxis for various etiologic agents are listed in Table 47-3.

Viral Pneumonitis

Infection is the most common cause of pulmonary interstitial disease in children, and viral agents are the leading cause of lower respiratory tract infection in infants and children. The viral agents listed in Table 47-4 account for the greatest percentage of pediatric pulmonary disease. Nearly 85% of all hospitalizations of children younger than 15 years occur during outbreaks of respiratory syncytial, parainfluenza, or influenza virus.

The diagnosis of a viral pneumonia in children is frequently based on the clinical presentation, epidemiologic setting, and exclusion of bacterial pathogens by negative cultures. A specific agent is identified in only approximately 50% of cases of presumed viral pneumonia. Pediatric viral respiratory tract infections occur most commonly during the winter, with distinct peaks during midwinter and early spring in temperate climates. Closed population groups provide for greater spread of respiratory viruses and increased recognition of viral pneumonias.

Pathophysiology

The mechanism of infection for most respiratory viruses appears to be a progressive spread from the larger airways to the alveoli. The respiratory epithelial cell is the major target of cytopathic effect. The normal ciliated columnar epithelium may become markedly dysplastic with loss of the overlying cilia.[51,52] Areas of ulceration then occur as segments of the mucosal surface desquamate into the bronchial lumen. Impaired mucociliary clearance occurs and altered stimulation of nerves mediating bronchial smooth muscle tone leads to increased airway resistance.[53] Enhanced mucus formation along with mucosal debris may lead to obstruction of the bronchioles, luminal narrowing, distal air trapping, and hyperinflation of various lung segments. In advanced disease with complete small airway obstruction, atelectasis results, causing hypoxemia as a result of intrapulmonary shunting and V/Q imbalance.

In persons with severe viral pneumonia, widespread parenchymal injury caused by a necrotizing alveolitis may occur. Alveolar round cell infiltrates occur often, with subsequent hyaline membrane formation and intraalveolar hemorrhage, which produces extensive parenchymal destruction and diminished lung compliance, decreased lung volumes, and intrapulmonary shunting.[54]

Table 47–2 Bacterial Pneumonia Therapy

Disease/Organism	Therapy
UNDETERMINED ORGANISMS	
Serious, life-threatening pneumonia, nonsuppressed host	Cefotaxime or ceftriaxone + azithromycin
	Bronchial lavage or needle aspiration of lung may be necessary to establish diagnosis
Suppressed neutropenic host	Imipenem/meropenem *or* Piperacillin or ceftazidime + aminoglycoside ± clindamycin
	Vancomycin not included in initial therapy unless high suspicion, ampho not used unless still febrile after 3 days/high suspicion. Bronchial lavage, needle/open biopsy may be necessary to establish diagnosis
Lung abscess	Clindamycin *or* Ticarcillin/clavulanate *or* Piperacillin/tazobactam
SPECIFIC ORGANISMS	
Pneumonia with Empyema	
Streptococcus pneumoniae, group A strep	
Penicillin susceptible	Cefotaxime or ceftriaxone + chest tube drainage
Penicillin resistant	Vancomycin ± rifampin + chest tube drainage
Staphylococcus	
Methicillin sensitive	Nafcillin or oxacillin + chest tube drainage
Methicillin resistant	Vancomycin ± chest tube drainage
Pneumonia without Empyema	
Haemophilus influenzae	Ampicillin or cefotaxime or ceftriaxone + chloramphenicol
Klebsiella pneumonia	Cefotaxime or ceftriaxone
Escherichia coli, Enterobacter	Aminoglycoside or cephalosporin
Legionella	Azithromycin or erythromycin ± rifampin
Pseudomonas	Aminoglycoside + anti-*Pseudomonas* penicillin *or* Aminoglycoside + ceftazidime
Mycoplasma pneumoniae	Erythromycin or azithromycin *or* Clarithromycin

Diagnosis

Although the clinical presentations of illness by respiratory viruses overlap, presumptive diagnosis of the specific etiology is based on clinical presentation, setting, and, most importantly, epidemiologic information. In the past, virus isolation or seroconversion was necessary for a definitive diagnosis. Today many respiratory viral infections can be diagnosed through the use of new techniques.

Viral specimens should be obtained as early as possible during the period of greatest viral excretion. Nasopharyngeal washings or swabs of the throat are most widely used. Cultures may be negative in up to 40% of patients during acute viral respiratory tract disease; failure to isolate a virus is not definitive evidence against the diagnosis of viral pneumonia. Serologic tests including complement fixation, hemagglutination inhibition, enzyme-linked solid-phase assays (enzyme-linked immunosorbent assays), and antibody assays have been used in the diagnosis of viral infection. Histologic evidence of infection in biopsy or postmortem specimens may be helpful, particularly when intranuclear inclusions are documented. Rapid diagnostic techniques focus on detection of the virus or its components in the sample. These new techniques include refinements in the use of immunofluorescence, enzyme immunoassay, time-resolved fluoroimmunoassay, latex agglutination assays, and use of nucleic acid hybridization methods, such as deoxyribonucleic acid (DNA) probes and PCR.[55-58]

Three major clinical syndromes are associated with lower respiratory tract viral illness:

1. Bronchitis: Acute bronchitis is a febrile illness associated with a new productive cough. Symptoms of upper respiratory tract infection may be present. Acute bronchitis can adversely affect respiratory function, particularly in patients with chronic pulmonary impairment, leading to hospitalization of persons with marginal lung function.
2. Bronchiolitis: Symptoms result from airflow obstruction caused by localized inflammation of the terminal respiratory bronchioles. The development of cough, tachypnea with intercostal retractions, fine, moist, inspiratory crackles, and expiratory wheezes are characteristic. Hypoxemia and cyanosis are often present.[59]
3. Pneumonia: Primary viral pneumonia is frequently a mild illness characterized by a mild cough and one or more segmental infiltrates on chest radiograph. Although it is usually a self-limited process, in some persons the pneumonic process may progress with extensive parenchymal injury, diffuse interstitial alveolar infiltrates, and severe hypoxemia. Bacterial superinfection is heralded by increased temperature, change in sputum, and signs of localized consolidation several days after the initial onset of symptoms.

Table 47–3 Preventive Measures

Organism	Immunization	Chemoprophylaxis
Cytomegalovirus	IVIG: prophylaxis in seronegative transplant recipients	Ganciclovir or valganciclovir
Haemophilus influenzae type b	Capsular polysaccaride vaccine *or* Conjugate vaccine	Rifampin in the face of incomplete immunization and exposure
Influenza	Inactivated virus produced in chicken embryos	Oseltamivir (A or B) *or* Amantadine/rimantadine (A)
Measels	Live virus vaccine *or* IVIG for immunocompromised patients	None
Streptococcus pneumonia	Purified capsular polysaccharide antigens of 23 pneumococcal serotypes vaccine *or* Multivalent protein conjugate vaccine	Penicillin VK for functional or anatomic aspleia until age 5 years
Pneumocystitis carinii	None	Trimethoprim-sulfamethoxazole *or* Pentamidine or dapsone
RSV	RSV-IVIG *or* Palivizumab (monoclonal antibody)	None
Group B strep	None	Intrapartum antibiotics

IVIG, Intravenous immunoglobulin; *RSV,* respiratory syncytial virus.

Table 47–4 Viral Agents Associated with Pediatric Interstitial Lung Disease

Agent	Frequency
Respiratory syncytial virus	+++++
Parainfluenza virus	++++
Adenovirus	+++
Influenza virus	+++
Cytomegalovirus	+
Enterovirus	+
Rhinovirus	+
Measles	+

Radiographic Findings

Differentiation of bacteria from viral pneumonia cannot be made solely on the radiographic appearance. Children with presumed viral pneumonia, however, may have several radiographic findings, including the following:

1. Peribronchial thickening and perihilar linear densities
2. Partial lobar or patchy involvement in multiple areas of the lung
3. Shifting regional infiltrates
4. Areas of hyperinflation and atelectasis

Hilar adenopathy is usually absent. Diffuse bilateral infiltrates similar to those reported in acute respiratory distress syndrome (ARDS) have been found in persons with severe influenza, adenovirus, and respiratory syncytial virus (RSV) pneumonias.[60] Pleural effusions can occur in both adenovirus and parainfluenza pneumonias. Pulmonary calcifications/nodules have been described in the convalescent phase of varicella and measles.

Specific Pathogens

We will review the most common viral pathogens that cause pneumonitis in children but have elected to exclude such viruses as Hantavirus that are beyond the scope of this

chapter. Please refer to more up-to-date journal articles for specific pathogens of interest (see also Chapter 102: Neuroendocrine-Immune Mediator Cooordination and Disarray in Critical Illness.).[25, 61]

Respiratory Syncytial Virus

RSV is the most common cause of bronchiolitis and pneumonia in the United States in children between the ages of 6 months and 3 years. The disease produced by RSV varies from upper respiratory tract infection to severe bronchiolitis and pneumonia with wheezing and respiratory failure.[59] Higher mortality rates and greater severity with prolonged symptoms occur in infants and children younger than 6 weeks of age and in those who have a history of prematurity, chronic lung disease, cardiopulmonary disease, congenital heart disease, pulmonary hypertension, or neuromuscular impairment and in those receiving chemotherapy or immunosuppressive therapy. [16,62-70] Signs of RSV pneumonia include wheezing, dyspnea, pulmonary infiltrates, and areas of atelectasis and hyperinflation on the chest radiograph. RSV infection may result in increased airway reactivity and airway resistance that persists for months. Significant respiratory tract shedding of virus continues for up to 21 days from the onset of illness. Nosocomial spread of RSV infection is common, and early diagnosis and appropriate isolation techniques are critical in hospitalized patients.

Methods for diagnosis of RSV include viral isolation in cell culture, immunofluorescence of exfoliated nasopharyngeal epithelial cells for detection of RSV antigens, and enzyme immunoassay for detection of RSV antigens in nasal secretions.[71,72] PCR technology is now available for diagnosis of RSV illness.

All hospitalized patients with bronchiolitis and RSV pneumonia should be monitored for hypoxia, hypercarbia, and the need for ventilatory assistance. Supportive care includes the use of humidified oxygen, secretion clearance, and hydration.[73,74] Mechanical ventilation for respiratory failure usually is well tolerated. Extracorporeal membrane oxygenation has been used successfully in infants who do not respond to conventional ventilation.[75,76] The routine administration of bronchodilators and corticosteroids is not warranted; use should be individualized based on clinical reponse.[74,77] Ribavirin, an antiviral agent, has been used to treat children with severe RSV pneumonitis, but its clinical effectiveness remains controversial.[66,78-89] Passive immunoprophylaxis has proved useful in high-risk populations in preventing RSV infection, as has palivizumab, a humanized mouse monoclonal antibody. [33,90-94] The incidence of bacterial superinfection in persons with RSV disease is low; therefore prophylactic antibiotics are not recommended for RSV disease.[63,95,96] It is not unusual for an infant with RSV to require hospitalization for 7 to 10 days following the onset of illness. Long-term complications of RSV infection may include persistent bronchial reactivity, with lower respiratory tract symptoms in more than 70% of infants in the year following hospitalization.[88] Whether moderately severe RSV infection predisposes a person to asthma later in life remains controversial.[97-101]

Parainfluenza Virus

Parainfluenza virus (types 1 and 2) is more often associated with laryngotracheobronchitis and croup than with pneumonia (usually type 3). Parainfluenza is second only to RSV as an etiology of lower respiratory tract disease responsible for the hospitalization of children.[102-107] The pneumonia associated with parainfluenza is typically mild; however, fatal cases with prolonged viral shedding have been reported in patients with severe combined immunodeficiency disease.[108-111] Conferred immunity following infection is low; repeat infection occurs in nearly 50% of patients by age 30 months, although they result in progressively milder illness. Parainfluenza virus, like RSV, has demonstrated ability to elicit an immunoglobulin IgE-specific antibody response.[104] Rapid identification of parainfluenza virus by either fluorescent and enzyme-linked immunologic techniques is possible, but results are variable depending on the viral type and antisera used. Viral culture may take up to a week. PCR methods are available for detection and differentiation, with high sensitivity and specificity. Treatment is supportive.

Adenovirus

Adenoviruses are responsible for approximately 3% of the pneumonias occurring in children. Clinical features are similar to other viral pneumonias except that the onset of illness is often gradual, occurring over several days. Of the 51 serotypes, types 3, 4, and 7 are the most common causes of lower respiratory tract disease in children. Adenovirus type 7 is most commonly associated with severe pneumonitis in infants and children and has a significant incidence of mortality and morbidity.[41,112-116] In 2007, a new strain of adenovirus 14 was isolated in previously healthy infants and young adults in the United States in whom fatal pneumonia developed.[117] A clinical presentation similar to that of bacterial pneumonia, with massive pleural effusion, rhabdomyolysis, and myoglobinuria, has been reported with adenovirus type 21.[118] In many infants with documented adenovirus respiratory tract infection, chronic pulmonary disease develops that manifests as persistent atelectasis, bronchiectasis, and recurrent pneumonitis with areas of hyperinflation and interstitial fibrosis. Bronchiectasis and restrictive lung disease have been documented in children following acute adenovirus infection. Adenovirus pneumonia is the most common cause of bronchiolitis obliterans in children, and unilateral hyperlucent lung syndrome has been reported.[119-124] Disseminated adenovirus occurs and usually is associated with infection by serotype 3, 7, or 21. It occurs most frequently in infants younger than 18 months and usually involves the heart, pericardium, liver, pancreas, kidneys, central nervous system, and skin.[125] Fatal cases of adenovirus and pneumonia can occur in previously healthy young individuals. Diagnosis is made by cell culture, and antigen and DNA detection by PCR. Adenovirus typing is available from some reference and research laboratories. Treatment is supportive.

Influenza

Three antigenically distinct influenza viruses exist—types A, B, and C. All three have hemagglutinin surface antigen, but only types A and B have neuraminidase surface antigen. Antigenic drift for types A and B produce minor changes in the surface antigens, resulting in endemic illness. Antigenic shift only occurs with influenza type A, resulting in a major change or new surface antigen, for which there may be low or no immunity in the population. Influenza type A is subtyped by its surface antigens, and currently three influenza strains are circulating world wide, including influenza A/H1N1, H1N2, and H3N2.[33,126]

Clinical signs of uncomplicated influenza pneumonia include coryzal symptoms followed by dyspnea, fever, cyanosis, cough, and wheezing. Children with influenza typically have a more sudden onset of "toxic" signs than do those with other viral diseases. Infection is associated with myalgia, encephalopathy, and cardiac involvement. Pathologically, influenza virus infection is similar to RSV in that the virus destroys ciliated respiratory epithelial cells with subsequent edema and an acute inflammatory response. Influenza has been associated with Reye syndrome and with significant bacterial suprainfections.[127] In patients in whom bacterial infection develops, there often is a period of apparent improvement before a sudden worsening that is heralded by the production of purulent sputum, return of fever, and development of pulmonary consolidation.[128] Fatal outcomes have been reported in previously healthy children as well as in high-risk groups.

Prevention of influenza disease is possible with either administration of multivalent influenza vaccine (influenza A/H1N1, A/H3N2, and B) or chemoprophylaxis with Oseltamivir and Zanamivir (influenza A, B, and A/H1N1) or amantadine hydrochloride and its closely related analogue rimantadine (influenza A). One study showed efficacy of aerosolized ribavirin in the treatment of persons with influenza B.[129,130] Diagnosis of influenza pneumonia may be made by a culture of the virus from respiratory secretions or with serologic techniques. Rapid diagnosis by means of immunofluorescence of exfoliated nasopharyngeal cells may be helpful, as well as by PCR, which may be available at some institutions. Treatment includes supportive care, monitoring of respiratory status, and administration of antiviral medications.

Measles

Measles is a highly contagious disease that is preventable by vaccine; the incidence fell below the endemic threshold in the United States in 2000.[131] Endemic outbreaks continue in developing countries and when international travelers import measles to nonimmunized persons in the United States.[33,131] Typical disease manifests as high fever, cough, runny nose, and generalized rash. Respiratory symptoms are nearly universal in this illness, making the prevalence of measles pneumonia difficult to determine. Moist crackles develop in most children, and approximately 20% have expiratory wheezes and hypoxia. In cases in which radiographs have been obtained, a fine reticular infiltrate was present, compared with the nodular infiltrates in children with atypical measles. Although the clinical syndrome usually resolves over 1 to 2 weeks, both radiographic and pulmonary function abnormalities may persist for months. Severe life-threatening tracheitis may occur during the course of measles or bacterial suprainfection.[132-134] In fatal cases, severe respiratory and nervous system disease is manifested, and lung tissue demonstrating interstitial pneumonitis with diffuse endothelial cells, pneumatocyte degeneration, and presence of multinucleated giant cells has been reported.[135]

Diagnosis is made by isolation of the virus, standard serology, or identification of viral ribonucleic acid by reverse transcription-PCR. All suspected cases should be reported to local and state health departments. No antiviral agent is available; treatment is supportive. Two doses of vitamin A (200,000 International Units) on consecutive days) has been shown to reduce pulmonary-specific and overall mortality rates in patients up to 2 years of age.[136] Administration of intravenous immunoglobulin may be of benefit to high-risk or immunosuppressed patients when it is started within 6 days of exposure.[33]

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) infection in children most commonly presents with recurrent bacterial infections. The major morbidity and mortality in pediatric acquired immune deficiency syndrome (AIDS) is associated with lung disease, ranging from opportunistic infections such as *Pneumocystis carinii* pneumonia to entities such as chronic interstitial pneumonitis.[137,138] Treatment for specific pulmonary pathogens are discussed throughout this chapter, but specific guidelines for HIV/AIDS treatment are lengthy, rapidly changing, and beyond the scope of this chapter. More specific and current information regarding HIV/AIDS are available at www.aidsinfo.nih.gov/guidelines. This Web site provides the most current information regarding HIV/AIDS clinical research, HIV treatment and prevention, and medical practice guidelines. This information also can be obtained by phone at 1-800-HIV-0440 within the United States or at 1-301-519-0459 outside the United States or by mail at AIDS Info, P.O. Box 6303, Rockville, MD 20849-6303.

Complications

The actual mechanisms by which viruses predispose the lung to secondary bacterial infection are not precisely understood. Viruses are capable of altering both cellular and noncellular defenses of the respiratory tract.[52,53,139] Viral infection of the epithelial cells appears to predispose the upper respiratory tract mucosa to bacterial colonization by allowing bacterial pathogens to adhere to injured cells.[51,52] Viral infection may cause significant impairment of both intracellular killing and ingestion of bacteria by the pulmonary macrophage. Significant defects in polymorphonuclear leukocyte chemotaxis and phagolysosome fusion occur during acute viral infection. The greatest impairment of macrophage function occurs 1 week after the onset of viral infection, which correlates with the peak incidence of bacterial suprainfection. Thus suprainfection during the course of viral lower respiratory tract disease appears to be the result of a combination of the cytopathic effects of the virus on the respiratory mucosa and various alterations in host immune response.

Significant life-threatening complications of viral lower respiratory tract disease are noted in Box 47-2. Respiratory failure with viral pneumonitis resembling ARDS is frequently seen in patients in the pediatric critical care unit. It often is associated with influenza or adenovirus but can occur with varicella, cytomegalovirus, and RSV.[60]

Diagnosis

A number of techniques are available for establishing a viral diagnosis. In the critical care setting, the decision to undertake these diagnostic measures should be guided by how awareness of the specific viral illness will affect the clinical management. Potential benefits include (1) a guide to selection of appropriate antiviral therapy and avoidance of unnecessary treatments with antibiotics and (2) initiation of appropriate infection control measures and use of vaccine or drug prophylaxis. Direct isolation of viruses is a sensitive method of diagnosis early in the course of disease when a

Box 47–2 Major Sequelae/Life-Threatening Complications Associated with Viral Pneumonitis

- Subacute sclerosing panencephalitis: measles
- Guillain-Barré syndrome: influenza, varicella
- Reye syndrome: influenza, VZV
- Encephalitis: adenovirus, measles, RSV, CMV
- Seizures: influenza
- Bacterial superinfection: influenza, VZV, Epstein-Barr virus, measles
- Asthma: RSV, parainfluenza, rhinovirus
- Apnea: RSV, influenza
- Bronchiolitis obliterans: influenza, adenovirus, measles
- Chronic obstructive pulmonary disease: RSV
- Fatal pneumonitis: influenza, measles, adenovirus, RSV, parainfluenza, CMV
- Tracheitis, life-threatening: measles, parainfluenza
- Appendicitis: adenovirus, measles
- Intussusception: adenovirus, CMV
- Hepatitis: adenovirus, influenza measles, CMV
- Nephritis: adenovirus, influenza, measles
- Myocarditis: adenovirus, influenza, measles
- Pericarditis: adenovirus, influenza, measles
- Arthritis: adenovirus
- Deafness: adenovirus
- Keratoconjunctivitis: adenovirus
- Myositis: influenza
- Stevens-Johnson syndrome: measles
- Coagulopathy: measles
- Thrombocytopenia: measles, CMV

CMV, Cytomegalovirus; *RSV,* respiratory syncytial virus; *VZV, Varicella zoster* virus.

large number of infectious particles are present in respiratory secretions. Nasopharyngeal washings are the preferred specimens for viral cultures because large quantities of secretions for culture are easily available. Unfortunately, viral isolation may require up to 2 weeks for positive culture results. Serologic testing or diagnosis depends upon demonstration of a rising antibody titer between acute and convalescent sera. Although serologic data may provide a diagnosis, they are of little value in guiding therapeutic critical care interventions. The more commonly used methods for viral diagnosis involve detection of viral antigens present in the respiratory secretions. These antigen-detection techniques using radioimmune or enzyme-linked assays can detect all riboviruses and adenoviruses that commonly produce lower respiratory tract infections. Antibody detection also has been used successfully in the diagnosis of lower respiratory tract viral disease (cytomegalovirus pneumonia).[140] A major advantage of tests capable of detecting viral components is that these studies can be performed rapidly and the results made available to the critical care physician in hours, thus allowing timely management.

Prevention and Treatment

Guidelines for influenza chemoprophylaxis and treatment are lengthy and rapidly changing. Specific and current information regarding the use of antiviral drugs is available at www.aapredbook.org/flu or www.cdc.gov/flu/professionals/antivirals/index.htm.

Vaccination

Influenza vaccine is directed at the currently circulating antigenic types of seasonal influenza A and B and influenza A/H1N1 and A/H3N2. Because of antigenic drift, it is necessary to vaccinate on a yearly basis to prevent seasonal influenza A and B. The Centers for Disease Control and Prevention recommends administration of influenza vaccine to groups at special risk for complications of influenza such as children with chronic cardiac, pulmonary, neurologic, or metabolic disorders and health care workers capable of nosocomial spread to high-risk patient groups.

Palivizumab is a monoclonal antibody vaccine directed against RSV that provides passive immunity. Current recommendations are to administer this vaccine to high-risk infants during the RSV season.[33] Passive immunization also is available for some viruses that can be associated with pneumonitis (see Table 47-3 for further details).

Chemoprophylaxis

Amantadine, rimantadine, oseltamivir, and zanamivir are approved for prophylaxis of viral respiratory tract infection caused by influenza. Amantadine and rimantadine have been shown to be effective prophylaxis for influenza type A; however, they are not active against influenza type A/H1N1 or influenza type B. Amantadine resistance has been reported in persons with influenza type A/H3N2. Oseltamivir and zanamivir have activity against influenza types A, B, and A/H1N1. Oseltamavir resistance has been reported among persons with influenza type A/H1N1 strains globally, but no significant resistance has been reported among persons with influenza type A/H1N1 strains circulating in the United States. All four drugs are recommended for persons at high risk for serious influenza infection who have not been vaccinated or who have received the vaccine within 2 weeks of the onset of an epidemic. They also are recommended for persons in whom appropriate immune response may not develop following vaccination and for persons who cannot receive the influenza vaccine because of allergic reactions.[33,141,142]

Therapy

A number of antiviral agents inhibit the replication of respiratory viruses in vitro, and some of these drugs have been used clinically in both experimental and naturally occurring respiratory infections (Table 47-5). Amantadine can be used to treat seasonal influenza A virus infections. Numerous studies have demonstrated that amantadine shortens the course of illness in uncomplicated influenza infections in otherwise healthy children if initiated within the first 48 hours of the disease. Amantadine is not effective against influenza type B or A/H1N1.[143] Rimantadine is effective against influenza type A, but it has not been approved for therapeutic use in children younger than 13 years and is not effective against influenza type B or A/H1N1. Oseltamivir and zanamivir both are effective against influenza type A, B, and A/H1N1.[144] These neuraminidase inhibitors have been shown to reduce the severity and duration of illness.[145-148] Resistance to oseltamivir has been reported in persons with influenza type A/H1N1 strains, but not A/H3N2 or B strains.[149-153] Zanamivir is effective against influenza type A, B, and A/H1N1, but it has not been approved for therapeutic use in children younger than 7 years.[33] Authorization

Table 47–5 Antiviral Agents Used in Viral Pneumonia

Agent	Indication	Route	Side Effects
Acyclovir	HSV, varicella Prophylaxis/treatment	IV, PO	Phlebitis, seizures, leukopenia, renal dysfunction
Valacyclovir renal	HSV, varicella Prophylaxis/treatment	PO	Bone marrow suppression, renal failure
Ganciclovir	CMV in immunocompromised host Prophylaxis/treatment	IV, PO	Renal failure, bone marrow suppression, seizure
Valganciclovir	CMV prophylaxis	PO	Same as ganciclovir
Amantadine	Influenza A Prophylaxis/treatment	PO	Nausea, dizziness, ataxia, diarrhea
Rimantadine	Influenza A Prophylaxis	PO	Similar to amantadine
Zanamivir	Influenza A and B Treatment, prophylaxis under study	Diskhaler	Bronchospasm
Oseltamivir	Influenza A and B Prophylaxis/treatment	PO	Nausea, vomiting, vertigo
RSV-IVIG	RSV prophylaxis (high-risk population)	IV	Allergic, fluid overload, not approved for CCHD
Palivizumab	RSV prophylaxis	IM	Anaphylaxis
Ribavirin	RSV (parainfluenza, influenza A and B, measles)	Small-particle aerosol	Conjunctival edema
Foscarnet	CMV retinitis, HSV resistant to acyclovir	IV	Renal dysfunction, nausea, bone marrow suppression
Pieconaril (under investigation)	Enterovirus and rhinovirus Prophylaxis/treatment	PO	Under investigation

CCHD, Cyanotic congenital heart disease; *CMV,* cytomegalovirus; *HSV,* herpes simplex virus; *IVIG,* intravenous immunoglobulin; *RSV,* respiratory syncytial virus.

for emergent use of intravenous Peramivir for confirmed A/H1N1 or nontypeable influenza A has been issued for pediatric patients who are not responding to current therapy, for whom the enteral or inhalation delivery route is prohibited, or who are allergic to amantadine. Peramivir is a neuraminidase inhibitor and should not be administered if the patient has a severe allergy to oseltamivir, zanamivir, or one of their metabolite components.

Ribavirin is a synthetic nucleoside analogue licensed for use in aerosol form for treatment of persons with severe RSV infection. This therapy may shorten the course of the illness and improve oxygenation in high-risk patients. A few children with severe combined immune deficiency have been treated with ribavirin with resulting clinical improvement and decrease in viral shedding. Ribavirin aerosol may be effective in shortening the course of both influenza type A and B in infections in college students, and it is possible that parainfluenza and the measles virus can be treated with ribavirin.[154] Various case reports of treatment in seriously ill adults with complicated viral infections suggest that ribavirin may be an effective treatment. Overall, the documented therapeutic benefit of antiviral agents has been inconclusive. Improvement is most apparent when the therapy was initiated early after the onset of infection. Future investigations are necessary to define the optimum dose/route of antiviral agents for each respiratory virus/pneumonia and to clarify the ability of antiviral therapy to modify serious lower respiratory tract infection in high-risk infants and children.

In persons with varicella or zoster, acyclovir reduces the period of viral shedding and the time needed to heal skin lesions, and it can prevent dissemination of localized zoster in immunocompromised children. Thus the use of acyclovir in immunosuppressed patients can be justified by the low toxicity of the drug and the potential severity of the illness. Ganciclovir (DHPG) is an antiviral drug with significant activity against cytomegalovirus.[155] It has been used successfully in immunocompromised patients with disseminated cytomegalovirus and pneumonia.[156] Symptomatic infection of the lower airway with herpes viruses is rare. When it occurs, it usually does so in an immunosuppressed child. Antiviral therapy for herpes viruses includes acyclovir, foscarnet, and adenine arabinoside.[157]

Fungal Pneumonitis

Fungal infections are becoming increasingly important in the differential diagnosis of pulmonary infections, particularly in immunocompromised hosts. The majority of pulmonary mycotic infections occur in two microbiologic and clinical groups (Box 47-3). In general, different patient groups are at risk for infection because of either opportunistic or pathogenic dimorphic pulmonary fungi. Primary pulmonary mycotic infections generally infect healthy children exposed to the pathogen in a particular geographic or environmental setting, whereas the opportunistic mycoses occur in children whose immunity is compromised.[158-160] The increase in opportunistic fungal infections can be attributed to numerous factors, including the following:

1. Selection of fungal organisms as flora by the use of broad-spectrum antibiotics
2. Leukopenia secondary to use of cytotoxic agents

Box 47–3 Major Pulmonary Mycoses

Primary (Endemic; Pathogenic to Normal Children)

Dimorphic Soil

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis
- Sporotrichosis

Nondimorphic Soil

- Cryptococcosis

Opportunistic (Ubiquitous; Abnormal Host)

- Aspergillosis
- Mucormycosis
- Candidiasis

3. Suppression of humoral and cell-mediated immunity by cytotoxic and suppressive therapy
4. Increased use of immunosuppressive drugs in patients with organ transplant or collagen vascular disease
5. An increasing number of patients with AIDS
6. An increased number of invasive surgical procedures in hospitalized children, which create portals of entry for fungi[19]

Primary Pulmonary Fungi

Fungi that cause primary pulmonary infection in otherwise healthy hosts are generally endemic mycoses found in a particular geographic distribution. The four major mycoses in this group are histoplasmosis, blastomycosis, coccidiomycosis, and paracoccidiomycosis.[15,161] Chemiluminescent DNA probes are available for identification of blastomycosis, coccidioidomycosis, and histoplasmosis. We review these primary pulmonary mycoses in the following section but exclude paracoccidiomycosis because this infection occurs primarily in South America, Central America, and Mexico. For information regarding paracoccidiomycosis infections, please refer to up-to-date journal articles.[162]

Pathogenesis

The dimorphic fungi cause infection following inhalation of spores (conidia) into the pulmonary system. In the lower respiratory tract the conidia transform into the yeast phase, which is susceptible to phagocytosis by the pulmonary macrophages. These yeast forms may persist in the nonimmune host. As the yeast-laden macrophages are transported via the lymphatics to the peribronchial and mediastinal lymph nodes, hematogenous dissemination may occur. However, with the primary pulmonary infection in the immunocompetent host, extrapulmonary infection is rare.

Progressive primary pulmonary infection in the absence of host defenses (such as in a patient who is immunocompromised or an infant) may lead to seeding of extrapulmonary sites, dissemination, and death if left untreated. Cellular immunity is the primary host defense against these deep mycoses, many of which are subclinical and require no therapy. However, children with severe life-threatening infections should be treated (Table 47-6).

Histoplasmosis

Histoplasmosis is caused by *Histoplasma capsulatum*, which is endemic in the east-central United States, particularly the Mississippi and Ohio River valleys. Primary pulmonary histoplasmosis is asymptomatic in more than 50% of patients. Patients usually become ill 2 weeks following exposure, manifesting influenza-like illness with fever, chills, myalgia, headache, and a nonproductive cough. Occasionally children have a skin rash, arthritis, and erythema nodosum.

The chest radiograph may show patchy areas of pneumonitis and prominent hilar adenopathy. After exposure to an usually heavy inoculum, a more diffuse pulmonary involvement may occur with extensive nodular infiltrates. Children with this condition frequently have significant dyspnea and may progress to respiratory failure. The chest radiograph frequently returns to normal after a primary pulmonary infection; however, a number of residual abnormalities may be seen, including multiple nodules with a dense core of calcium (a target lesion), scattered calcifications within lymph nodes, and occasionally small "buckshot" calcifications scattered throughout both lung fields.[163]

Diagnosis

The skin test is of epidemiologic value but is useless in individual case diagnosis because a positive test only indicates prior exposure to this disease. Neither are direct smears of the sputum helpful for diagnosis. Most cases are recognized by serologic studies and include immunodiffusion (M and H bands) and complement fixation. Unfortunately, the immune diffusion test is relatively insensitive, and a response may be delayed following a primary infection. The complement fixation test is more sensitive but less specific.[164] A titer of 1:32 or higher against the yeast antigen is diagnostic if the clinical picture suggests histoplasmosis. Children with rapidly progressive pneumonia that is not responding to antibacterial antibiotic therapy or those in impending respiratory failure need urgent diagnosis, and invasive procedures such as bronchoalveolar lavage (BAL), diagnostic lung aspiration, or open lung biopsy are necessary to obtain the required information.

Complications

Disseminated histoplasmosis refers to progressive extrapulmonary infection that occurs most frequently in children younger than 2 years and in patients with altered cellular immunity.[17,165] The clinical features of disseminated disease include fever, weight loss, hepatosplenomegaly, cough, diarrhea, gastrointestinal ulcers, and skin lesions. Anemia, leukopenia, and thrombocytopenia may occur as a result of bone marrow involvement in young children and may lead to rapid death. Chronic disseminated disease, which is uncommon and insidious, may present as a nonspecific afebrile illness without cough or radiographic abnormalities. Occasionally, disseminated histoplasmosis presents as a localized infection involving the central nervous system. Chorioretinitis and pleural effusion, along with isolated gastrointestinal findings involving terminal ileum, can occur.

Treatment

The usual primary pulmonary infection requires no treatment. Amphotericin B should be used for persons with a severe infection, especially if it is life-threatening or associated with

Table 47–6 **Antifungal Therapy**

Drug	Indications	Route	Side Effects
AmB	All life-threatening mycoses, empirical therapy in febrile granulocytopenic patients	IV	Fever, chills, nephrotoxicity, anemia, hypokalemia, thrombophlebitis
AmB lipid complex, AmB cholesteryl sulfate, AmB liposomal	Failure or intolerance to AmB, organ transplantation with renal insufficiency	IV	Same as AmB with decreased nephrotoxicity and infusion-related adverse events
Flucytosine (5-FC)	With AmB for life-threatening infections with *Cryptococcus, Candida* (central nervous system, ophthalmitis, disseminated, renal) or invasive disease refractory to AmB	PO	Neutropenia with elevated serum levels (if levels are not available, this agent should not be used)
Ketoconazole	Not indicated for acute treatment of severe invasive disease; alternative for mild blastomycosis, histoplasmosis, *Candida*, or coccidiomycosis	PO	Nausea, vomiting, hepatotoxicity, testosterone synthesis blockade
Miconazole	Deep infection: *Pseudallescheria* and *Scedosporium*	IV	Cardiac dysrhythmias, cardiovascular collapse with rapid infusion
Fluconazole	*Cryptococcus, Candida* (question in critically ill), coccidiomycosis	PO	Nausea, vomiting, dizziness
Itraconazole	Non–life-threatening blastomycosis, sporotrichosis, histoplasmosis, paracoccidioidomycosis	PO	Pediatric dosage not yet established; nausea, hypokalemia, edema, hypertension, adrenal insufficiency, epigastric pain
Voriconazole	*Apergillus* and *Cryptococcus,* resistant *Candida* spp.	IV	Visual changes, fever, nausea, vomiting, elevated liver enzymes
Caspofungin	Treatment for resistant *Aspergillus* and possible combination therapy for *Candida* and endemic mycoses	IV	Fever, phlebitis, nausea, headache, elevated liver enzymes

AmB, Amphotericin B.

respiratory failure. Upon clinical improvement, itraconazole should be given to complete the course of therapy. Chronic cavitary histoplasmosis can be treated with intravenous amphotericin B or a long-term course of oral itraconazole or ketoconazole. Pericarditis therapy should include antiinflammatory agents such as indomethacin or aspirin. Failure of pericarditis to improve with nonsteroidal antiinflammatory medication should not prevent use of a brief course of steroids because steroid use does not appear to predispose to dissemination.[166-168]

Blastomycosis

Blastomycosis is endemic to the southeastern region of the United States but extends northward along the western shores of Lake Michigan across to northern Wisconsin and Minnesota and into Canada. An intimate exposure to an infected site is required for infection rather than the casual exposure often found with histoplasmosis and coccidioidomycosis.[169-171] Most pediatric cases of blastomycosis occur in older children and adolescents in rural areas.

The pathophysiology is similar to that of histoplasmosis. The clinical course of primary pulmonary blastomycosis is variable. The symptoms are similar to those of acute bacterial pneumonia and include high fever, cough with productive purulent sputum, occasional pleuritic chest pain, and myalgias. Such symptoms generally last 2 to 3 weeks.

The chest radiograph frequently demonstrates patchy areas of alveolar consolidation affecting one or both lower lobes. Pleural effusions and cavitation can occur but are unusual. A rather dense lobar infiltrate similar to pneumococcal pneumonia is uncommon but occurs more frequently in pulmonary blastomycosis than with other pulmonary fungi. Clearing of the chest x-ray film may take 3 to 4 months.

Blastomycosis is not always self-limited, and progressive pulmonary infection can occur with acute dissemination to distant sites. In such instances the child remains febrile and toxic with rather rapid progression. Diffuse pulmonary involvement with acute miliary spread can lead to rapid respiratory failure and radiographic findings of ARDS.

Children may have asymptomatic primary pulmonary blastomycosis that is diagnosed only with reactivation blastomycosis involving the skin, bones, or other distant organ sites. Reactivation blastomycosis appears to be most common in the first 1 or 2 years immediately after the initial pulmonary infection and probably occurs in less than 5% of all infected patients. A chronic form of pulmonary blastomycosis may occur in patients who have no significant history of acute pneumonia but present with respiratory symptoms that have persisted for weeks or months. These persons have a chronic cough, productive sputum, nocturnal fevers, night sweats, weight loss, and dyspnea. Chest radiographs in persons with chronic blastomycosis may reveal a single large mass, often perihilar in location. A more common finding is a fibronodular infiltrate with small cavities and fibrosis radiating toward the hila. Such findings mimic tuberculosis.

Diagnosis

No reliable skin test exists for pulmonary blastomycosis. Sputum and material aspirated from BAL, lung aspiration, skin, or bone lesions may be examined directly after potassium

hydroxide digestion, and the pathognomonic yeast forms are identified. Such positive direct smears provide a rapid, accurate, inexpensive test. Serologic tests include immunodiffusion using purified antigen. The complement fixation test is less sensitive and less specific than the immunodiffusion test.[172] Most acute cases are diagnosed by direct sputum smears or from BAL. Needle aspiration under fluoroscopy usually is diagnostic in a child who is severely ill; a lung biopsy (either needle biopsy or open lung biopsy) and histopathology are necessary in some instances.

Complications

Patients whose illnesses are clinically similar to bacterial pneumonia frequently have a self-limited process. Life-threatening progressive respiratory failure similar to ARDS can occur. In such instances, diagnosis and therapy including mechanical ventilation must be initiated promptly. Dissemination occurs only in the most severe cases.[173,174] With dissemination, characteristic skin lesions (i.e., raised and crusted) may occur on the face and upper extremities. In persons with disseminated disease, bone involvement often includes the spine, ribs, and skull. The prostate, epididymis, or testes may be involved.

Treatment

Acute pulmonary blastomycosis does not require treatment in all cases. Treatment with intravenous amphotericin should be given if the patient is severely ill or if progressive illness occurs. Oral itraconazole and ketoconazole have been used for treatment of chronic pulmonary blastomycosis (similar to tuberculosis) but should not be used for severe life-threatening infections.[175,176]

Coccidioidomycosis

Coccidioidomycosis is a relatively common infection that occurs primarily in the southwestern United States. Sixty percent of patients with primary pulmonary infection have no symptoms or minimal symptoms. The pathogenesis is similar to that of histoplasmosis and other dimorphic fungi infections. Children 5 years or younger have a higher frequency of progressive disease than do older children and healthy adults. The clinical course of coccidioidomycosis is a flulike illness usually associated with fever, cough, and chest pain. There may be a transient maculopapular eruption similar to erythema nodosum in children. Radiographic abnormalities range from hilar adenopathy to patchy infiltrates with pleural effusion.

Diagnosis

Diagnostic studies include skin testing, which has some usefulness if the patient has compatible respiratory illness and a past negative skin test. Direct smears of potassium hydroxide-digested sputum are helpful if characteristic spherules are found. Antibody detection through complement fixation may be a useful measure of severity of disease.[172] In cases of suspected coccidioidal meningitis, complement fixation tests on cerebrospinal fluid should be obtained because many patients have a negative spinal fluid culture with positive complement fixation studies. Use of chemiluminescent DNA probes may aid in rapid diagnosis.

Complications

Complications include chronic progressive coccidioidal pneumonia, which is similar to tuberculosis but is uncommon in pediatric patients. Disseminated coccidioidomycosis does occur and is often accompanied by persistent fever and rapid progression with development of meningitis, bony lesions, and skin and soft tissue disease. A fulminant primary miliary spread of disease with severe respiratory failure and diffuse lung involvement has been observed in patients with altered immune status. The disseminated disease frequently has an insidious onset, following the primary pulmonary infection by weeks. The meninges are the most worrisome site of extrapulmonary involvement because coccidioidal meningitis requires intrathecal amphotericin B therapy, and cure is unlikely.[174,177-181]

Treatment

If the infection causes prolonged fever, progressive pulmonary disease, significant mediastinal adenopathy, or disseminated lesions, antifungal therapy with amphotericin B should be initiated. Ketoconazole has been used in skeletal, cutaneous, and other localized infection but not for meningitis. Coccidiomeningitis is the most difficult complication of this disease to treat; it requires intrathecal and systemic therapy with amphotericin B.

Opportunistic Pulmonary Mycoses

Pulmonary Aspergillosis

Invasive pulmonary aspergillosis occurs almost exclusively in immunocompromised patients.[15,182-185] Despite treatment, unless the underlying immune defect is ameliorated, invasive pulmonary aspergillosis is often fatal. Many cases are nosocomially acquired, usually in hospitals undergoing renovation or new construction.[171] Children with hematologic malignancies (e.g., myelogenous and lymphocytic leukemia) or organ transplantation are at the highest risk for development of invasive disease, presumably because of the abnormal immune cells and the cyclic neutropenia induced by repeated doses of chemotherapy. Persons with cheart and bone marrow transplants are at higher risk for aspergillosis infection than are persons with kidney transplants.

Neutropenia is an important risk factor for the development of aspergillosis because both the absolute neutrophil count and the duration of neutropenia have been related to the incidence of infection. Use of steroids and immunosuppressive drugs also appears to predispose to invasive aspergillosis.[186] Immune and myelosuppressed patients exposed to heavy aerosol concentrations of aspergillosis spores have an increased chance of the development of invasive pneumonia. Efforts should be made to eliminate the risk of airborne conidiospores in patient areas. If such elimination is not possible, then susceptible patients should be moved away from areas of excavation or construction.

Clinical signs of invasive aspergillosis are nonspecific. The usual presentation includes pulmonary infiltrates and fever that do not respond to empirical antibacterial therapy. Patients may exhibit dyspnea, a nonproductive cough, pleuritic chest pain, and pleural friction rubs. Symptoms usually are difficult to identify in small children, and auscultatory changes usually are found only with advanced disease. Hemoptysis is uncommon in children.

Diagnosis

Radiographs of the chest reveal virtually any infiltrative pattern, including patchy infiltrates, necrotizing pneumonitis, miliary nodules, and lung abscesses. Early findings may include

a round, patchy pneumonia that progresses to a wedge-shaped density characteristic of pulmonary infarctions.[187] Definitive diagnosis of invasive pulmonary aspergillosis requires histopathologic identification of fungus in tissue specimens.[188] Positive sputum cultures do not prove the presence of invasive disease even in compromised hosts, although isolation should be taken seriously and multiple positive cultures should be considered strong evidence of fungal infection in patients whose immunity is compromised. Serologic antibody tests have no value in the diagnosis of invasive aspergillosis. In severely ill children, fiberoptic bronchoscopy with bronchial lavage is the initial diagnostic test of choice in patients with suspected pneumonitis. If the results of fiberoptic bronchoscopy are nondiagnostic, a lung biopsy (open or needle) may be required.

Complications

Untreated invasive pulmonary aspergillosis usually is fatal in immunocompromised patients. Fatality rates greater than 80% are reported; however, survival may improve if appropriate therapy is initiated early in the disease. Death usually results from progressive pneumonitis, pulmonary infarction, and massive hemoptysis. On rare occasions, endocarditis, osteomyelitis, meningitis, or infection of the eye or orbit occurs.

Treatment

Therapy with amphotericin B should be initiated early in the course of the disease. Surgical resection usually is not indicated in the treatment of critically ill patients with uncontrolled disease. However, it may be considered in patients who have only partial response to antifungal therapy or with relapsing disease in a well-defined lung segment or in those identified with massive hemoptysis. In critically ill patients who are unresponsive to therapy or in whom aspergillosis develops while they are receiving amphotericin B, the addition of flucytosine or rifampin may be helpful.[189] Use of the lipid formulations of amphotericin is indicated in patients who are intolerant of or refractory to conventional amphotericin for reasons such as renal toxicity or persistent infusion-related adverse events.[190] Itraconazole is an option for use after an initial course of amphotericin B.[191] Change from amphotericin to the oral itraconazole must take into account the patient's status. New antifungal agents such as voriconazole have shown in vitro activity against aspergillus and are in phase II or III trials.[192,193]

Pulmonary Candidiasis

Of all the opportunistic pulmonary mycoses, candidiasis may be the most difficult to diagnosis and treat effectively because the *Candida* organism routinely colonizes the upper respiratory tract, resulting in positive cultures without significant disease. The prevalence of *Candida pneumonitis* has increased remarkably in the past 3 decades as a result of the increased use of broad-spectrum antibiotic therapy, immunosuppressive drugs, indwelling vascular lines, prosthetic devices, and organ transplantation.

Pathogenesis

Pulmonary candidiasis may occur by hematogenous seeding of the lung parenchyma from a distal infected site or through direct invasion of inhaled or aspirated organisms. *Candida* acquired through the hematogenous route demonstrates pulmonary lesions that are diffuse, bilateral, and miliary. The endobronchial form of infection does not have a significant interstitial component such as that seen with a hematogenous form. The endobronchial form radiographically demonstrates pulmonary lesions that are small, asymmetrical, patchy, and frequently found in the lower lobes.

Diagnosis

There are no pathognomonic signs and symptoms of pulmonary candidiasis. The diagnosis should be considered in an immunocompromised febrile patient with a pulmonary lesion, particularly if broad-spectrum antibiotics were used without a response. Oral pharyngeal involvement (thrush) indicates that the patient is harboring the organism in an invasive stage. Retinal lesions on ophthalmoscopic examination may help identify invasive *Candida*. A cutaneous lesion often seen in persons with invasive *Candida* is a discrete erythematous papule with an erythematous halo. The radiographic findings of *Candida* pneumonia are nonspecific. Early in the course of infection, patients have normal chest radiographs. The isolation of *Candida* in culture from an otherwise sterile body fluid or tissue and the identification of the organism in a biopsy specimen are diagnostic of invasive *Candida*. Serologic studies are of no diagnostic value. Tests for antibody, antigen, and metabolite detection remain investigational at this time. Proof of *Candida* pneumonia requires tissue examination or evaluation of alveolar lavage or protected brush samples from bronchoscopy as direct evidence of tissue invasion. If these studies fail to identify the disease process, the diagnosis of pulmonary candidiasis may be established with a lung biopsy.

Complications

As with other mycoses, pulmonary candidiasis may be complicated by systemic dissemination affecting other organs. Concomitant infection with other organisms, particularly bacteria, is not uncommon.

Treatment

Effective treatment includes correction of the patient's immunosuppression in addition to administration of amphotericin B. The concomitant and synergistic effect of flucytosine has been demonstrated with amphotericin B for most *Candida* species and is recommended for use in critically ill patients.

Pneumocystis Carinii Pneumonia

Pneumocystis carinii, which probably is a protozoan, produces a unique infection. In the early stages of the infection with cysts, trophozoites are found distributed within the alveoli, most commonly adjacent to the alveolar septum. Usually in this phase no clinical signs or symptoms are evident. With extension of infection, the number of organisms increases and bilateral diffuse distribution occurs throughout the lungs. Eventually desquamation of the alveolar septal cells occurs, with subsequent phagocytosis of the organisms by the alveolar macrophages. Minimal inflammation occurs in discrete areas of the alveolar septum at this stage of the disease, and a child may or may not be symptomatic. Ultimately the alveolar septum becomes thickened with inflammatory cells producing the clinical manifestations of childhood pneumocystosis.[194] In the infantile form there is extensive involvement of alveolar septa

with plasma cell and lymphocyte infiltration. The normal septal thickness may be increased 5 to 20 times, which results in occupation of much of the alveolus by the distended septum.

Clinical Features

The three forms of disease patterns in pneumocystosis are the childhood/adult form, the infantile form, and a more chronic fibrosing form observed in some HIV-infected patients.[195] The typical child/adult type of pneumocystosis occurs in children beyond infancy who have congenital or acquired immunodeficiency disorders or malignancies and in organ transplant recipients.[196-198] Clinical symptoms of pneumonitis include fever, cough, tachypnea, cyanosis, flaring of the nasal ala, and retractions. Chest auscultation usually reveals no adventitious sounds until the terminal stage of infection, at which time bilateral crackles may be present. The chest roentgenogram initially may be normal and changes may be seen only late in the course of the disease.[199]

In the infantile form of pneumocystosis, symptoms often begin insidiously, and presentations include poor feeding, failure to thrive, and diarrhea. Increasing tachypnea may be detected, with respiratory rates frequently in the range of 80 to 120 breaths per minute. A dry, nonproductive cough with increased retractions and flaring of the nasal alae becomes prominent. Diffuse crackles may be heard bilaterally on auscultation of the chest, and most infants remain afebrile. The clinical course in neonates and infants may be quite rapid, with progressive cyanosis and death resulting from respiratory failure within days. More commonly, however, the course extends over a period of several weeks, with a mortality rate varying from 20% to 50% without treatment.[198,200]

The chronic fibrosing type of *Pneumocystis* pneumonia identified in patients with HIV is associated with the presence of long-standing symptoms, localized radiologic changes, and interstitial fibrosis.[195]

Diagnosis

A definitive diagnosis requires documentation of *P. carinii* in lung tissue. The standard surgical open lung biopsy provides histologic details; however, the necessity for general anesthesia presents additional risk, particularly in the critically ill child. Identification of the organism in sputum is sufficient for the diagnosis, but inducing and obtaining sputum in young children often are difficult; in such cases bronchoscopy should be considered.[201] Fiberoptic bronchoscopy with BAL, although not achieving yields as high as open lung biopsy, offers a useful and safe alternative to open lung biopsy.[9,10,29] Transthoracic percutaneous needle aspirate and thoracoscopy have been used successfully and can be obtained without the use of a general anesthetic.[202,203] However, pneumothorax can be expected in up to 30% of children. Once a specimen is obtained, it can be stained with one of the array of preparations by which the organism can be confidently identified. Molecular techniques have been developed for detection of the organism based on PCR techniques amplifying *P. carinii* DNA and have been shown to be sensitive and specific detection methods. PCR assays can be applied to BAL samples, sputum, and nasopharyngeal aspirates with success.[204] Serum lactate dehydrogenase usually is elevated in patients with *P. carinii* pneumonia and appears to be related to the degree of lung injury.[205] The chest radiograph often may be normal early in the course of *P. carinii* pneumonia. However, as the disease progresses, the pattern demonstrates a diffuse bilateral alveolar disease process with hyperinflation and eventually development of air bronchograms. The bilateral densities frequently are more intense in the middle and lower lung fields. Only late in the course of disease do the upper lung fields become involved. Atypical lesions have been reported, including pneumonitis limited to lobar areas. Pneumatoceles and pleural effusions have been reported.[206]

Complications

P. carinii usually remains localized to the lungs, even with extensive disease. A disseminated form has been documented, with recovery of the organism from extrapulmonary sites including bone marrow, liver, and spleen. Life-threatening complications that can arise in patients with *P. carinii* pneumonitis include pneumothorax and pneumomediastinum. Pneumothorax, both spontaneous and iatrogenic, occurs frequently in patients with *P. carinii* pneumonitis. Some evidence indicates that upper lobe predominance of pneumothorax may be more frequent in those previously treated with inhaled pentamidine. Pneumomediastinum, with associated respiratory failure, may be noted in patients receiving assisted ventilation.

Treatment

Therapy for *P. carinii* should include specific anti-*Pneumocystis* chemotherapy, inhibition of the pulmonary inflammatory response, and enhancement of the immunologic status of the patient.[207-212] Several drugs have been used for treatment of pneumocystosis (Table 47-7).

Trimethoprim-sulfamethoxazole may be administered either orally or intravenously and is the drug of choice for treatment of this disease.[3,180] The second most widely used drug for treatment of *P. carinii* pneumonitis is pentamidine isethionate.[211,213] Its effectiveness has been well documented over several years, but it has an increased number of undesirable adverse effects and treatment failures compared with trimethoprim-sulfamethoxazole.[197] Administration of a

Table 47–7 *Pneumocystis Carinii* Pneumonitis Therapy

Drug	Route	Duration of Therapy (Days)	Comments
TMP-SMX	IV/PO	21	DOC
Pentamidine isethionate	IV	21	DOC
TMP dapsone	PO	21	Alternative
Trimetrexate folinic acid	IV	21	Alternative
Clindamycin primaquine	PO	21	Alternative
Atovaquone	PO	21	Alternative
Prednisone	IV/PO	21	Adjunctive agent

DOC, drug of choice; *IV,* intravenous; *PO,* by mouth; *TMP-SMX,* trimethoprim-sulfamethoxazole.

corticosteroid such as prednisone should occur at the initiation of specific anti-*Pneumocystis* therapy to improve survival and attenuate or prevent the initial decline in oxygenation. In addition to the specific therapies, efforts should be made to reverse the immune dysfunction that allowed occurrence of *P. carinii*, that is, reduce or discontinue immunosuppressive medications.

Chemical Pneumonitis

A large number of chemical and physical agents may produce intense inflammation of the lower respiratory tract in children. Chemical pneumonitis and/or pneumonia may be acquired in several different ways, such as by aspiration, inhalation, ingestion, or injection.

Aspiration Pneumonia

Aspiration pneumonia is composed of a diverse group of disorders that have in common the soiling of the lower respiratory tract by foreign, nongaseous substances. For purposes of this chapter, neither the solid foreign body nor the infectious component of aspiration is discussed.

Gastroesophageal reflux (GER) has been defined as the retrograde passage of stomach contents into the esophagus. This condition may be asymptomatic or it may be associated with significant regurgitation and vomiting, esophagitis, failure to thrive, and anemia.[214] Aspiration into the pulmonary tree can cause significant complications including apnea, pulmonary fibrosis, severe necrotizing pneumonias, recurrent bronchospasm, and death. Diminished lower esophageal sphincter pressure is often the result of physiologic immaturity; hence GER is more frequent in younger infants. This disorder also occurs in older children, especially those with central nervous and neuromuscular dysfunction. Other high-risk pediatric populations include patients with congenital abnormalities of the tracheal-bronchial tree and those with severe chronic pulmonary disease (Box 47-4).

Box 47–4 Pulmonary Aspiration and Gastroesophageal Reflux: Associated Disorders

Associated Disorders
- Bronchopulmonary dysplasia
- Asthma
- Cystic fibrosis
- Infantile apnea

Central Nervous System
- Convulsive disorders
- Anoxic encephalopathy
- Neurologic impairment
- Myopathies

Congenital Malformations
- Tracheoesophageal fistula
- Hiatal hernia

General
- Failure to thrive
- Achalasia
- Cardiopulmonary resuscitation
- Emergency surgery

Pathophysiology

The association of GER and lung disease has been well documented; however, the actual cause and effect of the relationship has not been firmly established. Massive aspiration of gastric fluid produces direct injury to the mucosal surface of the respiratory tract, resulting in diffuse alveolar damage, hemorrhage, and necrotizing bronchiolitis. This may be followed by a rapid interstitial reaction resulting in an acute inflammatory polymorphonuclear cell infiltration involving the interalveolar septa. Bronchiolitis obliterans and fibrosis can occur. In severe instances the initial onset of disease closely resembles that of ARDS with similar outcomes. Repeated aspiration of small amounts of gastric contents may lead to recurrent pneumonia, airway hyperreactivity, bronchitis, and bronchiectasis with eventual fibrosis and involvement of the pulmonary interstitium.

Clinical Findings

Clinical symptoms of GER vary with age.[214,215] In older children, heartburn, acid/bitter taste, retrosternal pain, or abdominal pain may be reported. Infants may be irritable and exhibit stridor, poor sleeping patterns, or intermittent apnea. Esophagitis can lead to microcytic anemia because of repeated episodes of gastrointestinal blood loss. Chronic respiratory symptoms may include coughing, wheezing with choking episodes occasionally resulting in apnea, or life-threatening events similar to those seen in infants with sudden infant death syndrome. In the hospitalized pediatric patient, significant aspirations may occur during or after general anesthesia. Severe aspiration may be seen in patients receiving tube feedings as a result of displacement of the feeding catheter.

Findings on a chest radiograph may vary from slight hyperinflation to a pattern of diffuse interstitial and alveolar densities. In mild cases a picture of bilateral diffuse infiltrates compatible with ARDS may be seen. Although a barium esophagogram can help to evaluate esophageal motility and detect esophagitis, it reflects only a single point in time. Therefore a negative study does not rule out the presence of GER. Radionuclide scans permit observation of esophageal function following administration of a radioactive tracer. Thus the frequency and severity of reflux and information on esophageal and gastric dysmotility may be obtained. If delayed aspiration occurs, the radionuclide may be observed in the lung fields on a delayed scan.[216] Esophageal motility and intraluminal pressures may be measured by esophageal manometry. Intraesophageal pH measurement is helpful in that it allows long-term monitoring of acid reflux by detecting frequency, duration, and intensity of reflux.[217,218] Esophagoscopy also is useful for assessing the extent of mucosal injury by allowing direct visualization and obtaining a mucosal biopsy. Use of BAL for assessment of lipid-laden macrophages has been useful in establishing or corroborating the diagnosis of aspiration in complex patients.[217,218]

Treatment

Treatment of patients with GER frequently includes placing the patient in an upright prone position and using thickened feedings. Use of antacid preparations, omeprazole, cimetidine, ranitidine, and other inhibitors of H_2 gastroreceptors may be helpful in decreasing acid production and neutralizing its effects on the esophageal mucosa. Omeprazole has on rare

occasions been associated with electrolyte disturbances. It also has been reported to possibly result in atrophic gastritis with prolonged use, but its use continues to increase despite these possible adverse effects.[219-223] Metoclopramide is used prior to meals to help improve lower esophageal function and aid gastric emptying. With the suspension of cisapride from the marketplace as an effective prokinetic agent because of potentially fatal toxicity, interest in erythromycin as a prokinetic agent has resurfaced, and many trials evaluating its dose and efficacy are under way.[224] Bronchodilators are used frequently to treat bronchospasm associated with GER. Because theophylline decreases the lower esophageal sphincter pressure, therefore aerosolized β_2 agonists are preferred. In instances where medical therapy was attempted and failed or in life-threatening situations, antireflux surgery is indicated. In such instances a fundoplication, partial plication, or percutaneous gastrojejunostomy is the appropriate treatment of choice.[214,215] The most favorable outcome and lowest incidence of morbidity in such instances are achieved when surgery is delayed until the patient is adequately nourished and optimal pulmonary status has been obtained.

Inhalation Injury

Acute inhalation injuries are a leading cause of fatalities in pediatric patients. Smoke inhalation accounts for the largest number of pediatric lives lost to inhalation injury each year. A significant number of inhalation injuries as a result of irritant gases occur through industrial or household accidents.[225] Serious pulmonary inhalation injury may be manifested immediately or delayed in onset (Table 47-8).[226-228]

Pathogenesis

Direct injury to the mucosal surface is the most common mode of pulmonary injury. Inhalation of noxious substances may cause extensive physical damage to the lungs and seriously impair subsequent gas exchange. The epithelial cells of air passages may become necrotic and desquamate, causing marked airway obstruction. Bronchospasm caused by irritation from the inhaled gases or particles may lead to further airway obstruction. Severe damage to the basement membrane may occur and cause subsequent leakage of intravascular fluid and blood into the alveolar and interstitial spaces. Injury may occur at all levels of the respiratory tract, depending on the physical and chemical properties of the irritant, the agent concentration, duration of exposure, and breathing pattern of the person exposed.[226,229,230] The clinical course usually has three phases: (1) the acute phase, which occurs within minutes or hours of the insult, resulting in pulmonary edema, hypoxemia, and respiratory failure; (2) the delayed phase, which occurs within the first few days and may include continuing effects of the lung injury such as pulmonary edema, airway obstruction, and superinfection; and (3) the phase in which long-term sequelae may be noted because of the hypoxic or ischemic injury to other organ systems and recurrent pulmonary problems resulting from reactive airways disease or interstitial fibrosis.

Table 47–8 Irritant Gases

Agent	Exposure/Environment
DIRECT MUCOSAL INJURY	
Acrolein	Plastic, rubber, textiles
Ammonia	Fertilizer, refrigerants, explosives
Chlorine	Bleaching, disinfectant
Formaldehyde	Disinfectant, paper, photography
Hydrogen chloride	Refining, dye making
Hydrogen fluoride	Etching, petroleum
Nitrogen dioxide	Welding, fertilizer, farming
Phosgene	Insecticide, dyes, chemicals
Sulfur dioxide	Bleaching, refrigeration
ASPHYXIATION INJURY	
Carbon dioxide	Mining, foundry
Carbon monoxide	Smoke, foundry, mining
Natural gas	Mining, petroleum

Clinical Findings

Clinical manifestations are nonspecific for inhalation of various irritant gases and may differ, depending on the individual child. Injury of the airways may be manifested as upper airway obstruction resulting in laryngotracheitis, bronchitis, and upper airway edema. More peripheral airway obstruction may present with classic findings of asthma and airway edema with hypersecretion. In cases of massive exposure the presenting symptoms may be those associated with acute respiratory distress syndrome, manifested by profound V/Q mismatch, cyanosis, dyspnea, and respiratory failure. Severe nasopharyngeal and laryngeal edema with hypersecretion may present as stridor.[227,229] Chest radiograph findings are nonspecific, ranging from scattered areas of atelectasis and infiltrate to dense bilateral alveolar infiltrates.

Treatment

Prompt physical removal from the offending agent and maintenance of upper airway patency are imperative. Endotracheal intubation is a high-risk procedure, and meticulous attention must be directed toward maintaining proper pulmonary toilet and removal of upper airway secretions and debris from the artificial airway once it is secured.

Oxygenation should be closely monitored. High oxygen concentrations, mechanical ventilation, and use of positive end-expiratory pressure may be necessary in the event of acute respiratory failure because the diminished compliance and formation of pulmonary edema occur rapidly. Use of steroids may be justified in the treatment of patients who have been exposed to oxides of nitrogen; however, use after exposure to other irritant gases has not been validated.

Bronchoscopy may be indicated and useful in assessing the severity of airway injury and as an aid to endotracheal intubation and treatment of major areas of atelectasis. However, use of BAL usually is not indicated except in instances in which significant particulate or carbonaceous material is likely. Humidification of air and oxygen mixtures to thin secretions is necessary, and chest percussion/postural drainage may help to mechanically clear the airways.

Use of prophylactic antibiotics in persons with inhalation injuries is not recommended. If pulmonary infection is suspected, prompt therapy with broad-spectrum antimicrobial agents should be started. Use of bronchodilators is advocated because of a high incidence of bronchospasm. No critical studies

have evaluated this therapy in persons with an inhalation injury; however, the risk associated with its use is low, and administration to the child with obvious airflow obstruction is warranted. Use of aerosolized β_2 agonists is preferred. Special attention is required in the presence of smoke inhalation with regard to treatment of carbon monoxide poisoning. Hyperbaric oxygen, if available, or sustained administration of 100% oxygen is recommended in the initial treatment of patients with significant carbon monoxide intoxication. Development of upper or lower airway edema may necessitate intubation and mechanical ventilatory support.[226,230,231] Administration of artificial surfactant may be beneficial in patients in whom ARDS develops.[232] Use of prophylactic steroids and antibiotics for persons affected by smoke inhalation is not recommended, especially if burn injuries are present, because complications are more frequent.

Prognosis

The prognosis of children with acute pulmonary injury produced by inhalation of toxic gases is generally good. Restrictive and obstructive pulmonary function abnormalities have been observed following recovery. Residual defects such as bronchiolitis obliterans, bronchiectasis, and reactive airways disease have been observed following smoke inhalation.

Ingestion/Injection of Pharmacologic Agents

Several chemotherapeutic agents and other commonly used drugs have potentially serious pulmonary toxicity (Box 47-5). Pulmonary toxicity is thought to be a direct effect in most instances, but immunologic and hypersensitivity mechanisms also may be involved. Toxicity may occur during therapy or after discontinuation of the agent.[233] The development of blebs in the capillary endothelium is followed by an interstitial fibrinous edema and mononuclear cell response with eventual hyaline membrane formation. Some studies have shown a significant decrease in type 1 pneumocytes with evolution of type 2 pneumocytes, septal thickening, and a proliferation of fibrous tissue with a decrease in the number of alveolar septa. Pleural thickening may accompany the pneumonitis.

Diagnosis/Clinical Findings

Characteristic clinical features of drug-induced pulmonary disease include fever, malaise, dyspnea, and a nonproductive cough. Initial radiographic studies may be normal but usually demonstrate a diffuse alveolar and/or interstitial involvement. Pulmonary function studies may be of either an obstructive or restrictive pattern. Hypoxemia enhanced by exercise is an early and clinically important finding because interstitial pneumonitis and pulmonary fibrosis constitute a major portion of drug-induced pulmonary disease. Histologic examination of lung tissue is frequently indicated to confirm the clinical diagnosis and to rule out other potential causes of pneumonitis such as *Pneumocystis*, viral, or fungal infections that often occur in children treated with these agents.

Other complications such as hypersensitivity lung disease, noncardiogenic pulmonary edema, bronchiolitis obliterans, alveolar hemorrhage, and pleural effusion may occur in these patients. Persistent and fatal lung dysfunction may follow drug-induced pulmonary damage. Therapy should be directed at early recognition of the problem, discontinuation of the offending agent, and supportive therapy. The benefit of steroid use for treatment of lung injury caused by pharmacologic agents has not been well defined. In persons with severe life-threatening disease, steroids are frequently used.

Box 47–5 Pharmacologic Agents Associated with Pulmonary Toxicity

Cytotoxic Agents

Antibiotics
- Bleomycin: IP/PF, H, PEFF
- Mitomycin C: IP/PF, PE, PEFF

Alkylating Agents
- Cyclophosphamide: IP/PF, PE, B
- Chlorambucil: IP/PF
- Melphalan: IP/PF

Antimetabolites
- Methotrexate: IP/PF, PE, H, PEFF
- Azathioprine: IP/PF
- G-mercaptopurine: IP/PF
- Cytosine arabinoside: IP/PF, PE
- Nitrosoureas
- Carmustine: PF

Noncytotoxic Agents
- Amiodarone: IP/PF
- Carbamazepine: H, B
- Gold salts: IP/PF, H
- Nitrofurantoin: AH, PEFF, H, B, IP/PF
- Diphenylhydantoin: H
- Sulfasalazine: H, FA, BO, B
- Penicillamine: DA, AH, H, BO

AH, Alveolar hemorrhage; *B,* bronchospasm; *BO,* bronchiolitis obliterans; *DA,* diffuse alveolitis; *FA,* fibrosing alveolitis; *H,* hypersensitivity lung reaction; *IP,* interstitial pneumonitis; *PE,* pulmonary edema; *PEFF,* pleural effusion; *PF,* pulmonary fibrosis.

Idiopathic Interstitial Lung Disease

ILD of undetermined etiology is rare in adults but is even more uncommon in children. Histologic classification of the idiopathic type of ILD can be somewhat confusing, and in past years, pediatric classification mirrored the adult classification scheme. As research progressed, some overlap was noted, but it was found that pediatric interstitial lung diseases have features that are very unique to pediatrics. Usual interstitial pneumonitis has never been identified in children as the diagnostic fibroblastic foci were not found in any of the cases that had initially been labeled UIP. Other interstitial pneumonias such as desquamative interstitial pneumonitis (DIP) and lymphocytic interstitial pneumonias (LIP) are seen in children but remain quite rare and have some features that are different from their adult counterparts. DIP in children is not associated with smoking, and the histologic picture is one of macrophage being the primary inflammatory cell that fills the alveolus, although histiocytes, lymphocytes, eosinophils, and plasma cells are also present. Hyaline membrane formation is not seen in DIP and the structural integrity of the alveolar unit usually is maintained. DIP tends to be responsive to steroids.[234] LIP is seen mostly in patients with immune deficiencies and connective tissue disorders. LIP tends to be insidious in onset and appears as a result of infiltration of the

interstitium by plasma cells, mature lymphocytes, and histiocytes. Nonspecific interstitial pneumonitis histologically is a mixture of inflammation and fibrosis. This entity has been identified in children. Cryptogenic organizing pneumonia (previously bronchiolitis obliterans organizing pneumonia) has been identified in children either as an isolated phenomenon or with infection, asthma, drug reactions, malignancies undergoing chemotherapy, bone marrow transplantation, and autoimmune disorders. Prognosis is usually excellent and patients have an excellent response to corticosteroids. Acute interstitial pneumonia is a rapidly progressive disorder with a histologic appearance consistent with the organizing form of diffuse alveolar damage. This diagnosis generally has a poor prognosis. Some interstitial lung diseases that are unique to infancy most likely in the past had been labeled under the aforementioned interstitial lung diseases but truly belong in their own classification scheme. These syndromes are persistent tachypnea of infancy (neuroendocrine cell hyperplasia of infancy), follicular bronchitis, cellular interstitial pneumonitis (pulmonary interstitial glycogenosis), chronic pneumonitis of infancy, and genetic abnormalities of surfactant function.[234] Detailed discussions of these disorders of infancy or the other interstitial lung diseases and their management is beyond the scope of this chapter but can be found in various review articles.[235-240] Patients who do not respond to medical therapy should be considered candidates for lung transplantation.

Pediatric Pulmonary Hemorrhage

Pulmonary hemorrhage (PH) is a potentially life-threatening event that can occur at any age. The clinical presentation varies from massive fatal hemoptysis to silent bleeding with respiratory distress and anemia. Rapid determination of the etiology of the PH and institution of specific therapy are often difficult. This section examines the less common causes of PH. PH resulting from trauma and infection will not be discussed.

Definition

PH is defined as extravasation of blood into airways and/or lung parenchyma. Massive PH in adults is defined as blood loss of 600 mL or more in 24 hours.[241-243] In infants, Esterly and Oppenheimer[244] characterized massive PH as the involvement of at least two pulmonary lobes by confluent foci of extravasated erythrocytes. Loss of 10% of a patient's circulating blood volume into the lungs regardless of age causes a significant alteration in cardiorespiratory function and should be considered massive. The diagnosis of PH following an episode of silent bleeding is established by pulmonary hemosiderosis, which is the abnormal accumulation of iron within lung parenchyma and alveolar macrophages.

Pathophysiology

Accumulation of blood in the airways following a significant episode of PH creates multiple problems. These problems include production of a diffusion barrier resulting in hypoxemia and reduction in the diameter of involved airways, which in turn increases airway resistance and may lead to airway obstruction.

Reduction in pulmonary compliance and impairment of ventilation may occur.[245,246] These changes in respiratory function increase both the ventilatory and myocardial work necessary to maintain a normal arterial oxygen tension. Interstitial fibrosis that develops following repeated episodes of PH results in reduced carbon monoxide diffusion and diminished static and dynamic lung compliance.

Etiology

Classification of the etiologies of PH provides a simple framework to proceed with diagnostic and therapeutic interventions (Box 47-6). Diffuse PH usually is associated with less total blood loss and can occur from either immune or nonimmune mechanisms. Diffuse, immune PH typically affects adolescents and, less commonly, school-aged children. Focal PH is commonly responsible for massive PH and carries a mortality rate greater than 50%.[243,247] Focal PH typically affects preschool-aged children but may occur in infancy.

Diffuse/Nonimmune Pulmonary Hemorrhage

PH in the neonate occurs in 0.7 to 4 per 1000 live births and is present in 6% to 26.3% of neonates at postmortem examination. Risk factors associated with PH in the neonate include asphyxia, infection/sepsis, central nervous system injury, weight less than 1500 g and/or small-for-gestational age, male sex, congenital heart disease, idiopathic respiratory distress syndrome, and coagulation disorders.[248,249] Intraalveolar hemorrhage appears to occur more commonly in neonates of older gestational age. Pulmonary hemorrhage in neonates as a primary occurrence is uncommon.[248] Pathogenesis of PH in the neonate is considered to result from the development of persistent pulmonary hypertension with right-to-left

Box 47–6 Causes of Pulmonary Hemorrhage

Diffuse

Nonimmune
- Neonatal
- Congenital heart disease
- Hematologic

Immune
- Lower respiratory and renal
  - Goodpasture syndrome
  - Idiopathic rapid progressive glomerulonephritis
- Upper and lower respiratory and renal
  - Wegener granulomatosis
- Multisystem organ involvement
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
  - Behçet syndrome
  - Henoch-Schönlein syndrome
  - Rheumatoid arthritis

Focal
- Foreign body aspiration and chronic retention
- Sequestration
- Arteriovenous fistula
- Bronchogenic and gastroenteric cysts
- Thrombus or embolus
- Neoplasms: angiomas, adenomas

intracardiac shunting of blood, resulting from hypoxia and acidosis. Left ventricular failure ensues, causing an increase in pulmonary capillary pressure and subsequent disruption of pulmonary capillary and alveolar membranes. Severe central nervous system injury may indirectly affect cardiac function, causing increased left ventricular end-diastolic pressure.[250]

Severe hemoptysis and life-threatening PH are very rare in the preadolescent child with congenital heart disease. However, a drastic increase in pulmonary capillary pressure in children with pulmonary atresia, unilateral pulmonary venous atresia, total anomalous pulmonary venous drainage, mitral stenosis, cor triatriatum, or hypoplastic left heart syndrome may result in massive PH.[250,251]

Although the lungs are an infrequent site for early manifestations of primary bleeding disorders,[241,244] a coagulopathy should be ruled out during the management of any patient with PH. In patients with leukemia, PH occurs most frequently when the platelet count is lower than 10,000/mm.

Diffuse/Immune Pulmonary Hemorrhage

The classic clinical triad of hemoptysis, microcytic hypochromic anemia, and diffuse alveolar-filling opacities on a chest radiograph (Figure 47-1) is found in most episodes of PH in this category. Although the lung may be the only organ affected, more frequently multiple organs are involved. In patients with PH, establishing which extrapulmonary organs are involved by the disease helps to narrow the differential diagnosis of which of the immune-mediated disorders is most likely present.

Diffuse parenchymal bleeding without evidence of extrapulmonary involvement occurs in patients with idiopathic pulmonary hemosiderosis, Heiner syndrome, and drug-induced PH. Idiopathic pulmonary hemosiderosis, a disease of childhood, is a diagnosis of exclusion. Clinically, episodes of PH recur, with 30% to 50% of patients eventually dying of exsanguination and/or respiratory failure.[252,253] Microscopic examination of the lungs is compatible with nonspecific injury rather than a specific cause such as vasculitis or immune deposits.[254] Heiner syndrome, which affects children between the ages of 6 months and 2 years, usually manifests as other symptoms, such as chronic rhinitis, recurrent otitis media, and growth retardation.[242,250] Tests for precipitating antibodies to milk proteins are positive. Symptoms resolve when milk and milk products are eliminated from the diet.[250]

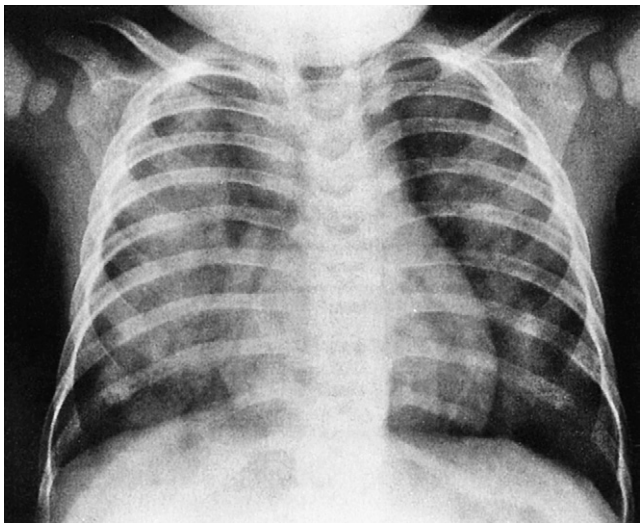

Figure 47–1. Chest radiograph of a patient with diffuse immune pulmonary hemorrhage.

Although uncommon, exposure to or inhalation of D-penicillamine, lymphangiography dye, trimellitic anhydride, cocaine, and exogenous surfactant[255-257] has been associated with development of PH. Acute PH of an undetermined etiology occurring in infants has been reported.[258,259]

Idiopathic rapidly progressive glomerulonephritis is usually a disease of older adults (mean age, 55 to 60 years).[253] In children with PH and either proteinuria, hematuria, or red cell casts, Goodpasture syndrome is the most likely etiology. The presence of a linear immunofluorescent staining of Ig and C3 along glomerular capillary walls and antibasement membrane antibody (ABMA) in the serum confirms the diagnosis of Goodpasture syndrome. Renal biopsy is the preferred primary method of confirming the diagnosis because an ABMA assay is not readily available at most institutions. AMBA is a cytotoxic plasma Ig that reacts immunologically with components of alveolar and glomerular basement membrane. Stress failure of pulmonary capillaries because of alteration of the alveolar and glomerular basement membrane may contribute to the likelihood of PH in these patients.[260] Fifty percent of patients with Goodpasture syndrome die of asphyxia as a result of massive PH. The presence of sinusitis and/or bilateral, multiple cavitary pulmonary nodules and evidence of glomerulonephritis in patients with PH help distinguish Wegener granulomatosis from the other vasculitides.[261] The immune-mediated causes of PH with multisystem organ involvement often have characteristic physical findings to suggest the diagnosis. Serositis, arthritis, facial erythema, fever, and glomerulonephritis are present prior to the development of PH in patients with systemic lupus erythematosus (SLE).[253,262] Ten percent of all cases of immune-mediated PH are associated with SLE.[253] The onset of PH in patients with SLE is abrupt. Pulmonary histology may or may not reveal a small vessel vasculitis characterized by neutrophilic infiltration of vessel walls and necrosis of capillaries and alveolar septa. Renal histology shows a vasculitis represented by focal and segmental glomerulonephritis with absent or minimal immune deposits.[263] The majority of patients who have SLE and PH die.[254] PH has been reported with most of the vasculitides, but the incidence is much lower than in the SLE population. Constitutional signs and symptoms, such as musculoskeletal involvement, blood dyscrasias, and dermatitis, are the predominant clinical features of polyarteritis nodosa, the second most likely vasculitis-associated disease to cause PH.[254] A segmental necrotizing (granular pattern) vasculitis is the characteristic lesion of polyarteritis nodosa, with PH a dominant feature.[264,265] Recurrent uveitis, mucocutaneous ulcerations, and genital ulcerations in a patient with PH suggests Behçet syndrome as the etiology. Other clinical features seen with Behçet syndrome include arthritis, gastrointestinal disease, cardiovascular involvement, and central nervous system disease.[266,267] A necrotizing vasculitis of small- to medium-sized arteries and veins and thromboses of the terminal vascular beds or vena cava confirm the diagnosis.

Although PH is an extremely rare complication of Henoch-Schönlein purpura or syndrome (when abdominal pain and

arthritis precede the purpura), it should be treated aggressively because it may be fatal. In a few patients with rheumatoid arthritis syndromes resembling idiopathic pulmonary hemosiderosis without evidence of vasculitis or renal disease have developed.[254]

Focal Pulmonary Hemorrhage

Congenital malformations that may be responsible for PH during infancy include angiomas and bronchogenic and gastroenteric cysts.[250] Angiomas are located in the subglottic area and present with symptoms of airway obstruction by age 6 months in almost 90% of cases. Bronchogenic cysts arise from abnormal branching of the tracheobronchial tree, are lined with ciliated columnar epithelium, are filled with mucoid fluid, and if they are in communication with the airway, they may demonstrate an air-fluid level. They are prone to infection and may bleed if contiguous vessels erode. Gastroenteric cysts, which are enteric duplication cysts lined with gastric mucosa, produce acid peptic secretions that may erode through adjacent vessels to cause bleeding. Pulmonary sequestration, arteriovenous fistula, and bronchial adenomas are congenital malformations that may present in childhood or later life with PH. With its tendency to become recurrently infected, a sequestered lobe may suffer erosion into its systemic arterial supply, causing massive PH.[250] Pulmonary arteriovenous fistula with or without telangiectasia (isolated or familial) may produce massive PH during childhood, but this usually does not occur until adulthood.[268,269] Adenomas are highly vascular tumors that, with minor trauma or inflammation, can cause PH. Acquired causes of focal PH include aspiration of an organic foreign body and development of a pulmonary arterial thrombus or embolus.[241,250] A patient presenting with PH and wheezing should lead the clinician to suspect a diagnosis of foreign body aspiration. Prolonged retention of an organic foreign body leads to hyperplasia of tortuous bronchial vessels, varicosities, and bronchiectasis, any of which may cause PH. Thrombi or emboli may develop in postoperative immobile children with central venous or pulmonary catheters, in female adolescents using oral contraceptives, or in patients with homozygous deficiency of antithrombin III, protein S, and protein C. Focal PH may develop in children with cystic fibrosis as a result of bronchiectasis.

Treatment

General

The primary objectives in treatment of PH are twofold: (1) to rapidly control the bleeding to prevent tissue hypoxia and/or ischemia resulting from airway obstruction and exsanguination and (2) to stabilize hemodynamics to prevent further damage to the kidneys or other extrapulmonary organs by the underlying disorder.[245,270] Initial management of the patient with severe PH should occur in the setting of a critical care unit because of the potential lethality of this event (Box 47-7). General care measures include use of the Trendelenburg position as tolerated, oxygen supplementation, mechanical ventilation, and hemostasis therapy when indicated. The Trendelenburg position may help clots propagate superiorly and exit the airway. This position may not be well tolerated by patients with respiratory or cardiac embarrassment.

Box 47–7 Treatment of Pulmonary Hemorrhage

General

- Admission to pediatric intensive care unit
- Positioning (intermittent Trendelenburg)
- Oxygen supplementation
- Mechanical ventilation (positive end-expiratory pressure)
- Hemodynamic monitoring
- Hemostasis replacement therapy
- Endobronchial tamponade (Fogarty catheter, cuffed endotracheal tube)

Specific

Immune

- Corticosteroids
- Other immunosuppressive agents (azathioprine, cyclophosphamide)
- Plasmapheresis (Goodpasture syndrome)
- Bilateral nephrectomy
- Deferoxamine, milk-free diet

Focal

- Surgical resection
- Selective embolization of bronchial vessels

Positive end-expiratory pressure during mechanical ventilation may become necessary to reverse hypoxemia and may provide a measure of tamponade to the site of hemorrhage.[243] Coagulation factors should be administered when indicated to lessen the severity of bleeding. Hemodynamic monitoring with a pulmonary arterial catheter may be beneficial in some instances because high pulmonary artery occlusion pressure may worsen PH of any etiology. Short-term control of bleeding may be obtained with insertion, under direct vision, of a balloon-tipped (Fogarty) catheter into the affected portion of the airway. Right upper lobe bleeding is best managed by intubating the left main stem bronchus with a cuffed endotracheal tube and inflating the cuff of the tube. Utilization of a "double lumen" or Carlens-type endotracheal tube also may be helpful in isolating the bleeding segment. However, the diameter of these tubes precludes their use in smaller children, and proper positioning may prove difficult.[245,271] Rigid bronchoscopy not only is the best means of identifying the source and type of bleeding but also has therapeutic applications.[245,272] The rigid scope readily establishes an adequate airway and can be used for large-volume isotonic saline solution lavage and for suctioning large volumes of blood. Fiberoptic bronchoscopy should be reserved for diagnostic purposes, including definitive identification of the bronchopulmonary segments involved and BAL. BAL provides useful information by permitting culture of the lavage for bacteria, fungi, mycobacteria, and viruses and quantitative assessment of the hemosiderin content of the alveolar lavage. Interpreting the presence or absence of hemosiderin-laden macrophages should be done cautiously because they may not appear for up to 48 hours following an acute episode of bleeding and usually disappear by 2 weeks.

Specific

Despite the different etiologies in the category of immune-mediated PH, the response to corticosteroid therapy is swift (within 24 to 48 hours) as assessed by transfusion requirements, hemoglobin concentration, hemoptysis, and absence

of new infiltrates.[254] Although controlled clinical trials have not been performed to validate this temporal relationship suggestive of therapeutic benefit, the risk of administering a short course of high-dose corticosteroids in this setting is low. Hence, the corticosteroids adrenocorticotropic hormone (10 to 25 units/day), methylprednisolone (2 to 4 mg/kg/day), or hydrocortisone (4 mg/kg/day) should be administered early in a patient with an acute, life-threatening episode of immune-mediated PH. Once remission is achieved, corticosteroids should be tapered until they are discontinued or until symptoms recur. In cases of inadequate response to corticosteroids alone, other immunosuppressive agents (e.g., azathioprine, cyclophosphamide, and chlorambucil) have been administered with some success in persons with the immune-mediated PH syndromes.[250] Azathioprine (1.2 to 5 mg/kg/day) with prednisone (5 to 20 mg every 6 hours) is a typical treatment combination. Cyclophosphamide is the drug of choice for treatment of patients with Wegener granulomatosis.[263,273-275] Once a specific diagnosis is made for the various etiologies of immune-mediated PH, directed therapies are available, including immunosuppression and plasmapheresis. These therapies are beyond the scope of this chapter and are discussed in the literature.[263,274,275] Administration of intravenous vasopressin to a patient with massive hemoptysis may temporarily control the bleeding. Surgical resection of a bleeding focus remains the procedure of choice if feasible. Surgical resection is the generally recommended treatment of uncorrectable, unilateral pulmonary vein atresia, bronchiectatic lung resulting from a foreign body, recurrent infection, and vascular tumors.[245] Severe bleeding at the time of resection resulting in single lung ventilation increased the mortality rate from 12% to 25% in one series. Pulmonary embolectomy should be considered for patients with an acute large embolus, especially if fibrinolysis is contraindicated.[245,276,277] For focal PH resulting from increased bronchial circulation, selective embolization or occlusion of bronchial vessels with glass microspheres, small pledgets of absorbable gelatin sponge, or polyvinyl alcohol sponge may provide temporary hemostasis. Embolization should be considered in the unstable or poor surgical candidate with focal PH. Complications of embolization include inadvertent central nervous system or coronary artery occlusion and transverse myelitis with resulting paraplegia.

Summary

PH that does not occur in the familiar setting of trauma or infection can be classified according to extent of pulmonary involvement, that is, diffuse or focal. PH occurs most commonly during the neonatal period as a result of diffuse nonimmune mechanisms. PH in the neonate is a preterminal complication of severe disorders of the cardiovascular and respiratory systems. The best initial approach to diagnosis and specific therapy in the older child is determining the extent of extrapulmonary organ involvement. Diseases that lead to focal hemorrhage are more likely to cause massive hemoptysis, typically affect younger children, and may be amenable to surgical resection. If the suspected cause of PH is a diffuse, immune-mediated process, a trial of corticosteroids should be administered early because of the rapid, dramatic response seen in patients with some disorders. A systematic approach to diagnosis in persons with PH will improve the odds of a favorable outcome for patients with this rare phenomenon.[245,271]

References are available online at http://www.expertconsult.com.

III

Chapter 48

Diseases of Pulmonary Circulation

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PEARLS

- The onset of breathing and lung inflation at birth with a resultant increase in oxygen tension decreases pulmonary vascular resistance, which is essential for establishing a normal postnatal circulatory pattern.
- Elevated pulmonary vascular resistance relative to systemic vascular resistance, which may result from either vasoconstriction or structural remodeling of the pulmonary vasculature, characterizes persistent pulmonary hypertension of the newborn (PPHN).
- An increase in pulmonary vascular smooth muscle can occur in utero or after birth and result in peripheral extension of the smooth muscle onto vessels that do not normally have muscle layers. This process may contribute to the pathology of PPHN.
- The gold standard in defining PPHN rests on the echocardiographic findings of right to left shunting of blood at the foramen ovale and/or ductus arteriosus, as well as evidence of elevated pulmonary arterial pressures.
- High-frequency oscillatory ventilation, surfactant therapy, and nitric oxide have decreased considerably the need for extracorporeal membrane oxygenation in infants with PPHN.
- In children, it is important to establish an accurate diagnosis with respect to etiology, because therapy may depend on the etiology of pulmonary hypertension.
- Echocardiography is a useful screening tool in children with suspected pulmonary arterial hypertension (PAH). Before committing to therapy specific to childhood PAH, diagnosis needs to be confirmed by catheterization.
- Calcium channel blockers are useful only for patients who respond to vasodilator testing during cardiac catheterization.
- Overall exercise capacity, symptoms as assessed by World Health Organization classification, and hemodynamic parameters of right ventricular function help not only in the management of these patients but also correlate well with survival.
- Recent advances in the medical management of PAH has widened the therapeutic modalities available for children including prostanoids, oral endothelin receptor antagonists, PDE-5 inhibitors, and some forms of combination therapies.
- Aggressive medical therapy combined with prompt and meticulous follow-up will improve quality of life and survival of children with pulmonary hypertension.

Early referral to expert centers is crucial to patient survival.

Etiology and Treatment of Pulmonary Hypertension

This chapter addresses the neonatal and pediatric aspects of pulmonary hypertension (PH). First, unique aspects of fetal and postnatal development of pulmonary vasculature, transitional circulation, and developmental regulation of pulmonary vascular tone are discussed. This background helps in understanding the pathophysiology and treatment of pulmonary vascular disorders in newborns and children.

Developmental Pulmonary Vascular Anatomy

Embryology

The vascular network of the developing endodermal pair of lung buds is derived from the surrounding mesenchyme of the splanchnic mesoderm beginning at 4 weeks of gestation. These vessels accompany the developing airways, differentiate into arteries, and join the larger pulmonary arteries that originate from the sixth aortic arch. The veins arise separately within the loose mesenchyme of the lung septa and subsequently connect to the developing left atrium.

Distinctions can be recognized between the proximal and distal pulmonary vasculature both in terms of their embryonic origins and the morphogenetic processes by which they develop. The sixth branchial arch is the embryonic origin of the proximal pulmonary vasculature, and it develops by the process of vasculogenesis. Vasculogenesis is the differentiation and segregation of angioblasts within the mesenchyme, which forms early vascular channels (arteries, veins, and lymphatics), depending on local influences from the epithelium and the mesenchyme. The lung mesenchyme is the embryonic origin of the distal vasculature, which develops by angiogenesis. Angiogenesis is the formation of new vessels from preexisting vascular channels by proliferation and migration of endothelial cells at the tips, which form multiple capillary sprouts. Abnormal maturation or maturational arrest in pulmonary arterial development is reflected in functional derangement that can appear in the newborn period. Persistent pulmonary hypertension of the newborn (PPHN) has been reported in association with pulmonary arterial maturational arrest at week 5 of gestation.[1] Normal growth and development of the pulmonary circulation in utero is critical for achieving successful transition to postnatal life.

Multiple factors influence development and growth of pulmonary vasculature in utero, including growth factors. Growth factors such as vascular endothelial growth factor[2] and fibroblast growth factor[3] appear to be responsible for orderly growth and branching morphogenesis of blood vessels. Quantity, timing, and location are critical determinants of the net effects of these agents. The mechanical stress that endothelial cells must withstand may be the predominant force responsible for development of large vessels after onset of circulation.[4]

Vascular Smooth Muscle

In the normal fetal and term lung, fully muscularized thick-walled preacinar arteries extend to the level of terminal bronchioles, whereas the intra-acinar arteries (i.e., those accompanying respiratory bronchioles) are partially muscular (surrounded by a spiral of muscle) or nonmuscular. Arteries at alveolar ducts and alveolar walls are nonmuscular. Preacinar arteries in the fetus late in gestation and in the newborn have thicker coats of smooth muscle relative to the arterial diameter than do similar arteries in adults, although the fetus actually has less distal extension of smooth muscle in smaller arteries than do older children or adults.[5] Figure 48-1 shows the diagrammatic representation of the extension of arterial smooth muscle within the acinus in a normal term newborn and in infants with severe PPHN.[6] An increase in intrauterine vascular smooth muscle, resulting from peripheral extension of smooth muscle into vessels that do not normally contain muscle layers, may contribute to the pathophysiology of PPHN[7] (see Figure 48-1). Increased muscularization of the pulmonary arteries has been described in infants with severe meconium aspiration syndrome (MAS) with PPHN.[8] Neonates who die of PPHN may have a striking distal extension of smooth muscle in the intra-acinar region, thickening of the media and adventitia, and excessive accumulation of the matrix protein in the pulmonary vessels.[9] The increase in vascular smooth muscle and its peripheral extension can occur either prenatally or postnatally. In utero ductal ligation 1 to 2 weeks prior to delivery results in severe PPHN at birth associated with distal extension of vascular smooth muscle in newborn lambs[10] (Figure 48-2) similar to the changes seen in human infants dying with severe PPHN.

Developmental Pulmonary Vascular Physiology

Hemodynamic Features of Fetal Circulation

Oxygenated blood (Pao_2 approximately 30 to 40 mm Hg) returning from the placenta in the umbilical vein[11] splits in the liver with slightly more than half passing through the ductus venosus to the inferior vena cava (IVC). The oxygenated blood streams along the medial aspect of the IVC as it enters the right atrium (Figure 48-3). Approximately two thirds of the IVC flow is directed toward the foramen ovale by the eustachian valve and the septum primum and enters the left atrium. The remaining third of the IVC flow mixes with the blood from the superior vena cava and enters the

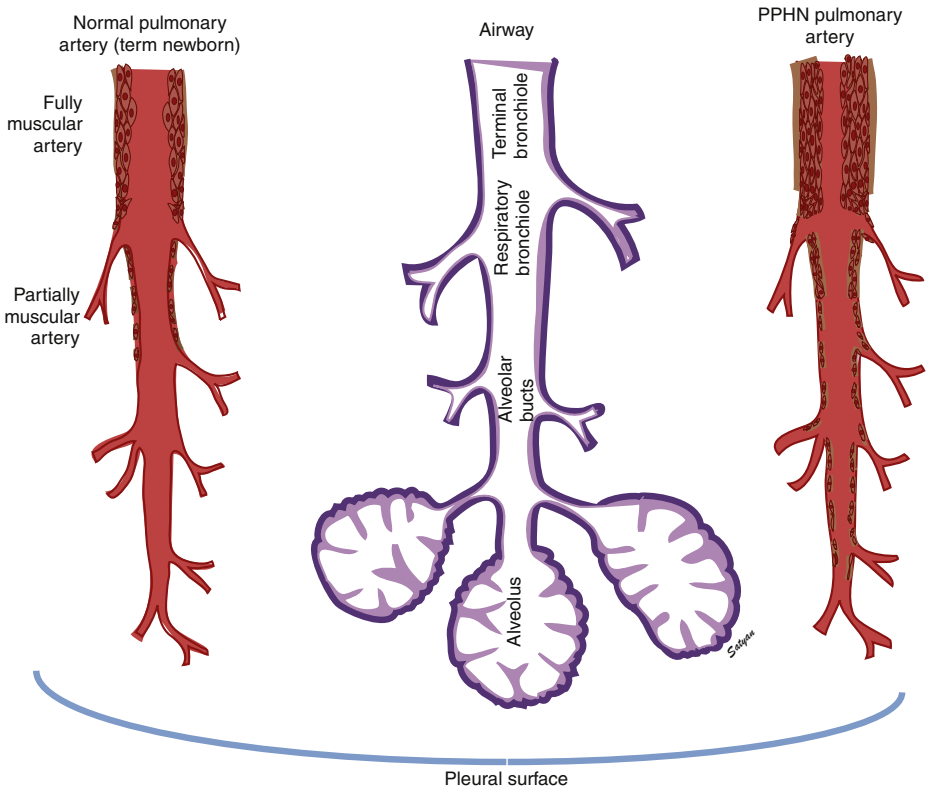

Figure 48–1. Diagrammatic representation of a normal pulmonary artery from a term newborn infant showing a fully muscular media to the level of the terminal and respiratory bronchiole. A partial muscular layer extends further distally but the terminal portion of the arterial tree is devoid of smooth muscle. A pulmonary artery in an infant with severe persistent pulmonary hypertension of the newborn shows an increase in the thickness of the muscular layer and distal extension of muscle. *(Copyright Satyan Lakshminrusimha.)*

right ventricle. The majority of the right ventricular (RV) output enters the ductus arteriosus and the descending aorta. A small portion enters the lungs via the pulmonary arteries.[12] The ratio of blood flow to the pulmonary arteries to the flow that traverses the ductus arteriosus is determined by the fetal pulmonary vascular resistance (PVR).

The fetal pulmonary circulation fulfills a unique function. Close to term, fetal lungs in the lamb receive about 5% to 10% of combined ventricular output to meet the metabolic demands of an actively growing organ. More recent data in human fetuses using Doppler echocardiography suggest that approximately 25% of combined ventricular output may enter the lungs near term.[13] The presence of large fetal shunts, the foramen ovale and the ductus arteriosus (see Figure 48-3), allows the fetal lung to regulate the amount of blood flow it receives by active vasoconstriction. The distribution of combined ventricular output, measured in fetal lambs ranging from 60 to 150 days gestational age, indicates that the lungs receive only about 3.5% of total output at 0.4 term, but the fraction increases to almost 8% at term.[14] This remarkable

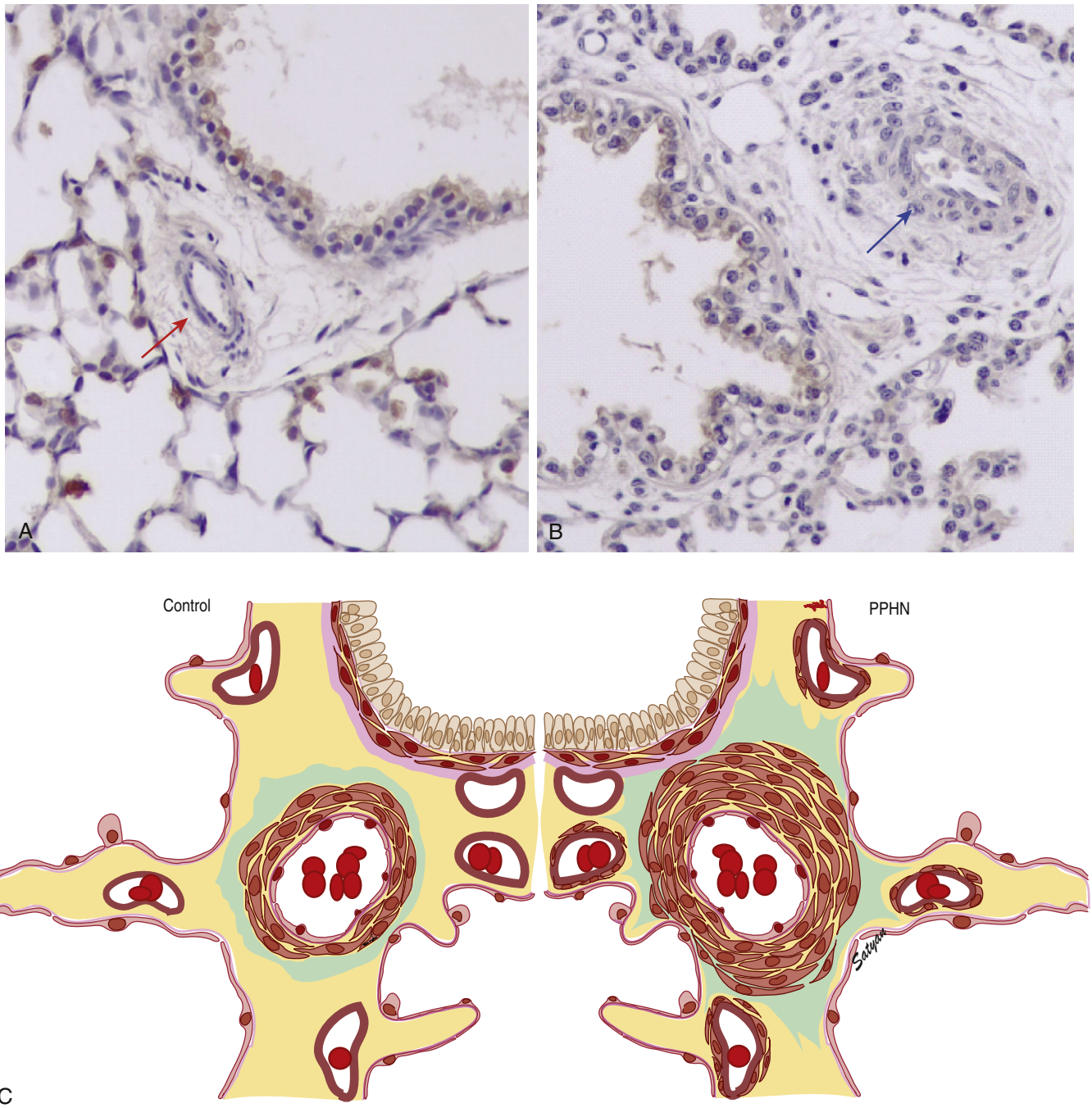

Figure 48–2. Histology (hematoxylin and eosin stain) showing increased muscularization surrounding pulmonary arteries (*blue arrow*) following antenatal ductal ligation in lambs resulting in persistent pulmonary hypertension of the newborn (**B**). Control twin lamb (**A**) with a normal pulmonary artery (*red arrow*) is shown for comparison. The cartoon (**C**) shows increased muscularization and distal extension of muscle in persistent pulmonary hypertension of the newborn. *(Copyright Satyan Lakshminrusimha.)*

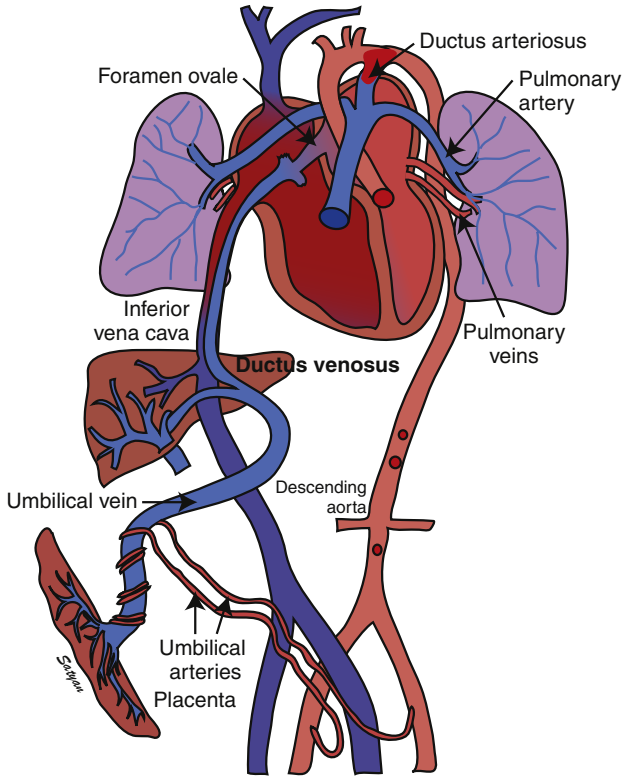

Figure 48–3. Fetal circulation showing the shunting of blood at the ductus venosus, foramen ovale, and ductus arteriosus. *(Copyright Satyan Lakshminrusimha.)*

increase in fetal pulmonary perfusion presumably is related to growth of the fetal lung. The lung increases in weight by sixfold from midgestation to term, and the number of pulmonary vessels increases more than tenfold.[15,16] Thus the tremendous increase in cross-sectional area of pulmonary vasculature permits pulmonary blood flow (Qp) to increase throughout gestation. However, Qp remains relatively constant when corrected for wet lung weight with advancing gestation.[17] A gradual increase in pulmonary arterial pressure (PAP), accompanied by a relatively constant flow per unit lung tissue, results in increasing fetal PVR with advancing gestation.[17] A major part of this increase comes from elevated pulmonary vascular tone associated with low Po_2 in the fetal lung.[18,19] Maintaining high PVR in utero is important because the function of gas exchange is performed not by the lungs but by the placenta.

Regulation of Pulmonary Vascular Tone in Utero

Low oxygen tension and various mediators play a crucial role in maintaining elevated fetal PVR.[20] Vasoconstriction in response to low oxygen tension contributes to high PVR in the fetal lamb as it approaches term.[18,19] Decreasing oxygen tension in fetuses at 103 to 104 days of gestation does not increase PVR, but it doubles resistance in fetuses at 132 to 138 days. Conversely, increasing oxygen tension does not change PVR before 100 days of gestation, but it decreases resistance markedly and increases blood flow to normal newborn levels at 135 days of gestation.[17]

Arachidonic acid metabolites are some of the most powerful vasoconstrictors known. Prostaglandin (PG) $F_{2\alpha}$ and thromboxane A_2 (TXA_2) are synthesized by the fetal lung via the cyclooxygenase pathway[21] and are pulmonary vasoconstrictors in the fetal and newborn lungs. However, TXA_2 does not appear to be responsible for maintenance of high PVR in the fetus.[22] Blocking PG or thromboxane synthesis does not decrease fetal PVR but prevents the decrease in PVR in response to rhythmic distension of the lung in fetal lambs.[23] The cytochrome P450 metabolism of arachidonic acid results in the formation of epoxyeicosatrienoic acids, dihydroxyeicosatetraenoic acids, and 20-hydroxyeicosatetraenoic (HETE) acids. Of these compounds, HETE acids have been shown to constrict pulmonary circulation in newborn piglets.[24] However, inhibition of 20-HETE did not reduce basal PVR in fetal lambs.[25] Thus it does not appear that cyclooxygenase and CYP450 metabolites of arachidonic acid cause the high vascular tone of the fetal lung.

Leukotrienes are formed from arachidonic acid through the 5-lipooxygenase pathways. Lipoxygenase activity has been demonstrated in human fetal lung as early as 12 to 18 weeks of gestation.[26] Leukotriene inhibition has been shown to decrease PVR in fetal lambs by 45%.[27] It also reverses hypoxic pulmonary vasoconstriction in newborn lambs but not in newborn piglets.[28,29] The specific role of leukotrienes in maintaining high PVR in immature fetuses is unclear. It is possible that they play a role in pathologic states such as hypoxia or inflammation.

Endothelins (ETs) are 21-residue peptides[30,31] whose role in regulating vascular tone and vasomotor responses has been studied intensively in the past decade. Three distinct ET isoforms have been described: endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3), cleaved from ET precursors big ET-1, big ET-2, and big ET-3, respectively, by an ET-converting enzyme. ET-1 synthesized by vascular endothelial cells is a potent vasoconstrictor,[32] and its effects in both animal and human studies vary with the tone of the pulmonary vessels, dose of ET-1, and the maturation of vessels.[33,34] Of the ETs, ET-1 is the best characterized, and its actions of fetal pulmonary circulation are best studied. Both ET-1 and ET-2 have been shown to dilate the fetal (normally high tone) pulmonary vasculature and constrict the bed when the tone is reduced by ventilation.[35] Thus it appears that the response of the pulmonary vasculature to ETs is tone-dependent. In contrast, infusion of big ET-1, the precursor of ET-1, into fetal lambs causes sustained pulmonary vasoconstriction,[36] suggesting that this might be the predominant effect of endogenous ET-1.[37] Currently at least two receptor subtypes, ET_A and ET_B, are thought to mediate responses to ETs (Figure 48-4). The ET_B receptor plays a role in vasodilation and the ET_A receptor plays a role in vasoconstriction. Selective blockade of the ET_A receptor causes fetal pulmonary vasodilation.[38-40] Some investigators suggest a significant role for an endothelial ET_B receptor in vasodilation and a smooth muscle ET_B receptor and ET_A receptor in vasoconstriction.[41,42] Vasoconstriction induced by ET-1 is mediated by calcium,[43] whereas the vasodilator properties are mediated by endothelium-derived nitric oxide (NO).[42,44] ET-1 may play a role in the change that occurs in the pulmonary vasculature at birth. It is possible that prenatally, endogenous ET-1 primarily stimulates ET_A receptors to cause vasoconstriction and that ET_B receptors are less active in fetal life.[38] However, ET_B receptors mediate the vasodilator

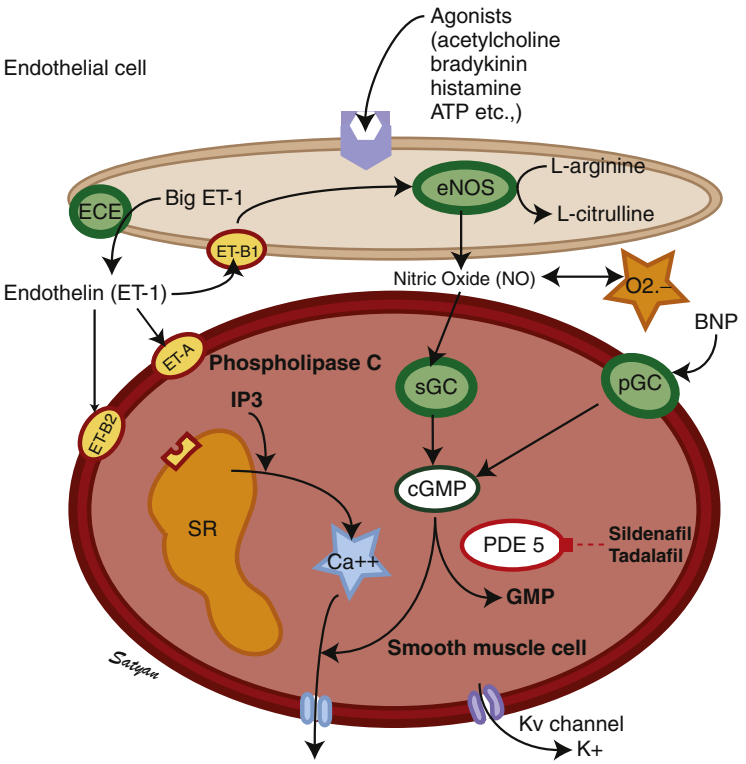

Figure 48–4. Endothelin and nitric oxide pathways in pulmonary arterial endothelial and smooth muscle cells. *ATP*, Adenosine triphosphate; *BNP*, B-type natriuretic peptide; *cGMP*, cyclic guanosine monophosphate; *eNOS*, endothelial nitric oxide synthase; *ET-A and ET-B*, endothelin A and B receptors; *GMP*, guanosine monophosphate; *IP_3*, inositol triphosphate; *Kv*, voltage gated potassium channel; *O2.–*, superoxide anions; *pGC*, particulate guanylate cyclase; *sGC*, soluble guanylate cyclase; *SR*, sarcoplasmic reticulum. *(Copyright Satyan Lakshminrusimha.)*

responses to ET-1 in the fetus, and there is a suggestion that an abundance of ET_B receptors may be of physiologic importance in decreasing PVR at birth.[40]

Transitional Circulation

The first stage of transitional circulation is essentially a fetal pulmonary circulation that is characterized by high pressure and low flow because of both passive and active elevation of PVR (Figure 48-5, *A*). The passive resistance most likely is related to compression of pulmonary capillaries by fetal lung liquid, but there is also a high degree of active vasomotor tone resulting from various mediators and hypoxic stimuli. Thus PVR exceeds systemic vascular resistance (SVR), resulting in right atrial and ventricular pressures exceeding left atrial and ventricular pressures. High PVR results in right-to-left shunting of blood across the foramen ovale, and most of the blood ejected by the right ventricle flows across the ductus arteriosus into the descending aorta. Persistence of elevated PVR after birth without the benefit of placental oxygenation results in the profound hypoxemia that characterizes PPHN.

The second stage of normal transition is accomplished when the fluid-filled fetal lungs are distended with air during the first breath (Figure 48-5, *B*).[20] A rapid decrease in PVR occurs with mechanical distension of the pulmonary vascular bed. The entry of air into the alveoli improves oxygenation of the pulmonary vascular bed, further decreasing PVR.[45] At birth PVR decreases dramatically, which leads to an eightfold increase in Q_p. The increase in Q_p raises left atrial pressures above right atrial pressures, closing the foramen ovale. SVR increases at birth, in part because of removal of the low resistance bed of the placenta. As PVR becomes less than systemic, flow across the ductus reverses. Within the first 5 minutes after birth, oxygen-induced vasodilation and lung expansion decrease PVR to approximately half of systemic resistance. Over the first few hours after birth, the ductus arteriosus closes, largely in response to the increase in oxygen tension. At this point the normal postnatal circulatory pattern is established.

The third stage of the transitional circulation occurs for 12 to 24 hours after birth and accounts for the greatest reduction in PVR. In the final phase of neonatal pulmonary vascular transition, further decline in PVR is accompanied by rapid structural remodeling of the entire pulmonary bed from the main pulmonary arteries to the capillaries.[46] During this remodeling, changes in the shape and geometric orientation of endothelial and smooth muscle cells cause luminal enlargement. Maturation of smooth muscle function, thinning of endothelial cells (Figure 48-5, *C*), and more gradual changes in elastic and connective tissue occur during the next few weeks.

Factors Responsible for Decrease in Pulmonary Vascular Resistance at Birth

The onset of ventilation with rhythmic inflation of the lungs at birth with a resultant increase in oxygen tension in the lungs leads to a decrease in PVR. Each of these stimuli has been shown to decrease vascular resistance and increase blood flow in the lungs of fetal lambs.[45] Increasing oxygen tension alone by using a hyperbaric chamber decreased PVR and increased

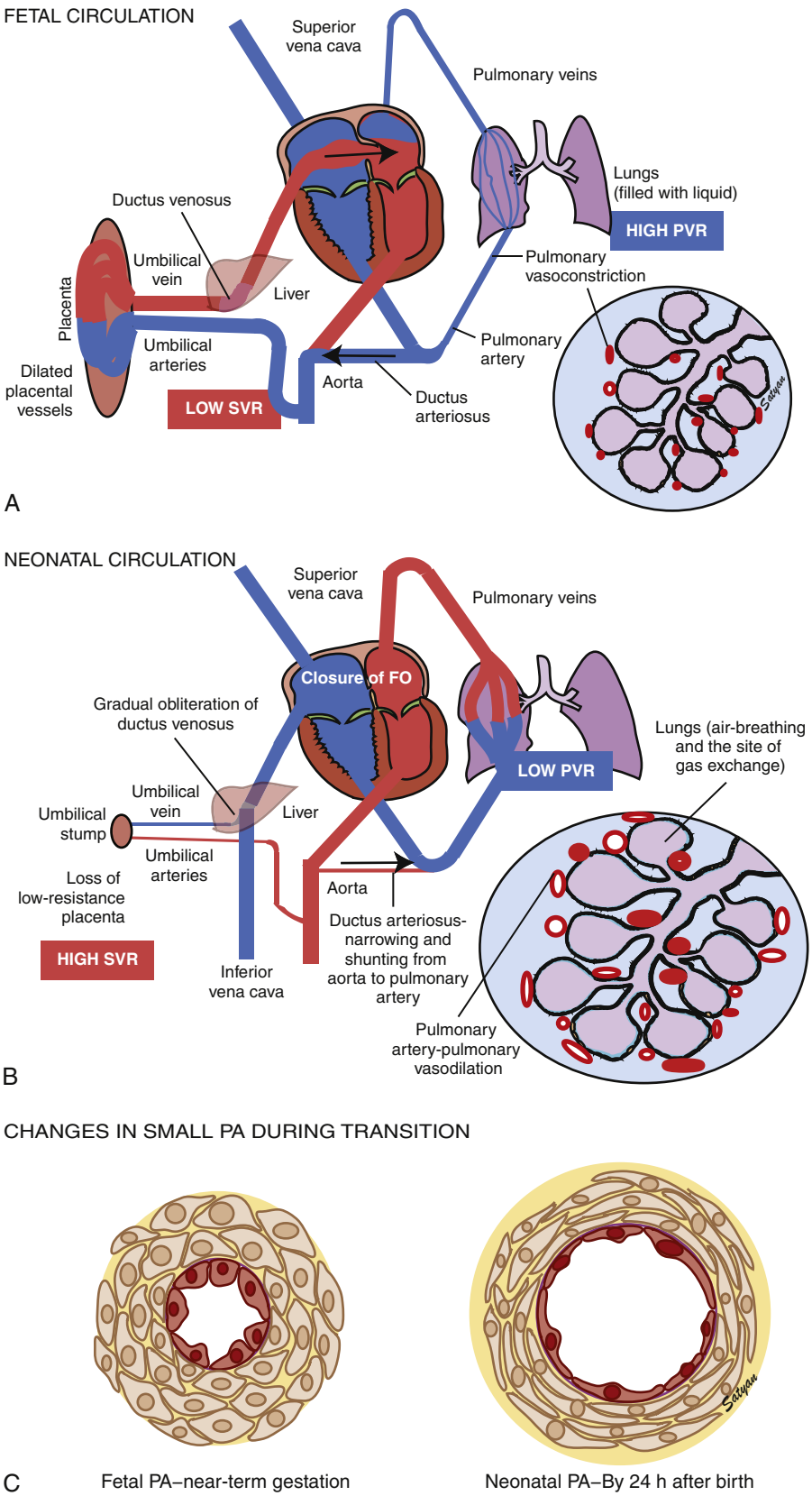

Figure 48–5. Transitional circulation. Fetal circulation (**A**) is characterized by high pulmonary vascular resistance (PVR), low pulmonary blood flow, and low systemic vascular resistance (SVR). After birth, with the clamping of the umbilical cord, low resistance placental circulation is removed and SVR increases and with pulmonary vasodilation, PVR decreases (**B**). During the first few hours of postnatal life, morphologic changes occur in the pulmonary arterial endothelial cells and smooth muscle cells. These changes contribute to further reduction in PVR (**C**). *(Copyright Satyan Lakshminrusimha.)*

Q_p by tenfold in mature fetal lambs.[17] Inflation of lungs with gas may decrease resistance, at least in part by mechanical effects. Oxygen may dilate in part by direct effects on vascular endothelial and smooth muscles.[20,47]

The drop in PVR soon after birth is accompanied by production of prostacyclin (PGI_2) and NO. Arachidonic acid metabolites such as PGs, generated through the cyclooxygenase pathway, are potent pulmonary vasodilators in the fetus. PGI_2 synthesized by endothelial cells appears to relax smooth muscle by producing cyclic adenosine monophosphate (cAMP). PGI_2 and its metabolites are more potent vasodilators than PGE_2. Even though blockade of PG synthesis, either by indomethacin[48,49] or meclofenamate,[23] blunts the decrease in PVR, it does not completely disrupt the transition to gas exchange. In addition, cyclooxygenase through the PGE_2 pathway plays an important role in maintaining patency of the ductus arteriosus. PPHN has been observed in infants of mothers receiving aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) that inhibit cyclooxygenase activity.[50] In this situation, the inhibitor acts through prenatal constriction of the ductus arteriosus or by decreasing PGI_2 synthesis at birth.[51] The cAMP signal transduction pathway is shown in Figure 48-6.

Acetylcholine,[52] bradykinin,[53] and histamine[54] are fetal pulmonary vasodilators, which in many species act by an endothelium-dependent mechanism (see Figure 48-4). They stimulate the production of NO by vascular endothelium. NO activates soluble guanylate cyclase to produce the second messenger cyclic guanosine monophosphate (cGMP). cGMP induces relaxation of vascular smooth muscle through activation of a cGMP-dependent protein kinase that produces a lowering of cytosolic ionic calcium, in part through activation of potassium channels.[55] There is strong evidence that NO is an important mediator of the decrease in PVR at birth. NO is a potent dilator of the fetal pulmonary circulation.[56] The dilation of the fetal pulmonary circulation caused by an increase in oxygen tension is mediated in large part by endogenous synthesis of NO.[57] In late gestation lambs, prolonged administration of nitric oxide synthase (NOS) inhibitors, which blocks endogenous NO synthesis, does not affect basal PVR but markedly blunts the decrease in PVR observed at birth.[58]

Evidence suggests that many other mediators can act as pulmonary vasodilators during fetal life and at birth. The purines adenosine triphosphate and adenosine are potent pulmonary vasodilators in the fetal lamb that may also be involved at birth.[59-63] Natriuretic peptides such as atrial natriuretic peptide, B-type natriuretic peptide, and C-type natriuretic peptide dilate fetal pulmonary vasculature by increase cGMP through particulate guanylate cyclase.[64] Arachidonic acid metabolites such as epoxyeicosatrienoic acids, which are generated through the cytochrome P450 pathway, are potent pulmonary vasodilators.[65] Because pulmonary vasodilation at birth is a vital step in establishing postnatal life, it is logical that there would be sufficient redundant vasodilators to compensate for failure or inadequacy of any single pathway.[37]

Persistent Pulmonary Hypertension of the Newborn

PPHN is a serious clinical condition that can result from diverse etiologies and is characterized by failure of the pulmonary circulation to adapt to extrauterine life.

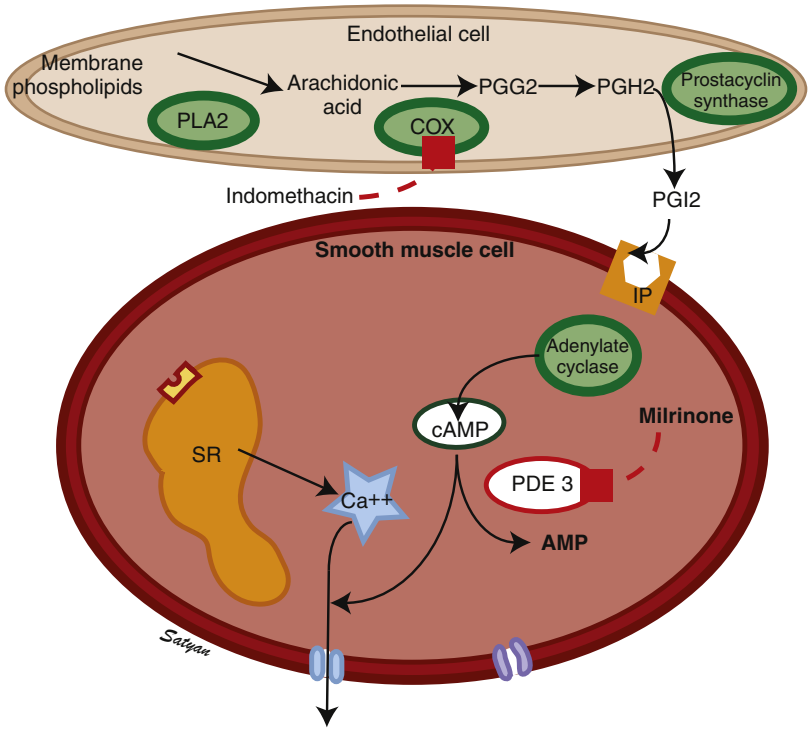

Figure 48–6. Prostaglandin pathway in the pulmonary arterial endothelial and smooth muscle cells. *AMP,* Adenosine monophosphate; *cAMP,* cyclic adenosine monophosphate; *COX,* cyclooxygenase enzyme; *IP,* prostacyclin receptor; *PDE 3,* phosphodiesterase 3 enzyme; *PGG_2 and PGH_2,* prostaglandins; *PGI_2,* prostacyclin; *PLA_2,* phospholipase A2. *(Copyright Satyan Lakshminrusimha.)*

Pathophysiology

Elevated pulmonary to systemic vascular resistance ratio (PVR/SVR) resulting from either vasoconstriction, structural remodeling of the pulmonary vasculature, intravascular obstruction, or lung hypoplasia (Figure 48-7) characterizes PPHN. This leads to right-to-left shunting of blood across the foramen ovale and ductus arteriosus, resulting in hypoxemia. Numerous disease states with diverse etiologies can result in a similar final pathophysiology. About 10% of cases with PPHN are idiopathic, with no associated pulmonary airspace pathology. However, PPHN is usually associated with other acute respiratory conditions, such as MAS, respiratory distress syndrome (RDS), pneumonia, or congenital diaphragmatic hernia (CDH) (Figure 48-8). Hypoxemia in these conditions can be due to ventilation/perfusion (V/Q) mismatch

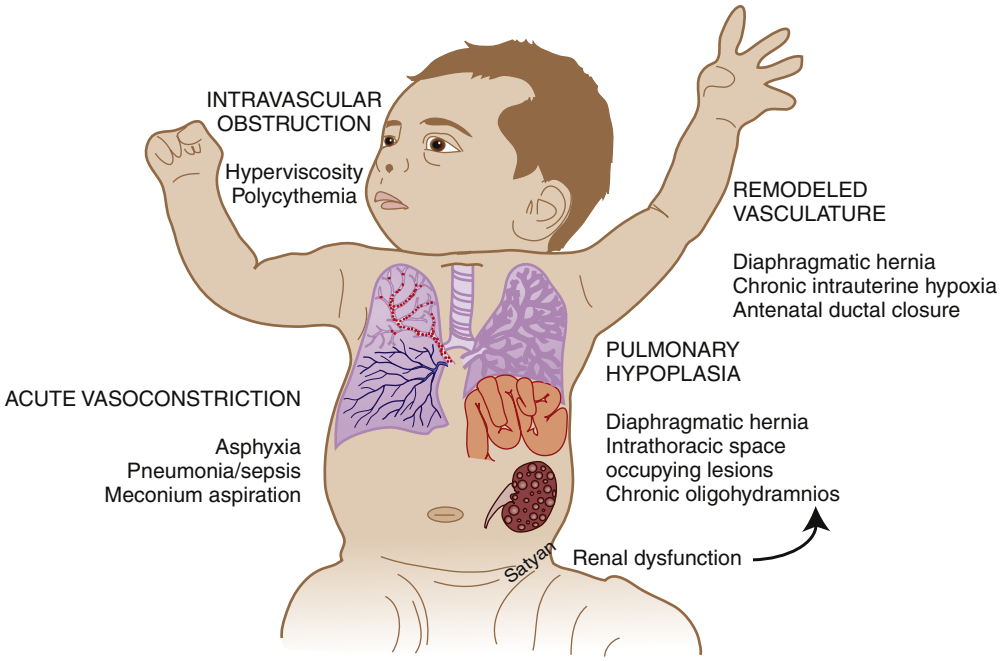

Figure 48–7. Mechanisms of persistent pulmonary hypertension of the newborn. *(Copyright Satyan Lakshminrusimha.)*

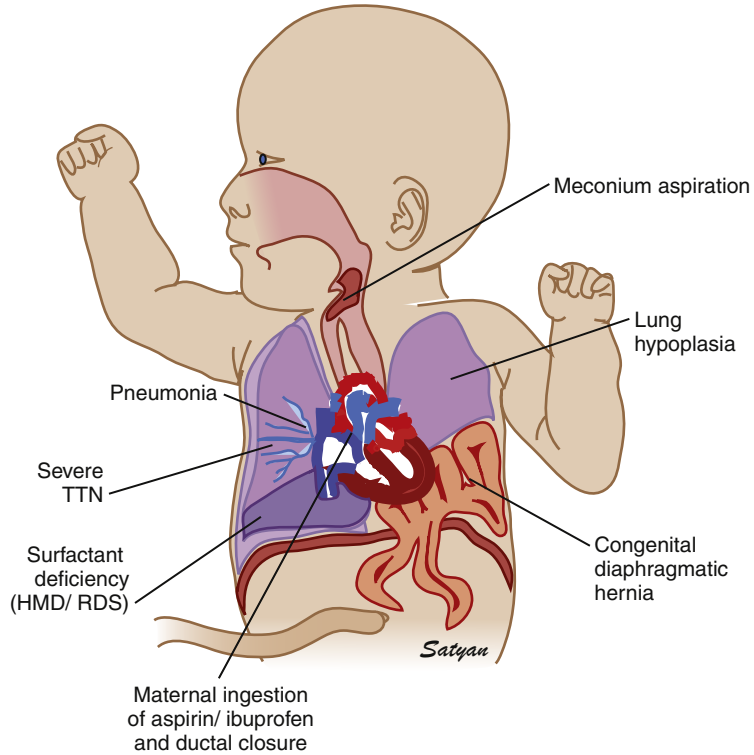

Figure 48–8. Clinically common conditions associated with persistent pulmonary hypertension of the newborn. *(Copyright Satyan Lakshminrusimha.)*

and intrapulmonary, as well as extrapulmonary, right-to-left shunting of blood. In some newborns with hypoxic respiratory failure, a single mechanism predominates (e.g., extrapulmonary right-to-left shunting in idiopathic PPHN). However, more commonly, several of these mechanisms contribute to hypoxemia. In MAS, obstruction of the airways by meconium results in decreasing V/Q ratios and increasing intrapulmonary right-to-left shunt. Other segments of the lungs may be overventilated relative to perfusion, causing increased physiologic dead space. The same patient also may have severe PPHN with extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale. The PPHN in patients with MAS may result from the alveolar hypoxia, from inflammatory mediators, or from abnormal pulmonary vascular muscularization.

Pneumonia or meconium aspiration may release inflammatory mediators that induce vasoconstriction. Vasoconstrictors such as leukotrienes, platelet-activating factor, thromboxanes,[66] and ET-1[67] have been found to be elevated in patients with PPHN. Chronic intrauterine ET_A receptor blockade following ductal ligation decreases pulmonary arterial pressure in utero and decreases RV hypertrophy, and distal muscularization of small pulmonary arteries increases the fall in PVR at delivery in newborn lambs with PPHN.[39] Thus ET-1 acting through the ET_A receptor stimulation might contribute to the pathogenesis and pathophysiology of PPHN. Derangements in the NO pathway of vasodilation also can result in the physiologic characteristics of PPHN. Pulmonary endothelial nitric oxide synthase (eNOS) gene and protein expression and enzyme activity are decreased in fetal lambs with PPHN induced by antenatal ductal ligation.[68] In addition, the response to stimulators of eNOS is lost.[69] In these lambs with PPHN, the vascular response to NO itself is also diminished,[70] whereas the response to cGMP is normal. Thus the decreased responsiveness appears to result from decreased vascular smooth muscle sensitivity to NO at the level of soluble guanylate cyclase. The cGMP pathway of signal transduction is shown in Figure 48-4. Because NO both vasodilates and inhibits vascular smooth muscle growth, diminished eNOS expression may contribute to both abnormal vasoreactivity and excessive muscularization of pulmonary vessels in patients with PPHN.

PH sometimes occurs because of an abnormal pulmonary vascular bed despite the absence of alveolar hypoxia and hypercapnia and of lung inflammation. These infants can be grouped according to the degree of muscularization and the number of pulmonary arteries.[71] In infants with hypoplastic lungs, as in those with congenital heart disease (CHD) and oligohydramnios sequence, PPHN may arise primarily as a consequence of a decreased number of vessels causing a decreased cross-sectional area of the pulmonary vascular bed, leading to flow restriction (see Figure 48-7). Patients with alveolar capillary dysplasia may have a similar vascular hypoplasia. These cases may be complicated by increased muscularization of the vessels.

Antenatal exposure to NSAIDs such as aspirin and ibuprofen has been associated with PPHN.[50] More recently, an association between the use of selective serotonin reuptake inhibitor class of antidepressants after 20 weeks of gestation and PPHN has been found.[72,73] Prenatal exposure to fluoxetine (a selective serotonin reuptake inhibitor) induced fetal PH in rats.[74] The exact mechanism of this association is not clear. Polycythemia and hyperviscosity also may increase PVR and contribute to PPHN. Similarly, hypothermia, acidosis, and hypoxemia can aggravate PPHN.

Clinical Presentation

PPHN must be included in the differential diagnosis of hypoxic respiratory failure in term or near-term infants. Prenatal and perinatal history may provide clues to the etiology of PPHN. These clues include the presence of meconium, acidosis, and asphyxia at delivery, maternal risk factors for infection such as prolonged rupture of membranes, maternal fever, or positive group B streptococcus status. Maternal use of over-the-counter medications that contain PG synthesis inhibitors such as aspirin may be important. Postmaturity also appears to be a risk factor.

Labile hypoxemia is the hallmark of PPHN (Figure 48-9). A newborn infant who is extremely labile, with frequent desaturation episodes and wide swings in arterial Po_2 without changes in ventilator settings, should suggest the possibility of PPHN. Lability also can occur in the face of significant parenchymal disease when V/Q mismatch is severe. Auscultation of the heart in babies with PPHN may reveal a single S2, which can be loud, and a systolic murmur of tricuspid regurgitation. Chest radiograph findings may vary depending on the etiology of PPHN. Hypoxemia out of proportion to the degree of parenchymal disease severity on chest radiography should suggest PPHN. Measurement of preductal and postductal arterial oxygenation can confirm PPHN. A difference in arterial Po_2 20 mm Hg or greater or oxygen saturation 10% or greater should be considered significant. Minimal or no difference in oxygen tension does not exclude PPHN because shunting at the atrial level produces no ductal gradient and probably is the most common site of shunting. Thus in clinical practice, the gold standard in defining PPHN rests on the echocardiographic findings of right-to-left shunting of blood at the foramen ovale and/or the ductus arteriosus, as well as estimates of PAP. Doppler measurements of atrial and ductal level shunts provide essential information when managing a newborn with hypoxic respiratory failure.[75] For example, left-to-right shunting at the foramen ovale and ductus arteriosus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should be directed at optimizing lung inflation. Similarly, presence of right-to-left shunting at the ductal level and left-to-right shunting at the atrial level suggests PPHN with left ventricular dysfunction with some pulmonary venous hypertension (see Table 48-1). This finding may be associated with CHD.[76]

Treatment

General Measures

Understanding the dynamic pathophysiology underlying right-to-left shunting is important to the successful management of PPHN. In patients with PPHN, even mild stress can cause Po_2 to plummet within minutes. Vigorous and persistent resuscitative measures are often necessary to promote pulmonary vasorelaxation. Accordingly, neonates and children with PPHN are often very sensitive to activity and agitation. Minimal stimulation and sedation with narcotics such as fentanyl and morphine are commonly used to achieve this goal. However, paralysis should be avoided because it is associated with

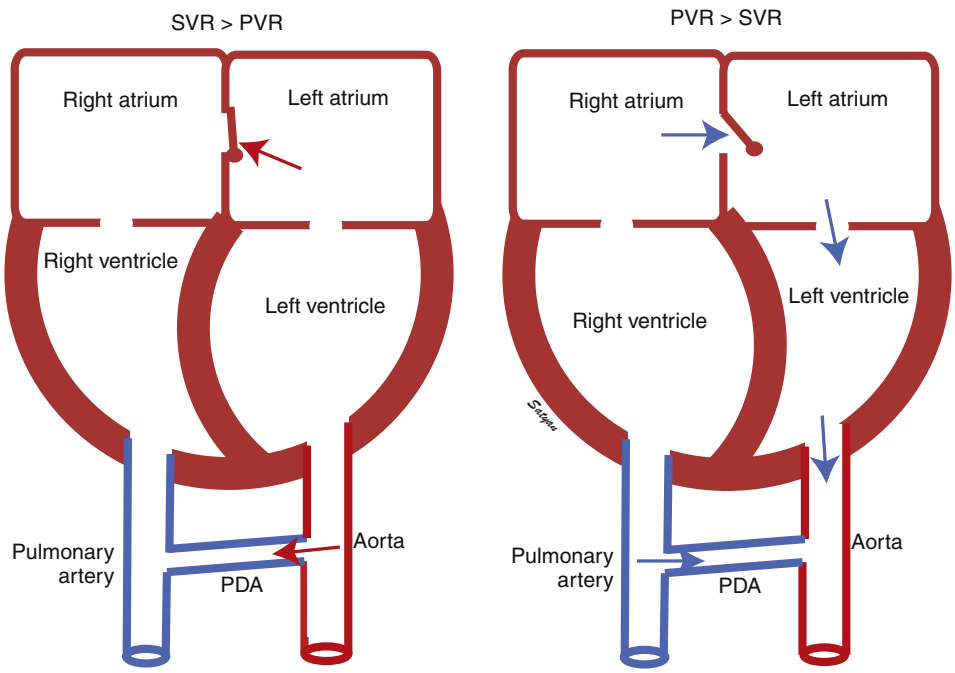

Figure 48–9. Physiology of labile oxygenation in persistent pulmonary hypertension of the newborn. When systemic vascular resistance (SVR) is higher than pulmonary vascular resistance (PVR), there is no right-to-left shunt. When PVR is close to or exceeds SVR, variable right-to-left shunt at foramen ovale and ductal levels results in labile hypoxemia. *(Copyright Satyan Lakshminrusimha.)*

Table 48–1 Differential Diagnosis of Hypoxemia in a Neonate Based on the Direction of Shunt at Atrial and Ductal Level on Echocardiography

Ductal shunt	Atrial shunt	Diagnosis	Management
R → L	R → L	PPHN	Oxygenation and inhaled NO
L → R	L → R	Parenchymal lung disease and V/Q mismatch	Lung recruitment, specific therapy NO may be beneficial
R → L	L → R	LV dysfunction (common in CHD)*	Milrinone
L → R	R → L	Tricuspid atresia/ stenosis or pulmonic atresia/ stenosis	PGE_1 + surgery
R → L (large PA)	R → L (small LA and no tricuspid regurgitation)†	TAPVR	Surgery

CHD, Congenital heart disease; *LA,* left atrium; *LV,* left ventricular; *NO,* nitrous oxide; *PA,* pulmonary artery; *PPHN,* persistent pulmonary hypertension of the newborn; *TAPVR,* total anomalous pulmonary venous return; *V/Q,* ventilation/perfusion; *R → L,* right to left; *L → R,* Left to right.

*Kinsella JP, Ivy DD, Abman SH: Pulmonary vasodilator therapy in congenital diaphragmatic hernia: acute, late, and chronic pulmonary hypertension, *Semin Perinatol* 29(2):123-128, 2005.

†Lakshminrusimha S, Wynn RJ, Youssfi M, et al: Use of CT angiography in the diagnosis of total anomalous venous return, *J Perinatol* 29(6):458-461, 2009.

increased mortality.[77] The lability in Pao_2 may result from the fact that when pulmonary and systemic arterial pressures are similar, small alterations in the ratio of the two can produce large changes in extrapulmonary shunting (see Figure 48-8).[78] Systemic blood pressures should be maintained at a high normal range for age and gestation, because an increased systemic resistance may decrease the degree of right-to-left shunting. Hypotension resulting from hypovolemia should be treated aggressively with volume replacement. If hypotension persists despite volume replacement, inotropic support with dopamine, dobutamine, and epinephrine may be required. All patients with PPHN benefit from a core group of therapies that includes management of hypothermia, hypocalcemia, acidosis, hypoglycemia, and polycythemia. In cases of PPHN resulting from perinatal asphyxia, correcting alveolar hypoxia, hypercarbia, and metabolic acidosis with administration of oxygen, conventional ventilation, and a buffer should restore normal pulmonary vasodilation. Surprisingly, few prospective randomized trials have been conducted of most of the therapeutic modalities advocated for the treatment of PPHN. Older therapies such as hyperventilation and alkalosis were introduced into clinical practice based on animal studies or short-term studies that included very small numbers of patients and used physiologic response rather than patient outcome as the end point. Only the newer therapies of inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO) have been rigorously evaluated in controlled clinical trials. In a National Institute of Child Health and Human Development (NICHD) observational study,[77] the use of hyperventilation varied among the 12 NICHD centers from 33% to 92%, and alkali infusion ranged from 27% to 93%. Similar variation was seen in the use of inotropic agents (46% to 100%) and intravenous vasodilators (13% to 81%). High-frequency ventilation (HFV) use ranged from 0% to 73%, and ECMO use varied

from 0% to 85%. Some of the variation is expected given the wide range of pathophysiology contributing to PPHN. A more likely explanation for the wide variation seen, however, is the overall lack of proven efficacy of many of these therapies.

Hyperventilation and Alkali Infusion

Animal studies documented the sensitivity of the pulmonary vasculature to both hypoxia and acidosis.[79] Short-term studies during cardiac catheterization showed reductions in PAP and elevation of oxygen tension following hyperventilation.[78,80] Based on these studies, hyperventilation became the mainstay of ventilation of term infants with hypoxic respiratory failure and PPHN. In some patients the benefits of hyperventilation may be outweighed by risks of barotrauma or volutrauma. Moreover, subsequent observations have raised concern of impaired cerebral perfusion and neurosensory deafness at extremes of alkalosis.[81,82] Studies of infants with PPHN maintaining normal Pco_2 (40 to 60 mm Hg) indicate similar or better outcomes and with less chronic lung disease.[83,84] Many neonatologists have moved away from the practice of hyperventilation in neonates with PPHN. Animal studies have shown that the beneficial effects of hyperventilation result from altered pH rather than from changes in Pco_2 or minute ventilation.[85,86] At one time alkali infusion to maintain alkaline pH to induce pulmonary vasodilation was a standard practice. In the aforementioned NICHD observational study, the group treated with alkali had a greater chance of treatment with ECMO compared with those treated with hyperventilation and an increased rate of supplemental oxygen at 28 days.[77] Alkali infusion with bicarbonate increases CO_2 production, necessitating higher ventilator support. Lack of patient outcome data with both hyperventilation and alkali infusion and availability of better therapeutic options have led to less use of these outdated management strategies.

Oxygen

Oxygen is a specific and potent pulmonary vasodilator, and increased oxygen tension is an important mediator of reduction in PVR at birth. Alveolar hypoxia and hypoxemia increase PVR and contribute to the pathophysiology of PPHN. Avoiding hypoxemia by mechanical ventilation with high concentrations of oxygen continues to be the mainstay of PPHN management. However, exposure to hyperoxia may result in formation of oxygen free radicals and lead to lung injury. Recent evidence suggests that brief exposure to 100% oxygen in newborn lambs results in increased contractility of pulmonary arteries[87] and reduces response to inhaled NO.[88,89] The biological half-life of endogenous NO is related to the local concentration of superoxide anions (see Figure 48-4).[90] Administration of intratracheal recombinant human superoxide dismutase (an antioxidant that breaks down superoxide anions) results in improved oxygenation in lambs with PPHN.[91,92] Based on these studies, it appears that avoiding hyperoxia is as important as avoiding hypoxia in the management of PPHN.

The optimal Pao_2 in the management of PPHN is not clear. Wung and colleagues[84] have suggested that gentle ventilation with avoidance of hyperoxia and hyperventilation results in good outcome in neonates with respiratory failure. Decreasing Pao_2 below 45 to 50 mm Hg results in increased PVR in newborn calves[79] and lambs.[89] In contrast, maintaining Pao_2 greater than 70 to 80 mm Hg does not result in additional decrease in PVR in both control lambs and lambs with PPHN. In animal studies, hypoxemia results in pulmonary vasoconstriction and normoxemia reduces PVR but hyperoxemia does not result in additional pulmonary vasodilation. However, to date, randomized studies comparing different Pao_2 targets have not been conducted in infants with PPHN.

Lung Recruitment Strategies

Surfactant. Clinical reports suggest that surfactant therapy improves oxygenation in term infants with RDS, pneumonia, and MAS.[93,94] Surfactant administration results in reduced need for ECMO in infants of 36 weeks or greater gestation at birth. Near-term and term infants delivered by elective repeat cesarean section may be one subset of patients who are at risk for deficiency or dysfunction of surfactant and progressive hypoxic respiratory failure.[95] If the cause of PPHN is parenchymal lung disease such as RDS, meconium aspiration or pneumonia, exogenous surfactant may be beneficial in improving oxygenation and reducing the need for ECMO.[94]

High-Frequency Ventilation. Many clinicians use HFV to manage infants with PPHN. Considering the important role of parenchymal lung disease in specific disorders resulting in PPHN, adequate lung inflation and optimal ventilation are as essential as pharmacologic vasodilator therapy. In the case of inhaled vasodilators, optimal inflation and ventilation may be necessary for drug delivery.[96] Infants with PPHN from a variety of causes have been successfully treated with HFV.[97] High-frequency oscillatory ventilation (HFOV) decreases $Paco_2$ and increases oxygenation in infants with PPHN. HFOV may improve oxygenation through safer use of higher mean airway pressures to maintain lung volume and prevent atelectasis. Two studies have evaluated the effectiveness of HFV compared with conventional ventilation in rescuing infants with respiratory failure and PPHN from potential ECMO therapy.[98,99] Neither mode of ventilation was more effective in preventing ECMO in these infants. In clinical pilot studies using iNO, combination of HFOV and iNO resulted in the greatest improvement in oxygenation in some newborns who had severe PPHN complicated by diffuse parenchymal lung disease and underinflation.[100] A randomized controlled trial demonstrated that treatment with HFOV and iNO was often successful in patients who failed to respond to HFOV or iNO alone in severe PPHN, and the differences in responses were related to the specific disease associated with PPHN. Infants with RDS and MAS benefit most from a combination of HFOV and iNO therapy.[101,102]

Nitric Oxide. In 1996 the Food and Drug Administration (FDA) approved iNO for use in neonates who are 35 weeks' gestation and older with PPHN. The physiologic rationale for using iNO for treatment of PPHN[103,104] is based on its ability to achieve potent and selective pulmonary vasodilation without decreasing systemic vascular tone (Figure 48-9). Once iNO enters the intravascular space, it combines with hemoglobin to form methemoglobin and does not exert a vasodilator effect on the systemic circulation. Inhaled NO also exerts a microselective effect and reduces V/Q mismatch. Being an inhaled vasodilator, NO enters only ventilated alveoli and redirects pulmonary blood by dilating adjacent pulmonary arterioles and reduces V/Q mismatch (Figure 48-10). Studies

in newborn lambs have shown that prolonged administration of NO increased survival rates without increasing the incidence of acute lung injury in lambs with PPHN.[105]

Three randomized trials on the use of iNO in newborns with PPHN and respiratory failure were published in 1997. In a randomized controlled clinical trial of patients with PPHN reported by Roberts and colleagues,[106] oxygenation doubled in 58% of treated patients in response to 80 ppm iNO. In addition, twice the proportion of the treated group avoided ECMO compared with the control group. In the Neonatal Inhaled Nitric Oxide Study, 235 infants older than 34 weeks' gestation who were diagnosed with hypoxic respiratory failure were randomly assigned to receive 20 ppm iNO or were assigned to a control group. Infants whose partial pressure of arterial oxygen increased by 20 mm Hg or less were studied for a response to 80 ppm iNO or control gas. The end point of this trial was death or ECMO. Although the mortality rate was no different in either treatment arm, there was a 40% reduction in the need for ECMO among infants treated with iNO compared with control subjects.[107] Only 6% of infants who failed to respond to treatment with 20 ppm of iNO responded to the higher dose in this study. In a study by Kinsella and colleagues,[102] 205 infants with PPHN were randomly assigned to receive iNO and conventional ventilation or to receive HFOV alone. Those who did not respond to either therapy received the combination of iNO and HFOV. Treatment with HFOV in combination with iNO was successful in some patients who did not respond to one treatment alone. The differences were partly related to the specific disease (RDS and MAS) associated with PPHN.[102] Because adequate lung inflation appears to be necessary for optimal response to iNO, lung recruitment strategies with HFOV should augment the response to iNO. Clark and colleagues[108] reported a 38% reduction in ECMO and no difference in mortality among 248 infants randomly assigned to receive 20 ppm iNO for 24 hours followed by 5 ppm for no more than 96 hours. A meta-analysis of the results of seven randomized trials of iNO use in newborns with PPHN demonstrated that 58% of hypoxic near-term and term infants responded to iNO within 30 to 60 minutes.[109] Mortality was not reduced in any of the NO studies analyzed, but use of ECMO as a rescue therapy in nonresponders was significantly decreased.

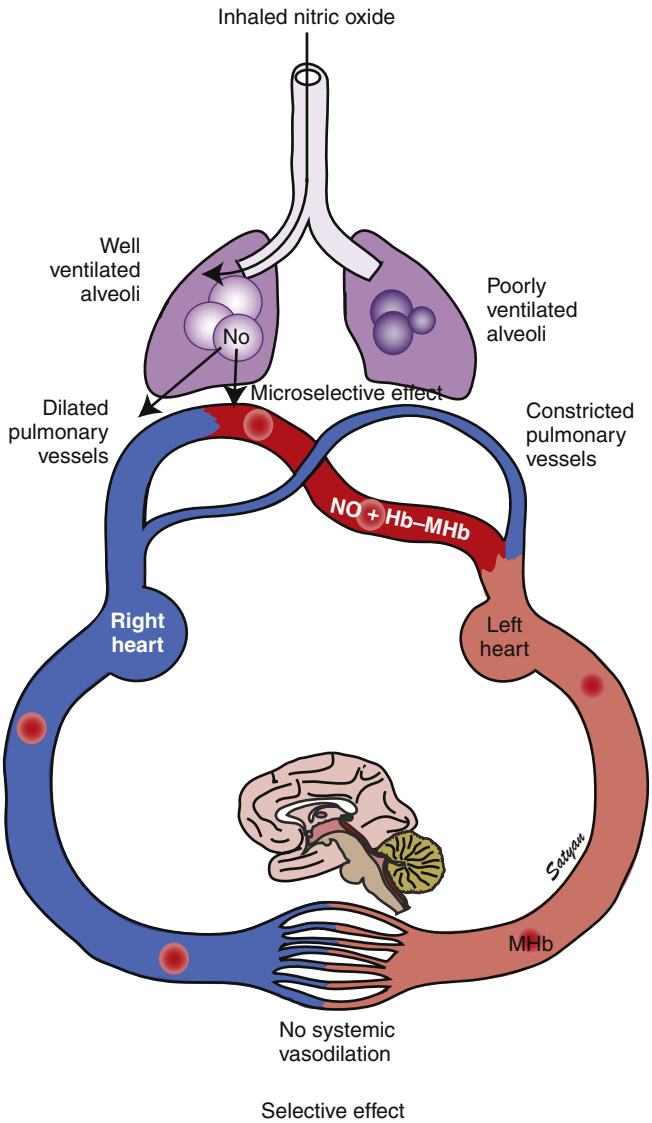

Figure 48–10. Selective and microselective action of inhaled nitric oxide (NO). Inhaled NO is a selective dilator of the pulmonary circulation without any significant systemic vasodilation because it combines with hemoglobin to form methemoglobin (MHb). Because it is an inhaled vasodilator, it selectively goes to the well-ventilated alveoli and improves blood flow to these alveoli and reduces ventilation/perfusion mismatch (microselective effect). *(Copyright Satyan Lakshminrusimha.)*

Inhaled NO by itself is toxic at higher concentrations. Potential adverse effects include methemoglobinemia, pulmonary edema, and platelet dysfunction. NO reacts with superoxide anion to form peroxynitrite, which causes lipid peroxidation and other oxidative injury to cell membranes. NO_2 is even more toxic. Careful monitoring of both NO and NO_2 levels during administration is mandatory. Because the optimal dosing and timing of iNO administration remains unclear and the potential toxicities are dose-related, lower doses might afford both safety and efficacy in the management of these infants. Two studies using 2 ppm iNO yielded contradictory results. In one study, 2 ppm iNO diminished the clinical response to 20 ppm.[110] In the other study, the initial exposure to a very low dose did not compromise the response to higher doses.[111] In a study involving direct measurements of PAP during cardiac catheterization, iNO produced peak improvement in oxygenation at 5 ppm, whereas peak improvement in the pulmonary-to-systemic arterial pressure ratio did not occur until an iNO dose of 20 ppm, which suggests that an initial dose of 20 ppm is optimum for the treatment of PPHN.[112] The use of higher doses of iNO is associated with increased methemoglobin levels, especially at 80 ppm but not at 40 or 20 ppm.[113] The results of randomized controlled trials support the use of iNO at starting does of 20 ppm in near-term and term infants. In summary, iNO offers substantial benefit to a large proportion of near-term and term newborns with hypoxic respiratory failure who do not respond to ventilatory support, lung recruitment, and oxygen.

The timing of initiation of iNO in patients with hypoxic respiratory failure is not clear. Severity of hypoxemia in neonates is measured by oxygenation index (OI = Mean airway pressure in cm of water × FIO_2 × 100/PaO_2 [in mm Hg]). An OI of 40 is often used as an indication for ECMO therapy. An OI of 25 is associated with a 50% risk of requiring ECMO or dying.[37] Thus the acceptable indication for treatment with

iNO include an OI greater than 25 with echocardiographic evidence of PPHN or a higher OI with or without evidence of right-to-left shunt. However, it has been suggested that initiating iNO at a lower OI may be associated with reduced need for ECMO.[114] Konduri and colleagues[115] randomly assigned neonates who were born at 34 weeks' gestation or later, required assisted ventilation, and had an OI of 15 or greater and less than 25 to receive early iNO or to receive simulated initiation of iNO (control). Infants who had an increase in OI to 25 or more were given iNO as standard therapy. Arterial oxygen tension increased by more than 20 mm Hg in 73% of infants who received early iNO (n = 150) and in 37% of infants in the control group (n = 149) after study gas initiation. Infants in the control group received standard iNO and deteriorated to an OI score greater tha 40 more often than did infants who were given early iNO. The incidence of death (early iNO group, 6.7% vs. control group, 9.4%), ECMO (10.7% vs. 12.1%), and their combined incidence (16.7% vs. 19.5%) were similar in both groups.[115] Follow-up evaluations showed no differences between the 2 groups in the incidence of neurodevelopmental impairment (early iNO group, 27%; control group, 25%) and hearing impairment (early iNO group, 23%; control group, 24%). Mental development index scores were similar in the two groups; however, psychomotor developmental index scores were significantly higher in the control group (early iNO group, 89 ± 17.7; control group, 93.5 ± 18.4).[116] These findings suggest that caution must be exercised while initiating iNO at lower OI levels.

Inhaled NO should be weaned gradually to avoid rebound PH.[117] A flow diagram showing the protocol for weaning iNO at The Women and Children's Hospital of Buffalo is shown in Figure 48-11.

The outcome of infants treated with iNO collectively supports both the efficacy and safety of this mode of treatment. Reports identify significant medical and neurodevelopmental sequelae of PPHN with or without iNO and point out the necessity for coordinated multidisciplinary follow-up for these infants. The overall rate of neurodevelopmental handicap in infants treated with NO was 46%, with 25% mildly affected and 21% severely affected at age 1 year in one study.[118] In another study, mild and severe neurodevelopmental handicaps were 14% and 12% at age 1 year and 9% and 12% at age

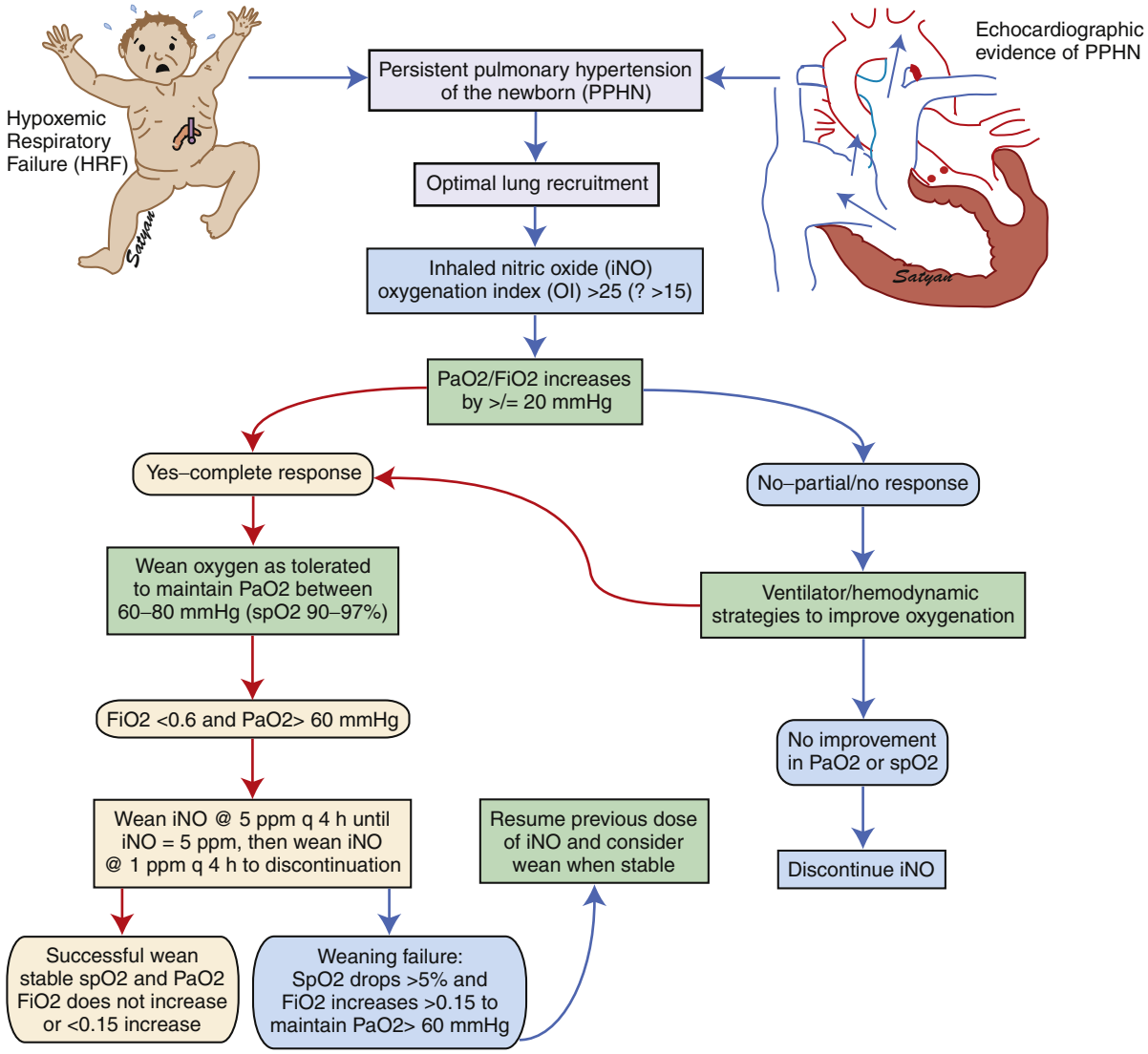

Figure 48–11. Weaning protocol for inhaled nitric oxide in use at The Women and Children's Hospital of Buffalo, NY.

2 years.[119] In these studies sensorineural hearing loss was present in 6% to 19% of infants with PPHN treated with iNO. No difference was noted between control and treatment groups for these outcomes. Published reports on the use of iNO in ECMO centers have not substantiated early concerns that iNO would adversely affect outcome by delaying ECMO utilization. Inhaled NO treatment may play an important role in stabilizing patients before ECMO is initiated, thus improving the chances of ECMO cannulation without further clinical deterioration. The Committee on the Fetus and Newborn of the American Academy of Pediatrics has suggested that iNO use be limited to tertiary care centers where ECMO is available.[120] In non-ECMO centers, a system should be in place to continue iNO during transport even if a response occurs, because not all physiologic responders avoid ECMO. For the same reason, the combination of HFOV and iNO should be used cautiously in non-ECMO centers.

Inhaled NO is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood (such as hypoplastic left heart syndrome). Also, patients with preexisting left ventricular dysfunction treated with iNO, even for short durations, have a high risk of pulmonary edema (package insert, INOmax, 2009).

Phosphodiesterase Inhibitors

Vasodilators such as NO and prostacyclin relax vascular smooth muscle by increasing intracellular concentrations of the second messengers cGMP (see Figure 48-4) and cAMP, respectively (see Figure 48-5). However, nearly 40% of patients with PPHN do not demonstrate a sustained improvement in oxygenation with this management. Because iNO is not universally effective, there has been considerable interest in understanding and targeting other biochemical pathways that regulate pulmonary vasoconstriction in PPHN. Inhibition of the cGMP degrading phosphodiesterase (PDE_5) by sildenafil and inhibition of the cAMP degrading phosphodiesterase (PDE_3) by milrinone offer additional tools to achieve pulmonary vasodilation in patients with PPHN. Two studies have evaluated the use of oral sildenafil in PPHN.[121,122] In centers lacking iNO therapy, oral sildenafil (dose range 1 to 3 mg/kg every 6 hours) has been shown to improve oxygenation and reduce mortality. A recent study showed that intravenous (IV) sildenafil was effective in improving oxygenation in patients with PPHN with and without prior exposure to iNO.[123] Systemic hypotension was the most common adverse effect. Administration of a loading dose slowly over 3 hours followed by a maintenance dose of sildenafil reduced the risk of systemic hypotension. These data suggest a beneficial effect for oral as well as IV sildenafil in patients with PPHN. Because oral or IV agents are not selective to pulmonary circulation, caution must be exercised about the risk of systemic hypotension with oral sildenafil. IV sildenafil is not available currently in the United States, but the same caution regarding systemic hypotension exists. The use of oral sildenafil for treatment of PH is approved by the FDA for adults but not for children.

Milrinone is the prototype PDE_3 inhibitor and is commonly used in adult and pediatric intensive care settings as an inotropic vasodilator. Agents that increase cAMP levels in pulmonary arterial smooth muscle cells (such as milrinone and prostacyclin) provide an alternate pathway of pulmonary vascular relaxation and potentially result in improved oxygenation in patients with poor response to iNO. In newborn lambs with PPHN, milrinone effectively relaxes pulmonary arteries[124] and improves oxygenation.[125] There is a marked increase in PDE_3 activity and reduced cAMP in pulmonary arteries following ventilation of lambs with iNO.[126] Milrinone can be effective in PPHN by inhibiting PDE_3 and increasing cAMP, causing direct pulmonary vasodilation and a synergistic effect with iNO. Milrinone may also improve cardiac function by positive inotropy (improved contraction), lusitropy (improved relaxation), and reduced ventricular afterload. Bassler and colleagues[127] and McNamara and associates[128] described 13 patients with PPHN refractory to iNO from Ontario, Canada, who were treated effectively with intravenous milrinone. This therapy is associated with a risk of hypotension and intraventricular hemorrhage and is not currently approved by the FDA.

Extracorporeal Membrane Oxygenation

If the heart and lungs cannot support the newborn, they can be bypassed with ECMO. Several randomized trials have indicated improved survival of infants supported with ECMO. In a large prospective trial conducted in the United Kingdom, 121 infants with severe respiratory failure were randomly assigned to ECMO or conventional management.[129] Survival in the patients treated with ECMO was significantly greater than in the control group (68% vs. 41%). Neurologic outcome was similar among survivors of either treatment arm, indicating that ECMO likely did not contribute to morbidity in this group of critically ill infants. ECMO has been shown to be both clinically[129] and economically[130] justifiable for mature newborn infants with severe respiratory failure. ECMO is not a specific treatment for any disease but rather a method of supportive treatment, in which the patient is kept alive while the lungs and their vasculature recover. As newer treatment modalities including HFOV, surfactant therapy, and NO have become available for treatment of hypoxemic respiratory failure, ECMO use in newborns has decreased considerably.[131,132] Because of serious inherent risks, such as systemic and intracranial hemorrhage, for infants with PPHN, the procedure presently is reserved for newborn infants with reversible pulmonary disease in whom alternative therapies have failed. However, ECMO should be initiated before the infant is moribund.

Considerable progress has been made in the last two decades in understanding the pathophysiology of PPHN and its management. While the need for ECMO for neonates with PPHN is decreasing, this syndrome continues to be associated with high mortality and morbidity, emphasizing the need for novel treatment strategies to improve outcome in PPHN. Vascular mediators such as phosphodiesterase inhibitors currently are being used experimentally in infants. Newer experimental therapies such as antioxidants, Rho-kinase inhibitors, L-citrulline, and inhaled prostacyclin analogs are under investigation.

Pulmonary Arterial Hypertension in Children

After the newborn period, pulmonary arterial hypertension (PAH) in children is an uncommon disease characterized by elevated PAP either at rest or during exercise. Progressive obliteration of the pulmonary vascular bed is the hallmark

of PAH. Primary pulmonary hypertension (PPH) is a rare disease in children that predominantly affects adolescents and young people in whom no apparent cause for PAH can be identified. In secondary PAH, a coexisting disease can be identified that presumably explains the PAH. As per World Health Organization (WHO) classification,[133] the term PAH refers to a disease spectrum with a similar clinical and pulmonary histopathology that includes PPH and PAH, which cannot be distinguished from PPH. This includes patients with PPH, both sporadic and familial, as well as pulmonary arterial hypertension associated with collagen vascular disorders, congenital systemic to pulmonary shunts, human immunodeficiency virus, CHD, portal hypertension, hemoglobinopathies, myeloproliferative disorders, and appetite suppressants (Box 48-1). Familial PAH often results from a mutation in the bone morphogenic protein receptor-2 and is inherited as an autosomal dominant disease with incomplete penetrance. These groups together comprise WHO Group I PAH. Other WHO categories include Group II, PH with left heart disease; Group III, associated with lung disease and/or hypoxemia; Group IV, PH due to chronic thrombotic and/or embolic disease; and Group V, miscellaneous cause of PAH. Despite recent advances leading to early recognition and new therapies, PAH remains a serious life-threatening condition. Most of the abnormalities in PAH have been linked to the recent advances in our understanding of smooth muscle cell physiology, endothelial and platelet dysfunction, vascular remodeling, and genetics to provide insight into its pathophysiology. It is important to establish an accurate diagnosis with respect to etiology of PAH because therapy may vary with etiology. For instance, thromboembolic disease is often amenable to surgery with excellent results from thromboendarterectomy. Similarly, secondary PAH may result from a left-sided heart lesion with pulmonary venous hypertension.

Box 48–1 Revised WHO Classification of PH

1. Pulmonary arterial hypertension (PAH)
   - 1.1. Idiopathic (IPAH)
   - 1.2. Familial (FPH)
   - 1.3. Associated with (APAH):
     - 1.3.1. Connective tissue disorder
     - 1.3.2. Congenital systemic-to-pulmonary shunts
     - 1.3.3. Portal hypertension
     - 1.3.4. HIV infection
     - 1.3.5. Drugs and toxins
     - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
   - 1.4. Associated with significant venous or capillary involvement
     - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
     - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   - 2.1. Left-sided atrial or ventricular heart disease
   - 2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   - 3.1. Chronic obstructive pulmonary disease
   - 3.2. Interstitial lung disease
   - 3.3. Sleep disordered breathing
   - 3.4. Alveolar hyperventilation disorders
   - 3.5. Chronic exposure to high altitude
   - 3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
   - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2. Thromboembolic obstruction of distal pulmonary arteries
   - 4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous (sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

HIV, Human immunodeficiency virus; *PH,* pulmonary hypertension; *WHO,* World Health Organization.

From McLaughlin VV, Archer SL, Badesch DB, et al: Expert consensus document on pulmonary hypertension, *J Am Coll Cardiol* 53(17):1573-1619, 2009.

Pathophysiology

PAH is a syndrome resulting from restricted flow through the pulmonary arterial circulation, which leads to pathologic increases in PVR and ultimately to right heart failure. The mechanisms responsible for the development of PAH are complex and incompletely understood. In persons with PPH, hyperreactive lung vessels in which various stimuli initiate vasoconstriction may explain the subsequent development of characteristic vascular lesions.[134] The vascular endothelium is regarded as an important source of locally active mediators that contribute to the control of vasomotor tone. The thromboxane/PGI_2 and NO/ET-1 system are two of the important balances that control pulmonary vasomotor tone. Endothelial injury/dysfunction may lead to vascular remodeling and progressively increasing vascular obstruction and loss of vascular luminal cross-section and obliteration (Figure 48-12). Risk factors that are associated with PPH include the use of anorexic drugs, family history of PH, infection with human immunodeficiency virus, cirrhosis, and the use of cocaine or intravenous drugs.[135]

ET-1 is a potent vasoconstrictor and stimulates pulmonary artery smooth muscle cell (PASMC) proliferation. Plasma levels of ET-1 are increased in patients with PAH and correlate with the severity of PAH and prognosis.[136] Of the two ET-1 receptors, ETa receptors, which are expressed mainly in the smooth muscle, mediate vasoconstriction and cell proliferation, whereas ETb receptors, which are expressed mainly in the endothelial cells, are important for clearance of ET-1, release of NO and PGI_2, and inhibition of endothelin-converting enzyme-1.[30,137] In experimental studies of hypoxia-induced[138] and monocrotaline-induced PH,[139] chronic ET receptor blockade lowered PAP and the incidence of vascular and pulmonary injury and improved NO-mediated pulmonary vasodilation. Studies with L-ω-nitroarginine methyl ester–induced PH suggest that ET-1 is linked to the dysfunction of the L-arginine/NO pathway[140] because ETa selective[141] but not combined ET blockade[142] improves endothelial function. Thus selective inhibition of ETa receptors improves the endothelial L-arginine/NO pathway that agrees with observations in humans.[143] ET-1 expression in pulmonary arteries is increased in patients with primary and secondary PH.[144,145] ET-1 increases at high altitudes in mountaineers and correlates

with pulmonary pressures and oxygen tension.[146] ET increases even more in mountaineers prone to high altitude pulmonary edema.[147] Increased local production[145] and elevated circulating levels of endothelin[148] have been demonstrated in patients with Eisenmenger syndrome,[149] PPH,[150] and in PAH associated with CHD.[151]

PGI_2 is a powerful vasodilator and an inhibitor of platelet aggregation, whereas TXA_2 is a vasoconstrictor and induces platelet aggregation leading to microvascular thrombus formation and hence vascular injury. Because TXA_2 and PGI_2 have opposing effects on platelet aggregation and pulmonary vascular smooth muscle, an imbalance in their biosynthesis could contribute to the progressive increase in PVR seen in older untreated patients with pulmonary hypertensive CHD.[152] Decreased urinary excretion of 2,3-dinor-6-keto prostaglandin $F_{1\alpha}$, a metabolite of PGI_2, occurs in patients with PPH.[153] In patients with PAH, the balance between these two molecules is shifted toward TXA_2,[153] favoring thrombosis, proliferation, and vasoconstriction. A decrease in expression of the enzyme PGI_2 synthase (PGI_2-S) in the lung may be an important manifestation of pulmonary endothelial dysfunction in patients with severe PH. PGI_2-S is decreased in small- and medium-sized pulmonary arteries, and the loss of expression of PGI_2-S may represent one of the phenotypic alterations present in the pulmonary endothelial cells in patients with severe PAH.[154] Pulmonary PGI_2-S overexpression in transgenic mice protects against development of hypoxic PH.[155] PGI_2-S may play a major role in modifying the pulmonary vascular response to injury. Intratracheal transfer of human PGI_2-S gene has been shown to augment pulmonary prostacyclin synthesis, ameliorate monocrotaline (MCT)-induced PH and improve survival in MCT rats.[156]

Potassium (K+) channels play an important part in smooth muscle cell electrophysiology, which has implications for the development of PAH. The inhibition of voltage-gated K+ (Kv) channels results in an accumulation of positively charged K+ ions within the cell, hence depolarizing the cell and activating the voltage-gated, L-type calcium channel.[157] Calcium then enters the cell, activating the contractile apparatus, leading to vasoconstriction, and possibly initiating cell proliferation. Acute hypoxia seems to initiate vasoconstriction in part by inhibiting the Kv channel in PASMC.[157] In humans with PPH, Kv1.5 messenger ribonucleic acid (mRNA) levels are reduced in PASMC.[158] This down-regulation of Kv1.5 is associated with inhibition of the K+ current, membrane depolarization, and elevation of cytosolic Ca++. Thus decreased expression or function of K+ channels in PASMC in patients with PPH could initiate and/or maintain pulmonary vasoconstriction and play a role in the pathogenesis of PPH.[158] The use of anorexic agents like aminorex, fenfluramine, and dexfenfluramine is associated with the development of PPH,[135] and these agents are thought to act by blocking the Kv channel.[159] Kv2.1 is inhibited by dexfenfluramine, a weight-loss drug that is associated with the development of PAH.[159] Anorexigen-induced Kv channel inhibition and membrane depolarization can contribute to pulmonary vasoconstriction.[160,161] Fenfluramine reduces the Kv1.5 mRNA levels by 50% in PASMC from normotensive patients,[162] suggesting that inhibited gene transcription and expression of Kv channels may play an important role in anorexigen-induced PAH.

Matrix metalloproteinases (MMP) and extracellular matrix are thought to be important in vascular remodeling and hence proliferation of SMCs. Endothelial abnormalities early in the course of PAH may permit extravasation of factors that stimulate SMC production of vascular serine elastase.[163,164] This results in the liberation of matrix-bound SMC mitogens, such as basic fibroblast growth factor, and enhances matrix degradation by activating other MMPs. The MMPs stimulate the production of mitogenic cofactor, tenascin, leading to phosphorylation of growth factor receptors and smooth muscle cell (SMC) proliferation. When MMPs are inhibited, tenascin levels fall, leading to apoptosis.[163] Direct inhibition of MMP-2 and serine elastases lead to complete regression of experimental PH in rats,[165] suggesting that they regulate vascular tone. MMP-2 and MMP-9 can activate platelets,[166] and intravascular MMP-2 can enhance the formation of vasoconstrictors and inhibit the action of endogenous vasodilators.[167]

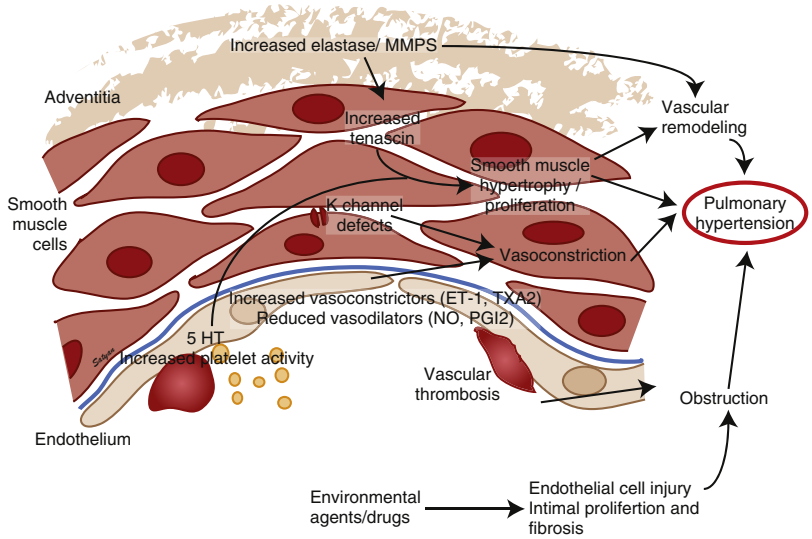

Figure 48–12. Schematic depicting the pathways involved in the pathogenesis of pulmonary arterial hypertension in children. *ET-1*, Endothelin-1; *MMPs*, matrix metalloproteinases; *NO*, nitric oxide; *PGI_2*, prostacyclin; *TXA_2*, thromboxane A_2; *5 HT*, 5 hydroxytryptamine. *(Copyright Satyan Lakshminrusimha.)*

A number of other less well-studied factors potentially are involved in the pathogenesis of PH. Abnormalities of the thrombomodulin/protein C anticoagulant system with a decrease in soluble thrombomodulin and an increase in fibrinolytic inhibitor plasminogen activator 1 have been noted in patients with PPH.[168] Whether hypercoagulability occurs in response to PAH or can actually initiate PAH is unclear, but it likely contributes to disease progression. Serotonin (5-hydroxytryptamine or 5-HT) and serotonin transporter (5-HTT) have been shown to promote development of hypoxic PH by stimulating PASMC growth.[169] 5-HTT activity may play a role in the pathogenesis of PASMC proliferation in PPH, and a 5-HTT polymorphism may confer susceptibility to PPH.[170] Mutations in the 2 genes in the transforming growth factor-β receptor pathway BMPR2 and activin-like kinase 1, have been implicated in the pathogenesis of familial PAH.[171,172] Many different BMPR2 mutations occur in familial PAH. These mutations, which lead to loss of function in the SMAD signaling pathway, are prevalent in familial PAH.[171] Activin-like kinase-1 mutations, detected in a group of patients with hereditary hemorrhagic telangiectasia and PAH,[172] are also thought to result in growth-promoting alterations of SMAD-dependent signaling.

Pulmonary Vascular Histopathology

PAH is a panvasculopathy predominantly affecting small pulmonary arteries and is characterized by a variety of arterial abnormalities, including intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation ,and plexiform arteriopathy (Figure 48-13). Heath-Edwards introduced the first comprehensive classification of PAH based on the histopathology of pulmonary vasculature[173] in children with CHD or idiopathic PH (Table 48-2). Grade I referred to changes seen in patients with CHD associated with PH from birth. Grades II to IV were classified as a result of raised PAP. Grades V and VI often overlap and represent advanced disease. Rabinovitch[174] introduced a morphometric classification system in 1978 by studying lung biopsies of 50 patients with CHD (Table 48-3). The presence and severity of pathologic lesions correlated with increased pulmonary blood flow (PBF), elevated PAP, and elevated PVR. The most familiar patterns of pulmonary vascular lesions begin with medial hypertrophy followed by cellular proliferation and concentric laminar intimal fibrosis. Eventually dilatated lesions, fibrinoid necrosis, and plexiform lesions develop, and the disease is referred as Eisenmenger syndrome.[175] The

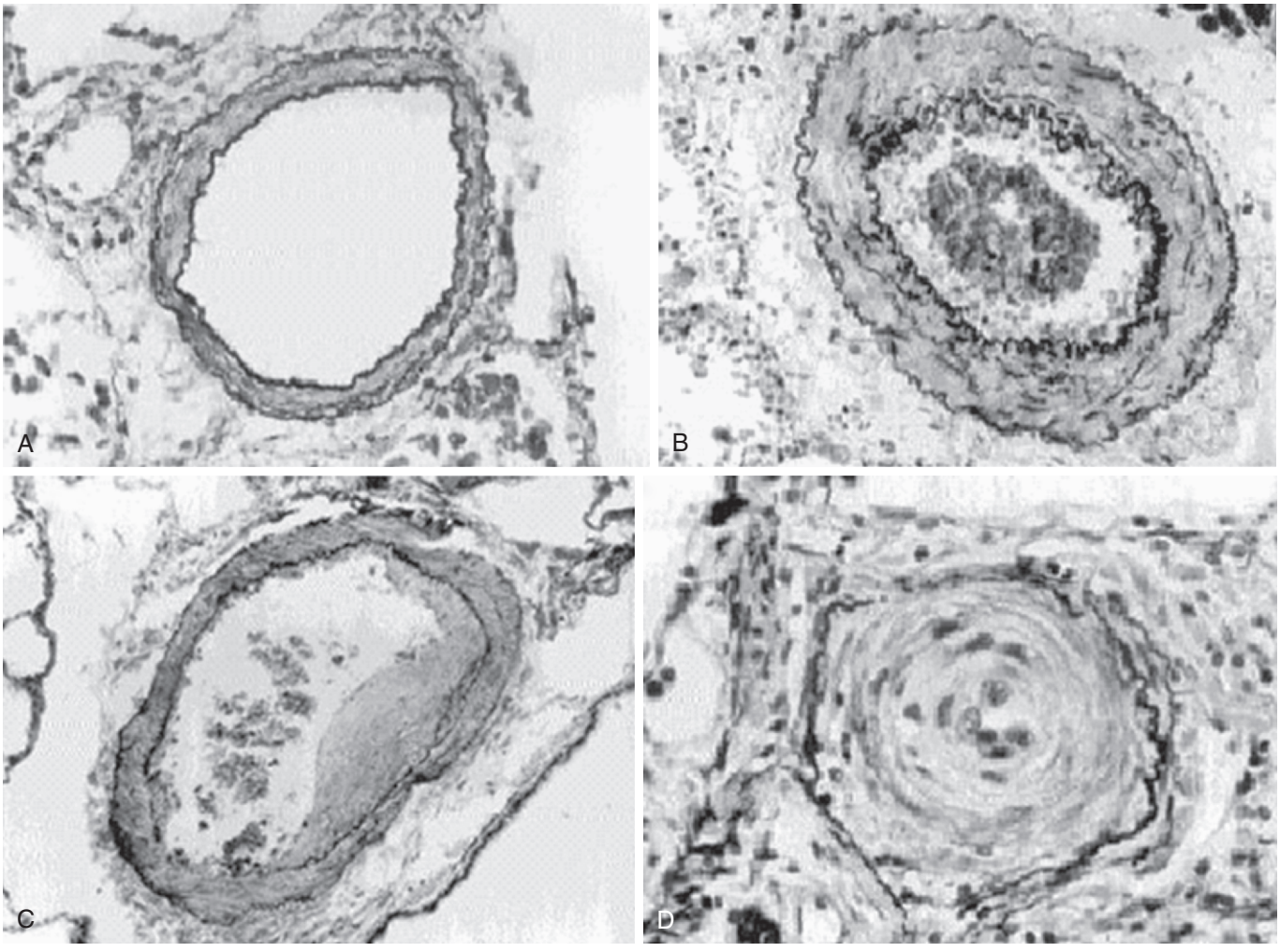

Figure 48–13. **A,** Normal small pulmonary artery with typically thin muscular wall. **B** through **D** show some of the changes that can occur in primary pulmonary hypertension. **B,** Wall or small pulmonary artery thickens. **C,** Fibrous or scarred tissue appears on inner wall of small pulmonary artery. **D,** Bands of scarred tissue build up on inner wall of small pulmonary artery, substantially narrowing the blood vessel.

Table 48–2 Heath-Edwards Classification of Pulmonary Vascular Disease

Grade	Pulmonary Vascular Pathology
I	Retention of fetal-type pulmonary vessels
II	Medial hypertrophy with cellular intimal proliferation
III	Medial hypertrophy; intimal fibrosis; early generalized vascular dilatation in severe instances
IV	Progressive generalized arterial dilation and occlusion by intimal fibrosis with the formation of complex dilation lesions (plexiform lesions)
V	Chronic dilation with formation of numerous dilation lesions including veinlike branches of hypertrophied arteries, cavernous and angiomatous lesions, and pulmonary hemosiderosis
VI	Necrotizing arteritis

Table 48–3 Morphometric Classification of Pulmonary Vascular Disease

Grading	Vascular Pathology
Grade A	Abnormal extension of smooth muscle along smaller peripheral arteries with intra-acinar extension (arteries accompanying respiratory bronchiole, alveolar duct and alveolar wall) (corresponds to Heath-Edwards grade I); associated with ↑ PBF without evidence of ↑ PAP
Grade B	In association with abnormal extension of the muscle, the medial muscular coat of the intra-acinar and preacinar arteries is thicker than normal (corresponds to Heath-Edwards grade I); when mild not associated with PAH; when more than twice normal is associated with PAH
Grade C	In association with abnormal extension and increased thickness of the muscular coat, the number of intra-acinar and preacinar arteries are reduced in number (high alveolar-arterial ratio); associated with moderate to severe elevation in PVR

PAH, Pulmonary arterial hypertension; *PAP,* pulmonary artery pressure; *PBF,* pulmonary blood flow; *PVR,* pulmonary vascular resistance.

progressive vascular lesions that occur in patients with PPH are identical to those that occur with CHD involving systemic to pulmonary shunts.[173] Based on these findings, similar therapeutic approaches have been used in children who have PPH and those who have PAH associated with CHD.

In patients with CHD, morphologic criteria[175] and pulmonary hemodynamics are both used to determine the stage beyond which surgical correction is no longer indicated because established disease will cause an unacceptable high operative risk or will continue to progress despite surgical repair.[176] Abnormalities in muscularization and growth of pulmonary arteries obtained at biopsy during surgical repair from patients with CHD correlated with preoperative hemodynamic data of increased pulmonary blood flow, pressure, and resistance.[175] Pulmonary vascular structural changes assessed by morphometry[175] (see Table 48-3) and Heath-Edwards classification[173] (see Table 48-2) in lung tissue obtained by biopsy at the time of surgical repair correlated with the postoperative hemodynamic findings of PAP and PVR measured 1 day and 1 year after surgery. One year after repair, mean PAP and PVR were normal in all patients whose conditions were surgically corrected before 9 months of age regardless of the severity of pulmonary vascular changes. PAP and PVR were increased in all patients whose conditions were repaired after 2 years of age with grade C morphometric findings and to a severe degree if associated with Heath-Edwards grade III. Thus although Heath-Edwards grade usually can be used to identify patients at risk for PH in the early postoperative period, both the morphometric and Heath-Edwards grades as well as age of the patient at the time of repair can be used to determine whether PAP and PVR eventually return to normal or remain elevated.

Congenital Heart Disease

Pulmonary vascular disease remains a significant cause of morbidity and mortality in children with CHD. Congenital heart lesions resulting in increased PBF or pulmonary venous obstruction produce pulmonary artery smooth muscle hypertrophy and hyperplasia and pulmonary vasoconstriction.[178] Unless PH is treated either by medical or surgical means, pulmonary vasoconstriction may persist, progress to vascular obliteration, and produce a high morbidity. Pulmonary hypertensive crisis in the immediate postoperative period is a life-threatening complication in children with certain types of CHD, despite a good surgical repair.[179] Even though early surgical repair has been advocated to prevent later pulmonary vascular obstructive disease, it does not abolish the occurrence of PH in the immediate postoperative period.[180] Microemboli, platelet aggregation, compliment activation, pulmonary leukosequestration, excess production of vasoactive mediators, atelectasis, and hypoxia during cardiopulmonary bypass all contribute to elevated PVR in the immediate postoperative period. The effects on the pulmonary vasculature may be insidious over several hours, presenting as low cardiac output and right heart failure or more acutely as pulmonary hypertensive crisis. In such situations, the PAP increases to systemic or suprasystemic levels, systemic blood pressure falls, and the arterial oxygen saturation drops. In one large center, half of the postoperative cardiac children who had pulmonary hypertensive crises died during their hospitalization.[181] In the newborn, parenchymal lung disorders including pulmonary edema, intrapulmonary shunting, and pneumonia may coexist with heart disease, resulting in hypoxic respiratory failure following cardiopulmonary bypass.

Pulmonary endothelial damage is an early histological event in children with CHD and pulmonary hypertension.[182] Reduced pulmonary vasodilation to acetylcholine demonstrates a physiologic impairment of endothelial function in these children.[183] Loss of local endothelial NOS activity may be one of the contributing factors in postoperative pulmonary hypertensive crisis. It has been suggested that cardiopulmonary bypass also may contribute to endothelial dysfunction. Arteries with endothelial damage are particularly sensitive to exogenous NO, and response to inhaled NO in the postoperative period suggests that the capacity for smooth muscle relaxation and pulmonary vasodilatation is intact in these children.[184] Even though NO-induced vasodilation varies among children with PH and elevated PVR, a decline in selective

response seems to parallel the progression of established vascular disease and thus may help in selecting patients to undergo surgery.[185] An increase in the number of ETa receptors in lung arteries and lung parenchyma has been noted in patients with increased PVR and low PBF.[186] Up-regulation of the ET-1 system may play a role in the pathogenesis of secondary PH associated with CHD in children.[186]

Clinical Presentation

Often no correlation exists between the time PPH is thought to have started, the age at which it is diagnosed, and the severity of symptoms. The disease seems to progress fairly rapidly, especially in children. Frequent tiredness, dyspnea, dizziness, and fainting spells are the typical early symptoms. Some of the other symptoms include edema of legs, cyanosis, palpitations, and chest pain. Exertional dyspnea, chest pain, and syncope result from the inability to increase cardiac output in the presence of increased oxygen demand. Examination findings compatible with PH in children include jugular venous distention, systolic murmur of tricuspid regurgitation, loud second heart sound at the base of the heart, and a diastolic murmur of pulmonary regurgitation (Graham Steel murmur). In patients with PAH and right heart failure hepatomegaly, ascites and peripheral edema may be seen. Initially the RV hypertrophies to maintain cardiac output at rest, although the ability to increase cardiac output during exercise may be impaired. As pulmonary vascular disease progresses, RV dysfunction ensues, resulting in right heart failure. Although the left side of the heart is not directly affected by pulmonary vascular disease, progressive right heart dilatation can impair left ventricular filling.[187] Depending on the degree of physical limitation by symptoms, the functional level of patients is graded from I to IV, with higher grades representing severe disease and worse prognosis. The New York Heart Association (NYHA) classification of dyspnea has been modified by the WHO to categorize PH by the severity of symptoms that, unlike PAP, correlate well with survival (Table 48-4).

Table 48–4 WHO Functional Classification for Pulmonary Hypertension (Modified After NYHA Classification)

WHO Class	Description
Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity; they are comfortable at rest; less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms; these patients manifest signs of right heart failure; dyspnea and/or fatigue may be present even at rest; discomfort is increased by any physical activity

NYHA, New York Heart Association; *WHO,* World Health Organization.

Diagnostic Approach

The diagnosis of PAH is made based on a clinical and a comprehensive diagnostic evaluation. Chest radiographs, pulmonary function tests, and sleep study will help in ruling out pulmonary causes of PH. Chest radiographs may demonstrate enlarged central pulmonary arteries, right heart enlargement, or evidence of a left-sided heart lesion. Etiologic clues of parenchymal lung disease or an airway lesion may be demonstrated. Pulmonary function tests and exercise testing are important not only for diagnosis but also for monitoring progression of the disease. Other tests that may help in the diagnosis include autoantibody testing for collagen vascular disorders, HIV testing, and liver function tests in cases of portopulmonary hypertension. An electrocardiogram will show right axis deviation and RV hypertrophy with strain. If PH is suspected based on history, risk factor assessment, and physical examination, an echocardiogram is the next appropriate study.

Doppler echocardiography may offer clues to the potential etiologies of PH, particularly left-sided heart lesions. RV systolic pressures greater than 35 to 40 mm Hg in a patient with unexplained dyspnea may warrant further evaluation of PAH. Common echocardiographic findings of PAH include right atrial and rRV enlargement, reduced RV function, tricuspid regurgitation, flattening of intraventricular septum, and underfilling of the left ventricle. In a clinical setting, findings of Doppler echocardiography suggest the diagnosis of PAH, but right heart catheterization (RHC) may eventually be required for an accurate assessment of PVR to confirm the diagnosis. Other noninvasive modalities such as computed tomography (CT) and/or magnetic resonance imaging (MRI) should be explored before subjecting the patient to a catheterization procedure. CT scanning may suggest an etiology of PAH such as a severe airway or parenchymal lung disease. Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of PH and should be sought in all patients with clinically significant PH because it is curable with surgery. CT and V/Q scans help in the diagnosis of CTEPH. Presence of ground-glass opacities, particularly with a centrilobular distribution, septal lines, and adenopathy on a CT scan are suggestive of pulmonary venoocclusive disease in a patient displaying symptoms of PH.[188] Pulmonary venoocclusive disease is an unusual form of PH, characterized by elevated PAP with a normal pulmonary capillary wedge pressure and evidence of venous congestion on chest radiograph. Cardiac MRI accurately assesses size and function of the RV with a high degree of reproducibility and hence is used as a prognostication tool in the management of PAH.[189] Despite the aforementioned noninvasive investigations, catheterization may be needed to define the hemodynamic profile, to confirm the diagnosis of PAH, to perform vasoreactivity testing on confirmation of diagnosis, and most important, to begin a specific management plan for the treatment of PAH.

The current hemodynamic definition of PAH is a mean PAP greater than 25 mm Hg; a pulmonary capillary wedge pressure, left atrial pressure or left ventricular end-diastolic pressure of 15 mm Hg or less and a PVR greater than 3

Wood units.[190] Any patient with suspected PAH requires a careful invasive assessment of pulmonary hemodynamics. Many causes of elevated PA pressure (PH) are not caused by pulmonary vascular disease. Pulmonary hypertension commonly occurs with high transpulmonary flow states such as exercise, anemia, pregnancy, sepsis, portopulmonary syndrome, or thyrotoxicosis. In these states, the pulmonary vascular bed is anatomically normal and the PH resolves when the cardiac output returns to normal levels. The consensus document on PH requires elevated PVR as opposed to simply elevated mean PAP in the setting of a normal left heart filling pressures. PVR is a more robust diagnostic criterion for PAH because it reflects the influence of transpulmonary gradient and cardiac output and is only elevated if the vascular obstruction occurs within the precapillary pulmonary circulation. PVR is a useful measure to apply to patients with increased mean PAP. PVR distinguishes passive PH (i.e., elevated mean PAP and normal PVR) from PPH caused by pulmonary vascular disease (i.e., elevated mean PAP and elevated PVR). By definition, PVR and PAP are both elevated in PAH.[133]

All patients suspected of having PAH after noninvasive evaluation should undergo RHC prior to initiation of therapy specific to PAH. Although RHC and pulmonary angiography are invasive, they can be performed safely by experienced operators even in patients with severe PH and right heart failure. In a recent review of 7218 RHC procedures collected retrospectively and prospectively, 76 serious events (1.1%) were reported. Most of them were related to venous access (e.g., hematoma or pneumothorax), followed by arrhythmias and hypotensive episodes related to vagal reactions or pulmonary vasoreactivity testing with a overall procedure-related mortality of 0.05% (4/76).[191]

Acute Vasodilator Testing

Vasoreactivity testing in an essential component in the diagnostic evaluation of PAH, because this has therapeutic implications. Responders are more likely to respond to oral calcium channel blockers (CCB) than are nonresponders and seem to have a better prognosis.[192] Acute vasodilator testing (AVT) is usually performed during the same procedure as the diagnostic RHC. AVT is performed using iNO, intravenous PGI_2,[194] or intravenous adenosine.[195] Inhaled NO is the commonly used drug for AVT at doses of 20 to 40 ppm for 5 minutes. Hemodynamic measurements are recorded prior to and after administration of iNO, and the drug is discontinued completely. Based largely on the data from Sitbon and colleagues,[192] the European Society of Cardiology and American College of Chest Physicians guidelines propose that the acute response to vasodilator testing be defined as a decrease in mean PAP by at least 10 mm Hg to an absolute level of less than 40 mm Hg without a decrease in cardiac output.[196] While these criteria are insufficient to capture all patients who may be responsive to long-term CCB therapy, it will reliably identify those who are least likely to benefit from oral CCB therapy and therefore provide the greatest degree of safety.[133] Patients with PAH due to conditions other than idiopathic PAH, such as BMPR2 genotype or anorexigen-induced PAH, have a very low rate of long-term responsiveness to oral CCB therapy. Accordingly, the decision to proceed with AVT in such patients should be individualized. AVT is not indicated and may be harmful in patients with significantly elevated left heart filling pressures.[133]

Treatment

General Measures

Treatment of PAH has evolved considerably during the past decade, and treatment algorithms have been formulated by the American College of Chest Physicians for adult patients.[196] Unfortunately, because of limited data in children with PAH, management decisions often are extrapolated from adult studies. Without treatment, the natural history for children with idiopathic PAH is worse than that for adults; however, with treatment, the outcome appears better in children than in adults. In the absence of studies specifically reporting the clinical response of children to PAH therapy, similar clinical strategies have been suggested for the management of PAH in children. Treatment goals in children are similar to those in adults. They include improvements in patient symptoms such as dyspnea, enhancing exercise capacity measured objectively by an assessment of exercise endurance in older children (such as a 6-mile walk test), improving hemodynamic profile (lowering PAP), preventing the progression of the disease, and improving survival rates.

Treatment of PPH is usually treatment for life. The therapeutic regimen has to be tailored in a given child and adjusted according to the clinical and hemodynamic response. Optimizing the management in these children will improve the quality of life and survival. Most important is the avoidance and treatment of hypoxemia. Patients are advised to avoid heavy physical exercise because this may evoke exertional syncope. Exposure to high altitude may contribute to hypoxic pulmonary vasoconstriction and may not be well tolerated. Because hypoxemia is a potent pulmonary vasoconstrictor, most experts recommend supplemental oxygen to maintain oxygen saturation greater than 90%. A sodium-restricted diet is advised and is particularly important to manage volume status in patients with RV failure. Routine immunizations, such as against influenza and pneumococcal pneumonia, are advised. The hemodynamic fluctuations of pregnancy, labor, and delivery are potentially devastating to patients with PAH with a demonstrated maternal mortality of 30% to 50%.[197] Current guidelines recommend that pregnancy be avoided or terminated early in women with PAH.[196] It is important to discuss effective methods of birth control with women with PAH who have child-bearing potential, although the preferred method is not clear. It also is advisable to avoid elective major surgeries, especially during periods of progression or bad control of the disease. Conventional treatment of children with PPH consists of an anticoagulant and an oral vasodilator, usually a CCB and supplemental oxygen.[198] Anticoagulation with Warfarin has been shown to be beneficial in these patients.[199] In a more recent study, anticoagulant therapy had a positive influence on long-term survival and a significantly improved quality of life in patients with PPH, particularly in patients with a history of anorectic drug intake.[200]

Therapy in secondary PH is directed at the cause of PAH. Closure of the heart defect will resolve the PAH resulting from increased PBF. Management of pulmonary venous hypertension includes controlling left ventricular failure and relieving the cause of venous obstruction (commonly

left heart obstructive lesions). Medical management includes administering oxygen, diuretics, and digoxin. Vasodilator therapy is the mainstay in the management of pulmonary vascular obstruction. Even small reductions in RV afterload following vasodilator therapy will produce substantial improvement in RV output in patients with PH. The goal of vasodilator therapy in patients with PAH is to reduce PAP and increase cardiac output without symptomatic systemic hypotension. The response to vasodilators is important in making a decision for surgical correction (lung or heart/lung transplantation). Patients with severe intractable cases of left ventricular dysfunction may need heart transplantation.

Pulmonary Vasodilators

Calcium Channel Blockers. CCBs are the drugs most frequently used in the treatment of PH outside of the neonatal period. The response to CCBs is better in children than in adults with PPH. Acute response to the vasodilator drug during cardiac catheterization will help in determining the desirability of using chronic oral CCBs. A positive response to a vasodilator is taken as a decrease in mean PAP of 20% or more with no fall in cardiac index. Patients who meet criteria for oral CCBs should be followed closely for both safety and efficacy of CCB therapy. If the patient meets the definition of an acute response but does not improve to functional class I or II while receiving CCB therapy, the patient should not be considered a chronic responder and alternative PAH therapy should be considered. Long-acting nifedipine, diltiazem, or amlodipine are the most commonly used CCBs. Verapamil should be avoided because of its potentially negative inotropic effects. The response to acute vasodilator testing is higher in children compared with adults (41% vs. 12% in adults).[201] The acute response in children is also age dependent. Oral CCBs help in reducing PAP in about 40% of children with PPH.[202] In the remaining 60%, acute vasodilator testing with agents such as iNO or intravenous PGI_2 failed to demonstrate responsiveness, and these children have not benefited from chronic oral CCB therapy.[202] Chronic CCB therapy improved survival and quality of life in children who acutely respond to vasodilator drug testing.[203] A 5-year survival rate for patients treated with chronic oral CCB who respond acutely to vasodilator testing was 97%, versus 35% for those who do not respond acutely.[202] Chronic use of CCBs in patients with fixed PVR and unfavorable hemodynamics may worsen right heart failure. Regular, noninvasive monitoring of PAP and cardiac function is as essential part of the management of these patients.

Prostanoids. PGI_2 is reduced in patients with PAH, and administering PGI_2 or its analogues (prostanoids) has been the mainstay in the management of these patients. Currently three prostanoids are commercially available: epoprostenol, treprostinil, and iloprost.

Epoprostenol. Prostacyclin (sodium epoprostenol) has been studied extensively during the past decade in patients with PPH[201,202,204,205] and secondary pulmonary hypertension.[206] Chronic administration of prostacyclin is usually well tolerated with minimal decrease in systemic pressures and modest decrease in PAP. Higher doses can lead to high cardiac output states, suggesting that it has important positive inotropic effects.[204] In patients who are nonresponders to vasodilator testing and responders who fail to improve while taking CCBs, continuous intravenous infusion of PGI_2 improves survival.[202] Long-term, continuous IV administration of PGI_2 has been shown to improve survival, quality of life, and exercise capacity and to significantly reduce PAP in children with PPH.[202,207] Ongoing studies suggest that in some children who were previously believed to have fixed pulmonary vascular disease with irreversible obstruction, their condition may be reversible with long-term IV administration of prostacyclin, perhaps via remodeling of the pulmonary vascular bed.[202,208] Although in the late 1980s and early 1990s the aim of chronic prostacyclin therapy was to act as a bridge to lung or heart/lung transplantation,[209] continuous prostacyclin now is being used as an alternative therapy to transplantation in selected children.[201] Chronic PGI_2 infusion improves hemodynamics and quality of life in patients with PH associated with CHD for whom conventional therapy fails.[210] Continuous IV PGI_2 is the only one of the "specific" therapies currently approved for use in patients with chronic PH. However, drawbacks to this therapy exist. Tolerance develops in some patients, requiring dose escalation, which results in additional adverse events and increased drug costs. More importantly, complications are associated with administration of PGI_2, such as risk of serious infections, catheter thrombosis, and rebound PAH due to pump failure with subsequent interruptions in therapy. Given its considerable complexity, epoprostenol use should to limited to centers experienced with its administration and with systematic follow-up of patients.

Treprostinil. The propensity for serious catheter-related infections with epoprostenol administration led to the development of treprostinil, a stable prostacyclin analogue for subcutaneous infusion with a half-life of about 4 hours. Chronic subcutaneous infusion of treprostinil improved indices of dyspnea, signs and symptoms of PH, and hemodynamics and had an acceptable safety profile in patients with PAH.[211] Dosage used in this study was 1.25 ng/kg/min to 22.5 ng/kg/min via subcutaneous infusion with use of a micro infusion pump with a catheter placed in the subcutaneous tissue. The FDA approved subcutaneously administered treprostinil in 2002 for use in persons with functional class II, III, and IV PAH. More recently, IV treprostinil has been studied in an open-label, uncontrolled fashion. Even though the drug proved to be of benefit in the treatment of persons with PAH,[212] a Centers for Disease Control and Prevention report recently raised concern for an increased risk of bloodstream infections, particularly with gram-negative organisms, in patients receiving IV treprostinil.[213] Given the complexity of administration of both IV and subcutaneous treprostinil, administration should be limited to centers experienced with this agent.

Iloprost. Iloprost is a stable prostacyclin analog with a serum half-life of 20 to 25 minutes. Aerosolization of prostacyclin or its stable analog iloprost causes selective pulmonary vasodilatation, increases cardiac output, and improves venous and arterial oxygenation in patients with severe PH.[214] Thus it may offer a new strategy for treatment of this disease. Long-term treatment with aerosolized iloprost has been shown to be safe and has sustained effects on exercise capacity and pulmonary hemodynamics in patients with PPH.[215] In a placebo-controlled trial, iloprost inhalation (2.5 μg or 5 μg per inhalation; median dose of 30 μg per day) improved pulmonary hemodynamics and quality of life in patients

with severe PH.[216] Inhaled iloprost represents a significant advance from intravenous PGI_2 in the management of PAH. Aerosolized iloprost might be an alternative to iNO for early testing of vascular reactivity and for the postoperative treatment of acute PH in children with CHD.[217] Common adverse effects of inhaled iloprost include cough, headache, flushing, and jaw pain. Iloprost was approved by the FDA in 2004 for use in persons with functional class III and IV PAH. Its short half-life and frequent inhalations do not make it an ideal candidate for chronic treatment of PPH in children.

Beraprost. Beraprost is a prostacyclin analog for oral administration. It has been shown that beraprost reduces PVR in patients with PPH[218-220] and also may be effective in the treatment of secondary precapillary pulmonary hypertension.[221] Oral administration of beraprost sodium also may improve exercise capacity and ventilatory efficiency in patients with both primary and chronic thromboembolic pulmonary hypertension.[222] Limited studies suggest the efficacy of oral beraprost in infants and children with PH resulting from congenital heart defects.[223]

Endothelin Receptor Antagonists. ET-1 mediates vasoconstriction and smooth muscle cell proliferation contributing to the development of PAH. Its action is mediated mainly through the ET_A receptor. Both nonselective (ET_A and ET_B receptor) and selective (ET_A receptor) antagonists are being evaluated in animal and clinical studies.

Bosentan. Bosentan (Tracleer), an oral antagonist of both ET_A and ET_B receptors, is the most widely studied endothelin receptor antagonist in clinical trials. In a placebo-controlled randomized trial, bosentan increased exercise capacity and improved hemodynamics in patients with PH.[224] Patients given bosentan had a reduced Borg dyspnea index and an improved WHO functional class indicating exercise tolerance.[224] In another large double-blind, placebo-controlled multicenter study, bosentan given for 16 weeks was well tolerated, improved exercise tolerance, and increased time to clinical worsening.[225] Similar improvements in exercise capacity, symptoms, and clinical worsening were seen in the larger Bosentan Randomized Trial of Endothelin Antagonist Therapy of Pulmonary Hypertension study.[226] Bosentan was well tolerated at a dose of 125 mg twice daily in these adult patients. Studies in children of the physiologic and long-term effects of bosentan appear to be warranted. Potentially serious hepatotoxicity and teratogenicity has been reported with bosentan that requires close monitoring and cautious use. Because of the risk of hepatic toxicity, the FDA requires that liver function tests be performed at least monthly and hematocrit be checked every 3 months for these patients. There is concern that the endothelin antagonists as a class may be capable of causing testicular atrophy and male infertility. Younger males who may consider conceiving should be counseled regarding this possibility prior to taking these drugs.

Selective ETA Receptor Antagonists. Sitaxsentan and ambrisentan are the two commercially available selective ET_A receptor antagonists. In patients with PAH who were in NYHA functional class II, III or IV, sitaxsentan improved exercise capacity as assessed by the 6-mile walk test and improved functional class after 12 weeks of treatment.[227] The incidence of liver abnormalities was more favorable for the 100-mg dose group (0%) compared with placebo (3%) and the 300-mg group (10%). The Sitaxsentan to Relieve Impaired Exercise-2 study again demonstrated that the 100-mg dose of sitaxsentan improved exercise capacity as assessed by the 6-mile walk test and improved functional class compared with placebo. Although a 50-mg dose of sitaxsentan had a lower incidence of liver enzyme abnormalities, it was not different from the placebo group.[228] In a double-blind study, ambrisentan was evaluated at four dosages (1, 2.5, 5, or 10 mg) once daily for 12 weeks. Results of the 6-mile walk test improved over baseline with ambrisentan.[229] Two phase III clinical trials of ambrisentan in persons with PAH have been completed. These trials randomly assigned 202 and 192 patients with PAH, respectively, to placebo and ambrisentan. Doses of 5 and 10 mg of ambrisentan were compared with placebo in the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-blind, Efficacy Study (ARIES), and doses of 2.5 and 5 mg of ambrisentan were compared with placebo in ARIES-2.[230] After 12 weeks, improvements were noted in the primary end point of the 6-mile walk test in both the studies. Ambrisentan was approved by the FDA in 2007 for patients with PAH with functional class II and III symptoms. As a class, endothelin receptor antagonists have a potential for liver injury and teratogenicity. Monthly monitoring of liver function tests, a monthly pregnancy test in women of childbearing potential, and a periodic hemoglobin measurement are required. Precautions regarding contraception and testicular atrophy are similar to those for bosentan.

Nitric Oxide. The acute responsiveness to iNO seems to predict the subset of patients who might be responsive to oral CCBs and thus is a relatively safe and easy test to perform during cardiac catheterization.[231] Experience with long-term use of iNO in children with PAH is limited. Inhaled NO, however, is expensive and requires a fairly sophisticated delivery and monitoring system. Nonetheless, iNO dilates the pulmonary circulation while avoiding unwanted and dangerous systemic vasodilation and is economical and extremely effective in the management of PH in critically ill patients in intensive care units.[232] Inhaled NO has been used to assess the vasodilator capacity of the pulmonary vascular bed in children with CHD and elevated PVR.[184,233] Low-dose iNO (2 to 20 ppm) has been effective in the management of postoperative PH following corrective surgery in infants with CHD.[234] NO at higher doses (20 to 80 ppm) produced selective pulmonary vasodilatation in children with CHD and pulmonary hypertension.[235] Hemodynamic benefit with NO has been shown in newborns with total anomalous pulmonary venous connection and congenital mitral stenosis and in postoperative patients with preexisting left-to-right shunts and other lesions.[236] It can be used to help discriminate anatomic obstruction to pulmonary blood flow from pulmonary vasoconstriction, and it may be used in the treatment or prevention of pulmonary hypertensive crisis after cardiopulmonary bypass in neonates.[236,237] A trial of iNO may diminish the need for ECMO in patients with cardiopulmonary failure following cardiac surgery.[238,239] In children with PH and CHD, both iNO and aerosolized iloprost were equally effective in selectively lowering PVR.[217]

Phosphodiesterase Inhibitors

Type 5 phosphodiesterase (PDE-5) is primarily responsible for degradation of cGMP to inactive metabolite GMP. PDE-5 appears to be particularly abundant in pulmonary vessels.

One way of augmenting the concentration of cGMP in pulmonary vessels is by inhibiting the activity of PDE-5. PDE-5 inhibitors such as sildenafil and tadalafil might therefore be expected to prolong the vasodilating effects of cGMP. Sildenafil is a potent and selective inhibitor of cGMP-specific PDE-5[240] and has been shown to cause selective pulmonary vasodilatation in an ovine model of acute pulmonary hypertension.[241] Several agents that inhibit PDE-5 are shown to augment the response to NO.[242-245] Dipyridamole, a nonselective PDE-5 inhibitor, in combination with iNO, augments the decrease in PVR index and blunts the severity of acute hypoxic pulmonary vasoconstriction in children with PH.[246] When administered alone in children with PH, dipyridamole reduces the PVR index primarily through an increase in cardiac index.[246] In the Sildenafil Use in Pulmonary Arterial Hypertension study, 278 patients with PAH were randomly assigned to either placebo or sildenafil (20, 40, or 80 mg) orally 3 times daily for 12 weeks.[247] Results of the 6-mile walk test increased from baseline in all sildenafil groups. In all sildenafil groups, mean PAP was reduced and functional class improved. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil versus placebo. Long-term data in 222 patients (available for the 80-mg group) completing 1 year of treatment with sildenafil monotherapy showed sustained improvement from baseline at 1 year in the 6-mile walk test. The FDA-approved dose of sildenafil in patients with PAH is 20 mg administered three times daily for adults. Adverse effects include headache, flushing, dyspepsia, and epistaxis. The question of whether higher doses might confer additional hemodynamic benefit has generated considerable debate, and such doses continue to be studied in clinical trials. Another long-acting PDE-5 inhibitor, tadalafil, is currently undergoing clinical study. Like sildenafil, tadalafil has been approved by the FDA for erectile dysfunction. However, it continues to be investigated in patients with PAH.

Combination Therapy

Combining two agents may be clinically useful. As previously noted, agents that inhibit degradation of cGMP (PDE-5 inhibitors) may act synergistically with iNO. Similarly inhibiting PDE-3, a principal metabolizer of cAMP, might be expected to augment the response to PGI_2. Inhaled milrinone, either alone or in combination with inhaled PGI_2, selectively dilated the pulmonary vasculature without systemic effects in cardiac surgical patients with PH.[248] The goal of combination therapy is to maximize efficacy and to minimize toxicity. The safety and efficacy of combination therapy in persons with PAH is a subject of active investigation. In one recent study, inhaled Iloprost has been studied in patients who remained symptomatic (NYHA functional class III or IV) while undergoing stable bosentan therapy for at least 3 months.[249] After 12 weeks, the primary efficacy measure, a postinhalation 6-mile walk test, improved significantly in the Iloprost group compared with the placebo group. Improvements in mean PAP, functional class, and clinical worsening also were found. More recently sildenafil or placebo was evaluated in 267 patients with PAH who remained symptomatic while receiving a stable dose of epoprostenol for at least 3 months.[250] Patients treated with sildenafil experienced a placebo-adjusted improvement in the 6-mile walk test, mean PAP, and time to clinical worsening.

Pulmonary Thromboendarterectomy

Patients with suspected PAH should undergo evaluation for CTEPH. The screening tool of choice is the perfusion scanning. If indicative of CTEPH, pulmonary angiography should be performed. Patients are considered to be candidates for pulmonary thromboendarterectomy if they have surgically accessible disease and present an acceptable surgical risk. The surgery must be performed at a center experienced in performing this procedure with excellent technical skills and support systems in place.

Atrial Septostomy

Despite advances in medical treatment for PAH, many patients experience progressive functional decline, largely because of worsening right heart failure. Fortunately, it is uncommon to see patients in the pediatric age group in end-stage PAH compared with adults. In these patients, interventional and surgical options, including atrial septostomy and lung or combined heart and lung transplantation, should be considered. In patients with symptomatic cor-pulmonale secondary to pulmonary vascular disease, atrial septostomy can improve symptoms and may serve as a palliative bridge to heart and/or lung transplantation.[251,252] Several case series have reported hemodynamic and clinical improvement following atrial septostomy.[251,252] Improved cardiac output appears to be the principal hemodynamic benefit. Improvements in NYHA functional class and the 6-mile walk test also have been reported.[253] The success rates for bridging patients to transplantation, with septostomy, ranges from 30% to 40%.[251,252] The procedural mortality rate is high, however, with an estimate of 15% based on published series. Currently, atrial septostomy is recommended for patients with severe PAH and intractable right heart failure despite maximal medical therapy, including optimized PAH-specific agents and inotropes. The goals of the procedure are palliation and restoration and maintenance of clinical stability until a transplant can be performed.

Lung and Combined Heart/Lung Transplantation

Before PGI_2 became available as the long-term therapy, lung transplantation was the only option for survival for patients with severe PH. Single-lung, double-lung, and heart-lung transplantation have all been advocated as the operation of choice in persons with PPH. Transplantation is offered after maximal therapeutic effort with vasodilators and oxygen has been attempted and when the estimated 2-year survival is less than 50%.[254] Most centers now perform bilateral lung or heart-bilateral lung transplantation for persons with PPH. Intravenous PGI_2 has been used as a bridge to stabilize the patient until transplantation is accomplished. Of the 70 lung transplants performed in 1997, PH accounted for 7% of infants and 18% of older children requiring transplantation.[255] Survival rates have improved considerably in the 1990s, suggesting both technical improvements and earlier referral for transplantation. Recent data from the International Society for Heart and Lung Transplantation (January 1998 to December 2001) indicate an overall survival following lung transplant of 70% to 80% at 1 year and 50% at 3 years in children younger than17 years. Survival in all patients with PPH following lung transplant was 72% at 1 year and 58% at 3 years. In a single-center study, survival following heart-lung

transplant in patients with PPH was 72% at 1 year, 67% at 2 years, and 42% at 5 years.[256] Because outcomes for infants listed for lung or heart/lung transplantation is similar to that of children, very young age should not be considered a contraindication to lung or heart/lung transplantation.[257] Earlier diagnosis and listing may decrease pretransplant mortality.[257] Even though the early outcome following lung transplantation has improved considerably, long-term complications, including infections, bronchiolitis obliterans, and complications of immunosupression remain significant problems.[258] Aggressive medical therapy combined with early recognition of lung transplant candidates will improve quality of life and overall survival of these children.

Prognosis and Survival in Pulmonary Arterial Hypertension

Most of the studies have been focusing on short time end points, such as 12 weeks' duration or the 6-mile walk test, and long-term follow-up guidelines for these patients is lacking. Figure 48-14 summarizes the treatment algorithm of PAH with an emphasis on initial diagnosis and initial management of these patients from the expert consensus document for PH.[133] Although therapies to manage PAH are evolving rapidly, long-term experience with epoprostenol has suggested the importance of early follow-up, because patients who remain in NYHA functional class III or IV despite therapy have poor outcomes and should be considered for a lung transplant.[259]

Some of the earlier studies found that NYHA functional class, 6-mile walk, and hemodynamic variables were all related to prognosis and survival. All of these parameters were studied as primary end points in many prospective trials. The National Institutes of Health cohort study showed that among 194 patients who received a diagnosis of idiopathic PAH, the risk of death was higher among patients in NYHA functional class III or IV than among those in functional class I or II. Median survival among patients presenting with NYHA functional class I or II symptoms was nearly 6 years versus 2.5 years for functional class III and 6 months for functional class IV symptoms.[260] Other studies have confirmed the importance of functional class as a prognostic variable, even during treatment.[261] Patients who improved to functional class I or II with epoprostenol had a better prognosis than did patients who remained in functional class III or IV.[261]

In the pivotal epoprostenol idiopathic PAH trial, performance in the 6-mile walk test was found to be an independent predictor of survival, leading to use of this test as the primary end point in many trials.[262] All large published evaluations implicate hemodynamics as an important predictor of survival.[259,261] In the National Institutes of Health registry, three hemodynamic variables that were associated with an increased risk of death included increased mean PAP (>55 mm Hg), increased right atrial pressure (>12 mm Hg), and decreased cardiac index (<2.0 L/min/m^2).[260] Similarly, responders to vasodilator testing have an excellent prognosis with up to a 95% survival at 5 years.[192] In a recent single-center study of 65 children with PAH, the 5-, 10- and 15-year survival rates were 96%, 92%, and 65%, respectively, and no significant correlation between outcome and immediate response to the vasodilators was found.[263]

While echocardiography has been a pivotal screening test, studies evaluating the prognostic value of echocardiography have been limited to relatively small series. The presence of any degree of pericardial effusion has been proven to be a consistent predictor of mortality.[264] More recently, tricuspid annular plane systolic excursion on echocardiography has been shown to be a robust measure of RV function and a powerful predictor of patient survival among those with PH.[265] Tricuspid annular plane systolic excursion of less than 1.8 identifies patients with more advanced RV dysfunction in patients with PH. In addition, these patients had reduced survival over a median follow-up of 19 months. Cardiac MRI

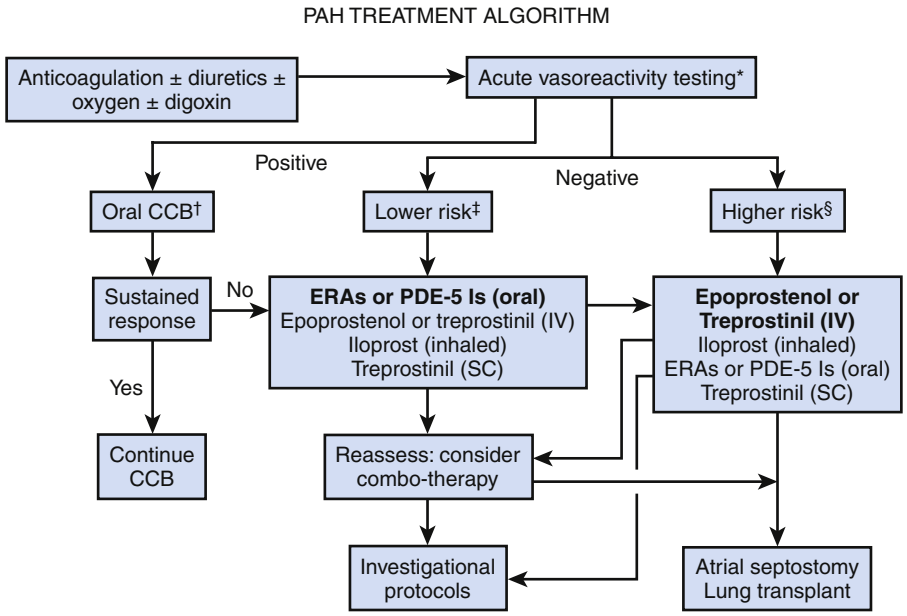

Figure 48–14. Treatment algorithm for pulmonary arterial hypertension. *(From McLaughlin VV, et al: Expert Consensus Document on Pulmonary Hypertension, J Am Coll Cardiol 53(17):1573-1619, 2009; adapted with permission from Elsevier.)*

accurately assesses size and function of the RV with a high degree of reproducibility. RV function is an important prognostic indicator in persons with PAH, and MRI of poor RV function was found to be an independent predictor of mortality and treatment failure.[189] Cardiac MRI holds promise as a noninvasive tool to assess for evidence of RV response and remodeling with treatment. Brain natriuretic peptide and NT-proBNP appear to be significantly elevated and are independent predictors of poor prognosis.[266]

Assessing safety and efficacy of therapy in young pediatric patients is problematic, and even in older children assessment of exercise capacity is difficult. In addition, because of the biologic variability and the progressive nature of the disease in children, making longer-term observations regarding therapy is problematic. All of these factors make clinical investigations in children more difficult, but the potential rewards for having a significant impact on overall quality of life as well as long-term survival far outweigh the hurdles in developing newer management options for children.

References are available online at http://www.expertconsult.com.

Mechanical Ventilation and Respiratory Care

Shekhar T. Venkataraman

PEARLS

- Modern pediatric respiratory care requires a major institutional commitment in resource allocation for the state-of-the-art management of the patient undergoing mechanical ventilation.
- A team approach among the physician, the nurse, the respiratory therapist, and the family is required, in which the role and responsibilities of each of the team members is clearly defined and respected.
- Everyone is equally important for the care of the patient undergoing mechanical ventilation. Physician's medical expertise is of no value in the absence of appropriate nursing care and respiratory therapy.
- As new technologies are developed, every team member must become familiar with them so that they can be applied safely and effectively.
- Family involvement is crucial to provide emotional and psychological support to the child.

Vesalius, in 1555, was one of the first to suggest that artificial respiration in humans is possible by blowing air through a tube of reed or cane positioned in the trachea.[1] Positive pressure ventilation was first used in conjunction with general anesthesia in the 1920s.[2] Outside the operating room environment, mechanical ventilation during the 1920s was provided by negative pressure methods.[3] The utility of prolonged artificial respiration was first proven in the management of polio victims, where it was primarily used to maintain breathing until patients could recover their muscle strength.[4] Since then, tremendous advances have been made not only in the design and sophistication of mechanical ventilators, but also in the application of artificial respiration in its varied modes for a variety of illnesses and indications. This chapter will review the following: (1) applied physiology of breathing, (2) a conceptual framework for the design and function of mechanical ventilators, (3) a modern classification to understand the modes of mechanical ventilation, (4) practice parameters for mechanical ventilator support based on the pathophysiology, (5) philosophy and the practice of weaning, (6) the theory and practice of adjunctive respiratory care, (7) the theory and practice of high frequency ventilation, and (8) home respiratory care. The topic of noninvasive mechanical ventilation is covered elsewhere (Chapter 50).

Applied Respiratory Physiology

Lung Volumes and Capacities

Air gets in, air gets out; oxygen is taken up, carbon dioxide is eliminated; this is the essence of breathing, spontaneous or otherwise. Tidal volume is the volume of gas that is moved in and out of the lungs per breath. The normal tidal volume is 6 to 8 mL/kg, regardless of age. Total lung capacity (TLC) is the volume of gas present in the lung with maximal inflation. The normal range for TLC is 60 to 80 mL/kg. Vital capacity is the volume of gas that can be maximally expired from TLC. The normal vital capacity is about 30 to 40 mL/kg in infants and 45 to 55 mL/kg in adults. Functional residual capacity (FRC) is the volume of gas that is present in the lung at the end of expiration. FRC results from the balance between forces that favor alveolar collapse and maintain alveolar inflation. The normal FRC is about 30 mL/kg. Residual volume is the volume of gas present in the lung at the end of a maximal expiratory effort and cannot be expelled from the lung. Closing capacity (CC) refers to the volume of gas present in the lung at which small conducting airways begin to collapse. When FRC exceeds CC, the small airways and the alveoli remain open because the lung volume remains above CC. On the other hand, when CC exceeds FRC, the small airways and alveoli tend to collapse. In children older than 6 years, FRC exceeds CC. In infants and in children younger than 6 years, CC exceeds FRC. This explains the propensity for atelectasis in infants and young children.

Physiology of Inflation and Deflation

Thoracic structures impede lung inflation. Therefore a certain amount of force is required to overcome this impedance. One of the major determinants of impedance to lung inflation is elasticity of the lung and chest wall. Compliance, a measure of elasticity, is defined as the change in volume per unit change in transmural pressure. Lung compliance is defined as the change in lung volume for a unit change in transalveolar pressure (alveolar pressure minus the pleural pressure). Chest compliance is the change in thoracic cage volume produced by a unit change in transthoracic pressure (ambient pressure minus the pleural pressure). Specific lung compliance refers to

Box 49–1 Factors Associated with Decreased Total Respiratory Compliance

Decreased Lung Compliance
Surfactant deficiency or alteration
Respiratory distress of the newborn
Adult respiratory distress syndrome
Interstitial inflammation
Diffuse pneumonitis
Fibrosis
Pulmonary edema
Alveolar edema
Interstitial edema
Hyperinflation
Airway obstruction-both upper and lower
Excessive CPAP/PEEP or auto-PEEP
Atelectasis

Decreased Chest Compliance
Restrictive pleural disease
Pleural collection of air or fluid
Fibrosis
Increased intercostal muscle tone
Upper motor neuron disease
Drugs
Restrictive chest diseases
Deformations: kyphosis, scoliosis, or both
Ankylosis
Restrictive bandages

Diaphragmatic Restriction
Abdominal distension
Abdominal binding
Increased abdominal pressure: peritoneal dialysis, post-laparotomy, etc.

CPAP-PEEP, Continuous positive airway pressure-pulmonary end-expiratory pressure.

lung compliance that is normalized to the lung volume or body weight and is similar in children and adults. Disease processes that result in an abnormal lung or chest wall compliance are given in Box 49-1. The second major determinant of impedance to lung inflation is airway resistance. Airway resistance is defined as the change in transpulmonary pressure (proximal airway pressure minus the alveolar pressure) required to produce a unit flow of gas through the airways of the lung. In the infant, the airway resistance is equally distributed between the upper and lower airways. With increasing age, most of the airway resistance resides in the upper airways. Two additional factors impede inflation. One is inertia of the respiratory gas, or inertance.[5] The other is the frictional resistance to deformation of the lungs, thoracic cage, and abdominal contents.[5] Frictional resistance is also known as the *nonelastic viscous resistance*. Therefore, taking into consideration all the forces that impede lung inflation, the total pressure (Ptp) required to inflate the lung can be mathematically expressed as follow,s termed the *equation of motion*:

$$P_{tp} = P_{Compliance} + P_{resistance} + P_{Inertance} + P_{Frictional\ resistance}$$

where $P_{Compliance}$ is the pressure required to overcome the compliance of the respiratory system, $P_{resistance}$ is the pressure required to overcome the resistance of the airways, $P_{Inertance}$ is the pressure required to overcome inertance, and $P_{Frictional\ resistance}$ is the pressure required to overcome the frictional or tissue resistance to deformation of the lungs, thoracic cage, and abdominal contents.

$$P_{Compliance} = Volume / Compliance \text{ or } Volume \times Elastance$$

where *Elastance* is the reciprocal of compliance.

$$I.\ P_{resistance} + P_{Frictional\ resistance} = Total\ respiratory\ resistance \times Flow$$

Normally, $P_{Inertance} + P_{Frictional\ resistance}$ is negligible. In certain pathologic conditions, such as pulmonary edema, interstitial lung disease, and pulmonary fibrosis, frictional resistance may be increased. Therefore with the effect of inertance neglected, a simplified equation of motion can be expressed as follows:

$$Ptp = (Volume / Compliance) + (Total\ Resistance \times Flow)$$
$$\text{or } (Volume \times Elastance) + (Total\ Resistance \times Flow)$$

It takes a finite amount of time to inflate the lung with a given volume of gas. This factor is directly proportional to the compliance and the resistance. Time constant is the product of compliance and resistance, and it defines the time taken to cause a given change in lung volume with a constant distending pressure. The rate of inflation and deflation of the lung is normally exponential; one time constant is the time taken to cause a 63% change in volume, and three time constants is the time taken to cause a 95% change in volume.[5] Normal expiration is passive because of the elastic recoil of the lung. Elastic recoil of the lung is attributable to alveolar surface tension and tissue elasticity. Surface tension is greatest at high lung volumes, and lowest at FRC. Elastic recoil of the lung provides most of the force required to expel the gas from the lungs. Again, the time taken to expel a certain tidal volume depends on the time constant of the respiratory system. Because inspiratory and expiratory resistances are different, inspiratory and expiratory time constants may be different.

Work of Breathing

During normal tidal breathing, the work of breathing is performed entirely by the inspiratory muscles (Figure 49-1), and almost all of the work is performed during inspiration. Nearly half of the work of breathing during inspiration is dissipated as heat to overcome frictional resistance to deformation.[5] The remaining inspiratory work is stored as potential energy that is used to perform the expiratory work. Increased airway resistance and decreased chest and lung compliances would require a greater Ptp to inflate the lung to the same lung volume. This imposes a greater workload on the respiratory muscles and increases the oxygen cost of breathing. When the oxygen supply/demand balance to the respiratory muscles is perturbed, respiratory failure may ensue because of muscle fatigue.

Determinants of Gas Exchange

The determinants of systemic arterial oxygenation are inspired oxygen concentration and tension, lung volume, cardiac output, ventilation/perfusion (V/Q) matching, and the magnitude of venous admixture or intrapulmonary shunting. Lung volumes are increased during inspiration and fall during expiration. During expiration, the presence of alveolar surfactant prevents alveolar collapse. A critical opening pressure is required to maintain both the patency of the terminal airways

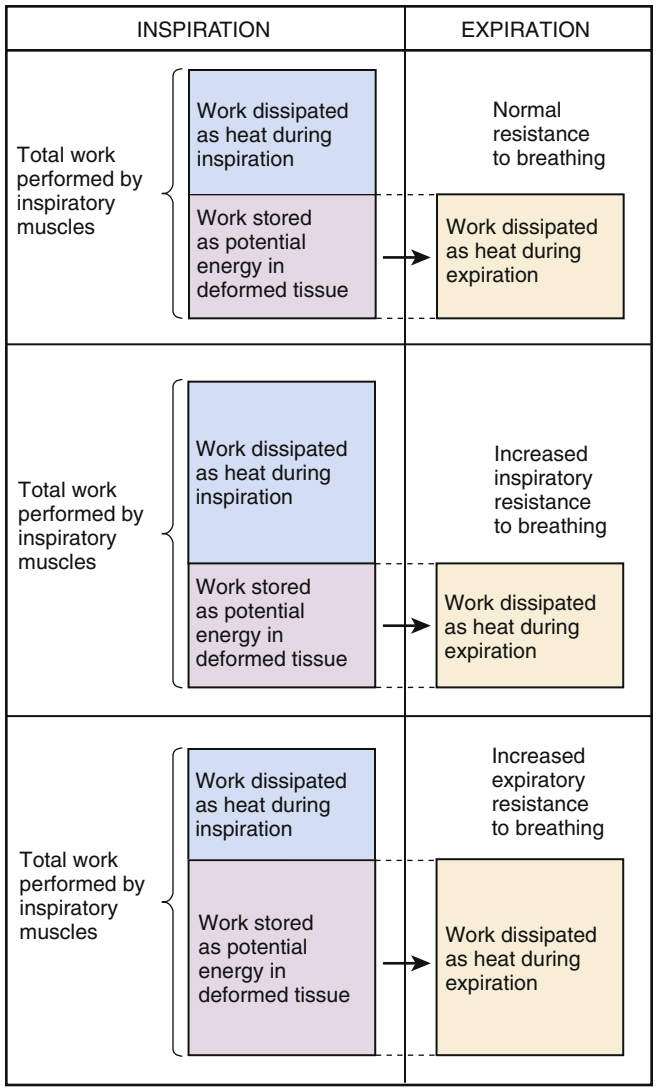

Figure 49–1. Work of breathing of respiratory muscles. The area in each box represents the amount of work performed. The left side shows the total amount of work performed with normal resistance, and increased inspiratory and expiratory resistances to breathing. *(From Nunn JF: Applied respiratory physiology, ed 3, London, 1987, Butterworth.)*

and alveolar volume. When the airway pressure is below the critical opening pressure, the terminal airway closes and the alveoli collapse because of continued absorption of gases into the bloodstream. Surfactant deficiency, loss, or alteration promotes alveolar collapse and increases the critical opening pressure. In parenchymal lung disease, which is characterized by an increased critical closing pressure, alveoli collapse during expiration if the airway pressures cannot be maintained above the critical opening pressure. Alveolar collapse leads to inadequate oxygenation from increased intrapulmonary shunting resulting from V/Q mismatch.

Inadequate ventilation results from a minute alveolar ventilation that is insufficient to meet the metabolic production of carbon dioxide. $Paco_2$ reflects the balance between metabolic production of carbon dioxide and its elimination. Failure of carbon dioxide elimination usually results from hypoventilation due to decreased central drive, lower airway obstruction, parenchymal disease, and muscle weakness (Box 49-2). Increased metabolic production of carbon dioxide usually results from hypermetabolic states and excessive caloric intake, especially high carbohydrate alimentation.

Box 49–2 Causes of Ventilatory Pump Failure

Decreased Respiratory Muscle Capacity

Decreased respiratory center output (CNS disorders)
Phrenic nerve injury
Decreased muscle strength or endurance
Malnutrition
Prolonged neuromuscular blockade
Muscle fatigue
Electrolyte abnormalities

Increased Respiratory Muscle Load

Increased work of breathing
Hyperinflation
Lower airway obstruction
Decreased respiratory system compliance
Increased ventilatory requirements
Increased carbon dioxide production (e.g., excessive carbohydrate intake)
Increased dead space
Hypercatabolic states (e.g., sepsis)

Indications for Mechanical Ventilation

Respiratory Failure

The primary indication for institution of assisted ventilation is respiratory failure. Apnea or respiratory arrest is an extreme form of respiratory failure and an absolute indication for mechanical ventilation. Respiratory failure is generally defined as the presence of (a) inadequate oxygenation, (b) inadequate ventilation, or (c) both. *Inadequate oxygenation*, objectively, is defined as partial pressure of arterial oxygen (Pao_2) less than 60 torr or an arterial hemoglobin oxygen saturation of less tha 90% in room air. Oxygenation can also be expressed as the ratio of PaO_2 to fractional concentration of oxygen in inspired gas (Fio_2). *Inadequate oxygenation* can also be defined as a Pao_2/Fio_2 ratio of less than 300. Other indexes include an alveolar/arterial oxygen gradient of more than 300 torr with an Fio_2 of 1.0 and a calculated or measured intrapulmonary shunt fraction greater than 15%. Inadequate oxygenation due to intrapulmonary shunting can be overcome with the addition of increased inspired oxygen concentration, provided the magnitude of the shunt is less than 15% (Figure 49-2). Intrapulmonary shunt can be decreased by with the reexpansion of collapsed alveoli or with the decrease of the fraction of pulmonary blood flow going to the collapsed alveolar segments. *Inadequate ventilation* is defined as $Paco_2$ greater than 45 torr with an arterial pH of less than 7.35 in the absence of chronic hypercapnia. Impending respiratory failure, characterized by rapidly rising $Paco_2$, progressive respiratory distress, $Paco_2$ out of proportion to the respiratory effort, or fatigue of respiratory muscles, is a relative indication for mechanical ventilation. Intubation and institution of mechanical ventilation in impending respiratory failure are likely to be more controlled than when full-blown respiratory failure develops. Therefore in critically ill children, establishing mechanical ventilation before respiratory failure develops is preferable. Chronic respiratory failure is defined as requirement for mechanical ventilation for more than

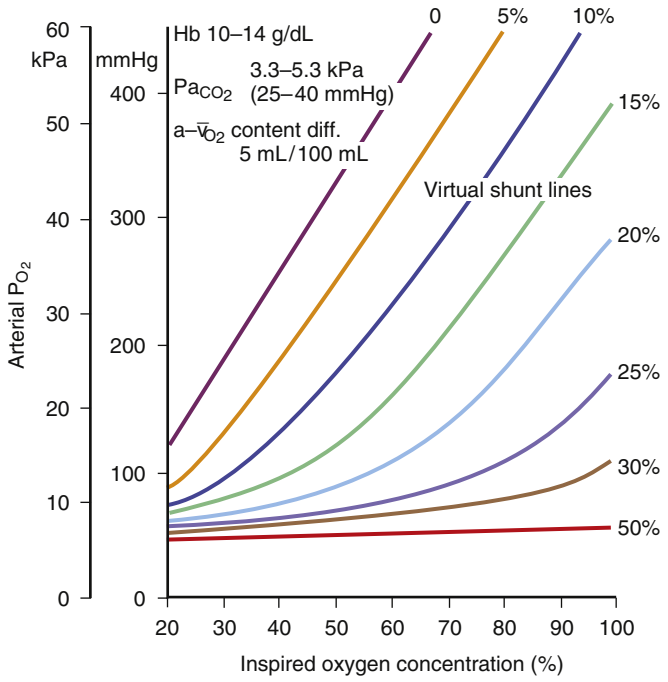

Figure 49–2. Iso-shunt diagram. This shows the relationship among the magnitude of intrapulmonary shunt, the inspired oxygen concentration, and the arterial oxygen tension for a hypothetical patient. *(From Nunn JF: Applied respiratory physiology, ed 3, London, 1987, Butterworth.)*

28 days. Children with chronic lung disease often fail to grow despite adequate caloric intake. In these patients, mechanical ventilation may decrease the work of breathing enough to allow the child to grow.

Cardiovascular Dysfunction

Moderate to severe cardiovascular dysfunction is another major indication for mechanical ventilation. The cardiovascular and respiratory systems must act in concert to maintain adequate gas exchange and thereby meet the metabolic demands of the whole body. Therefore the two systems cannot be functionally divorced from each other (until death do these part, unless one is undergoing extracorporeal membrane oxygenation [ECMO]). Cardiovascular dysfunction results in decreased respiratory reserve, in increased respiratory work, and may ultimately result in respiratory failure. Positive pressure ventilation decreases lactic acid production by respiratory muscles during circulatory shock, and withdrawal of ventilatory support results in a marked increase in cardiac work.[6,7] Therefore mechanical ventilation not only may decrease the work of breathing under these circumstances but also decrease the oxygen demand of the heart.

Neurologic and Neuromuscular Disorders

Acute neurologic disorders may require mechanical ventilation for many reasons. First, neurologic disorders may result in decreased ventilatory drive and therefore result in acute hypercapnia. Second, loss of airway protective reflexes may require an artificial airway for maintaining airway integrity and for providing an access for suctioning pooled secretions. Third, mechanical ventilation may be instituted to deliberately cause hyperventilation in disorders associated with intracranial hypertension to produce hypocapnia and respiratory alkalosis. Fourth, certain acute neuromuscular disorders such as Guillain-Barré syndrome, transverse myelitis, botulism, and drugs may result in decreased ventilatory effort because of muscle weakness and may result in hypoventilation and hypercarbia. Mechanical ventilation is usually instituted under these circumstances until the patient recovers from the primary disorder. Mechanical ventilation is also instituted for various chronic neuromuscular disorders such as muscular dystrophy and for permanent neurologic disorders such as spinal cord transection for prolonged home ventilator support.

Design and Functional Characteristics of Mechanical Positive-Pressure Ventilators

A detailed review of the physical characteristics and functional design of ventilators is beyond the scope of this chapter, and the reader is referred to several excellent reviews on this subject.[8-13] In 1991, Chatburn proposed a new system for understanding the design of mechanical ventilators.[10] A Consensus Conference on the Essentials of Mechanical Ventilators was held in Cancun, Mexico, in February 1992 and the proceedings published in the September issue of the *Respiratory Care Journal*. The goals of the conference were to (1) provide a standard nomenclature, (2) identify essential support features, (3) identify essential heat and humidity requirements, (4) identify essential monitoring/alarm features, and (5) identify what constitutes an order for mechanical ventilation. There are four key reviews that have increased our understanding of a standard nomenclature to classify mechanical ventilators and modes of ventilation.[10a-13] The scheme to classify mechanical ventilators was based on features of input power, control scheme, and the output variables (Box 49-3). Subsequent modifications to include newer modes of ventilation are described elsewhere.[11-13] The following is a brief summary that incorporates some of the elements of Chatburn's classification.

Ventilator as a Machine

The concept is a simple one—*a ventilator is simply a machine that performs external work*. This requires energy to be applied to the device which is then altered, transmitted, and directed in a predetermined manner to perform the work of breathing. This work can either replace the patient's work of breathing completely or partially or augment a patient's breathing efforts. Therefore a ventilator is a mechanical device that is used to move gas into the lungs by increasing P_{tp}. Positive pressure ventilators create P_{tp} by raising the airway pressure (P_{aw}) above the intrapleural pressure (P_{pl}), whereas negative pressure ventilators create P_{tp} by decreasing P_{pl} below P_{aw}. All ventilators include an input power, a drive system, a control system, a cycling mechanism, and a system to provide positive end-expiratory pressure (PEEP).[8-13] The accessories include a heated humidifier and an oxygen blender. The input power provides the energy to operate the ventilator and is usually electric or pneumatic. The drive system provides the force required to generate a gas flow. For gas flow to be provided, a pressure gradient needs to be created between the ventilator and the lungs. This is most commonly accomplished with compressed gases at high pressures from wall outlets or cylinders or a small

Box 49–3 Outline of Ventilator Classification System

I. Input
  A. Electric
    1. AC
    2. DC (battery)
  B. Pneumatic
II. Power conversion and transmission (drive mechanism)
  A. Compressor
    1. External
    2. Internal
  B. Motor and linkage
    1. Electric motor/rotating crank and piston rod
    2. Electric motor/rack and pinion
    3. Electric motor/direct
    4. Compressed gas/direct
  C. Output control valves
    1. Electromagnetic poppet valve
    2. Pneumatic poppet valve
    3. Electromagnetic proportional valve
    4. Pneumatic diaphragm
III. Control scheme
  A. Control circuit
    1. Mechanical
    2. Pneumatic
    3. Fluidic
    4. Electric
    5. Electronic
  B. Control variables and waveforms
    1. Pressure
    2. Volume
    3. Flow
    4. Time
  C. Phase variables
    1. Trigger variable
    2. Limit variable
    3. Cycle variable
    4. Baseline variable
  D. Modes of ventilation and conditional variables
IV. Output
  A. Pressure
    1. Rectangular
    2. Exponential
    3. Sinusoidal
    4. Oscillating
  B. Volume
    1. Ramp
    2. Sinusoidal
  C. Flow
    1. Rectangular
    2. Ramp
      a. ascending ramp
      b. descending ramp
    3. Sinusoidal
  D. Effects of the patient circuit
V. Alarm systems
  A. Input power alarms
    1. Loss of electric power
    2. Loss of pneumatic power
  B. Control circuit alarms
    1. General systems failure (ventilator inoperative)
    2. Incompatible ventilator settings
    3. Inverse I/E ratio
  C. Output alarms
    1. Pressure
    2. Volume
    3. Flow
    4. Time
      a. high/low ventilatory frequency
      b. high/low inspiratory time
      c. high/low expiratory time (high expiratory time or apnea)
    5. Inspired gas
      a. high/low inspired gas temperature
      b. high/low Fio_2

From Chatburn RL: *Classification of mechanical ventilators, respiratory care equipment,* Philadelphia, 1995, JB Lippincott.

compressor designed to be used with individual ventilators. Alternatively, some ventilators have a built-in compressor such as a piston and cylinder (e.g., Emerson IMV), a diaphragm (e.g., Engtrom Erica), a system of bellows (Siemens Servo 900C), or a rotating vane (Bear 2). When a ventilator depends on an external source of compressed gases to power the ventilator, it acts mainly as a control system and will not function if the external source fails. On the other hand, a ventilator that has an internal compressor does not need an external source of gas to inflate the lung. The pressure generated within the ventilator can be thought of as the driving pressure that forces the gas into the lungs through the conducting system involving the ventilator circuit and the patient's airways. During mechanical ventilation, for a single breath, P_{tp} may be generated either by the ventilator or a spontaneous breath or a combination of both. Therefore the equation of motion can be reexpressed as:

$$P_{tp} = P_{mus} + P_{vent} = (\text{Volume} \times \text{Elastance}) + (\text{Total Resistance} \times \text{Flow})$$

where P_{mus} is the pressure exerted by the respiratory muscles and P_{vent} is the pressure exerted by the ventilator. Compliance and resistance are assumed to remain constant during lung inflation and are called parameters. Pressure, volume, and flow in the respiratory system change with time and are therefore referred to as variables. Figure 49-3 shows the classification scheme that is based on the equation of motion.

A ventilator can also be viewed as a form of mechanical controller that "controls" either pressure (in a pressure generator) or flow (in a flow generator). A pressure generator is a ventilator that generates a fixed pattern of pressure within the ventilator and at the mouth regardless of the lung conditions, leaving the flow waveform free to vary. This occurs when the generated pressure is low (generally between 20 and 50 cm H_2O), which results in a high initial flow rate that decays to zero as the alveolar pressure approaches the generated pressure. The generated pressure can be constant, nonconstant, increasing, or decreasing. The Hand-E-Vent (Ohio Medical Products), Bird Asthmatik (Bird Corporation), the Bennett PR-1, and the Bennett PR-2 ventilators are examples of pressure generators. A flow generator is a ventilator that generates a high driving pressure (3 to 50 psig corresponding to 200 to 3500 cm H_2O) and controls the inspiratory flow of gas into the patient by interposing a high series resistance system between

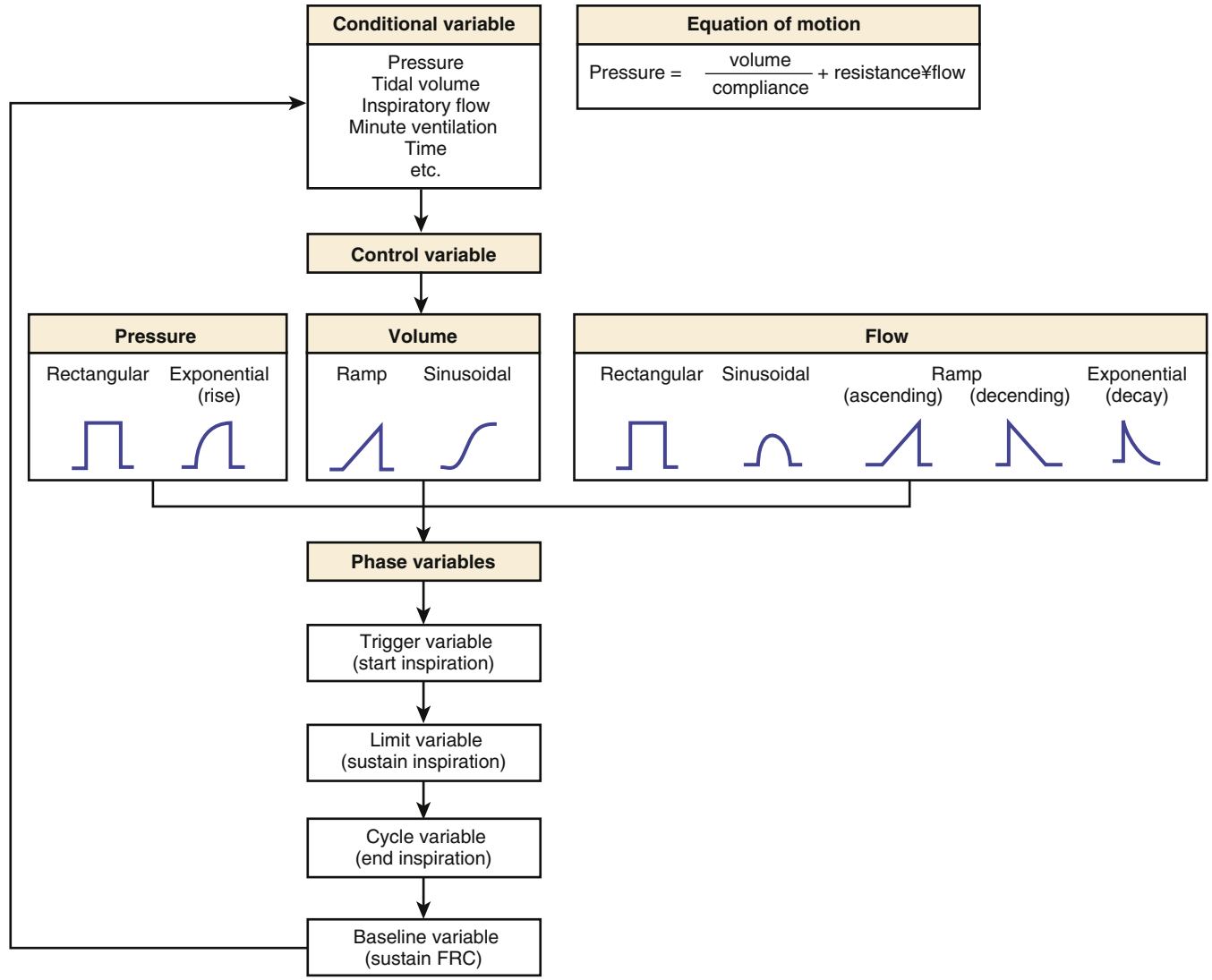

Figure 49–3. Chatburn classification system based on a mathematical model known as the equation of motion for the respiratory system. This model indicates that during inspiration the ventilator is able to directly control one and only one variable at a time (e.g., pressure, volume, flow). Some common waveforms provided by current ventilators are shown for each control variable. Pressure, volume, flow, and time are also used as phase variables that determine the parameters of each ventilatory cycle (e.g., trigger sensitivity, peak inspiratory flow rate or pressure, inspiratory time, baseline pressure). *(From Chatburn RL:* Classification of mechanical ventilators, respiratory care equipment, *Philadelphia, 1995, JB Lippincott.)*

the generated pressure and the patient. The flow generated may be constant, nonconstant, increasing, or decreasing.

The pattern of gas flow from the ventilator to the patient depends on the driving mechanism and the driving pressure in the ventilator. Four distinct flow patterns can be recognized: (1) a constant flow, (2) a decelerating flow, (3) an accelerating flow, and (4) a sinusoidal or sine-wave flow (Figures 49-4 to 49-6). A constant inspiratory flow is generated when the driving pressure is very high (e.g., 50 psig) relative to the airway pressure. The drive mechanism is usually a high-pressure gas system (compressed air or oxygen at 10 to 50 psig). The driving force may exceed 1000 cm H_2O and is severalfold higher than the typical proximal airway pressure that is required to inflate the lungs. An adjustable resistance controls the pressure and the flow to the proximal airway. The airway pressure and lung volume increase linearly until inspiration is terminated. Bird Mark 7 and Monaghan 225/SIMV are examples of high pressure drive systems with constant inspiratory flows. Constant flow can also be generated by a linear-driven piston, which moves at a constant rate of speed during inspiration (e.g., Bourns LS 104-150 Infant Ventilator). A decelerating inspiratory flow is created when the driving pressure is relatively low (<60 cm H_2O). In this case, a pressure-reducing valve controls the driving pressure to the desired level. As the airway pressure and lung volume increase during inspiration, the pressure gradient between the drive mechanism and the proximal airway decreases. Consequently, as inspiration continues, the inspiratory flow from the ventilator decreases and finally stops at the end of inspiration. The Bennett PR-1 and PR-2 are examples of low-pressure drive systems that produce decelerating inspiratory flows. A sine-wave or sinusoidal inspiratory flow is created when the drive mechanism is a rotary driven piston. As the rotary wheel turns, the piston is moved to and fro in the cylinder in an accelerating and then a decelerating fashion. The inspiratory flow produced also has a similar profile. Emerson 3-PV and 3-MV ventilators are examples of rotary piston devices. The notion that one specific flow pattern is more beneficial than

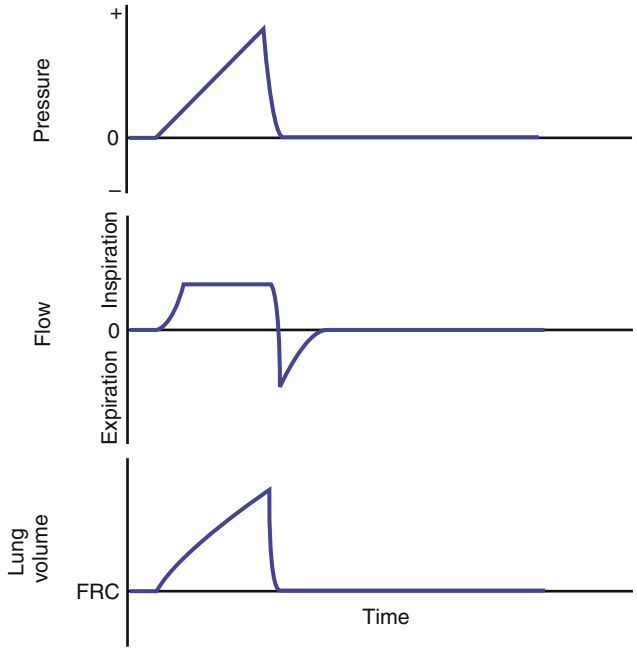

Figure 49–4. Constant inspiratory flow. The flow quickly reaches a plateau and remains constant throughout the inspiratory phase. The airway pressure and lung volume increases relatively linearly. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

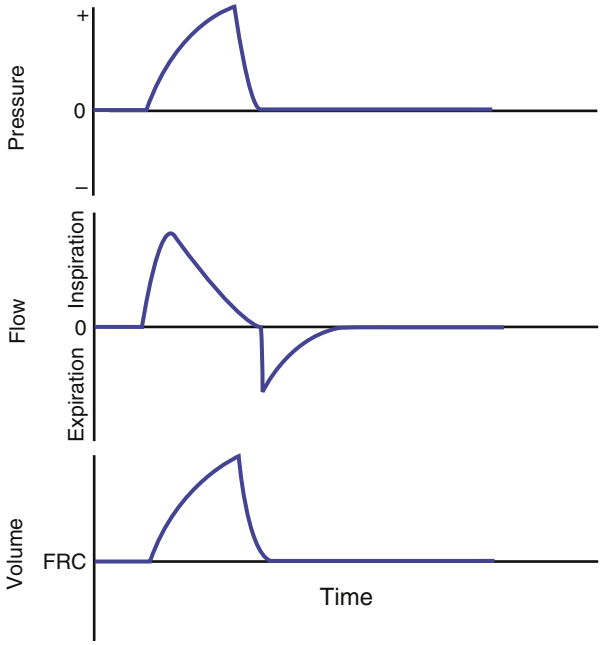

Figure 49–5. Decelerating inspiratory flow. Inspiratory flow is maximal early in inspiration and gradually falls to zero at the end of inspiration. The airway pressure and lung volume rise exponentially. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

the others is controversial. A detailed description of this topic is beyond the scope of this chapter, and the reader is referred to several excellent reviews.[8-13] Ventilators can also be classified as a single-circuit or a double-circuit device. A single-circuit device refers to a ventilator in which the gases go directly from the drive mechanism to the patient (e.g., Emerson-PV

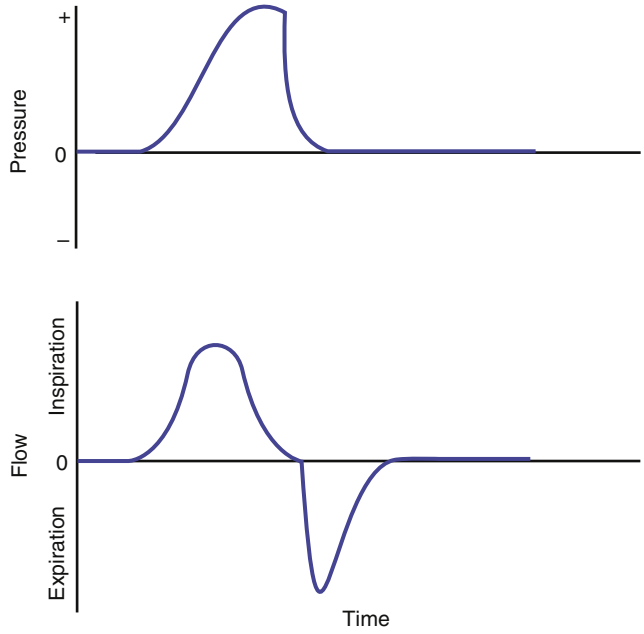

Figure 49–6. Sinusoidal, or sine-wave, inspiratory flow. Inspiratory flow increases gradually and then falls gradually to zero. The airway pressure and lung volume increase in an S-shaped fashion. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

and 3-MV models, Bird Mark series, and the Siemens Elema 900 series ventilators). On the other hand, a double-circuit device refers to a system in which the drive mechanism is used to compress another system that then delivers the tidal volume (e.g., Engstrom 150 and 300 series, Bennett MA-1, and Monaghan225/SIMV ventilators).

All ventilators are equipped with mechanisms to provide four basic functions: (1) inflate the lungs, (2) terminate lung inflation, (3) allow lungs to empty, and (4) start lung inflation.[10,11] The ventilator performs these functions through four phases: (1) the inspiratory phase, (2) the changeover from the inspiratory to the expiratory phase, (3) the expiratory phase, and (4) the changeover from the expiratory phase to the inspiratory phase. The criteria for determining the phase variables during a mechanical breath are shown in Figure 49-7. The inspiratory phase is started when a variable measured in the circuit or at the airway reaches a preset value. This variable can be pressure, volume, flow, or time. This is called the trigger variable. Pressure- or flow-triggering requires a patient effort. On the other hand, time-triggered breaths do not require a patient effort but can be synchronized to the patient's efforts. During inspiration, a tidal breath is delivered to the lung. The volume of the tidal breath delivered to the patient depends on several factors: (1) the P_{tp} generated, (2) the compliance and resistance of the ventilator circuit, (3) the impedance to inflation of the patient's lungs, (4) leaks in the circuit, (5) leaks around the endotracheal tube, and (6) limitation or regulation of inspiratory phase variables (pressure, flow, or volume). Limitation or regulation of the inspiratory pressure, volume, or flow does not terminate inspiration. Modern ventilators such as the Siemens Servo 300 can control more than one phase variable during inspiration. Termination of inspiration depends on the cycling mechanism. Cycling refers to the mechanism by which inspiration is terminated and expiration is initiated. All ventilators require

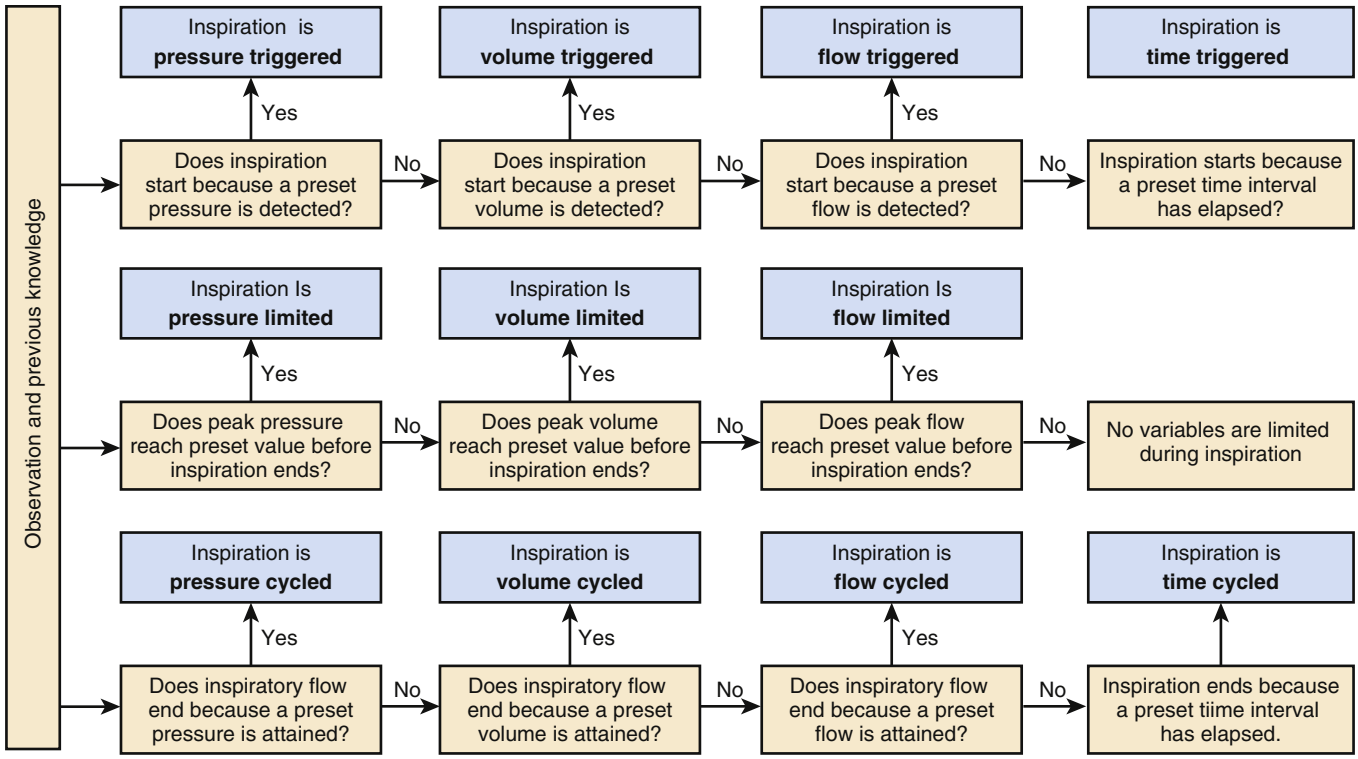

Figure 49–7. Criteria for determining phase variables during a ventilator-assisted breath. *(From Chatburn RL:* Classification of mechanical ventilators, *respiratory care equipment, Philadelphia, 1995, JB Lippincott.)*

a trigger mechanism to cycle. The trigger for cycling may be a predetermined time (time cycling), a predetermined pressure (pressure cycling), a predetermined volume (volume cycling), or a predetermined flow (flow cycling). Most conventional ventilators used in infants and children today are time-cycled or volume-cycled ventilators.

Modes of Ventilation

Mode of ventilation can be defined as the manner in which a ventilator achieves the objectives of mechanical ventilation.[12] In 2007, Chatburn proposed an update which simplified the nomenclature so that all modes of ventilation can be adequately described.[13] Box 49-4 describes the classification scheme from that review.[13] A breath refers to the occurrence of a positive airflow into the lungs (inspiration) and a negative airflow out of the lungs (expiration), which results in ventilation of the lungs. The positive and negative airflow are relative to a baseline. As described previously, all breaths have four important components. They are inspiratory trigger, phase of inspiration, termination of inspiration and the start of expiration (otherwise called *cycling*), and the phase of expiration.

There are two types of breaths: spontaneous and mandatory. A breath where the patient determines both the inspiratory timing and cycling is defined as a spontaneous breath (i.e., when the initiation and termination of a breath is under the control of the patient's breathing efforts). A spontaneous breath is both patient triggered and patient cycled. A spontaneous breath may be either unassisted or assisted. An unassisted spontaneous breath refers to a breath where the patient determines both the timing and size of the breath. T-piece breathing or breaths during continuous positive airway pressure (CPAP) are examples of unassisted spontaneous breathing. The size of the breath is determined solely by the effort of the patient with no additional help from the ventilator. An assisted spontaneous breath refers to a breath where the ventilator does some of the inspiratory work indicated by an increase in airway pressure above the baseline (i.e., a spontaneous breath with an inspiratory pressure that is greater than the expiratory pressure is referred to as an assisted mechanical breath). For an assisted breath, the patient must initiate a breath, and then the ventilator is triggered to provide a positive pressure breath. The trigger can be either pressure or flow. With an assisted spontaneous breath, the patient determines the timing but the ventilator contributes to the size of the breath. Pressure-supported breaths are examples of assisted spontaneous breaths. Mandatory breaths refer to those breaths that are not spontaneous. A mandatory breath may be initiated by the ventilator with a preset frequency or minute ventilation, or it can be initiated by the patient. Mandatory breaths can be triggered by either the machine or the patient. With a mandatory breath, the termination of the breath is under the control of the ventilator. A mandatory breath is always cycled by a preset time, pressure, or volume and is not under the control of the patient. Whether the mandatory breath is initiated by the ventilator or by the patient, the characteristics of the breath (changes in flow, pressure, and volume) and the inspiratory time of the breath are the same.

There are eight possible breathing patterns based on three possible control variables (volume, pressure, and dual control) and three breath sequences.[12,13] These are shown in Table 49-1. Continuous spontaneous ventilation (CSV) refers to a breath sequence in which all the breaths are spontaneous. Continuous mandatory ventilation (CMV) refers to a breath sequence in which all the breaths are mandatory breaths. During CMV, spontaneous breaths are not

Box 49–4 Chatburn's Classification Scheme for Modes of Ventilation

I. Breathing pattern
  A. Primary breath control variable
    1. Volume
    2. Pressure
    3. Dual
  B. Breath sequence
    1. CMV
    2. IMV
    3. CSV
II. Type of control strategy (control type)
  A. Hierarchical set point control
  B. Hierarchical servo control
  C. Adaptive set point control
III. Specific control strategy
  A. Phase variables
    1. Trigger
    2. Limit
    3. Cycle
  B. Operational logic
    1. Conditional variables
    2. Output variables
    3. Performance function (i.e., function that is maximized or minimized for adaptive strategies)

Modified from Chatburn RL, Primiano FP Jr: A new system for understanding modes of mechanical ventilation, *Respir Care* 46:604–621, 2001; and Chatburn RL: Classification of ventilator modes: update and proposal for implementation, *Respir Care* 52:301–323, 2007.

permitted or do not occur between mandatory breaths. If the patient is breathing spontaneously during CMV, each spontaneous breath may trigger a mandatory breath. Assist-control refers to a mode of ventilation when a patient receives a combination of ventilator-initiated and patient-initiated mandatory breaths. The total number of mechanical breaths will be the sum of the preset frequency of ventilator breaths and the number of patient-triggered breaths. For example, if the preset frequency is 15 breaths/min and the patient triggers an additional 15 breaths/min, the total number of mandatory breaths will be 30 breaths/min. Mandatory breaths may be superimposed on spontaneous breaths (such as during high frequency) or vice versa (such as during airway pressure release ventilation). Intermittent mandatory ventilation (IMV) refers to a breath sequence where breaths are either mandatory or spontaneous. Volume control CSV is not possible because the definition of a spontaneous breath would conflict with the definition of volume control. When all minute ventilation is provided by the ventilator, it is referred to as total ventilatory support. When some of the minute ventilation is provided by spontaneous breathing and the rest by the ventilator, it is referred to as partial ventilatory support. Total ventilatory support is provided when the patient does not take any spontaneous efforts because of a primary disease process (e.g., quadriplegia, muscle disease), pharmacologic therapy (e.g., induced neuromuscular blockade), or suppression of spontaneous breathing efforts (e.g., hyperventilation). Total ventilatory support is provided entirely by CMV. On the other hand, partial ventilatory support can be provided by CMV, AMV, or a combination of both.

Table 49–1 Breathing Patterns

Breath-Control Variable	Breath Sequence	Acronym
Volume	Continuous mandatory ventilation	VC-CMV
	Intermittent mandatory ventilation	VC-IMV
Pressure	Continuous mandatory ventilation	PC-CMV
	Intermittent mandatory ventilation	PC-IMV
	Continuous spontaneous ventilation	PC-CSV
Dual	Continuous mandatory ventilation	DC-CMV
	Intermittent mandatory ventilation	DC-IMV
	Continuous spontaneous ventilation	DC-CSV

Modified from Chatburn RL, Primiano FP Jr: A new system for understanding modes of mechanical ventilation, *Respir Care* 46:604–621, 2001; and Chatburn RL: Classification of ventilator modes: update and proposal for implementation, *Respir Care* 52:301–323, 2007.

Mandatory Mechanical Ventilation

During inspiration, the control variable is pressure (pressure control), volume (volume control), flow (flow control), time (time control), or dual control. The two most common forms of controlled mandatory mechanical ventilation modes that are used in infants and children are pressure-regulated and volume-regulated mandatory modes of ventilation. Figure 49-8 shows pressure-time curves for some of the mandatory modes of ventilation.

Volume-Regulated Mandatory Breaths

Volume-regulated ventilation can be delivered either by volume-cycled breath, where inspiration is terminated after a preset volume is delivered and inspiratory time is allowed to vary, or by volume-regulated time-cycled breaths, where the cycling mechanism is preset time and the tidal volume delivered is regulated by adjusting the inspiratory flow rate. In volume-regulated ventilation, the tidal volume is delivered throughout inspiration. The peak inspiratory pressure (PIP) is variable and depends on the flow rate, the total resistance, and the total compliance of the ventilator circuit and the patient's lungs. Changes in resistance or compliance will be reflected by an increase in PIP, and the ventilator can be set to alarm at a pressure limit that is generally set 5 to 10 cm above the PIP.

Most modern ventilators deliver the preset tidal volumes reliably, but the tidal volumes delivered to the patient on a breath-to-breath basis may not always be constant. The tidal volume delivered by the ventilator is distributed between the ventilator circuit, the airways, and the patient's lungs. The compliances and resistances of the ventilator circuit, the endotracheal or tracheostomy tube, and the patient independently and together affect the distribution of tidal volume delivered by the ventilator. A decrease in the compliance or an increase in the resistance of the ventilator circuit will affect the actual tidal volume delivered to the patient. The ventilator circuit includes an internal volume and the external tubing.

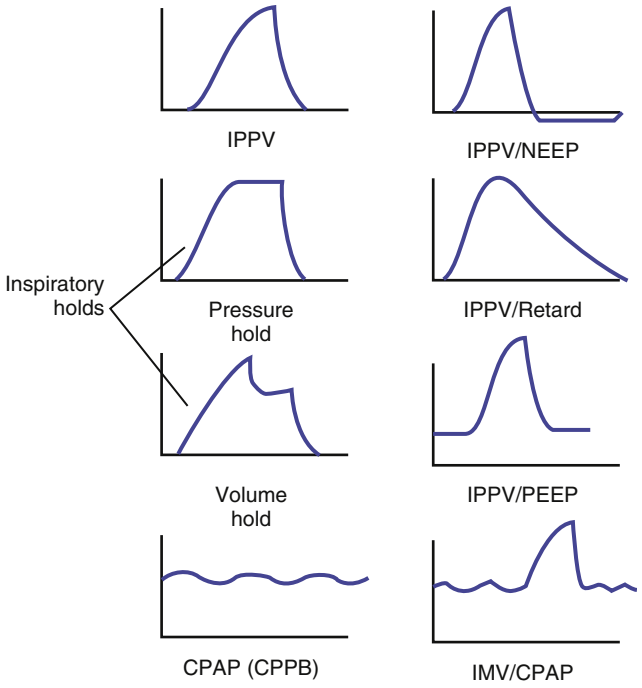

Figure 49–8. Pressure-time curves of some of the mandatory modes of ventilation. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

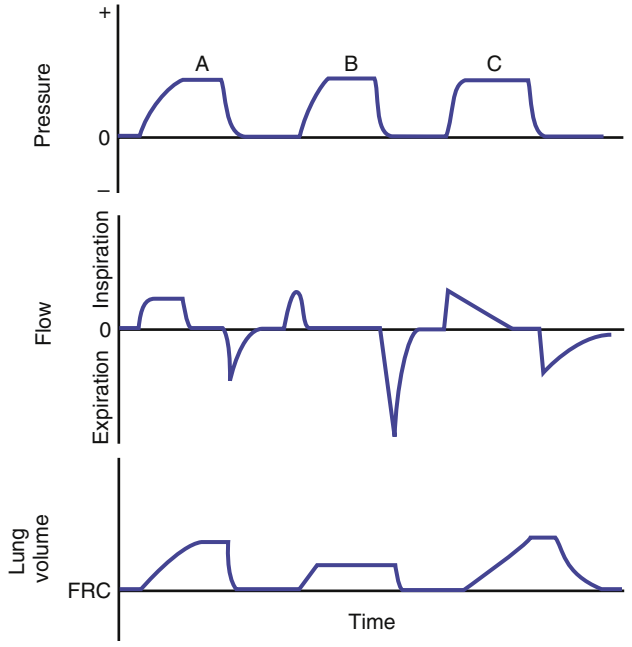

Figure 49–9. Pressure-control ventilation. Inspiratory flow pattern is constant. Airway pressure and lung volume rise relatively linearly. The airway pressure reaches a preset pressure limit and does not change throughout inspiration. Lung volume follows the time course of the pressure curve with a slight lag. **A,** Normal lung. **B,** Lung with decreased compliance. **C,** Lung with increased resistance. With decreased compliance the tidal volume delivered is decreased. With increased resistance, it takes longer to deliver the tidal volume. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

The actual tidal volume or the effective tidal volume (VT_{eff}) delivered to the patient can be approximated by the following formula:

$$VT_{eff} = VT_{del} - VT_{circuit}$$

where VT_{del} is tidal volume delivered by the ventilator and $VT_{circuit}$ is the volume of gas that is distributed to the ventilator circuit. VT_{del} is equal to the inspired tidal volume, when there is no leak in the total respiratory system. When there is a leak in the system, however, such as with the use of uncuffed endotracheal tubes, then VT_{del} is less than the inspired tidal volume. $VT_{circuit}$ can be estimated by the following formula:

$$VT_{circuit} = C_{vent} \times (PIP - PEEP)$$

where C_{vent} is the compliance of the ventilator circuit. An increase in resistance or compliance of the ventilator circuit (including the endotracheal tube) or the patient's airways or lungs will increase the time constant to inflation. If the inspiratory time is less than five times the time constant of the whole respiratory system, which includes the ventilator circuit and the patient's airways, then the VT_{del} will be less than the preset tidal volume. During inspiration, after the tidal volume is delivered, an inspiratory hold will maintain inspiratory pressure and prolong the duration of inspiration (see Figure 49-8). During exhalation, expiratory flow curves depend on the type of expiratory resistance or PEEP valve in the system.

Pressure-Regulated Mandatory Breaths

Pressure-regulated ventilation can be either pressure-cycled or pressure-limited time-cycled ventilation. In pressure-cycled ventilators, inspiration is terminated when a preset pressure limit is reached. In this mode of ventilation, the inspiratory time may vary depending on the changes in resistance and compliance of the total respiratory system. This mode of ventilation is not widely used these days except for intermittent positive-pressure breathing treatments. Pressure-limited, time-cycled ventilation is most commonly used in the neonate with respiratory distress syndrome and in children with acute respiratory distress syndrome (ARDS). In this mode, inspiratory and expiratory times are constant, and the PIP reaches a preset limit quickly early in inspiration and is then maintained at that level during the rest of the inspiratory phase. Usually a high flow rate is used (4 to 10 L/kg/min). The tidal volume delivered depends on the compliance and resistance of the ventilator circuit and the patient's lungs. Pressure-controlled ventilation results in higher mean airway pressure for the same amount of minute ventilation. Figure 49-9 shows the time course of changes in airway pressure, inspiratory flow, and lung volume with normal lungs, lungs with decreased compliance and with increased resistance. As shown in Figure 49-9, with PIP remaining the same, lung volume delivered is affected by changes in lung compliance and airways resistance. Factors that would increase mean airway pressure during pressure-controlled ventilation are shown in Figure 49-10.

Continuous Flow Versus Demand Flow

Some ventilators that can provide pressure-regulated ventilation have both inspiratory and expiratory valves. Once PIP is reached, both inspiratory and expiratory valves close and the lung is held in inflation until the end of inspiration. For use in infants, ventilators were modified to provide continuous flow throughout the respiratory cycle.[14] A continuous flow device refers to a ventilator in which the flow of respiratory gas occurs throughout the respiratory cycle. Most infant ventilators are continuous flow devices (e.g., Infant Star, Baby Bird). In most continuous flow infant ventilators, inspiratory

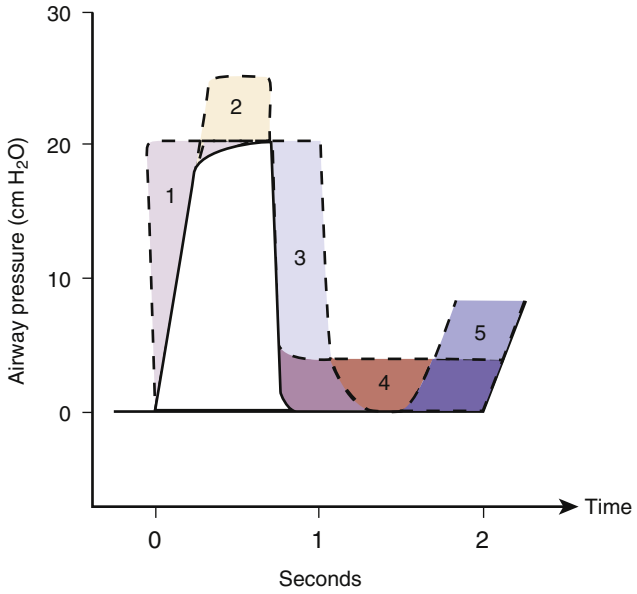

Figure 49–10. Factors that increase mean airway pressure during pressure controlled ventilation: (1) increased inspiratory flow rate, (2) increased preset pressure limit, (3) increased inspiratory time, (4) increased PEEP, and (5) increased ventilator rate. Note that with each maneuver, the area under the curve increases. Area under the curve represents mean airway pressure. *(From Goldsmith JP, Karotkin EH, editors:* Assisted ventilation of the neonate, *Philadelphia, 1988, WB Saunders.)*

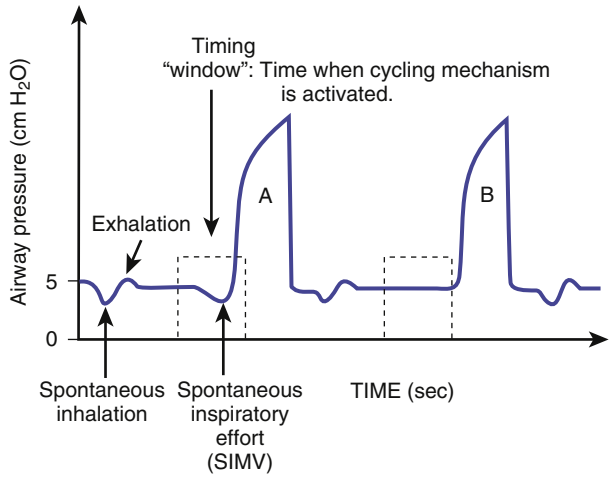

Figure 49–11. Synchronized intermittent mandatory ventilation (SIMV). At set intervals, the ventilator's timing circuit becomes activated and a timing "window" appears (*shaded area*). If the patient initiates a breath in the timing window, then the ventilator will deliver a mandatory breath. If no spontaneous effort occurs, then the ventilator will deliver a mandatory breath a fixed time after the timing window. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

valves are lacking, and the cycling is controlled by the exhalation valve. Closure of the exhalation valve begins inspiration, and the flow of gas going through the circuit is diverted to the patient. If the inspiratory flow rate is low (1 to 3 L/kg) and if the PIP is not limited, the tidal volume delivered by the patient can be calculated from the inspiratory flow rate and the inspiratory time. This would result in a time-cycled, volume-regulated breath. For pressure-control ventilation, the flow rates used are usually higher (4 to 10 L/kg). Once the preset PIP is reached, the excess flow is vented through a pressure relief valve, and the lungs are maintained in inflation throughout the rest of inspiration. During exhalation, there is continuous flow of gas, allowing the patient to breathe from the circuit rather than open a demand valve. A demand flow ventilator refers to a ventilator that allows inspiratory flow of gas to the patient between ventilator breaths through a demand valve that is opened by the patient's inspiratory efforts. Work of breathing is higher with a demand flow ventilator compared with a continuous flow device because of the effort required to open the demand valve.

Intermittent Mandatory Ventilation

Intermittent mandatory ventilation (IMV) refers to a pattern of controlled ventilation in which spontaneous breathing is permitted. Between mandatory machine breaths, the patient can breathe spontaneously and the required gas flow is delivered through either a continuous flow or a demand system. The concept of IMV where spontaneous breathing occurred with a preset mechanical ventilator rate was first developed by Kirby et al.[14] in 1971 with the use of a continuous flow circuit in the management of respiratory distress syndrome of the neonate. IMV was first described by Downs et al.[15] in 1973 to describe a mode of ventilation that allowed the patient to breathe spontaneously with a preset ventilator rate. The spontaneous breaths are not assisted by a ventilator breath. Therefore the tidal volumes generated by the spontaneous breaths depend on the patient's effort alone and not on the ventilator support. The total ventilatory support time and duration of weaning were significantly reduced in infants using IMV compared with CMV.[16,17] Two systems are currently available to deliver IMV: one uses continuous flow, and the other uses a demand valve. Ventilators such as the InfantStar incorporate a continuous flow circuit that can be adjusted to the inspiratory flow demand of the patient. The ideal flow rate would result in minimal pressure swings associated with spontaneous inspiration and expiration. Most modern ventilators incorporate a demand valve that needs to be opened to satisfy the inspiratory flow requirements of the patient. This increases the inspiratory work of breathing. This can be minimized by the application of a small amount of pressure support. When IMV is synchronized to the patient's inspiratory efforts, it is referred to as synchronized IMV (SIMV) (Figure 49-11). The ventilator accomplishes this by creating a timing window just before the next mandatory breath is scheduled to be delivered. If the patient takes a spontaneous breath in this timing window and the ventilator senses this breath on the basis of the trigger sensitivity, then the mandatory breath is synchronized with the patient's effort. Each time a synchronized breath is delivered, the machine recomputes the time required to deliver the next mandatory breath. In SIMV, the total number of mandatory breaths will only be equal to the preset frequency of mandatory breaths. SIMV breaths can be both volume regulated or pressure limited.

Continuous Positive Airway Pressure/ Positive End-Expiratory Pressure

CPAP refers to the maintenance of positive airway pressure throughout the respiratory cycle with no positive pressure breaths being delivered to the patient. PEEP refers to the maintenance of positive airway pressure above atmospheric pressure at the airway opening at end expiration.[18]

CPAP/PEEP can be applied by a variety of devices. These include (1) an underwater column, (2) a water-weighted diaphragm, (3) a Venturi valve, (4) a spring-loaded valve, (5) a pressurized exhalation valve, (6) a magnetic valve, and (7) a fixed or adjustable orifice. Devices that retard expiratory flows (e.g., Venturi valve, fixed or adjustable orifice) tend to produce higher mean airway pressure than those that do not retard expiratory flow rates.

CPAP may be provided by several means:

1. Endotracheal CPAP[9,19]: This is the most reliable method of applying CPAP. The advantages of endotracheal CPAP are precise control of airway pressure and Fio_2; access to the airway for tracheobronchial toilet; maintenance of enteral feeding through a nasogastric tube; and, if necessary, immediate institution of mechanical ventilation. The disadvantages are those associated with those of endotracheal intubation and the long-term presence of an artificial airway.
2. Nasal CPAP: Specially designed nasal prongs,[20] a single cannula or a shortened uncuffed endotracheal tube inserted into the nasopharynx, and nasal masks,[21] provide a means of applying CPAP. Because of the location in the nasopharynx, there will be a loss of pressure in the hypopharynx so that the actual CPAP delivered to the trachea may vary. This technique is easy to apply and can be instituted by less-skilled personnel. This technique is most useful in infants who are obligatory nose breathers. Mouth breathing reduces the efficiency of this technique considerably. Nasal prongs are more prone to obstruction with thick secretions and require proper humidification and frequent suctioning. Nasal prongs have also been reported to increase the work of breathing.[22]
3. Face mask CPAP: A tight-fitting mask is placed on the face covering the nose and the mouth. CPAP is provided with the application of positive airway pressure to the mask. This technique is only useful in patients who are alert and cooperative, without a tendency for nausea and vomiting. A tight-fitting mask may produce pressure lesions on the face if applied too tight. Gastric distention with vomiting and aspiration are potential problems.

The primary effect of CPAP/PEEP is an increase in end-expiratory lung volume due to the increased P_{tp}. In lung diseases characterized by increased closing volume and decreased FRC, alveoli are unstable and tend to collapse. Recruitment of collapsed alveoli requires a P_{tp} greater than that required to sustain inflation once the alveoli are open. An increase in FRC above the closing volume restores this balance, prevents alveolar collapse, and maintains alveolar stability (Figure 49-12). This reduces the magnitude of V/Q mismatching because of improved distribution of alveolar ventilation.[23,24] Airway closure and alveolar collapse can be prevented if the level of CPAP/PEEP is above the critical opening pressure. In lung disease with nonuniform or heterogeneous parenchymal involvement, CPAP/PEEP may hyperinflate normal lung segments, and this hyperinflation results in redistribution of blood toward the diseased segments, increasing intrapulmonary shunt on one hand and increasing alveolar dead space on the other (Figure 49-13).

Selection of Parameters for Mandatory Breaths

The first parameter is the tidal volume. A practical approach to determining an adequate tidal volume is to evaluate the desired degree of chest expansion during manual ventilation and to reproduce that when the patient is connected to the

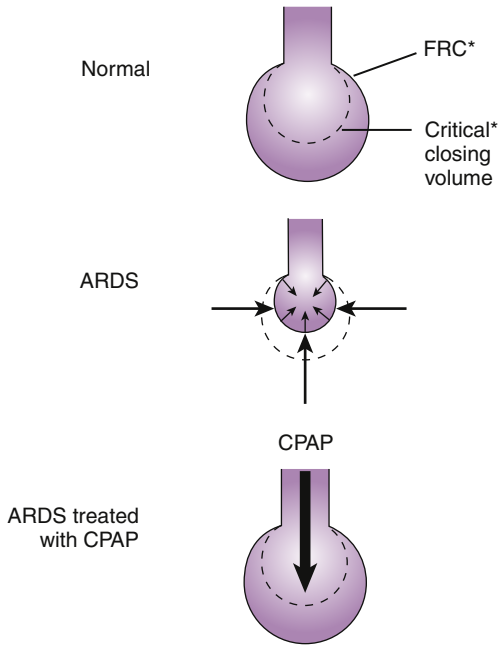

Figure 49–12. Effect of CPAP on FRC. **A**, In normal lungs, FRC is greater than critical closing volume. **B,** In ARDS, FRC is less than critical closing volume. CPAP restores FRC to be greater than critical closing volume and prevents alveolar collapse. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

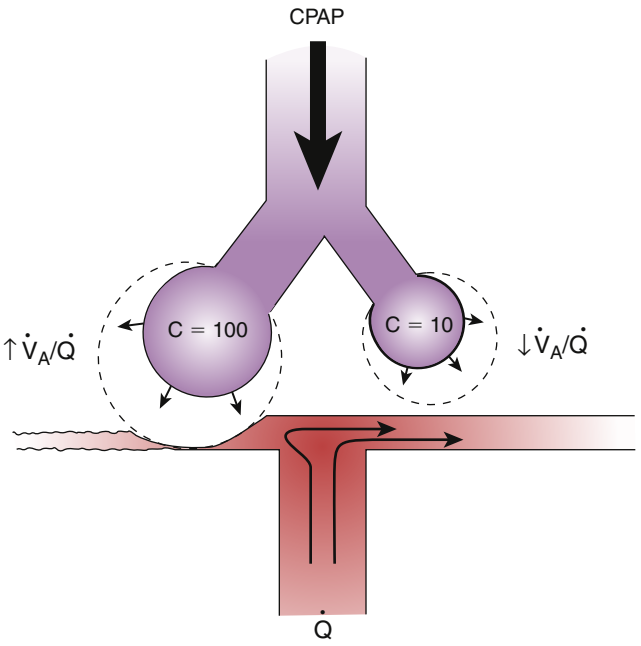

Figure 49–13. Effect of CPAP on nonhomogenous lung disease. CPAP increases FRC in the lung segment with decreased alveolar ventilation-perfusion ratio (*VA/Q*) and decreases shunt reaction. CPAP overdistends lung segments with high VA/Q and redistributes blood toward the segments with low VA/Q increasing the amount of shunt. The net effect depends on the balance between the two. *(From Kirby RR, Smith RA, Desautels DA:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

ventilator. A desirable VT_{eff} for most patients is 8 to 10 mL/kg. Patients with normal lung compliance may require a preset tidal volume of 12 to 15 mL/kg to produce a VT_{eff} of 8 to 10 mL/kg. Ideally, the end-inspiratory alveolar pressure should be less than 30 cm of H_2O. The end-inspiratory alveolar pressure can be measured using an inspiratory hold maneuver. With an inspiratory hold, inspiratory flow is stopped, both inspiratory and expiratory valves are closed and the proximal airway pressure equilibrates with the alveolar pressure. The end-inspiratory hold pressure is called the *pause pressure, plateau pressure*, or simply *end-inspiratory airway pressure*. A large VT_{eff}, especially those that results in an end-inspiratory airway pressure greater than 40 cm of H_2O should be avoided. During mechanical ventilation, end-inspiratory alveolar pressure can be estimated through the measurement of the end-inspiratory airway pressure with an end-inspiratory hold maneuver.

Ventilator rate is the next parameter to be selected. The initial rate selected depends on the age of the patient and the ventilatory requirements of the patient and may subsequently be adjusted according to the $PaCO_2$. The initial ventilator rate for a newborn infant usually ranges from 25 to 30 breaths per minute; for a 1 year old, between 20 and 25 breaths/min; and for an adolescent, from 15 to 20 breaths/min. The inspiratory time is selected to provide an inspiratory/expiratory time (I/E) ratio of at least 1:2 in most patients. Inspiratory time can be set either as a percentage of the total respiratory cycle or as a fixed time in seconds depending on the ventilator. Inspiratory time must be selected to allow sufficient time for all lung segments to be inflated. In heterogenous lung disease with varying regional time constants, a short inspiratory time may not be sufficient to inflate all lung segments and may contribute to underventilation and underinflation. Similarly, sufficient expiratory time must be provided for all lung segments to empty. If inspiration starts before the lung has completely emptied, this will result in air trapping and inadvertent positive end-expiratory pressure. The I/E ratio can be adjusted according to the pathophysiological cause of the lung disease. In infants with bronchiolitis and in children with asthma, the expiratory time may have to be lengthened to avoid air-trapping.

PEEP is the next parameter to be selected. The level of PEEP will depend on the clinical circumstance. PEEP increases mean Paw during both volume-controlled and pressure-controlled ventilation, which results in a higher mean lung volume. The goals of PEEP are (1) increasing end-expiratory lung volume above closing volume to prevent alveolar collapse, (2) maintaining stability of alveolar segments, (3) improving oxygenation, and (4) reducing work of breathing. The optimum PEEP is the level at which there is an acceptable balance between the desired goals and undesired adverse effects. The desired goals are (1) reduction in inspired oxygen concentration to "nontoxic" levels (usually ≤50%); (2) maintenance of PaO_2 or SaO_2 (arterial oxygen saturation) of more than 60 mm Hg or more than 90%, respectively; (3) improvement of lung compliance; and (4) maximal oxygen delivery.[25-27] Arbitrary limits cannot be placed on the level of PEEP or mean airway pressure that will be required to maintain adequate gas exchange. When the level of PEEP is high, peak inspiratory pressure may be limited to prevent it from reaching dangerous levels that contribute to air leaks and barotrauma.

Fio_2 is the next parameter to be selected. Fio_2 is adjusted to maintain an adequate PaO_2. High concentration of oxygen can produce lung injury and should be avoided. The exact threshold of inspired oxygen that increases the risk of lung injury is not clear. An Fio_2 less than 0.5 is generally considered safe. In patients with parenchymal lung disease with significant intrapulmonary shunting, the major determinant of oxygenation is lung volume, which is a function of the mean airway pressure. With a shunt fraction of more than 20%, oxygenation may not be substantially improved by higher concentrations of oxygen.

Assisted Mechanical Ventilation

As defined previously, all assisted ventilation requires the patient to trigger the ventilator to provide a breath. With assisted ventilation, every breath that reaches a trigger threshold will result in a mechanical breath that is predetermined. There are two forms of assisted ventilation. The first kind of assisted breath is one where a mandatory breath is triggered by the patient's effort. In this form of assisted breath, the breath is patient-triggered but machine cycled. The second kind of assisted breath is one where the breath is both patient-triggered and patient-cycled. The second kind of assisted breath is also classified as *pressure control continuous spontaneous ventilation* (PC-CSV) (see Table 49-1). There are various ways to assist spontaneous breaths with a PC-CSV breathing pattern. They include (1) pressure support: spontaneous breaths assisted with setpoint control; 2) volume assist: spontaneous breaths assisted with adaptive pressure control; (3) automatic tube compensation: spontaneous breaths assisted with servo control; (4) proportional assist ventilation: spontaneous breaths assisted with servo control; and (5) SmartCare: spontaneous breaths assisted with knowledge-based control.[12,13] Following is a description of the most common mode of assisted ventilation that is used today.

Pressure-Support Ventilation

Pressure-support ventilation (PSV) is a form of assisted ventilation in which the ventilator assists the patient's own spontaneous effort with a mechanical breath with a preset pressure limit. Figure 49-14 shows the important components of a pressure support breath. As with any form of support that is designed to respond to the patient's effort, the inspiratory pressure assist of PSV requires a signal to trigger the demand valve to initiate flow.[28] The patient's spontaneous breath creates a negative pressure (pressure triggering) or a change in flow through the circuit (flow triggering), which triggers the ventilator to deliver a breath. With initiation, the machine delivers high inspiratory flow to achieve a peak airway pressure level that is selected by the operator.[29-31] The pressure-limit stays constant as long as the patient's inspiratory effort is maintained with a variable gas flow rate from the ventilator.[30,31] As inspiration continues, the inspiratory flow rate decreases. A threshold reduction in the flow rate is a signal for the termination of the inspiratory assist, with the opening of an expiratory valve, after which passive exhalation occurs.[29-31] The termination signal can be a predetermined percentage of the peak inspiratory flow (10% or 25%) or a fixed flow (usually 5 L/min).[32-34] Many ventilators also incorporate backup flow termination criteria, such as the duration of inspiration greater than 5 seconds or an increase in the airway pressure above the set pressure support level (e.g., when a patient attempts to cough). In summary, PSV is patient triggered,

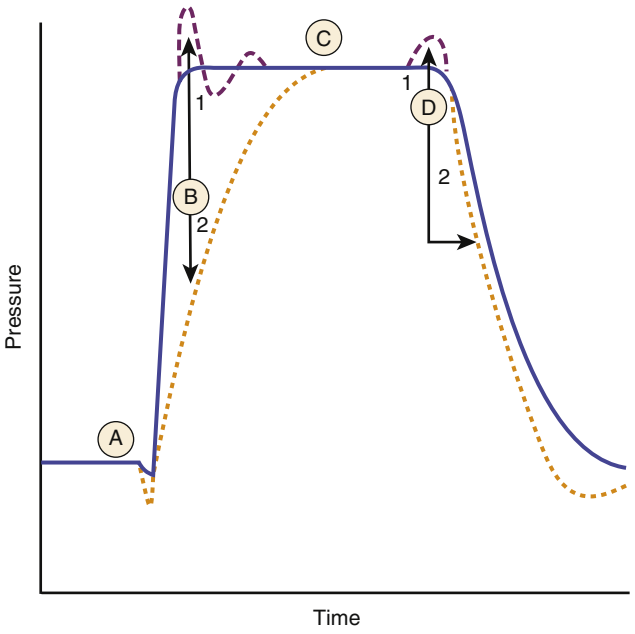

Figure 49–14. Components of a pressure-support breath. *Point A* is the patient's effort indicated by a negative deflection. When the ventilator senses this trigger (change in pressure or flow), it will deliver flow to reach the desired pressure-support level (*point B*) as rapidly as possible. Ventilator-delivered flow is then servo-adjusted to patient demand to maintain this pressure plateau (*point C*). Inspiration is terminated when a minimal flow criterion is reached (*point D*) and airway pressure returns to baseline. *(From MacIntyre NR: Pressure support ventilation. Mechanical ventilation and assisted respiration. In Grenvik A, Downs J, Rasanen J, et al, editors:* Contemporary management in critical care, *New York, 1991, Churchill Livingstone.)*

pressure limited, and flow cycled. PSV is entirely dependent on the patient's effort; if the patient becomes apneic, the ventilator will not provide any mechanical breath.

Other Modes of Ventilation

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is a method of mechanical ventilation introduced by Stock and Downs.[35,36] It was based on the premise that most patients with acute lung injury (ALI) or adult respiratory distress syndrome (ARDS) required positive pressure support to maintain an adequate lung volume and required minimal, if any, ventilatory assistance.[35,36] These authors theorized that if a sufficiently high level of CPAP were provided with a high gas flow rate, it would maintain an adequate lung volume and oxygenation while ventilatory needs would be met entirely by spontaneous breathing. If ventilatory assistance were to be required, CPAP level could be abruptly reduced for a short period of time and this could be repeated several times in a minute to enhance ventilation. So, the original circuit included a CPAP device and a mechanism to release airway pressure periodically to some desired low pressure. Simplistically, this can be thought of as pressure-limited, time-cycled ventilation, in which the preset pressure limit is equal to the level of CPAP required and the PEEP is usually ambient pressure or a selected lower airway pressure, with reversal of I/E ratio. Spontaneous breathing occurs at both levels of airway pressure. In the original description, the gas flow through the circuit was continuous and allowed unrestricted spontaneous breathing. It was recommended that the flow rate be kept slightly above the peak inspiratory flow rate of a spontaneous breath. Minute ventilation occurs with both spontaneous breaths and the periodic inflation and deflation that occur with the two levels of airway pressure. Gas exchange can occur throughout the respiratory cycle. Several studies with acute respiratory failure have shown that APRV results in improvement in gas exchange with much lower airway pressures.[35,37-39] Lower peak airway pressures are the consistent major advantage of ARPV. Because airway pressures are lower, APRV results in less adverse cardiovascular effects than IMV, when both are added to CPAP.[37,39] Some of the modern ventilators have incorporated features that allow spontaneous breathing through a demand-flow system during both the inspiratory and expiratory phases of a pressure-controlled, time-cycled breath. These are called by different names such as *biphasic positive airway pressure* and *intermittent mandatory pressure-release ventilation*. These different modes have been classified under the acronym APRV. Some ventilators incorporate pressure-support to be provided for the spontaneous breaths during these modes. It is clear that the patient-ventilator interactions are clearly different between the original APRV circuit and the modern APRV systems. Generally, demand-flow systems increase the trigger work of breathing and therefore are not necessarily unrestricted, especially in infants and children. At the present time, not enough information is available in infants and children.

Mandatory Minute Volume Ventilation

Mandatory minute volume ventilation (MMV) was first introduced by Hewlett et al.[40] in 1977. In this mode, the patient is guaranteed a preset delivered minute ventilation. If the spontaneous minute ventilation exceeds the preset value, then the ventilator reduces the rate to zero and does not deliver a mechanical breath. If there is no spontaneous minute ventilation, then the ventilator will deliver sufficient breaths to match the preset minute ventilation. If the spontaneous minute ventilation is insufficient to match the preset value, then the ventilator will provide the remainder of the minute ventilation. Different mechanisms are used by manufacturers to achieve this goal. In the Ohmeda CPU1 ventilator, the preset minute ventilation is compared with the patient's total minute ventilation (spontaneous and mechanical) every 24 cycles and then adjusted. In the Engstrom Erica ventilator, it is done on a breath-by-breath basis. Currently, there is not much experience with MMV in pediatric patients. The indications of MMV are in patients after abdominal surgery, especially with complications; patients who are recovering from respiratory muscle paralysis (e.g., Guillain-Barré syndrome, myositis, myasthenia gravis); and patients who have widely fluctuating respiratory drive (encephalopathy).

Dual Control Modes

Dual Control Within a Breath. These modes allow the ventilator to deliver a pressure-controlled breath or switch from a pressure-controlled breath to a volume-controlled breath within the breath. This is shown in Figure 49-15. This mode is referred to as VAPS (Bird 8400ST and Tbird, Bird Corp., Palm Springs, Calif.) and pressure augmentation (PA) (Bear 1000). Both of these techniques can operate during

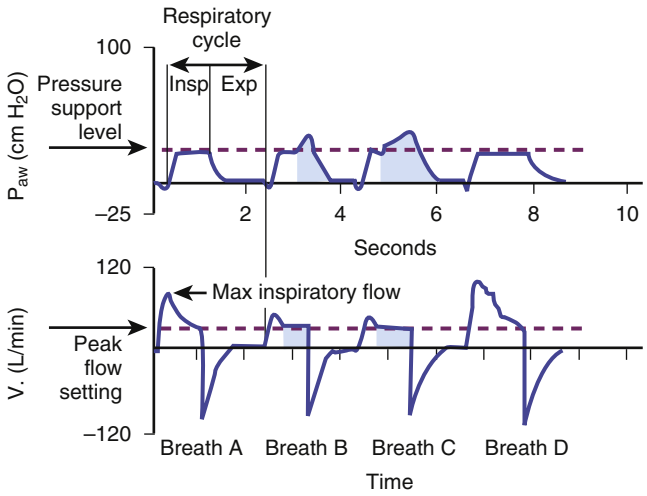

Figure 49–15. Pressure and flow waveforms illustrating VAPS. *(From Branson RD, MacIntyre NR: Dual-control modes of mechanical ventilation,* Respir Care *41:294–305, 1996.)*

mandatory breaths (pressure limited, time cycled) or pressure-supported breaths. During VAPS and PA, the clinician must set the respiratory frequency, peak flow, PEEP, inspired oxygen concentration, trigger sensitivity, and minimum desired tidal volume. During VAPS or PA, the ventilator's inspiratory flow waveform is constant (square). Additionally, the pressure support setting must be set. During pressure support, VAPS and PA can be considered a safety net that always supplies a minimum tidal volume. A VAPS or PA breath may be initiated by the patient or time triggered. After the breath is triggered, the ventilator attempts to reach the pressure support setting as quickly as possible. This portion of the breath is the pressure control portion and is associated with a rapid variable flow, which may reduce the work of breathing. As this pressure level is reached, the ventilator's microprocessor determines the volume that has been delivered from the machine (note: this is not exhaled tidal volume), compares this measurement with the desired tidal volume, and determines whether the minimum desired tidal volume will be reached. If the ventilator determines that the ultimate delivered tidal volume will be equivalent to the set tidal volume, the breath is delivered as a pressure support breath. If the ventilator determines that the ultimate delivered tidal volume will be less than the set tidal volume, then the breath changes from a pressure-limited to a volume-limited breath. At that point, inspiratory flow remains constant and the ventilator increases the inspiratory time until the desired volume has been delivered. Inspiratory pressure will increase above the set pressure support setting. Setting the high-pressure alarm remains important during VAPS. If pressure increases abruptly, the high-pressure alarm setting is reached, and the breath is pressure cycled (see Figure 49-15). VAPS breath can allow the patient a tidal volume larger than the set volume.

Mandatory Dual-Control Breath-to-Breath Modes. Dual-control breath-to-breath mode with mandatory pressure-limited time-cycled breaths is referred to as pressure-regulated volume control (PRVC) (with Siemens 300), adaptive pressure ventilation (APV) (with Hamilton Galileo), autoflow (Evita 4), or variable pressure control (Venturi), depending on the manufacturer. In this form of pressure-limited, time-cycled ventilation, delivered tidal volume is used as a feedback control for continuously adjusting the pressure limit. All breaths in these modes are time or patient triggered, pressure limited, and time cycled. One difference between devices is that the Siemens 300 only allows PRVC in the CMV mode. The newer Servo-i ventilator and the other ventilators allow dual control breath to breath with CMV or SIMV. During SIMV, the mandatory breaths are the dual control breaths. PRVC is selected on the mode selector switch, and the desired tidal volume is set. A "test breath" is delivered, and total system compliance is calculated. The next three breaths are delivered at a pressure limit that is 75% of that necessary to achieve the desired tidal volume on the basis of the compliance calculation. The ensuing breaths increase or decrease the pressure limit at less than 3 cm H_2O per breath in an attempt to deliver the desired tidal volume. The pressure limit fluctuates between 0 cm H_2O above the PEEP level and 5 cm H_2O below the upper-pressure alarm setting. The ventilator sounds an alarm if the tidal volume and maximum pressure limit settings are incompatible. With changes in lung compliance and resistance, the delivered tidal volume may not be equivalent to the set tidal volume. If the delivered tidal volume is less than the set tidal volume, the pressure-limit is increased to achieve the set tidal volume until the pressure limit is equal to a level 5 cm H_2O below the upper pressure limit alarm. The upper pressure-limit alarm must be adjusted with this in mind. It should be set to the maximum allowable pressure plus 5 cm of H_2O. When the delivered tidal volume is larger than the set tidal volume, then the ventilator will lower the pressure limit to achieve the set tidal volume. There is no lower limit for the reduction in the pressure-limit level. This mode of ventilation appears to be most beneficial when there are rapid changes in lung compliance (such as after surfactant administration).[41-43] Clinically controlled trials are required to evaluate the benefits of PRVC ventilation in acute lung disease, in ventilation of healthy lungs (i.e., in patients undergoing neurosurgical procedures), and during weaning from the ventilator.

Assisted Dual-Control Breath-to-Breath Mode. Dual-control breath to breath in the pressure support mode is simply closed-loop pressure support ventilation, with tidal volume as the input variable. It is referred to as volume support (Siemens 300) and variable pressure support (Venturi). All breaths are patient triggered, pressure limited, and flow cycled. Volume support is selected with the mode selector switch, and the desired tidal volume is set. The ventilator initiates volume support by delivering a "test breath" with a peak pressure of 5 cm H_2O when a patient effort is sensed. The delivered tidal volume is measured, and total system compliance is calculated. The subsequent three breaths are delivered at a peak inspiratory pressure of 75% of the pressure calculated to deliver the minimum tidal volume. Each subsequent breath uses the previous calculation of system compliance to manipulate peak pressure to achieve the desired tidal volume. From breath to breath, the maximum pressure change is less than 3 cm H_2O and can range from 0 cm H_2O above PEEP to 5 cm H_2O below the high-pressure alarm setting. The primary cycling mechanism is flow cycling of the pressure-supported breath. Similar to the PRVC mode previously described, the pressure-support level is adjusted to maintain the set tidal volume with changes in compliance and resistance. In addition to the

volume-support settings, a mandatory ventilator frequency must be set. This frequency is set according to the age of the patient; the frequency for ages younger than 6 months is 16 to 20 breaths per minute; for 6 months to 2 years, 14 to 18 breaths/min; for 2 to 5 years, 12 to 16 breaths/min; and for older than 5 years, 10 to 16 breaths/min. A secondary cycling mechanism is activated if inspiratory time exceeds 80% of the set total cycle time. There is also a relationship between the set ventilator frequency and tidal volume. The minute ventilation calculated by the set tidal volume and the backup ventilator rate gives the minimum minute ventilation that needs to be achieved. If the patient is breathing at a frequency faster than the set ventilator rate, then the only adjustment that is made by the ventilator is to manipulate the pressure-support level to achieve the desired tidal volume. The total minute ventilation in this instance will be larger than the minimum level that needs to be achieved. When the patient's breathing rate is less than the set frequency, then the total minute ventilation will decrease to a level below the set minimum level. Then, the tidal volume target is automatically increased by raising the pressure-support level up to a maximum of 150% of the initial set value. If the tidal volume has to be increased beyond the 150% of the initial set value or the minute ventilation cannot be maintained at the set minimum level, then the ventilator will alarm and switch to the PRVC mode to ensure that at least the set minimum minute ventilation is delivered.

AutoMode

AutoMode combines mandatory and assisted dual-control breath-to-breath modes. The patient's effort or lack of breathing effort determines whether the breaths are flow cycled or time cycled. AutoMode is available on the Siemens 300A ventilator. Simplistically, AutoMode can be thought of as the combination of volume support and PRVC in a single mode. When the patient is breathing spontaneously, then the patient is in volume-support mode. If the patient becomes apneic or is paralyzed, the ventilator provides PRVC. The apneic threshold setting is 12 seconds for adults, 8 seconds for children, and 5 seconds for neonates. The change from PRVC to volume support or from volume support to PRVC is accomplished at equivalent peak pressures.

Automatic Tube Compensation

Automatic tube compensation (ATC) is a technique of overcoming the imposed work of breathing caused by artificial airways available in the Evita 4 ventilator. It accomplishes this by using the known resistive characteristics of the artificial airways. ATC is essentially pressure support in which the ventilator adjusts the pressure support to compensate for the imposed work of breathing by the artificial airways and the flow demand of the patient. The equation for calculating tracheal pressure (P_{trach}) is $P_{trach} = P_{aw} - (K \times V^2)$, where P_{aw} is airway pressure, V is flow, and K is the tube coefficient describing the nonlinear pressure/flow curve of the ETT.

To select the level of ATC required, the operator needs to input type of tube, endotracheal or tracheostomy, and the percentage of compensation desired (10% to 100%). Most of the interest in ATC revolves around eliminating the imposed work of breathing during inspiration. Under static in vitro conditions, pressure support can eliminate the endotracheal resistance, but in vivo, where the inspiratory flow demands of the patient are changing, a single level of pressure support is unlikely to be effective. Moreover, there are no in vivo measurements of the minimal pressure support needed to overcome the endotracheal tube resistance. During periods of tachypnea, the level of pressure support no longer eliminates work imposed by the endotracheal tube. Additionally, the resistance of the endotracheal tube creates a condition early in the breath in which ventilator flow is high, tracheal pressure remains low, and undercompensation for imposed work occurs.[44] Late in the breath, when pressure begins to equilibrate during the pressure plateau, pressure support tends to overcompensate, prolong inspiration, and exacerbate overinflation.[44] During expiration, however, there is also a flow-dependent pressure decrease across the tube. ATC also compensates for this flow-resistive component and may reduce expiratory resistance and unintentional hyperinflation. During expiration, the calculated tracheal pressure is greater than airway pressure.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is a mode of mechanical ventilation that is based on the equation of motion. The design of PAV allows the ventilator to change the pressure output (pressure control) to always perform work proportionally to patient effort. PAV is simply PSV in which the level of pressure support is adjusted as a multiple of the sum of the volume and flow signals. The ventilator tries to maintain a constant percentage of work performed by the patient per breath irrespective of the volume of the breath or the inspiratory flow of the breath. Currently, there are major issues of interface and accurate breath-to-breath measurement of elastance and resistance and the need to take into account the confounding effects of endotracheal tube resistance, level of auto-PEEP, and the problem of nonlinearity of elastance and resistance.

High-Frequency Ventilation

Definitions

High-frequency ventilation (HFV) refers to diverse modes of ventilation characterized in general by supraphysiologic ventilatory frequencies (>60 cycles/min) and low tidal volumes (less than or equal to physiologic dead space during conventional ventilation). Four distinct methods of HFV are recognized: high-frequency positive pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV), high-frequency oscillatory ventilation (HFOV), and high-frequency chest wall oscillation (HFCWO).

1. **HFPPV** was first described by Oberg and Sjostrand[45] in 1969 and refers to ventilation at a frequency of 60 to 100 cycles/min with a tidal volume of 3 to 4 mL/kg using a ventilator with a small internal dead space, low internal compliance, and minimal compression of gases within the ventilator. HFPPV was initially instituted by insufflation through a catheter positioned within the endotracheal tube, with expiration occurring through an expiratory valve connected to the outer orifice. Since 1973, a pneumatic valve, based on the Coanda or wall effect, was developed in which the gas mixture was intermittently delivered through a sidearm branching off the main channel of the pneumatic valve connector (Figure 49-16). This main channel remains open for insertion of a bronchoscope or a laryngoscope.

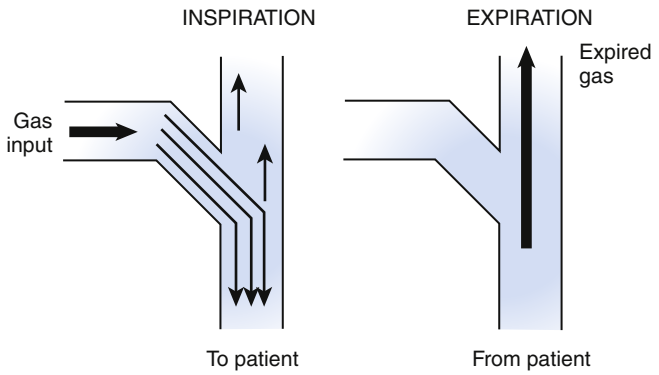

Figure 49–16. High-frequency positive-pressure ventilator. The inspiratory limb is angled so that the inspiratory gas can be directed to the patient. During inspiration, some gas escapes through the expiratory limb, preventing entrainment. During expiration, the gas flows out into the expiratory limb. *(From Shoemaker WC, Ayres S, Grenvik A, et al editors:* The textbook of critical care, *Philadelphia,1989, WB Saunders.)*

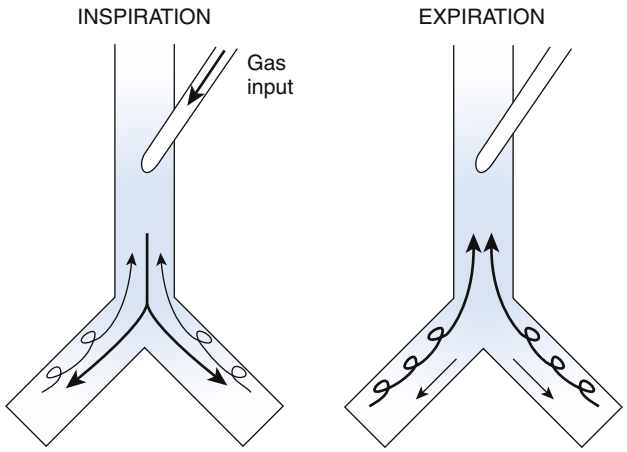

Figure 49–17. High-frequency jet ventilator. Gas is introduced into the trachea at a high pressure through a small catheter. *Arrows* represent coaxial and turbulent flow patterns. *(From Shoemaker WC, Ayres S, Grenvik A, et al editors:* The textbook of critical care, *Philadelphia, 1989, WB Saunders.)*

2. **HFJV,** which was first described by Sanders[46] in 1967 to assist bronchoscopy, refers to delivery of inspiratory gases through a jet injector at a high velocity into the trachea at a rate of 100 to 400 cycles/min (Figure 49-17). Tidal volumes delivered are usually 3 to 5 mL/kg.
3. **HFOV** was first described by Lunkenheimer[47] in 1972 and refers to ventilation at frequencies of 900 to 3600 cycles/min, with an alternating positive and negative pressure in the airway. This oscillatory flow may be produced by a piston pump or a diaphragm with tidal volumes of 1 to 3 mL/kg (Figure 49-18).
4. **HFCWO** was first described by Zidulka et al.[48] in 1983 and refers to a method of ventilation in which a rigid harness surrounds the chest and is oscillated at a frequency of 180 to 600 cycles/min; minute ventilation is controlled with adjustment of the inflation pressure and frequency. A variant of HFCWO is high-frequency body surface oscillation (HFBSO), in which the body is encased in an air-tight tank.

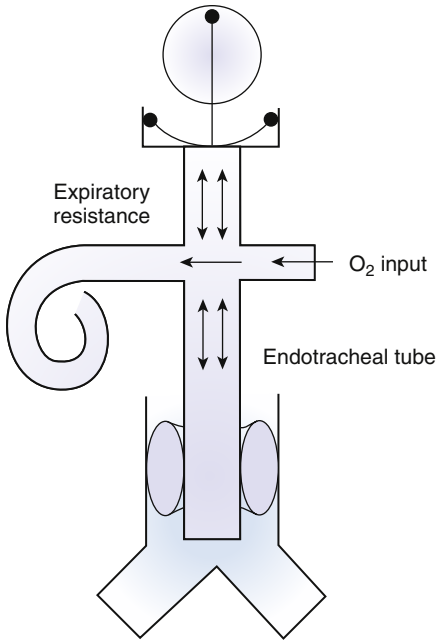

Figure 49–18. High-frequency oscillation system. Uses a reciprocating pump (*top*) to oscillate a column of gas that is a mixture of inspired and expired gases. Excess gas is vented through the overflow side port (*left*). *(From Shoemaker WC, Ayres S, Grenvik A, et al editors:* The textbook of critical care, *Philadelphia, 1989, WB Saunders.)*

Only HFPPV, HFJV, and HFOV have been extensively used clinically.

Mechanism of Gas Flow in High-Frequency Ventilation in the Normal Lung

The exact mechanism of gas transport in HFV is currently not clear. It is possible that each mode of ventilation may have differing mechanisms of gas flow from the proximal airway to the alveoli. If gas flow to the lungs is increased more than 200 times the minute volume of oxygen demand, the lung parenchyma can be made to oscillate.[49,50] At ventilatory frequencies less than 7 Hz, regional alveolar ventilation depends on segmental compliance and airway resistance. At a ventilatory frequency greater than 7 Hz, a frequency-dependent excitation of the lung parenchyma and airway conduits occurs,[51] and at frequencies greater than 10 Hz, ventilation becomes independent of regional compliance. When the gas in the airways is oscillated at high frequency, the airways begin to undergo spatial oscillation inside the chest. These oscillations are composed of periodic changes in length and width, movements of curved or angular bronchi, and wave motions in the bronchi. When the frequency of oscillation approaches the natural resonant frequency of the lung structures, the oscillations of the airways, and the lung parenchyma are amplified. These result in shaking and squeezing of the neighboring parenchyma, resulting in intraparenchymal and interparenchymal gas mixing.[52] Other mechanisms involved in gas transport during HFV include accelerated axial dispersion, increased collateral flow through pores of Kohn, intersegmental gas mixing or Pendelluft phenomenon, Taylor dispersion, asymmetric gas flow profiles, and gas mixing within the airway from the nonlinear pressure-diameter relationship of the bronchi.

Parameters to Be Selected

High-Frequency Jet Ventilation

The main controls in HFJV are the driving pressure inspiratory time, and rate. The driving pressure is usually initiated at a desired mean airway pressure and adjusted according to the level of lung expansion and gas exchange. Inspiratory time is usually kept to a minimum at 20%. A higher inspiratory time may be used but may result in air-trapping. The rate can be adjusted up to 600 breaths per minute depending on the jet ventilator used. PEEP is applied through a separate bias flow circuit with continuous flow. Fio_2 delivered to the patient is adjusted through regulation of the inspired oxygen concentration of the bias flow circuit. In certain circumstances, conventional ventilation can be combined with HFJV. Here, conventional ventilation provides "sigh breaths" of approximately 10 to 12 mL/kg to prevent atelectasis and maintain lung volumes during HFJV. The size of each breath increases with a higher driving pressure, increased inspiratory time, and a decreased frequency. Because there is entrainment of gas with HFJV, it is difficult to predict the effect of ventilator parameters on minute ventilation. Ventilation is most effective when the jet catheter is close to the carina. The main concerns with HFJV are airway injury and air-trapping. Airway injury can be minimized with placement of the tip of the catheter sufficiently proximal in the endotracheal tube and without close placement close to the carina. Air-trapping can be avoided with the minimal inspiratory time and the lowest driving pressure.[53]

High-Frequency Oscillatory Ventilation

Currently, the HFOV systems available in North America are the Viasys Critical Care 3100A and 3100B ventilators. The main difference between the two ventilators is the age range each of them supports. The 3100A is designed to support HFOV in neonates and small children. The 3100B is designed to support older children and adults weighing more than 35 kg. Input power for both the ventilators requires two pneumatic gas sources and one electrical source. The first pneumatic connection through a blender determines the Fio_2 delivered to the patients. The second pneumatic connection is for cooling the oscillator. The drive mechanism is a square-wave driver which has an electric linear motor and a piston. The stroke of the piston (both positive and negative) determines the amplitude. The position of the piston determines the mean airway pressure of the circuit.

The main controls in HFOV are mean airway pressure, oscillatory pressure amplitude, bias flow, frequency, and inspiratory time. With piston-driven oscillators, piston-centering is an additional control mechanism. Mean airway pressure determines the mean lung volume of the lung. Oscillatory amplitude is the total change in pressure around the mean airway pressure produced by forward and backward displacement of the piston. The pressures developed in the patients' airways are considerably dampened because of the impedance of the endotracheal tube. Similarly, the pressure profile is further dampened in the distal airways because of the impedance of the proximal airways. If the oscillatory frequency approaches the natural resonant frequency of the lung and airways, then there may be amplification of the pressure waves. The oscillatory amplitude determines the volume displacement with each stroke of the piston. If the volume of gas displaced is less than the dead space of the airways and lungs, then there is little chest displacement. If sufficient chest displacement is seen with each stroke, then the volume of gas displaced tends to be larger than the physiologic dead space and results in some direct alveolar ventilation. Frequency is the next parameter that can be controlled and is usually in the range of 5 to 10 Hz. For a given amplitude, a lower frequency will result in less attenuation of pressures along the airways and improve gas exchange. Inspiratory time is generally controlled at 33% of the total cycle time. In certain circumstances, a lower inspiratory time may be used. Bias flow is a continuous flow of fresh humidified gas and allows replenishing oxygen and removing carbon dioxide from the circuit. Determinants of oxygenation during HFOV are mean airway pressure and Fio_2. Minute ventilation during HFOV is directly proportional to the frequency and the square of the tidal volume. Tidal volume is determined by the amplitude and the duration of each stroke. With increased frequency, the time for each stroke is reduced, decreasing the tidal volume. When the ventilatory frequency is decreased, this increases the time for each stroke and thereby increases the tidal volume. The primary determinant of ventilation is oscillatory amplitude. Decreasing the frequency to reduce attenuation and increasing the inspiratory time are less effective strategies to improve carbon dioxide elimination.

High-Frequency Percussive Ventilation

High-frequency percussive ventilation (HFPV), a newer mode introduced during the past 20 years, combines the beneficial effects of HFV with conventional ventilatory support.[54-56] HFPV has been described as an exceptionally versatile form of HFV that delivers subphysiologic tidal volumes at rapid rates (up to 500 breaths/min) using the volume-diffusive respirator.[54-56] It has been shown to provide the same or improved oxygenation and ventilation at lower peak, mean, and end-expiratory pressures when compared with conventional ventilation.[54-56]

The high-frequency percussive ventilator (Percussionaire, Bird Technologies, Sandpoint, Idaho) is a pneumatically powered, time-cycled, and pressure-limited ventilator with inspiratory and expiratory oscillation. The ventilator is connected to a high pressure flow generator, fed by an air-oxygen blender. Two inspiratory circuits come off the ventilator—one a high-pressure and the other a low-pressure circuit. The low-pressure circuit is connected to the humidifier and a nebulizer system. The humidifier and nebulization system provides a gas mixture that is appropriately heated and fully humidified. The high-pressure circuit is a low compliant tubing. Both the circuits attach to a system called the Phasitron, which is a sliding Venturi that acts as both an inspiratory and expiratory valve. The phasitron is driven by a high-pressure gas supply at a high-frequency rate of 200 to 900 beats/min superimposed on a conventional I/E pressure-controlled cycle that is set at a desired rate. From the Phasitron, there are two branches—one is the inspiratory limb that attaches to the endotracheal tube and the other an expiratory limb. The Phasitron consists of a hollow cylinder in which there is a spring-controlled piston which is driven by the high-pressure circuit. There are two safety valves, one inspiratory and one expiratory that regulate the pressure delivered to the airway. There are seven control variables: (1) peak inspiratory pressure,

(2) positive end-expiratory pressure, (3) continuous positive airway pressure, (4) inspiratory time, (5) expiratory time, (6) percussive frequency, and (7) rate. The tidal volume delivery is a product of the PIP setting and subtidal volumes produced by the oscillatory function. During inspiration, lung volumes are progressively increased in a controlled, stepwise fashion by repetitively diminishing subtidal volume deliveries until an oscillatory plateau is entered and maintained.[4] At the end of inspiration, the lung is allowed to empty passively until the preset expiratory baseline is reached. Gas exchange has been noted to be as good, if not better, than CV at lower airway pressures. The endotracheal tube cuff should be left partially deflated to allow for a continuous air leak through the trachea.

Clinical Uses of High-Frequency Ventilation

The principal theoretical advantage for the use of HFV lies in the ability to ventilate effectively at low airway pressures. The most common use of HFV is in the operating room for use in airway operations; in laryngoscopies; in bronchoscopies; and in emergency airway management, in which airway movement has to be reduced to a minimum.[53] HFV has been used to manage neonates with idiopathic respiratory distress syndrome with the goal of decreasing the incidence of pulmonary barotrauma. Initial studies showed improvement in gas exchange with lower airway pressures, provided periodic sigh maneuvers were performed.[57-60] HFV has been also been shown to support adequate gas exchange with severe pulmonary interstitial emphysema (PIE) in neonates.[61,62] The initial enthusiasm for HFOV as a method for reducing pulmonary barotrauma in premature neonates with idiopathic respiratory distress syndrome requiring mechanical ventilation has been tempered by a recent multicenter trial in which HFOV did not prove to be superior to conventional mechanical ventilation.[63] One area of relatively proven benefit of HFV is in the management of bronchopleural fistulae. HFJV has proven useful in the management of bronchopleural fistula, with consistent improvement in arterial blood gas, when conventional ventilation had previously failed.[64] Recent studies have suggested a role for HFV in children after cardiac surgery and with ARDS.[65-70] HFJV has been shown to improve cardiac function after a Fontan procedure.[65] HFJV and HFOV have been shown to improve oxygenation and ventilation compared with conventional ventilation in children with respiratory failure.[67-70]

The most common approach to HFOV in infants and children is as a rescue therapy when conventional mechanical ventilation proves to be insufficient to recruit the lungs and maintain adequate gas exchange. There are many reported strategies with the use of HFV: (1) "high lung volume strategy," which requires HFV to be provided at a mean airway pressure that is at least 3 to 5 cm higher than with conventional ventilation; (2) combined HFV and conventional ventilation (usually used with HFJV), in which conventional tidal breaths are interposed during HFV usually at a rate of 5 to 8 breaths/min; or (3) application of HFV at the same mean airway pressure as conventional ventilation. The high lung volume strategy seems to be the most promising one at least for HFOV. When transitioning the patient to HFOV from conventional ventilation, the mean airway pressure on HFOV is set to 3 to 6 cm H_2O above the mean airway pressure on conventional ventilation. It is important to recruit the lung before placing the patient on HFOV. Amplitude is set by adjusting the Power control while observing for adequacy of chest wall vibrations. The goal for oxygenation is to employ a mean airway pressure that will allow reduction of Fio_2 to at least 0.6 while maintaining an arterial oxygen saturation of at least 90%. This may require titrating the mean airway pressure from the initial setting. Adequacy of lung recruitment is usually verified by ensuring that both hemidiaphragms are displaced to the level of the ninth posterior rib on a chest radiograph. After an appropriate degree of lung inflation as well as patency of the endotracheal tube are verified, ventilation needs to be addressed. Arterial $Paco_2$ can be maintained at the desired level by changing the amplitude or frequency. Ventilation is increased by an increase in amplitude and a decrease in frequency. It is also important to deflate the cuff of the endotracheal tube, if a cuffed tube is used. Adjusting the bias flow can also aid in ventilation but is seldom done in routine clinical practice.

Case series in neonates with respiratory failure showed that HFPV can result in improvement in oxygenation and ventilation with a reduction in Fio_2 and PEEP requirements.[71-73] One other purported advantage to HFPV is the mobilization of secretions. This has generated much interest from the burn community, particularly for the treatment of children and adults with inhalation injury.[74-80] Two prospective, randomized trials of HFPV have been reported in the pediatric burn population. Compared with the conventional ventilation, HFPV resulted in similar ventilation and improved oxygenation at significantly lower peak inspiratory pressures. Pneumonia and mortality rates were lower in the high frequency group.[75,76]

Approach to Mechanical Ventilation Based on Underlying Pathophysiology

Primary Respiratory Muscle Failure ("Respiratory Pump Failure")

The primary difficulty in these disorders is inadequate ventilation due to weakness of the respiratory muscles (pump failure). Tidal volumes and ventilatory rates are set to provide normal minute ventilation to maintain normocarbia. Complete control of ventilation may result in disuse muscle atrophy and complicate weaning from mechanical ventilation; therefore spontaneous breathing should be encouraged as much as possible. Assisted ventilation is a useful mode of ventilation in these disorders because the trigger sensitivity can be adjusted to encourage spontaneous breathing on the one hand and prevent muscle fatigue on the other. Fio_2 is usually kept to a minimum because these disorders are not associated with inadequate oxygenation. In chronic hypoventilation, hypercarbia is often acceptable, provided the arterial pH is within the normal range. PEEP is usually set at a relatively low level (3 to 5 cm H_2O).

Disorders with Airway Obstruction

Provision of an artificial airway relieves respiratory distress because of upper airway obstruction (e.g., epiglottitis, croup). Respiratory failure from lower airway obstruction poses a

special problem during mechanical ventilation. Depression of cardiac output and hypotension may occur during intubation because of the institution of positive airway pressure to already hyperinflated lungs. This causes further impedance to venous return and increased pulmonary vascular resistance. Volume-controlled ventilation is the preferred mode of ventilation. Inspiratory-expiratory ratio should be at least 1:2. The expiratory time required depends on the severity of the lower airway obstruction. If the expiratory time is inadequate to empty the lung, "auto-PEEP" or "inadvertent PEEP" will result. Inadvertent PEEP results in air-trapping and hyperinflation with its attendant complications. The level of PEEP selected for patients with lower airway obstruction is controversial. There are two schools of thought: "low PEEP" and "high PEEP." Low PEEP advocates usually apply a PEEP of 3 to 5 cm H_2O because of the concern for pulmonary barotrauma from air-trapping and alveolar hyperinflation. In lower airway disease, air-trapping often results in an end-expiratory alveolar pressure that is higher than the proximal airway pressure because of incomplete emptying of the alveoli. This results in "auto-PEEP" or "inadvertent PEEP." End-expiratory lung volume and therefore the level of alveolar inflation will not be affected by the level of proximal set PEEP as long as it is less than the amount of auto-PEEP. In adults with severe asthma, high levels of PEEP, which is closer to the level of auto-PEEP, have been shown to decrease the magnitude of air-trapping and work of breathing without significant complications.[81-83] In children with tracheomalacia or bronchomalacia, PEEP decreases the airway resistance by distending the airways and preventing dynamic compression during expiration. The use of low levels of PEEP compared with high levels has been described previously.

Parenchymal Lung Disease

ARDS, idiopathic respiratory distress syndrome, and interstitial pneumonias are examples of parenchymal lung disorders that are characterized by a reduction in FRC, an increase in closing volume higher than FRC, and diffuse subsegmental atelectasis. These diseases are characterized primarily by inadequate oxygenation because of V/Q mismatching and intrapulmonary shunting. Therapy should be directed toward maintaining lung volumes higher than closing volume throughout the respiratory cycle, increasing FRC higher than closing volume, and reducing V/Q mismatching and intrapulmonary shunting. The most effective method of achieving these goals is with an increase of mean lung volume, which is usually obtained with an increase of the mean airway pressure. During spontaneous breathing without any ventilatory assistance, CPAP is the most reliable method to increase lung volume. CPAP is effective in improving oxygenation in idiopathic respiratory distress syndrome[14] and ARDS.[84,85] During positive-pressure breathing, the level of PEEP required to maintain adequate oxygenation primarily depends on the severity of the underlying lung disease. The degree of intrapulmonary shunting, ventilation-perfusion mismatching, alveolar edema, alveolar collapse, and decreased compliance is directly proportional to the severity of lung disease. As the severity of lung disease increases, the airway pressures required to maintain adequate gas exchange also increase. Therefore arbitrary limits cannot be placed on the level of PEEP or mean airway pressure that will be necessary to maintain adequate gas exchange. Tidal volumes should be limited to 6 to 8 mL/kg. Studies in adults, including the ARDSNetwork study, have demonstrated that using high tidal volumes of 12 ml/kg is detrimental to patient outcome.[86,87] When high levels of PEEP are used, PIP may reach levels that contribute to pulmonary air leak and barotrauma. Attempts to decrease PIP with the reduction of tidal volume will result in decreased mean airway pressure, mean lung volume, and decreased minute ventilation. With a high airway pressure maintained throughout inspiration, pressure-control ventilation may provide higher mean airway pressure and maintain a higher mean lung volume compared with volume-control ventilation. A general rule of thumb is to consider switching to pressure-limited time-cycled ventilation when PEEP requirement is more than 10 cm H_2O. For hyperinflation to be avoided, the end-inspiratory pause pressure should not exceed 35 cm H_2O. Hypercapnia may be permitted under these circumstances provided arterial pH is adequate (permissive hypercapnia). It has been recommended that the optimal PEEP should be set above the critical closing or critical opening pressure of the airways. This can be deduced by the lower inflection point generated with static pressure-volume loops (Figure 49-19). As the lung is inflated from zero end-expiratory pressure, in many lungs there is an abrupt change in compliance as denoted by the "lower inflection point." It is generally thought that this is the critical opening pressure of the airways above which the alveoli and airways remain open. As the lung is further inflated in increments, the pressure-volume slope increases and then abruptly changes direction as noted in Figure 49-19 as the "upper inflection point." It is generally thought that the upper inflection point reflects overdistension of the alveoli. The general recommendation is to keep the PEEP level above the lower inflection point and to keep the end-inspiratory pause pressure below the upper inflection point. Currently, bedside use of static pressure-volume loops to set PEEP is not a standard practice in infants and

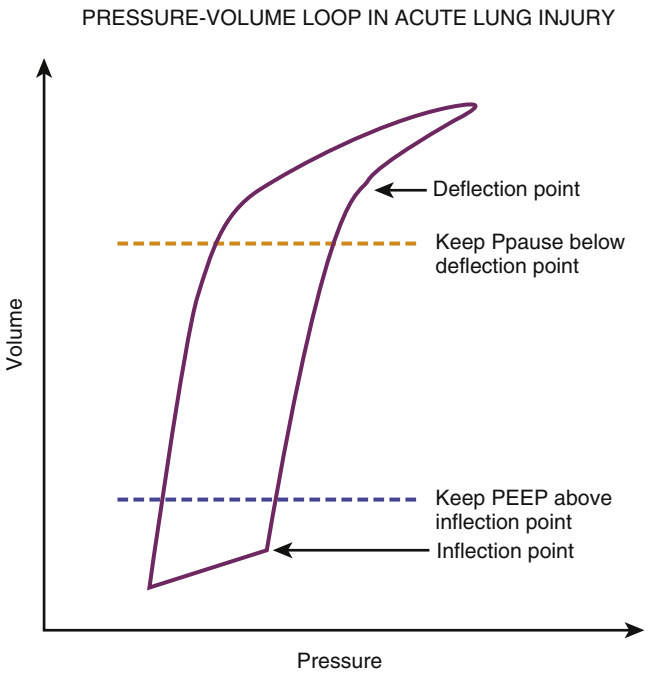

Figure 49–19. Optimal PEEP and peak alveolar pressure setting in ALI/ARDS on the basis of static pressure-volume loop. The goal is to keep the PEEP level above the lower inflection point and to keep the end-inspiratory pause pressure below the upper inflection point.

children. Therefore the level of PEEP should be set by titrating the level of PEEP and selecting the level by the maximal level of improvement in oxygenation compliance seen without affecting systemic hemodynamics. The repeated collapse and reopening of the lung units at low lung volume have been shown to contribute to ventilation-induced lung injury.[88-91] A strategy combining recruitment maneuvers, low-tidal volume, and higher PEEP has been shown to decrease the incidence of barotrauma or volutrauma.[88-91]

Alveolar Recruitment and Derecruitment

Alveolar recruitment with maintenance of lung volume by preventing derecruitment during mechanical ventilation is a goal in ventilating the lungs of patients with ALI and ARDS. The benefits of optimal lung recruitment and prevention of derecruitment are (1) a reduction in the intrapulmonary shunt fraction and venous admixture resulting in an improvement in arterial oxygenation; (2) improvement in lung compliance; and (3) prevention of repeated alveolar collapse and reopening, which may ameliorate or prevent ventilator-induced lung injury. The primary determinants of alveolar recruitment and derecruitment are transpulmonary pressure and PEEP both of which increase mean airway pressure. Mean lung volume depends on mean alveolar pressure. Mean airway pressure has been shown to be an excellent marker of mean alveolar pressure.[93] Increasing mean airway pressure will improve oxygenation if there is alveolar recruitment. Several techniques of alveolar recruitment have been described in the literature. These include manual inflation to high airway pressures, the increase of PEEP in a stepwise manner, application of a sign maneuver, the use of pressure-limited time-cycled ventilation with a high peak inspiratory pressure, and the combination of titrated levels of PEEP with increased inflation pressures. Ventilatory sighs are effective in recruiting alveoli in ARDS.[94] They are effective, however, only from an optimal level of PEEP that does not result in derecruitment. At optimal PEEP, a sigh maneuver increases end-expiratory lung volume and improves oxygenation.[95] Gattinoni et al.[96,97] showed and quantified alveolar recruitment induced by PEEP and showed that the primary role of tidal volume inflation was to open the lung and the primary role of PEEP was to avoid derecruitment. Not all patients have recruitable lungs. In some patients, the lungs may be maximally recruited and any further increase in airway pressures may either cause no change in lung mechanics or gas exchange or result in a deterioration of lung mechanics and gas exchange due to overdistension.[98] The low tidal volume and moderate PEEP approach used in the ARDSNetwork study has been shown to result in derecruitment in many patients. Richard et al. showed that increasing PEEP or performing periodic recruitment techniques counteracted the derecruitment in these patients.[99] Periodic high levels of PEEP, high inflation plateau pressures, or both have shown to be beneficial in improving lung mechanics and oxygenation, through alveolar recruitment.[100-102]

Prone Positioning

Prone positioning has been proposed as a means to improve gas exchange in patients with ARDS with severe hypoxemia. Oxygenation improves in most adult patients with ALI/ARDS when they are placed prone.[103-107] A large, multicenter trial of prone positioning for almost 7 hours per day did not show improvement in mortality rates in patients with ALI/ARDS; however, a post hoc analysis suggested improvement in those patients with the most severe hypoxemia.[106] A recent multicenter trial of prone positioning for almost 20 hours a day also suggested improvement in this patient subgroup that did not reach statistical significance.[108] Bruno et al.[109] reported the short-term effects of 1 to 2 hours of prone positioning in children with respiratory failure. They found that only 28% of the patients had a significant improvement in oxygenation.[109] Curley et al., in a preliminary single-center study in children with ALI/ARDS, showed that oxygenation improved with prone positioning in 84% of patients without any critical incident.[110] Relvas et al.[111] also reported a retrospective study on the effects of prone positioning in children with ARDS and showed that the improvement in oxygenation was much more sustained if the duration of prone positioning was between 18 and 24 hours than when the duration of prone positioning was between 6 and 10 hours. A recent multicenter study on prone positioning in children with ALI/ARDS showed that patient recruitment within 48 hours of meeting acute lung injury criteria, prone positioning for 20 hours per day for a maximum of 7 days did not show any differences in the number of ventilator-free days between the two groups. There were no differences in the secondary endpoints, including proportion alive and ventilator-free on day 28, mortality from all causes, the time to recovery of lung injury, organ failure–free days, and cognitive impairment or overall functional health at hospital discharge.[112]

Although some patients benefit by an improvement in oxygenation, there are no data on its efficacy in improving patient outcome. Although the magnitude of the response varies widely from marginal to dramatic, there is no adequate model predicting where a particular patient with ARDS will fall in the spectrum. Furthermore, patients' response times vary from immediate to several hours. As a result, little is known about the optimal time period to maintain the prone position. Some patients respond to a return to a supine position after a trial of prone positioning by reverting to their original oxygenation, others have a reduction in oxygenation that is better than the original supine value, and some patients show an improvement. Prone positioning may have potentially life-threatening complications, including accidental dislodgement of the endotracheal tube and central venous catheters. Marcano et al. reported that prone positioning resulted in cephalad movement of the endotracheal tube within the trachea in children with ARDS ranging from 10% to 57% of their thoracic tracheal length.[113] Their study also suggested that if the tip of the endotracheal tube is not deeper than one third of the thoracic tracheal length before prone positioning, it might slide into the cervical trachea as a result of prone positioning.[113]

Unilateral Lung Disease or Severely Differential Lung Disease

Unilateral or asymmetric lung disease in infants and children poses special problems during mechanical ventilation. Some of these patients may have severe intrapulmonary shunts leading to hypoxemia requiring mechanical ventilation. Because of regional differences in compliance and resistance, the time constants for inflation and deflation may vary widely between

lung segments. During conventional ventilation, tidal volume delivered tends to preferentially inflate the more compliant lung and underventilate the stiffer, more affected lung. This may result in overinflation of the relatively "normal" lung and cause redistribution of pulmonary blood flow away from the hyperinflated lung, thus exaggerating the ventilation-perfusion mismatching. Such overinflation may contribute to further barotrauma. In such circumstances, with unilateral or asymmetrical lung disease, simultaneous independent lung ventilation (SILV) may allow each lung to be ventilated according to its needs without affecting the opposite lung. Currently, independent lung ventilation (ILV) can be generally indicated in the treatment of unilateral lung disease, such as unilateral atelectasis or consolidation, emphysema, pneumonia, pneumothorax, and bronchopulmonary fistula, and postoperative care, ILV can be used for lung reexpansion after thoracic surgery, for correction of V/Q mismatch in the lung remaining dependent during surgery, and for the treatment of pulmonary complications arising during anesthesia and surgery (e.g., pneumothorax or aspiration syndrome).[67-73] A new possible indication for ILV can be the selective administration of drugs to one lung, such as antibiotics or surfactant. SILV requires a bilumen tube with one tube being the longer "bronchial" tube and the other shorter "tracheal" tube. Usually, the bronchial tube is advanced into the right main stem bronchus so that both lungs can be ventilated separately. In adults, SILV has been shown to be useful in the treatment of unilateral lung disease.[114-117] In infants and children, SILV has been limited because of the lack of a suitable bilumen tube. Marraro[118] reviewed their experience with SILV in infants and children younger than 1 year with a bilumen tube developed in their department, but it is currently available through Portex Ltd. (Mythe, Kent, UK). The indications included bronchopneumonia with unilateral prevalence, unilateral pneumonia, lobar atelectasis, and diaphragmatic hernia. Nine of 41 patients treated with SILV had rapid improvement in lung disease, whereas the other 32 recovered more slowly. No major complications were attributed to SILV. In newborns and infants, it is possible to provide ILV with a double-lumen endotracheal tube manufactured by Portex as special equipment. In children older than 6 to 8 years, selective bronchial intubation is possible using a cuffed double-lumen tube similar to that used in adults (26- to 28-Fr Bronchocath Mallinckrodt, Broncho-port Rusch). The Marraro Paediatric Endobronchial Bilumen Tube, produced by SIMS-Portex, may be used in neonates and children age 2 to 3 years.[119] It is uncuffed to maximize the internal diameter of the tube and has no carinal hook; this minimizes tracheal trauma.[118-120] ILV requires two ventilators that permit the application of different modes of ventilation and different PEEP levels for each lung. Synchronization of the beginning of the inspiratory phase and the inspiratory time can avoid mediastinal shifts that impede venous return and reduce cardiac output.[118-120]

Heart Failure

The goals in respiratory management in congestive heart failure are prevention and relief of alveolar collapse from alveolar and interstitial edema from pulmonary vascular congestion, as well as decreased oxygen demand on the heart with a reduction in the work of breathing. CPAP/PEEP will provide relief of atelectasis. Hyperinflation should be avoided because it may increase pulmonary vascular resistance and increase right ventricular afterload. The oxygen cost of breathing can be reduced with a decrease in the work of breathing. This can be provided by a judicious combination of controlled ventilation and sedation. By unloading the respiratory muscles, mechanical ventilation can also reduce the work of breathing. In extreme cases, muscle relaxation by neuromuscular blockers may provide additional reduction in oxygen cost of breathing. As a general principle, the greater the inotropic support a heart needs, the greater should be the respiratory support provided. Tidal volumes should be generally maintained on the lower range (8 to 12 mL/kg). In adults with congestive heart failure, positive intrathoracic pressure has been shown to improve cardiac output.[121,122] This effect has been attributed to decreased left ventricular afterload provided by positive airway pressure.

Postoperative Management After Repair of Congenital Heart Disease

After open heart surgery, many infants and children require mechanical ventilation during the postoperative period. The duration of requirement of mechanical ventilation depends on several factors such as age of the patient, complexity of the cardiac lesion, complexity of the operative procedure, duration of bypass, duration of circulatory arrest, and postoperative cardiopulmonary status. Prolonged intubation and mechanical ventilation are more likely in children younger than 1 year of age, with more complex heart lesions, prolonged bypass and prolonged circulatory arrest times, and postoperative respiratory failure and hemodynamic instability. In the immediate postoperative period, patients should be supported with controlled mechanical ventilation until hemodynamic functions improve. Adequate PEEP should be applied to prevent and relieve atelectasis. Initially, the ventilator rate should be appropriate for the age. As the hemodynamic function improves, the rate can be weaned, as dictated by the clinical status. The choice of ventilatory parameters depends on the goals for each patient. In patients with pulmonary hypertension or pulmonary vascular disease, hyperventilation to provide respiratory alkalosis will decrease pulmonary vascular resistance and right ventricular afterload. In patients with marginal cardiac output, high airway pressures are to be avoided. In patients who have undergone a Fontan procedure, early extubation is desirable, and if that is not possible, then spontaneous ventilation should be encouraged. Because these patients are totally dependent on venous return for their cardiac output, airway pressures must be kept at a minimum. High intrathoracic pressure may not only impede venous return, but also decrease pulmonary blood flow from increased pulmonary vascular resistance.

Diseases with Abdominal Distention

The presence of abdominal distention poses a special problem. Positive intraabdominal pressure tends to elevate the diaphragm, decrease Ptp alveolar lung volumes in the lung bases. For normal lung volumes to be maintained, a greater Ptp has to be generated. This increases the airway pressures during positive pressure ventilation and increases work of breathing during spontaneous breathing. During positive pressure ventilation, a higher Ptp may cause hyperinflation of the apical regions while restoring normal volumes in the bases. Therapy

should be directed primarily toward reducing the intraabdominal pressure.

Neurologic and Neuromuscular Diseases

Hyperventilation with respiratory alkalosis is an effective method of reducing intracranial pressure. High intrathoracic pressure may impede venous return from the brain by increasing central venous pressures; therefore high levels of PEEP are to be avoided. The goals of respiratory support in patients with acute neuromuscular diseases that are self-limiting are (1) provision of respiratory assistance to maintain adequate minute ventilation and (2) avoidance of disuse muscle atrophy from mechanical ventilation. Spontaneous breathing must be encouraged as much as possible. Neuromuscular blockade must be avoided.

Patient-Ventilator Asynchrony

When the patient is capable of spontaneous breathing or allowed to breathe spontaneously, monitoring and titrating mechanical ventilation to either minimize or eliminate patient-ventilator asynchrony are important. One of the primary goals of mechanical ventilation is to reduce the patient's work of breathing. This can be achieved only if the patient's respiratory muscles and the ventilator act in a coordinated manner. The patient should not be attempting to inspire when the ventilator is in the expiratory phase and should not be attempting to exhale when the ventilator is attempting to deliver a breath. Patient-ventilator asynchrony is defined as a mismatch between the inspiratory times of the patient and the ventilator. Asynchrony can occur during assisted ventilation, assist-control as well as synchronized intermittent mandatory ventilatory ventilation.

The types of asynchronies are as follows:

1. Ineffective triggering: Ineffective triggering refers to the failure of a patient's effort to trigger a ventilator breath. This may be due to muscle weakness which results in an effort that is below the trigger threshold, increased load on the muscles at the start of inspiration such as induced by intrinsic PEEP, or due to too high a trigger threshold. Ineffective triggering can be detected as a pressure drop in the airway with a flow decrease but not followed by a ventilator breath. Ineffective triggering can be resolved by setting the trigger sensitivity low enough to capture the patient's efforts but not result in auto-triggering (see the following section).
2. Auto-triggering: Auto-triggering refers to a ventilator breath that occurs in the absence of an inspiratory effort by the patient. Auto-triggering is usually generated by leaks in the ventilator circuit. It can be triggered by cardiogenic oscillations and other sources that cause a change in airway pressure or flow in the absence of an inspiratory effort.
3. Double triggering: Double triggering refers to the occurrence of a two consecutive ventilator breaths that are separated by a very short or absent expiratory period. This can occur when the ventilator inspiratory time is too short and the ventilator demand is high. It can also occur with condensation in the circuit.
4. Delayed triggering: Delayed triggering refers to the delay in the start of the ventilator breath after the patient's effort has been detected. This is usually intrinsic to the trigger-sensitivity and electronic response of the ventilator circuit.
5. Delayed cycling: Delayed cycling refers to the prolongation of the ventilatory inspiration breath beyond the start of the patient's expiration. This can occur during pressure-support ventilation and can induce adverse effects such as increasing hyperinflation and intrinsic PEEP due to a shortened expiratory time.
6. Premature cycling: Premature cycling refers to the ventilator terminating inspiration while the patient is still continuing to have inspiratory efforts. This most commonly occurs in the presence of a leak in the ventilator circuit or around the endotracheal tube. When the ventilator phase (inspiration or expiration) is not synchronized completely with the phase of the spontaneous breath, it is referred to as asynchrony. When the ventilator phase is only partially not synchronized with the spontaneous breath, it is referred to as dyssynchrony. The interplay between the respiratory pump and the ventilator can occur either within one breath or on a breath-to-breath basis.

Ideally, ventilator breaths should be synchronized with spontaneous breaths. Asynchrony between mechanical ventilation and spontaneous breathing is common, especially in small infants. The most common form of asynchrony is active exhalation during a ventilator-delivered inspiratory breath. This has several detrimental effects. These are increased expiratory work of breathing, decreased overall minute ventilation with hypercarbia, patient discomfort, and increased risk for air leak.[123,124] Patients exhibiting asynchrony during mechanical ventilation have shown improved oxygenation and ventilation after neuromuscular blockade.[125,126]

Use of Neuromuscular Blockade

Neuromuscular blockers are often used as adjunctive therapy to mechanical ventilation. Although spontaneous breathing is to be encouraged as much as possible, respiratory muscle paralysis becomes necessary at times as an aid to mechanical ventilation. The indications for the use of neuromuscular blocking agents during mechanical ventilation are (1) asynchrony between the patient and the ventilator; (2) use in controlled ventilation; (3) a decrease in oxygen demand of skeletal muscles, especially in patients with hemodynamic instability; and (4) prevention of coughing, especially in patients with intracranial hypertension. Neuromuscular blockade is also used in patients when ventilation is to be controlled so that the appropriate minute ventilation is delivered. Paralysis of respiratory muscles may also be required in patients after congenital heart surgery to reduce the oxygen demand on the heart. Prolonged neuromuscular blockade is to be avoided because it tends to promote muscle atrophy. This, in turn, will prolong weaning from mechanical ventilation.

Special Techniques of Respiratory Support

Altering Inspired Oxygen and Carbon Dioxide Concentration

A low alveolar oxygen tension increases pulmonary vascular resistance (hypoxic pulmonary vasoconstriction), and a high alveolar oxygen tension decreases pulmonary vascular

resistance.[127] With certain types of congenital heart disease such as hypoplastic left heart syndrome, it is critical to control pulmonary blood flow and prevent pulmonary overflooding. One approach is to decrease the Fio_2 to less than 0.21 with a blending of room air with nitrogen. The exact Fio_2 delivered must be monitored to avoid administering excessively low inspired oxygen. The other approach, especially in patients undergoing mechanical ventilation, both preoperatively and postoperatively, is to increase the inspired carbon dioxide concentration ($Fico_2$).[128] Increased $Fico_2$ also increases pulmonary vascular resistance. During mechanical ventilation, increased $Fico_2$ allows one to hyperventilate and prevent atelectasis without producing hypocarbia. One of the difficulties with a boost in $Fico_2$ is increased spontaneous ventilatory drive from an increased $Paco_2$. This increases the work of breathing and with marginal cardiac reserve may impose undue strain on the heart. Therefore in spontaneously breathing patients, neuromuscular blockade and total ventilatory support may be necessary with increased $FIco_2$ to avoid an increased workload on the heart.

Helium-Oxygen Mixture

Helium-oxygen mixture has much lower density compared with oxygen-nitrogen mixture and offers a reduced resistance to breathing. This property has been used in the successful treatment of upper airway obstruction after extubation in children, upper airway obstruction from laryngotracheobronchitis and postextubation subglottic edema in infants and children.[129] Helium is usually administered in at least 30% to 40% oxygen through a tight-fitting face mask. Use of an Oxyhood is not indicated because helium tends to separate and layer at the top of the Oxyhood with the patient breathing very little helium. Recently, helium-oxygen mixture has been shown to improve gas exchange in neonates with respiratory distress syndrome.[130] Oxygenation should be monitored during administration of helium-oxygen mixture to avoid hypoxia, especially in neonates.[131] In adults, helium-oxygen mixture has also been used in the management of severe lower airway obstruction in asthma. Because ventilator transducers are calibrated with an air-oxygen mixture, the true volumes delivered tend to be different from preset values. Therefore when helium-oxygen mixture is administered through the ventilator, direct volume measurements are necessary to ensure that the appropriate VT_{eff} is being delivered.

Inhaled Nitric Oxide

Inhaled nitric oxide produces selective pulmonary vasodilation. Indications for inhaled nitric oxide include diaphragmatic hernia, pulmonary hypertension after repair of congenital heart disease, primary pulmonary hypertension, and isolated right heart failure. In babies with severe hypoxemia and pulmonary hypertension, inhaled nitric oxide rapidly increases arterial oxygen tension without causing systemic hypotension.[132-135] Randomized controlled studies showed that nitric oxide inhalation safely improves arterial oxygen levels and decreases the need for ECMO therapy.[132-135] Oxygenation improves in approximately 50% of infants receiving nitric oxide. In addition, Kinsella and Abman[136] showed that high-frequency ventilation seems to augment the response to inhaled nitric oxide probably by better recruitment of alveoli. In children with ALI/ARDS, Ream et al.[137] showed an improvement in oxygenation in more than two thirds of the patients. Researchers of a randomized controlled trial of inhaled nitric oxide in children with acute hypoxemic respiratory failure have also reported an improvement in oxygenation.[138] Results from several adult studies, however, showed that several participants failed to show any improvement.[139-142] In these multicenter studies in children and adults, there were no differences in ventilator-free days and no effect on mortality between treatment groups. Not all patients respond to inhaled nitric oxide. It seems prudent to test whether a patient will respond to inhaled nitric oxide. At Children's Hospital of Pittsburgh, a 2-hour trial of inhaled nitric oxide with 20 to 40 ppm is administered to infants and children with ALI/ARDS with hypoxemic respiratory failure. A good response is defined as improvement in Pao_2/Fio_2 ratio of greater than 100%. A partial response is defined as an improvement in Pao_2/Fio_2 ratio between 50% and 100%. If the response is less than 50%, the patient is considered a nonresponder. Inhaled nitric oxide is then continued in only those patients who show a partial or good response. Nitric oxide binds to hemoglobin to produce methemoglobin. Therefore methemoglobin levels should be monitored during administration of nitric oxide. In addition, nitric oxide combines with oxygen to form nitrogen dioxide. Nitrogen dioxide is known to cause lung injury. Therefore the concentration of nitrogen dioxide should be monitored in the inspired gas to keep it below 1 to 2 ppm.

Adverse Effects of Mechanical Ventilation

Yin-Yang of Mechanical Ventilation

Mechanical ventilation has profound effects on various organ systems; some are beneficial and others have adverse effects. The beneficial and adverse effects can occur simultaneously; the net effect of mechanical ventilation results from the interaction of useful and deleterious effects. The beneficial effects in the lung are related to improvements in pulmonary mechanics and gas exchange. Adverse effects of positive pressure ventilation are related to (1) consequences of positive intrathoracic pressure, and (2) injury to the airway. Some of the important adverse effects of mechanical ventilation are shown in Box 49-5.

Airway Injury from Mechanical Ventilation

The presence of an endotracheal tube traversing the upper airway can be associated with significant airway injury. Oropharyngeal and nasopharyngeal injuries are rare. Ulceration of the ala nasi from pressure necrosis may occur following prolonged nasotracheal intubation, particularly if the skin perfusion of the ala nasi is compromised by very tight taping. Similar ulceration may occur at the angles of the mouth from tight taping of orotracheal tubes.[143,144] Palatal grooves and traumatic cleft palate can occur in infants.[145] Laryngeal injury may extend from minor swelling to ulceration of the mucosa of the vocal cords and aryepiglottic folds. Similarly, injuries in the subglottic region may extend from minor swelling to major ulceration. Healing of the severe injuries may lead to scarring, granuloma formation with airway obstruction,

Box 49–5 Adverse Effects of Mechanical Ventilation

Respiratory system

Airways
- Mucosal swelling
- Ulceration
- Granuloma formation leading to airway obstruction
- Infection

Lung
- Infection
- Adverse effects on gas exchange
- Effects on extravascular lung water
- Air leaks

Cardiovascular system

Heart
- Decreased venous return
- Decreased left ventricular compliance
- Decreased left ventricular afterload

Pulmonary circulation

Compression of alveolar vessels
Increased pulmonary vascular resistance

Other systems

Decreased renal blood flow
Decreased hepatic blood flow
Decreased cerebral venous drainage

which may be partial or complete. The majority of the subglottic tracheal lesions is due compression of the tracheal mucosa by the endotracheal tube. High-pressure cuffs, cardiovascular instability, upper respiratory tract infection, duration of intubation, and head and neck movement all increase the risk of tracheal injury. Airway injury can also result from suction catheters.[146] Necrotizing tracheobronchitis is a severe form of airway injury seen in patients on mechanical ventilation which is characterized by extensive ulceration and mucosal damage. The sequelae of tracheal injuries include tracheal stenosis, tracheomalacia, tracheoesophageal fistula, tracheoinnominate artery fistula.

Injury to the airway can be prevented by attention to several details. The endotracheal tube should be of the proper size, with a gas leak around it at less than 20 cm H_2O positive pressure. Excessive pressure on the skin should be avoided while taping of the endotracheal tube. Excessive patient movement should be prevented by adequate sedation and restraints. Endotracheal tube cuffs should be inflated with pressures less than 20 cm H_2O. Suctioning should be gentle, preferably with a catheter with multiple side holes. Suction catheters should not be routinely advanced beyond the tip of the endotracheal tube.

Effects on the Lung

Adverse effects of mechanical ventilation on the lung are due to the following factors: (1) high airway pressures, (2) overdistension of the alveoli, 93) altered mucociliary clearance, (4) lung water clearance, and (5) oxygen toxicity. The adverse effects of positive pressure ventilation may be manifested as (1) parenchymal injury, (2) altered ventilation-perfusion relationship leading to impaired gas exchange, and (3) increased risk for infection. Increased airway pressure may cause hyperinflation of the alveoli and predispose to alveolar rupture. Hyperinflation may increase alveolar dead space, impair cardiac filling, and compress alveolar vessels. *Pulmonary barotrauma* is a loose term that encompasses many entities of parenchymal injury. Alveolar rupture from overdistended alveoli is the most common manifestation of pulmonary barotrauma. Air leak may occur from the lung into the pleura (pneumothorax), the interstitium (pulmonary interstitial emphysema), the mediastinum (pneumomediastinum), the pericardium (pneumopericardium), the peritoneal cavity (pneumoperitoneum), and the subcutaneous tissue (subcutaneous emphysema). Even though the term implies high airway pressures as the main mechanism of parenchymal injury, pulmonary barotrauma is often multifactorial.[147-150] The physiologic consequences of extra-alveolar air may range from no adverse effect to life-threatening cardiorespiratory compromise. A pneumothorax may be small and inconsequential or may be large and under tension. Tension pneumothorax would need immediate evacuation of the pleural air. Pulmonary interstitial emphysema may decrease lung compliance and increase pulmonary vascular resistance.[151] Pneumomediastinum requires careful observation. The natural tendency of pneumomediastinum is to track along fascial planes either cephalad to produce subcutaneous emphysema or caudad to produce pneumoperitoneum or pneumoretroperitoneum. Pneumomediastinum rarely requires evacuation. Pneumopericardium can range from minimal inconsequential amount of air to life-threatening cardiac tamponade. Cardiovascular compromise is an indication for immediate evacuation of pericardial air.

A special form of pulmonary air leak is a bronchopleural fistula, where a fistulous track develops between the bronchus and the pleural space. This results in an almost continuous flow of air from the airway into the pleural space. The fistula flow is wasted ventilation and may result in hypercarbia. Attempts to increase minute ventilation by increasing tidal volume will only serve to increase the fistula flow by increasing the pressure gradient across the fistula. If attempts to decrease airway pressures with conventional ventilation are not possible without compromising gas exchange, a trial of high-frequency ventilation may be tried.

Barotrauma can be minimized by avoiding factors that predispose to pulmonary air leakage. The principal factors that can be controlled are airway pressures and lung volumes. As long as acceptable gas exchange is maintained, every effort must be made to reduce airway pressures to a minimum. Hyperinflation must be avoided. When the lung disease is severe, deliberate hypercarbia may be tolerated provided the arterial pH is normal. Inspired oxygen concentration should be maintained at nontoxic levels (usually <50%).

Effects on the Circulatory System

The cardiovascular effects of positive intrathoracic pressure are complex and depend on the underlying lung disease, uniformity of lung disease, transmission of airway pressure to the pleural space, lung volume, etc. Cournand et al.[169] were one of the first to demonstrate that positive pressure ventilation decreased cardiac output. Positive intrathoracic pressure decreases impedes right ventricular filling by decreasing the pressure gradient to venous return.[152-154] Positive airway pressure also increases pulmonary vascular resistance provided, the airway pressure exceeds left atrial or critical

closing pressure.[155] Positive intrathoracic pressure has also been shown to decrease left ventricular afterload.[121,122] The net effect is a combination of all the effects mentioned above and the reflex cardiovascular adjustments that accompany these changes. Positive-pressure breathing also decreases urine output, decreased hepatic, portal venous, and mesenteric perfusion.[156-160] Many of these effects can be offset by volume loading.

Respiratory Care During Mechanical Ventilation

Pulmonary Hygiene

The fundamental goals of pulmonary hygiene are clearance of secretions and prevention and relief of atelectasis. The most effective method of clearing secretions is a combination of changing body position and vigorous coughing by the patient.[161] When the patient is unable to cough effectively, it is common practice to resort to chest physiotherapy and active suctioning of the trachea. Suctioning the trachea usually requires disconnecting the patient from the ventilator, passage of a suction catheter into the endotracheal tube, and application of suction to the catheter while the catheter is withdrawn from the endotracheal tube. In patients with marginal oxygenation, suctioning may result in hypoxia; arrhythmias; hemodynamic instability; and, in rare instances, cardiac arrest.[162-164] This can be prevented by prior hyperoxygenation. Suctioning may also result in cardiac arrhythmias. Chest physiotherapy refers to a variety of respiratory maneuvers performed to aid in the clearance of airway secretions and promoting lung expansion. These are (1) postural drainage, (2) chest percussion and chest vibration, and (3) deep breathing exercises. The efficacy of chest physiotherapy in patients who have undergone intubation is unclear. In adults, some studies have shown a benefit when all the components of the chest physiotherapy regimen are performed.[165] In children with cystic fibrosis, no additional benefit was provided by chest physiotherapy maneuvers when compared with spontaneous coughing.[166] Recently, several devices have been proposed as an adjunct to the standard chest physiotherapy. They include an intrapulmonary percussive ventilator (IPV); a mechanical insufflator-exsufflator (CoughAssist); the FLUTTER mucous clearance device and Acapella devices; intermittent positive pressure breathing (IPPB); mechanical percussors; and the ABI Vest, formerly known as the ThAIRapy Vest. The IPV is used in mechanized chest physical therapy; the IPV device delivers high-flow jets of air to the airways by a pneumatic flow interrupter at a rate of 100 to 300 cycles/min through a mouthpiece. The patient controls variables such as inspiratory time, peak pressure, and delivery rates. Initial studies showed that in children with cystic fibrosis, IPV was as effective as standard aerosol and chest physiotherapy.[167,168] IPV was recently reported to improve atelectasis in children, compared with conventional chest physiotherapy.[169] A more recent study suggests that IPV may be more beneficial in secretion clearance in children with cystic fibrosis.[170] The mechanical insufflator-exsufflator (CoughAssist) is a portable electric device that uses a blower and a valve to alternately apply a positive and then a negative pressure to a patient's airway to assist the patient in clearing retained bronchopulmonary secretions. This device attempts to simulate a cough. Air is delivered to and from the patient through a breathing circuit incorporating a flexible tube; a bacterial filter; and a facemask, a mouthpiece, or an adapter to a tracheostomy or endotracheal tube. Miske et al.[171] reported that in children with neuromuscular disease and impaired cough, the use of a mechanical insufflator-exsufflator was safe, well tolerated, and effective in preventing pulmonary complications. The FLUTTER mucous clearance device and Acapella device are small handheld devices that provide positive expiratory pressure (PEP). Exhaling through the device creates oscillations, or "flutter," in pressures in the airway resulting in loosening of mucus. Other PEP devices are used with a small volume nebulizer and function in conjunction with medication delivery. A recent Cochrane review concluded that there was no clear evidence that PEP was a more or less effective intervention overall than other forms of physiotherapy, and there was limited evidence that PEP was preferred by participants compared with other techniques.[172] IPPB devices use pressure to passively fill the lungs when a breath is initiated. An incorporated manometer and mechanical valves serve to terminate the flow of inspired air when a predetermined pressure is reached on inhalation. IPPB breathing circuits are designed to nebulize inhaled medication. Most IPPB devices are powered by compressed air and are not suitable for home use. Mechanical percussors are typically electrical devices used in lieu of a caretaker's hands for chest percussion or vibration. Conventional chest physiotherapy is both labor intensive and time consuming. A high-frequency chest wall vibrating/oscillating device is currently available (the ABI Vest). Arens et al.[173] showed that in hospitalized patients with cystic fibrosis, high-frequency chest compression with the vest conventional chest physiotherapy was equally safe and effective when used during acute pulmonary exacerbations.

Humidification Systems

During spontaneous breathing, inspired air is warmed and almost completely humidified as it passes through the upper airways.[174] The use of an endotracheal or a tracheostomy tube bypasses the natural warming and humidifying functions of the upper airway. The mucosal surface below the artificial airway must then provide both humidification and heat to the inspired air. This may adversely affect mucociliary clearance.[174,175] If the inspired gases are not warmed to the body temperature, insensible water loss in the lung is increased. All gases used in respiratory therapy are dry with no moisture. Therefore these gases must have moisture added to them during delivery to the patients. When a gas is warmed, its relative humidity decreases.

Humidifiers can be classified into those that provide only humidity and those that provide both heat and humidity. There are several types of nonheated simple humidifiers. The simplest in design is the pass-over or blow-by humidifier. The second type is the bubble humidifier, probably the most common device used in respiratory therapy. In this device, the gas is directed below the surface of the water and allowed to bubble to the surface. A jet humidifier produces an aerosol; humidity is provided by evaporation of the aerosol particles. An underwater jet humidifier uses a combination of jet and bubble humidification principles. In the clinical setting, the amount of humidity provided by the simple humidifiers is about the same. Although the more efficient humidifiers increase humidification, they also tend to cool the inspired air.

Therefore the absolute humidity delivered tends to be similar among the simple humidifiers. Relative humidity of 100% at room temperature is less than 40% relative humidity at body temperature. When inspired gases are humidified with one of these devices, the balance of the moisture is provided by the airway mucosa. Therefore when the upper airway is bypassed by the presence of an artificial airway, then the inspired gases must be additionally heated to provide 100% humidity at body temperature. The factors that determine the efficiency of humidifying devices depend on (1) time of contact with the gas and water, (2) temperature of both the gas and water, and (3) the surface area of contact of the gas/water interface. The efficiency of humidification increases as the time of contact increases and as the surface area of contact increases. Increasing the temperature of the inspired gas before delivery decreases the humidity that needs to be provided by the airway mucosa and adds to patient comfort. Heated humidifiers use the same principle as the simple humidifiers and have in addition a heating element. The relative humidity with these systems can be as high as 100%. The heating system can be servo-controlled to adjust the heat according to the relative humidity.

Aerosol Therapy

Aerosolized drug administration is often used in the treatment of infants and children with respiratory diseases including reversible lower airway obstruction, pneumonias due to Pneumocystis carinii and respiratory syncytial virus, and hyaline membrane disease. Common drugs used as aerosol agents include β_2 agonists, atropine, ipratropium bromide, cromolyn sodium, antiviral agents, corticosteroids, antibiotics, surfactant, pentamidine, and mucolytics. A drug aerosol increases the therapeutic index of the drug by delivering it directly to the site of action with minimal side effects. The factors that affect deposition of aerosol particles are gravity, viscosity of the gas, kinetic activity of the particles, particle inertia, physical nature of the particle, temperature and humidity of the aerosol, and the ventilatory pattern. Compared with that in adults, deposition of aerosolized particles in infants and children is poor because of factors such as a small airway caliber, greater airway resistance, high respiratory rate with a short inspiratory time, increased chest wall compliance, ineffective coordination effort, and inconsistent breathholding maneuvers. Despite poor aerosol deposition, a clinical response to inhaled medications can often be seen. The dose and the delivery method should be individualized to each patient to ensure a good clinical response.

Nebulizers are devices that generate aerosols. Particle size has to be at least 1 to 5 μm for deposition in the distal airways. Currently, four types of delivery systems are available for clinical use that generate medication aerosols. These are the jet nebulizers (small-volume and large-volume nebulizer), ultrasonic nebulizers, metered-dose inhalers, and dry-powder inhalers. A jet nebulizer uses the Bernoulli principle to create an aerosol. The size of the particle depends on the jet flow rate and the size of the capillary tube. Baffles placed in the path of the aerosols tend to remove larger particles, allowing delivery of smaller particles to the patient. A pneumatic nebulizer is a device that creates the aerosol using the same principle as the jet nebulizer, but the aerosol particles are carried to the patient by a main gas flow. A pneumatic nebulizer may be a mainstream nebulizer in which the aerosol is generated in the path of the main gas flow or a sidestream nebulizer in which the aerosol is generated in a separate chamber and carried passively into the path of the main gas flow. The ultrasonic nebulizer uses a piezoelectric crystal that produces a highly concentrated output of aerosol particles and has been used primarily for cough and sputum production or bronchoprovocational challenges. Ultrasonic nebulizers have not been routinely used for drug delivery in infants and children. With the replacement of the saline solution with medication; however, the highly concentrated output from the ultrasonic nebulizer may perform better than a small-volume nebulizer in accomplishing greater deposition of medications in children. The metered-dose inhaler uses a pressurized canister that dispenses a single bolus of aerosolized medication. Such inhalers are convenient, cost effective, and versatile, and generally have an effective deposition rate of 10% to 15%. The canister is activated into the spacer and the medication remains suspended in the chamber until the patient inhales. A dry-powder inhaler delivers a large bolus of medication during a single inspiration maneuver and produces therapeutic effects similar to a metered-dose inhaler and an aerosol nebulizer. The dry-powder medication, released from a capsule and deposited into a small canister, is delivered to the lungs during inspiration. The inspired flow rate causes a turbulent state within the canister, and the powder is directed toward the respiratory tract.

Aerosolized medications are often delivered through mechanical ventilators for the treatment of bronchospasm. Aerosol delivery is inefficient when delivered through a ventilator. The endotracheal tube is the most significant barrier to effective delivery. The smaller the inner diameter of the tube, the less efficient is aerosol delivery. The nebulizer is most effective when it is synchronized to fill the inspiratory limb of the circuit with aerosolized particles during the exhalation phase of ventilation, thereby improving the delivery of medication during the subsequent inspiration. The inspiratory portion of the circuit serves as a spacer chamber, similar to the spacer used for metered dose inhalers. Some current ventilators offer a synchronized nebulization capability, in which a portion of the preset inspiratory gas is diverted to power the nebulizer. The effects of added volume delivered to the inspiratory limb should be taken into account and minimized with the addition of a pressure relief valve to the circuit. Metered-dose inhalers can be equally effective as nebulizers during mechanical ventilation.

Weaning from Mechanical Ventilation

Weaning from mechanical ventilation is defined as liberation from mechanical ventilation while spontaneous breathing is allowed to assume the responsibility for effective gas exchange. Weaning can be considered a success when a patient can maintain effective gas exchange, with complete spontaneous breathing and without any mechanical assistance. Weaning can be considered a failure when spontaneous efforts are incapable of sustaining effective gas exchange without mechanical ventilator support. Extubation is defined as the removal of an endotracheal tube. The timing of extubation should coincide with an assessment that the patient is capable of maintaining effective gas exchange without any mechanical ventilator support. Avoiding both premature extubation and unnecessary prolongation of mechanical ventilation is important.

When the indications that were met for provision of mechanical ventilation are no longer present, then the patient can be weaned from mechanical ventilation. Weaning should start when (1) the underlying disease process is improving; (2) gas exchange is adequate; (3) no conditions exist that impose an undue burden on the respiratory muscles, such as cardiac insufficiency, severe hyperinflation, severe malnutrition, and multiple organ system failure; and (4) the patient is capable of sustaining spontaneous ventilation as ventilator support is decreased without expending an excessive amount of energy. It is the patient who dictates the initiation of the weaning process and the pace of the weaning process. Patients cannot be arbitrarily forced to wean. Improvement of the underlying disease process can be assessed with measurement of indices of gas exchange, pulmonary mechanics, ventilation perfusion relationships, and radiographic findings. The patient's ability to take over the responsibility from the ventilator depends on several factors: (1) respiratory muscle strength, (2) stability of the cardiovascular system, (3) work of breathing, (4) general nutritional status of the patient, and (5) the presence or absence of an underlying hypercatabolic state (e.g., sepsis). Weaning cannot be accomplished unless all of these factors are optimal. The pathophysiologic determinants of weaning outcome include the following: (1) adequacy of pulmonary gas exchange; (2) respiratory drive; (3) respiratory muscle performance and capacity; (4) respiratory muscle load; (5) amount of dead-space ventilation; and (6) work of breathing and ventilatory requirements. Box 49-6 shows the specific parameters to be met before initiating weaning. There are currently two approaches to weaning. One is the "traditional" method of slowly reducing the ventilator support, including inspired oxygen concentration, to a minimal acceptable level and then assessing the patient's readiness to extubate. The other is the "modern" concept of assessing the patient's readiness to extubate as soon as the patient meets criteria to initiate weaning.

Traditional Method of Weaning

In the traditional method, the exact sequence of the weaning process will be dictated by the clinical circumstance. At each step of weaning, the patient must demonstrate an ability to sustain effectiveness of breathing. Minute ventilation is reduced primarily with a decrease in the ventilator rate.

Box 49–6 Criteria to Meet Before Initiating Weaning

1. Alert mental status
2. Good cough and gag reflexes
3. Core temperature below 38.5° C
4. Spontaneous respiratory effort
5. pH 7.32–7.47
6. PaO_2 >60 mm Hg or pulse oximetry reading <95%
7. Fio_2 ≤0.50
8. PEEP ≤7 cm H_2O
9. $PaCO_2$ <50 mm Hg
10. No further need for vasoactive agents
11. No clinical need for increased ventilator support in the past 24 hours
12. No planned operative procedures requiring heavy sedation in the next 12 hours

Mean airway pressure is then reduced to a minimum with a decrease in CPAP/PEEP. Most children are currently weaned with SIMV or IMV alone, with SIMV and added pressure support, or with pressure support alone. Despite earlier indications that weaning with IMV was useful,[176,177] current studies do not advocate weaning with IMV in adults.[178,179] In infants, provision of a continuous flow device has been shown to decrease work of breathing and aid in weaning.[14] PSV has been advocated as a weaning mode because it can result in better synchrony between the patient and the ventilator than IMV, volume-assisted ventilation, or pressure control ventilation.[180-183] Pressure support will allow ventilatory muscle loads to be returned gradually during the weaning process.[180-183] Because each breath is assisted, it alters the pressure-volume relationship of the respiratory muscles in such a way as to improve its efficiency.[180-183] The parameters that can be manipulated to titrate the muscle loading are the magnitude of the trigger threshold and the preset pressure limit. PEEP is provided to maintain FRC and prevent alveolar collapse. The amount of pressure support to be provided depends on the clinical circumstance. PSVmax, or the maximum pressure support needed to reduce the respiratory work to zero, requires a pressure limit that delivers a VT_{eff} of about 10 to 12 mL/kg. PSVmax is not necessary at the start of weaning. The level of pressure support that should be selected should allow for spontaneous respiration without undue exertion and still result in normal minute ventilation. No strict criteria can be established; they have to be applied and titrated on an individual basis. Weaning of PSV is accomplished with a decremental reduction of the pressure limit. Similar to that previously mentioned in the weaning guidelines, with each wean, the effect of weaning on muscle loading has to be evaluated clinically. An increase in respiratory rate is an early indication of increasing muscle load. Retractions and use of accessory muscles would indicate a more severe muscle load. If respiratory rate increases during the weaning process, the level of pressure support should be increased until there is reduction in the respiratory rate. A relative contraindication to the use of PSV is a high baseline spontaneous respiratory rate. There is a finite lag time involved from the initiation of a breath to the sensing of this effort and from the sensing to the delivery of a mechanical breath. In infants breathing at a relatively fast rate (>50 breaths/min), this lag time may be too long, and this may result in asynchrony between the patient and the ventilator.

"Modern" Method of Weaning

The premise underlying the modern method is that not all patients require a prolonged weaning process. Esteban et al.[178] showed that 76.2% of patients successfully underwent a 2-hour trial of spontaneous breathing, and 89.4% of them immediately underwent extubation. In a recently completed randomized, controlled trial of weaning modes in children, 42% of the patients initially tested with a minimal pressure-support trial passed the test and underwent extubation.[184] These studies validate the modern method of weaning patients from mechanical ventilation. If patients meet the criteria for weaning as outlined in Box 49-7, they can be subjected to a Readiness to Extubate Trial (RET) to test their ability to breathe spontaneously and maintain gas exchange. If the RET is successful, then the patient is ready to be extubated. If the patient fails an RET, there are two choices, either

continuation of invasive mechanical ventilation or extubation to noninvasive ventilation. If invasive mechanical ventilation in continued, then the RET can be repeated in 24 hours. The level of invasive mechanical ventilator support should keep the patient comfortable with no increased work of breathing.

Box 49–7 Criteria for Terminating a Readiness to Extubate Trial

1. Inability to maintain gas exchange
   - Pulse oximeter saturations <95% with 40% inspired oxygen
   - Needing >50% inspired oxygen to maintain oxygen saturations >95%
2. Inability to maintain effective ventilation
   - Measured exhaled tidal volume <5 mL/kg
   - An increase in $PaCO_2$ >50 mm Hg or an increase of >10 mm Hg
   - Respiratory acidosis with pH <7.3
3. Increased work of breathing
   - Respiratory rate outside of the acceptable range for age:
     <6 months: 20–60 breaths/min
     6 months to 2 years: 15–45 breaths/min
     2–5 years: 15–40 breaths/min
     >5 years: 10–35 breaths/min
   - Use of accessory respiratory muscles
   - Intercostals/suprasternal/supraclavicular retractions
   - A paradoxic breathing pattern
4. Other signs of distress
   - Diaphoresis
   - Anxiety
   - Heart rate >90th percentile for a given age
   - Change in mental status (agitation or somnolence)
   - Systolic blood pressure <third percentile for a given age

If a patient has any of these signs at any time during the breathing trial, the trial should be terminated and mechanical ventilation should be reinstituted.

If the decision is to extubate to noninvasive positive pressure support, then it would be prudent to test the patient on a level of pressure support that is necessary to maintain gas exchange and decrease the work of breathing. The criteria for terminating an RET are shown in Box 49-7.

Readiness to Extubate Trial

Currently, there are three methods of RETs: (1) T-piece trials, (2) CPAP trials, and (3) minimal pressure-support trials.[178,179,184-187] In T-piece trials, the patient is removed from the ventilator but does not undergo extubation. Humidified supplemental oxygen is provided to the airway without any positive pressure support through a T-piece (Figure 49-20). In this system, a corrugated tubing from the nebulizer/humidifier attaches to one end of the T-piece, and an extension of corrugated tubing attaches to the other end of the T-piece. The flow rate should be adjusted to produce a constant mist coming from the extension piece on the T-tube both during inspiration and expiration so that the patient's minute ventilation is matched by the device. Roughly, this corresponds to at least about three times the minute ventilation of the patient.

The RET can also be conducted without removing the patient from the ventilator with a low level (e.g., 5 cm H_2O) of CPAP or with a low level of PSV. Randolph et al.[184] described a minimal pressure support technique in which the level of pressure support was adjusted for the endotracheal tube size (3 to 3.5 mm = pressure support of 10 cm H_2O; 4 to 4.5 mm = pressure support of 8 cm H_2O; >5 mm = pressure support of 6 cm H_2O). On the other hand, in a study comparing minimal pressure support with T-piece trials, Farias et al.[185-187] used a pressure support of 10 cm H_2O for all patients. The duration of the trial can range from 30 minutes to 2 hours. The proponents of a "minimal pressure support" approach to the RET speculate

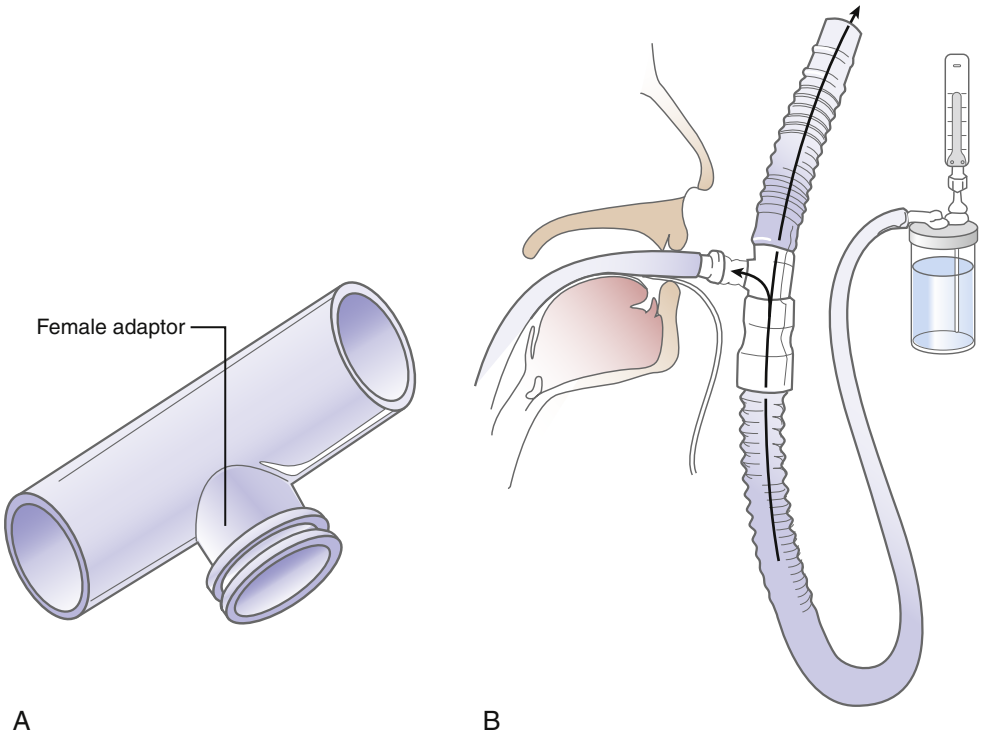

Figure 49–20. T-piece circuit. *(From Kofke WA: Postoperative respiratory care techniques. Part III. Weaning from mechanical ventilation and oxygen therapy,* Curr Rev RACN *13:161, 1992.)*

that this overcomes the resistance to breathing through the artificial airway. Ishaaya et al.[188] showed that minimal pressure support based on in vitro studies overestimated the amount of support required to overcome the resistance of the endotracheal tube and ventilator circuitry. There are no measurements in vivo validating this concept in children. In one study of adults, the authors reported a similar resistance to breathing through the upper airway after extubation as that with the endotracheal tube in place.[189] Resistance through the artificial airway is affected by many factors, including the inspiratory flow of the patient, the inner diameter of the tube, the use of either an endotracheal or a tracheostomy tube, and the presence of secretions in the tube. In children, Farias et al.[186] recently compared two methods of RET, one with pressure support of 10 cm H_2O and the other with a T-piece circuit. The extubation failure was not different between the two groups.[186]

Physicians are reluctant to subject infants and young children to a trial of complete spontaneous breathing with either CPAP or a T-piece circuit because of concern about the work of breathing imposed by the endotracheal tube and the breathing circuit. Proponents of this paradigm routinely extubate patients after a "minimal pressure support" RET. Willis et al.[190] showed, very elegantly, that the work of breathing associated with T-piece breathing was similar to that with complete spontaneous breathing after extubation. In fact, this study showed that the work of breathing with all the support modes including minimal pressure support mode was considerably less than that after extubation. Taken together, these studies suggest that with support modes the patient is receiving a substantial amount of assisted ventilation. Therefore an RET performed with a support mode may not truly represent complete spontaneous breathing and any evaluation made may overestimate the ability of children to breathe spontaneously when they are extubated. The studies by Farias et al.[185-187] have shown that RETs with a T-piece circuit are well tolerated by children. These should serve to dispel the myth that infants and children cannot be subjected to a T-piece trial before extubation. Despite these theoretical concerns, Farias et al. showed that patients extubated using either T-piece or pressure-support trials had similar rates of reintubation.[186] There is another school of thought that infants and children need not be subjected to a RET before extubation. Proponents of this practice routinely extubate infants and children from a "low" level of ventilator support. Studies in children, however, have shown that when the fraction of minute ventilation provided by the ventilator is more than 30%, the risk of extubation failure is increased.[191,192] It is preferable that the ability to breathe effectively be determined with complete spontaneous breathing without ventilator support. An important dictum to remember is that "the test for extubation readiness is not extubation."[193]

Extubation

When RET is successful, the patient can undergo extubation and be liberated from mechanical ventilation. The patient must be awake, be alert, and have airway protective reflexes. The patient must be breathing effectively, without undue exertion. Adequate gas exchange with a relatively low Fio_2 must be established. A stable cardiovascular system must be established. Metabolic, nutritional, and electrolyte balance must be ensured. Airway pressures must be reduced to a minimum.

Table 49–2 Threshold Values for Low- and High-Risk of Reintubation for Bedside Parameters of Respiratory Function

Respiratory Parameter	Low Risk (≤10%)	High Risk (≥25%)
Spontaneous tidal volume (mL/kg)	>6.5	<3.5
Fraction of inspired oxygen	<0.3	>0.4
Mean airway pressure (cm H_2O)	<5	>8.5
Peak inspiratory pressure (cm H_2O)	<25	>30
Dynamic compliance (mL/kg/cm H_2O)	>0.9	<0.4
Fraction of the total minute ventilation provided by the ventilator (%)	<20	>30
Mean inspiratory flow (mL/kg/sec)	>14	<8

Respiratory parameters were measured just before extubation. Risk of reintubation is percent of patients who were reintubated within 48 hours of extubation.

Extubation failure can be predicted using simple measures of respiratory function such as inspiratory drive, lung mechanics, gas exchange, and level of ventilator support before extubation.[191,192] A low risk is defined as an extubation failure rate of less than 10%, and a high risk of failure is defined as an extubation failure rate of at least 25%.[191,192] Table 49-2 lists the threshold values for the respiratory parameters with identified low- and high-risk values.[191,192] Additional parameters that may be useful in determining eligibility for extubation are an intrapulmonary shunt fraction less than 15% (requires pulmonary artery catheterization), a physiologic dead space less than 40%,[194] a vital capacity of at least 15 mL/kg, and a maximum negative inspiratory force of at least 30 cm H_2O.

Weaning Problems

Farias et al.[185-187] distinguish between two types of failure: trial failure and extubation failure. Trial failure is defined as a failure to sustain effective gas exchange and breathing during an RET of spontaneous breathing while the patient is still intubated. Extubation failure is defined as the requirement for reintubation within 48 hours after extubation. Some patients take longer than others to wean. Factors that prolong the weaning process are (1) slow resolution of the underlying disease process, (2) ventilatory pump failure, and (3) psychological factors. In many instances, weaning is delayed because of the slow resolution of the underlying disease process. Ventilatory pump failure can be due to increased respiratory workload, decreased respiratory muscle capacity, or a combination of both. Decreased ventilatory drive may result from respiratory center dysfunction caused by sedative agents; neurologic disease, particularly if it affects the brainstem; sleep deprivation; and metabolic alkalosis. Phrenic nerve injury usually results as a complication of birth trauma or operative procedures involving the heart and other thoracic structures.[195-197] This may result in either paresis or paralysis of one or both hemidiaphragms. When muscle weakness is present, weaning should generally be slow, allowing sufficient time for regaining muscle strength and endurance. Muscle training through an incremental increase in muscle work can be achieved by a gradual increase in the trigger threshold for assisted ventilation. Ventilatory requirements can be reduced with a decrease in carbon dioxide production

with a reduction in excess caloric intake. Muscle loading may occur during IMV because of patient asynchrony. Asynchrony between the patient's breathing and the mechanical breaths may occur during both phases of the respiratory cycle. When the patient exhales while the ventilator delivers a mechanical breath, the airway pressures will be higher and the mechanical breath is wasted. This increases the work of breathing during exhalation. Prolonged asynchrony may result in muscle fatigue and may contribute to prolonged weaning. Considering nonrespiratory factors that may affect extubation failure is important. In a study by Khamiees et al.,[199] although all patients passed an RET, poor cough strength and endotracheal secretions were synergistic in predicting extubation failure.

Tracheostomy and Weaning

Most airway resistance resides in the upper airways. The presence of an endotracheal tube markedly increases the airway resistance (Figure 49-21) and contributes to the work of breathing. Tracheostomy may aid in the weaning by several mechanisms. First, it reduces airway resistance by bypassing the upper airway. This reduces the work of breathing. Second, it increases patient comfort and allows better interaction between the patient and the caretakers, especially the parents. Third, it increases nursing comfort. Tracheostomy is not without risk. The procedure and complications of tracheostomy are described in detail elsewhere. Immediate complications are those related to bleeding, those related to pulmonary air leak, and those associated with anesthesia. Long-term complications include infections of the trachea and the lung, granuloma formation with subglottic stenosis from scarring, erosion of the trachea, and bleeding from erosion into a major thoracic vessel (e.g., innominate artery).

Home Respiratory Care

Chronic respiratory failure is defined as the requirement for mechanical ventilation for longer than a month. Because of improved medical care and technology, the prevalence of children surviving with chronic respiratory failure is increasing. In 1984, the Ad Hoc Task Force on Home Care of Critically Ill Infants stated that "the goal of a home care program for infants, children, or adolescents with chronic conditions is the provision of comprehensive, cost-effective health care within a nurturing home environment that maximizes the capabilities of the individual and minimizes the effects of disabilities."[200] Respiratory care requirements in these children may range from supplemental oxygen to long-term mechanical ventilation. Long-term care in a tertiary care center is expensive and can alternatively be provided in a specialized chronic care rehabilitation center or at home. In 1986, the American College of Chest Physicians published guidelines for the management of ventilator-dependent patients in the home and at alternate community sites.[201] Since the late 1970s and early 1980s, home care has been shown to be as safe as hospital care for infants with tracheostomies and infants and children requiring long-term mechanical ventilation.[202-208] The diagnoses included neuromuscular disease, spinal cord trauma, and respiratory failure from chronic cardiorespiratory disease.[183-189] Home care is psychosocially more acceptable to the families, less

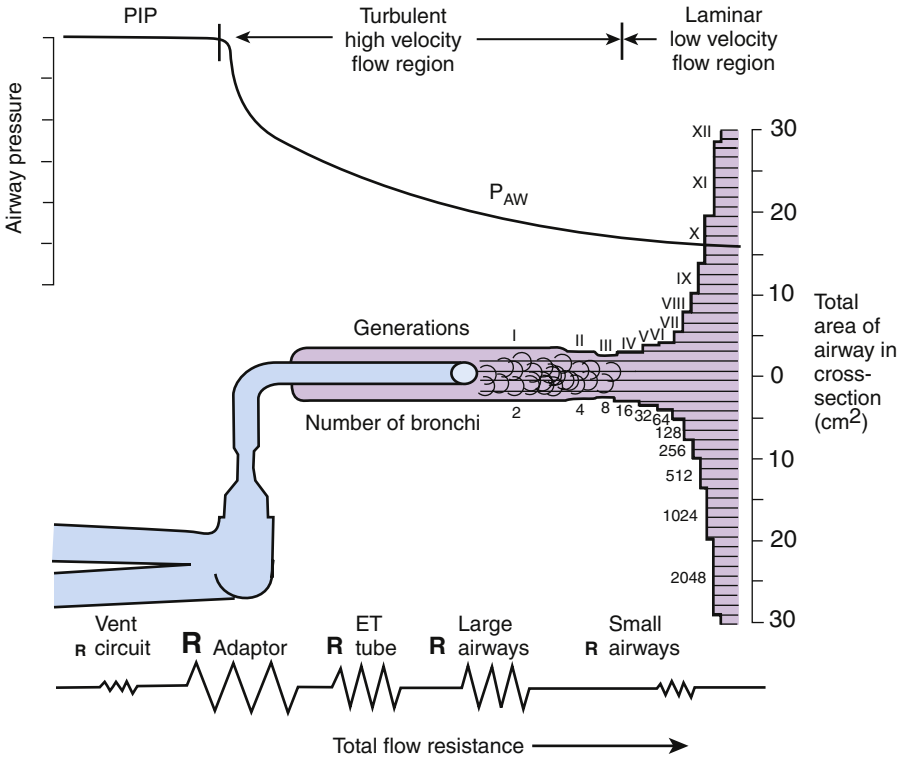

Figure 49–21. Representation of resistances and pressure drop across the entire respiratory system in an intubated patient. Approximately 60% to 80% of the total airway resistance in a spontaneously breathing patient resides within the first few generations of bronchi. Addition of an endotracheal tube and the ventilator circuit increases the resistance to breathing. *(From Goldsmith JP, Karotkin EH editors:* Assisted ventilation of the neonate, *Philadelphia, 1988, WB Saunders.)*

expensive, and may provide a better quality of life for respiratory technology-dependent children.[209,210]

Indications for Home Respiratory Care

The goals of long-term home respiratory care include (1) provision of comprehensive, cost-effective respiratory care, (2) enhancement of quality of life, (3) reduction of morbidity, and (4) wherever possible, extend life. The major indication for home respiratory care is chronic respiratory failure. This may occur in children with parenchymal or airway disease or in children with normal lungs. In children with normal lungs, respiratory failure is usually the result of central or peripheral nervous system dysfunction, neuromuscular disorders, or chest wall abnormalities. Patients who require home respiratory care generally fall under the following categories: (1) patients whose underlying disease is most likely to recover and therefore would need respiratory care during the recovery phase such as infants with bronchopulmonary dysplasia and children recovering from adult respiratory distress syndrome, (2) patients whose underlying disease is irreversible but not progressive such as patients with spinal cord injury, and (3) patients whose underlying disease is irreversible and progressive such as patients with muscular dystrophy. The approach to home care planning will be different depending on the natural course of the underlying disease.

Logistics of Home Care

Home care requires a team approach with interaction between several health care personnel (e.g., a primary physician, home care nurses, respiratory therapists, social workers, and sometimes the State Health Agency) and the family and the patient (Box 49-8). First, the patient must be ready for home care.[208,210,211] In some patients, a stable tracheostomy with a mature stoma is essential. Inspired oxygen requirement should not be greater than 35%. Pao_2 should be greater than 60 to 70 torr with a $Paco_2$ less than 60 torr with a normal arterial pH at relatively low ventilator settings. The family must demonstrate not only a desire to provide home care, but also a minimal ability to provide various aspects of home care. Health care personnel must be available in the local community to assist the family in providing care. The home must have adequate facilities to maintain and run all necessary equipment and supplies. Contingency plans must be made for emergencies. The location of the home has major implications for home care. The home must be easily accessible by standard transportation. A home care provider should be available on a 24-hour basis to respond to emergencies. The home must have adequate space to accommodate all the caretakers and the required equipment. Discharge planning must be thorough and take into account all the factors listed in Table 49-2. A detailed description of the various respiratory care equipment used for home care is beyond the scope of this chapter and the reader is referred elsewhere.[212,213] A thorough knowledge of the limitations of various devices is essential for the respiratory care personnel coordinating home care. Parents who are motivated to providing home care for their children are willing to take on the cumbersome responsibility of carrying all the necessary equipment from place to place just to have the benefit of having the child at home.

References are available online at http://www.expertconsult.com

Box 49–8 Factors to Consider in Children for Home Care

Patient selection
- Medical assessment
- Cardiopulmonary stability
- Positive trend in weight gain and growth curve
- Freedom from frequent respiratory tract infections

Characteristics of the family and child
- Awareness
- Motivation
- Commitment

Home requirements
- Safe electrical, plumbing, and heating systems
- Telephone
- Space

Health care support personnel
- Nurses
- Aides
- Family and friends

Funding
- Third party
- State
- Other

Multidisciplinary home care team from the discharging institution
- Physician specializing in technology-dependent patients
- Nurse specializing in technology-dependent patients
- Social worker
- Respiratory therapist specializing in technology-dependent patients

Other services
- Occupational therapy
- Physical therapy
- Speech therapy
- Dietary services
- Psychologist

Responsibilities of the home care team
- Coordinator
- Physician available on a 24-hour basis
- Referral to a local durable medical equipment company
- Instruction of parents and caretakers
- Assistance of family in securing funding

Family preparation
- Training in cardiopulmonary resuscitation
- Instruction in all aspects of home care plan
- Instruction in use and maintenance of equipment
- Psychological impact
- Techniques of instruction

Noninvasive Ventilation: Concepts and Practice

Shekhar T. Venkataraman

PEARLS

- Noninvasive ventilation can be used for both short-term and long-term indications depending on whether respiratory failure is acute or chronic.
- Not all patients are suitable candidates for noninvasive ventilation. Careful selection of patients is important for noninvasive ventilation to be successful.
- Equipment needs are different when noninvasive ventilation is provided in the hospital versus home.
- A properly fitting interface is crucial to the success of noninvasive ventilation.
- Family involvement is essential for success when long-term noninvasive mechanical ventilation is provided at home.

Conventional mechanical ventilation provided by endotracheal intubation or tracheostomy is a life-saving technique for the management of patients with respiratory failure. Endotracheal intubation and tracheostomy are associated with complications including injury to the airway and nosocomial infections. In addition, mechanical ventilation of children by endotracheal intubation often requires use of sedatives with attendant side effects and complications. *Noninvasive ventilation* (NIV) refers to a technique of respiratory support that is provided without an artificial airway in the trachea. NIV can be provided using either positive or negative-pressure ventilators. Positive pressure NIV is provided by an interface that increases the proximal airway pressure, whereas negative pressure NIV is provided by creating a negative pressure around the chest wall. In both instances, the transpulmonary pressure is raised causing airflow into the lungs. This review will describe the various noninvasive ventilatory techniques available, published reports on their efficacy, their advantages and disadvantages, and future directions. Throughout most of this chapter, NIV will refer to positive pressure noninvasive ventilation. Negative-pressure ventilation is described at the end of the chapter.

Historical Perspective

Dalziel, in 1832, reported the use of a bellows-operated box with a seal around the neck or shoulders to provide artificial respiration to a drowned seaman.[1] In 1867, Woillez designed the first workable noninvasive negative-pressure ventilator, which was operated manually.[2] Doe, in 1989 described a box used for resuscitating newborns.[3] Drinker developed the first tank ventilator in 1928 that was subsequently used with great clinical value in patients with poliomyelitis.[4] Negative-pressure ventilation was introduced for use with neonates in the 1960s.[5,6] In 1953, Lassen reported that positive-pressure ventilation administered using an endotracheal tube or a tracheostomy was more successful that negative-pressure ventilation in treating patients with poliomyelitis.[7] Major technologic advances in the design of positive-pressure ventilators led to the marked decrease in negative-pressure ventilation. Noninvasive positive-pressure ventilation by facemask was first used by Barach et al.[8] for the treatment of hypoxemic respiratory failure secondary to acute pulmonary edema. Gregory et al.,[9] in 1971, reported that constant positive airway pressure (CPAP) through nasal prongs was effective in improving oxygenation in neonates with hyaline membrane disease. Vidyasagar and Chernick showed that constant negative pressure applied about the chest and abdomen was as effective as CPAP in improving oxygenation in neonates with hyaline membrane disease.[10] Despite these early reports, noninvasive ventilation did not become popular until more recently. There is a renewed interest in noninvasive ventilation coinciding with technologic advances in the manufacture and design of noninvasive ventilators. NIV through a mask for neuromuscular disorders was pioneered in the 1980s by Rideau et al.[11] and subsequently by Bach et al.[12]

Indications

The indications for the use of NIV can be categorized into short-term and long-term NIV. Short-term NIV is indicated where positive pressure support is needed acutely in a hospital setting in acute care or critical care areas for conditions that are reversible within a few days. Long-term NIV is indicated in conditions where respiratory failure is likely to be chronic or progressive.

Short-Term Noninvasive Ventilation

The indications for use of NIV in acute care and critical care situations are given in Box 50-1. The selection guidelines are given in Box 50-2. The first step is to determine whether a

Box 50–1 Indications for Short-Term NIV

Acute hypoxemic respiratory failure
- Acute lung injury
- Acute cardiogenic pulmonary edema
- Pneumonia

Acute lower airway disease
- Acute asthma

Avoiding intubation
- Immunocompromised patients
- Restrictive chest diseases
- Neuromuscular disorders
- Postoperative respiratory failure
- Patients with orders not to intubate
- Postextubation respiratory failure

Facilitate weaning and extubation

Box 50–2 Selection Guidelines for Short-Term NIV

1. Potentially reversible condition
2. Need for *moderate* ventilatory assistance

Moderate to severe increase in work of breathing
- Tachypnea
- Retractions
- Paradoxical breathing
- Accessory muscle use

Gas exchange criteria
- Ventilatory failure ($Paco_2$ >45 mm Hg with a pH <7.35)
- Oxygenation failure (Pao_2/Fio_2 ratio <300)

3. No contraindications to NIV

Respiratory or cardiac arrest
Unstable (hypotension, shock)
Poor airway protective reflexes
Recent upper airway and esophageal surgery
Excessive secretions
Uncooperative
Agitation
Untreated pneumothorax
Inability for a good mask fit
Rapidly progressive neuromuscular weakness (e.g., Guillain-Barré syndrome)

patient has a reversible cause of respiratory failure. The second step is to determine whether the patient needs positive pressure support to maintain gas exchange. Before attempting NIV in acute respiratory failure, the clinician must answer the following questions:

1. Does the patient have any contraindications to the use of NIV (see Box 50-2)?
2. Does the patient need to be promptly intubated?

If the answers to both questions are no, then the patient can be considered for NIV. Additional questions that the clinician needs to consider are the following:

1. Does the patient only need increased positive airway pressure to recruit the lung to improve oxygenation?
2. Does the patient need additional ventilatory assistance based on the clinical signs and symptoms or gas exchange derangements?

If the patient only needs increased airway pressure to recruit atelectatic lung and to maintain lung volumes, then the patient can be placed on noninvasive CPAP through an appropriate interface. If the patient needs ventilatory assistance, the patient is a candidate for NIV.

Figure 50-1 shows the algorithm to be followed for initiation of NIV in acute respiratory failure. If NIV is used in acute situations, there should be a determination within 1 to 3 hours whether the patient has improved. Signs of success and failure are given in Box 50-3. A good response to NIV is indicated by: (1) reduction in respiratory rate, (2) reduction in work of breathing, (3) reduction in dyspnea, (4) improvement in pH, (5) improvement in oxygenation, and (6) reduction in $Paco_2$. Additionally, there may be hemodynamic effects such as a reduction in heart rate, improved blood pressures, and perfusion. Generally, for short-term use, NIV is used continuously until the patient improves or fails NIV. The goals of short-term NIV are given in Box 50-4.

Adult Studies on the Short-Term Use of Noninvasive Ventilation

Adult studies have shown that NIV can be used in hypoxemic respiratory failure (Pao_2/fraction of inspired oxygen [Fio_2] ratio <300) with bilateral parenchymal disease to prevent endotracheal intubation. Ferrer et al. showed that NIV reduced the intubation rate from 52% to 25% with a reduction in intensive care unit (ICU) mortality rate from 39% to 18%.[13] But, this finding must be tempered by studies that show that NIV may not reduce the need for endotracheal intubation.[14,15] CPAP, not strictly a form of ventilatory assistance, was described by Barach et al.[8] for the treatment of acute cardiogenic pulmonary edema. Since then, several studies have demonstrated that both CPAP and NIV can decrease the rate of intubation, improve work of breathing and improve gas exchange.[16-18] In adults with acute exacerbations of chronic obstructive pulmonary disease, NIV has been shown to improve both short-term and long-term outcomes.[19-21] It is reasonable to expect a similar response to acute asthma because many of the pathophysiologic features are similar. Uncontrolled studies and one randomized controlled study showed improvement in patients having an acute asthma attack.[22-24] It is desirable to reduce the probability of nosocomial infections in immunocompromised patients. Therefore, it is appealing to apply NIV to avoid endotracheal intubation in these patients. Adult studies have shown that NIV can reduce the rate of intubation and may improve short term mortality.[25-27]

Adult studies have shown that respiratory insufficiency that develops postoperatively in patients can be successfully treated with NIV. NIV reduces the rate of intubation and is more effective than CPAP or chest physiotherapy.[28,29] In patients after lung resection surgery, NIV reduced the rate of intubation and mortality compared with conventional therapy.[30] Children with restrictive chest diseases who develop respiratory failure after surgery such as spinal fusion are good candidates for NIV if they develop postoperative respiratory failure provided they do not have any other contraindications.

Endotracheal intubation and invasive mechanical ventilation are associated with complications including ventilator-associated pneumonia, ventilator-induced lung injury, and airway trauma. To minimize these complications, it is desirable to extubate the patient as quickly as possible. Generally, extubation coincides with the end of weaning (i.e., the patient is not placed on any form of positive pressure support

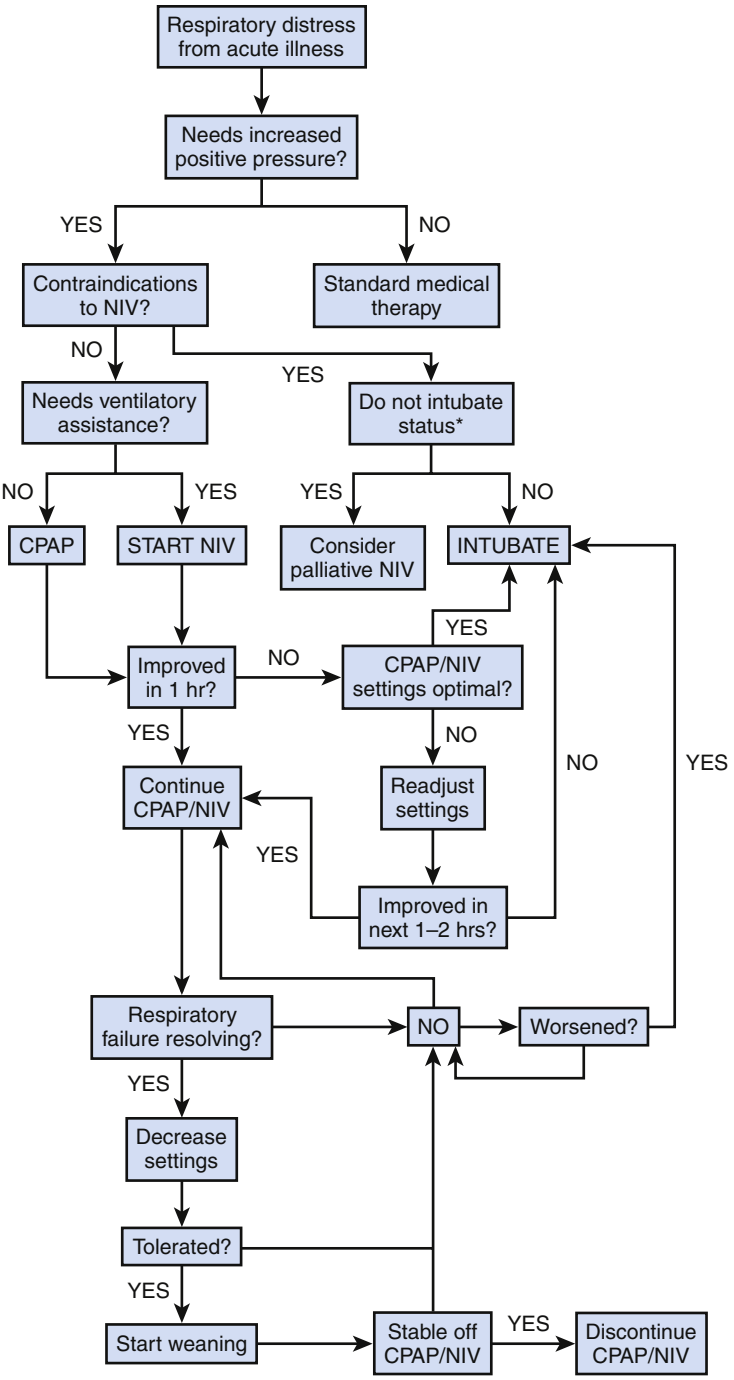

Figure 50–1. Algorithm for initiation and weaning of short-term continuous positive airway pressure and NIV.

postextubation). In some patients, who take a long time to wean, but require fairly low ventilatory assistance, it is possible to extubate them to NIV. Theoretically, it would reduce the incidence of complications associated with endotracheal intubation and invasive mechanical ventilation. Udwadia et al. were among the first to test this paradigm in 22 adult patients who were successfully stabilized on NIV after extubation.[31] Three adult studies have demonstrated that the use of NIV resulted in a reduction in the duration of mechanical ventilation, a reduction in the incidence of nosocomial pneumonia, and a reduction in the duration of hospital stay.[32-34] Similar pediatric studies are lacking. NIV to facilitate extubation should be carried out only if the patient meets the following criteria: (1) is awake and alert, (2) has intact bulbar function with a preserved cough reflex, (3) has minimal airway secretion, (4) is able to breathe spontaneously, (5) has stable hemodynamic status, (6) does not have gastric distension, and (7) has a requirement for 40% or less supplemental oxygen. Recently, some adult studies have examined the use of NIV for postextubation respiratory failure (i.e., respiratory failure that develops after extubation on complete spontaneous breathing). The rationale for the use of NIV in this circumstance is the avoidance of endotracheal intubation. In at least one study in adults, this approach was shown to increase the time from

Box 50–3 Signs of Success and Failure Within 1–2 Hours of Application of NIV for Short-Term NIV

Signs of Success

Reduction in respiratory rate to a range that is normal for age
Absence of retractions
Absence of paradoxical breathing
Improvement in gas exchange
- Improved pH
- Improved Pao_2/Flo_2
- Reduction in $Paco_2$

Signs of Failure

Signs of work of breathing
Gas exchange
Hemodynamic instability
Signs of respiratory fatigue
Change in mental status
Increased agitation

Box 50–4 Goals of NIV

Short-Term NIV

Relieve respiratory distress
Decrease work of breathing
Improve gas exchange
Avoid intubation

Long-Term NIV

Ameliorate symptoms
Improve gas exchange
Improve quality of life
Improve sleep duration and quality
Improve survival

respiratory failure to intubation with an increase in mortality rate.[35] It is difficult to extrapolate from adult studies to pediatrics. It is possible that some children may benefit from the institution of NIV for postextubation respiratory failure.

Pediatric and Neonatal Studies

In 1981, Sullivan et al.[36] first demonstrated that nasal CPAP was effective in reversing obstructive sleep apnea in four adults and one teenager. Guilleminault et al.,[37] in 1986, reported that nasal CPAP reversed or reduced obstructive sleep apnea in some children. There were problems related to poor cooperation from parents and difficulty in preventing leaks around the nasal mask. Since the first report, several studies have shown that nasal CPAP was effective in obstructive sleep apnea in infants and children.[37-42] In 1995, Guilleminault et al.[43] reported that nasal CPAP was successful in 70 of 72 infants with sleep-disordered breathing. In many instances, it provided an interim solution while allowing the patient to grow and postponing surgery.

Patients in a fairly wide age range appear to tolerate NIV therapy in the acute setting, provided they are adequately monitored and sedated. In 1993, Akingbola et al.[44] published a case report describing effective NPPV therapy in two pediatric patients with acute respiratory distress. Since that time, NIV has been applied to pediatric patients with a variety of respiratory disorders associated with acute hypoxemic respiratory failure, including pneumonia, pulmonary edema, postoperative respiratory decompensation in sleep apnea syndrome, status asthmaticus, spinal muscular atrophy, and end-stage cystic fibrosis.[45-51]

Padman et al.[52] published a preliminary report on 15 patients ages 4 to 21 years who had respiratory failure because of cystic fibrosis (four patients) and neuromuscular disease (11 patients). In 14 patients, the placement of an artificial airway was avoided. They observed significant improvement in hospital days, respiratory rate, heart rate, serum bicarbonate, arterial carbon dioxide, dyspnea, activity tolerance, and quality of sleep. In 1995, Fortenberry et al. reported a retrospective study on the efficacy and complications of biphasic positive airway pressure (Bi-PAP) in 28 children with acute hypoxemic respiratory insufficiency.[47] Bi-PAP significantly decreased respiratory rate and improved both oxygenation and ventilation. The use of Bi-PAP decreased hospitalization rate and increased patient comfort. Only three of 28 patients required intubation or reintubation. Padman et al. conducted a prospective study in 34 patients with impending failure all of whom required airway or oxygenation/ventilation support and required admission to the pediatric ICU.[50] A decrease in respiratory rate, heart rate, and dyspnea score, and an improvement in oxygenation were noted in more than 90% of patients studied. The frequency of intubation in these patients was only 8%. Birnkrant et al.[51] reported their experience with Bi-PAP in six patients with spinal muscular atrophy and three patients with other causes of respiratory failure. This uncontrolled study showed that in these patients noninvasive positive-pressure ventilation facilitated extubation. Teague et al.[53] reported that NIV treatment acutely improved oxygenation and reduced cardiorespiratory distress in 19 of 26 patients. This group of "NIV responders" had significantly shorter lengths of stay in both the ICU and hospital. However, the seven nonresponders required endotracheal intubation as respiratory distress progressed despite sedation. Teague et al.[53] also showed that NIV improves gas exchange in children with upper airway obstruction In a prospective, randomized, controlled trial of NIV in children with acute respiratory failure, Yan et al.[54] showed that NIV improved hypoxemia and the signs and symptoms of acute respiratory failure and reduced the rate of endotracheal intubation. Thill et al.,[55] in a randomized, crossover study in children with lower airway obstruction, showed that NIV decreased signs of work of breathing such as respiratory rate, accessory muscle use, and dyspnea as compared with standard therapy with no serious associated morbidity. Pancera et al.[56] recently published their experience with NIV in immunocompromised pediatric patients. NIV as the first-line therapy was compared to invasive mechanical ventilation. Seventy-five percent of the patients treated with NIV did not require endotracheal intubation showing that NIV is a viable first-line therapy for respiratory failure in immunocompromised patients for preventing endotracheal intubation.[56] More recently, NIV has been suggested as an alternative to endotracheal intubation for the perioperative management of scoliosis correction in patients with muscular dystrophy.[57]

Interfaces

A properly fitting facial appliance is essential for the optimal application of NIV. There are currently several devices in use: (1) oral-nasal mask, (2) nasal mask, (3) total face mask,

(4) Adam's circuit, (5) head hood, (6) nasal prongs, and (7) mouthpieces. A correctly sized interface minimizes leaks, improves effectiveness of positive pressure support, and improves comfort.

Oral-Nasal Masks

This is the most common interface used to provide NIV. The ideal face-mask should (1) be made of a clear material to allow visual inspection, (2) conform to the contours of the patient's face, (3) be easily moldable from its factory shape, (4) be soft and not apply excess pressure on the skin of the face, and (5) maintain its deformed shape (has "memory") when it is removed. The mask should extend from the bridge of the nose to just below the lower lip. The mask is secured using an anchoring system that goes around the head.

Nasal Masks

A nasal mask rests between the bridge of the nose and above the upper lip. As a rule, the smaller the mask, the better the fit. Patients who are unable to keep their mouth closed may use chin straps to close the mouth.

Total Face Mask

This mask covers the whole face including the eyes. The advantage of a total face mask is that it does not have to conform to the shape of the face and therefore does not have to be molded to fit every patient. The disadvantage is that it has an increased deadspace and therefore, there may be difficulty in eliminating CO_2.

Adam's Circuit

This device uses a "nasal pillow" that attaches to a manifold that is placed over the top of the head. Some patients prefer this to the nasal mask. "Nasal pillows" are available in various sizes.

Head Hood

Also called a *helmet,* the head hood has been used successfully in a number of European ICUs. It appears best suited for application of CPAP. Dead space is a major concern and therefore should be reserved for patients in the ICU.

Equipment

A detailed description of the devices available for NIV at home is beyond the scope of this chapter and the reader is referred to several excellent reviews.[58,59] This discussion focuses on the characteristics of positive-pressure ventilators that can be used for providing NIV. Negative-pressure ventilators are discussed elsewhere in the chapter. The ventilators that are used for NIV can be classified into three categories: (1) conventional ICU ventilators with a double limb circuit without leak compensation, (2) devices with a single limb circuit with leak compensation, and (3) devices that combine the above two categories to include both leak compensation and having a double-limb circuit. Category 1 devices can only be used in the hospital. Category 2 and 3 devices can be used both in the hospital and at home. The examples of these devices would be any of the conventional ICU ventilators that can provide pressure support with positive end-expiratory pressure (category 1), Respironics Bi-PAP (category 2), and the Pulmometrics LTV ventilator (category 3). The performances of these ventilators vary widely in delivered tidal volumes, air-leak compensation, response to simulated effort, inspiratory trigger, expiratory cycling, rebreathing, response to high ventilatory demands, and patient-ventilator synchrony.[60] Category 1 or ICU ventilators operate with high-pressure gas sources with an oxygen blending system. Category 2 and 3 devices can operate without a high-pressure gas source. Bilevel ventilators do not have a blender; therefore the delivered Fio_2 is unpredictable depending on the oxygen flow rate, ventilator settings, amount of leak, site of oxygen enrichment, and the type of exhalation port.[61]

Optimizing Patient-Ventilator Interaction

Optimal patient-ventilator interaction requires that the ventilator be able to detect the patient's inspiratory efforts as quickly as possible and terminate inspiration (expiratory cycling) as close to the beginning of the patient's expiration as possible. Inspiratory trigger function differs significantly among the ventilators.[62-64] Factors affecting the inspiratory trigger function include trigger response to the inspiratory flow, leak-induced auto-triggering, and pressure-time and flow-time waveform heterogeneity.[62-64] Strategies to optimize expiratory cycling include setting a suitable threshold for the inspiratory time and adjusting the expiratory cycling flow threshold. Patients with obstructive lung disease tend to do better with high inspiratory flow, whereas patients with neuromuscular disease seem to do better with low inspiratory flows.[65] An adjustable backup rate is available in most modern ventilators used for NIV. This is particularly useful when sedation is used to improve patient compliance with NIV. Leaks around the interface reduce its effectiveness. Some amount of leak around the interface is expected with NIV. Complete elimination of air leak is not desirable because it comes at the expense of a very tight-fitting mask that may lead to patient discomfort and skin breakdown. Ventilators differ in their capacity to compensate for leaks. One of the drawbacks of a large airleak is auto-triggering. Humidification is important to prevent mucosal drying. Humidification can be provided using a heated humidifier, HME, or a pass-over humidifier.

Ventilator Settings

With CPAP, the pressure level is selected based on clinical need. There should be relief of symptoms within 1 to 2 hours of application of CPAP. With short-term NIV, two strategies have been employed. One approach is to start with a high inspiratory pressure (about 20 to 25 cm H_2O). The goal of such an approach is rapid relief of symptoms. If successful, a lower level that also is tolerated is selected. This approach is called the *high-low approach*. The other approach starts with a lower inspiratory pressure (about 8 to 10 cm H_2O) and gradually increased to produce relief of symptoms. The aim of this approach is to maximize patient comfort and tolerance. This is called the *low-high approach*. Within the first 1 to 3 hours, subsequent adjustments may be necessary depending on the

patient response. Expiratory pressure is used routinely during short-term NIV. Maximal FIo_2 with bilevel ventilators is usually about 45% to 50%. If a higher FIo_2 is required, and endotracheal intubation is not indicated, then an ICU-type ventilator may be used.

Complications and Concerns During Short-Term Noninvasive Ventilation

Aerophagia and gastric distension can occur with NIV. The higher the pressure used, the greater the chance of gastric distension. Regurgitation of gastric contents and aspiration into the lungs are major concerns with the use of an oronasal total face mask and a helmet. Close monitoring is needed to prevent aspiration. A nasogastric tube to keep the stomach decompressed is necessary in these acutely ill patients. Pressure sores related to the masks are the other major concern. It should be possible to pass one or two fingers between the headgear and the face. Care should be taken to avoid fitting the interface too tightly. A spacer with soft padding can reduce the incidence of pressure sores on the face.

Circuit and Carbon Dioxide Rebreathing

Single limb circuits that are employed with bilevel ventilators can result in significant CO_2 rebreathing. All single-limb circuits have an exhalation port that is placed close to the patient interface through which exhaled gas will escape. If the exhaled gas flow exceeds the rate of escape through the exhalation port, exhaled air is rebreathed with the next inspiration. This results in significant CO_2 rebreathing and can cause hypercarbia. Rebreathing also depends on the level of expiratory positive airway pressure (EPAP), the location of the exhalation port, and the design of the exhalation port. Earlier devices had significant CO_2 rebreathing of the exhaled air, especially if the expiratory positive airway pressure levels were set too low. In the newer designs, this problem has been reduced. The closer the exhalation port to the patient interface, the less the rebreathing of CO_2. In fact, if the exhalation port is located in the mask itself, it results in the lowest amount of CO_2 rebreathing. Dual-limb circuits eliminate the risk of rebreathing.

Long-Term Noninvasive Ventilation

Long-term NIV is indicated in conditions that result in chronic respiratory failure. This can be either progressive or nonprogressive. Generally, long-term NIV is intermittent with periods off NIV. The most common form of long-term NIV is nocturnal NIV with off-periods during the daytime. The goals of long-term NIV are given in Box 50-4. The indications for long-term NIV are given in Box 50-5.

Physiologic Effects and Outcomes of Long-Term Noninvasive Ventilation

Intermittent NIV consistently improves daytime gas exchange.[66,67] Patients with neuromuscular and chest wall disorders often have sleep-related disturbances.[68] NIV ameliorates hypoventilation, intermittent sleep apneas, and other sleep-disordered breathing.[69] In children with neuromuscular disorder, symptoms of daytime sleepiness, headache, and sleep quality improved after initiation of NIV.[70] Hospitalization rates and health care costs decreased. Quality of life remained stable after NIV, despite disease progression.[70] NIV, applied appropriately, improves the quality of life with restrictive thoracic disorders.[71] Children with spinal muscular atrophy (types 1 and 2) often develop thoracoabdominal asynchrony, especially during sleep. NIV improved sleep breathing parameters and thoracoabdominal coordination during sleep in spinal muscular atrophy Types 1 and 2.[72] Long-term NIV combined with mechanically assisted coughing has also been shown to increase survival in patients with Duchenne muscular dystrophy.[73]

Box 50–5 Indications for Long-Term NIV

Restrictive thoracic diseases
- Chest wall deformity—kyphoscoliosis

Slowly progressive neurologic disorders
- Postpolio syndrome
- Muscular dystrophies
- Spinal muscular atrophy

Nonprogressive chronic respiratory failure
- High spinal cord injury

Ventilator Settings

As with short-term NIV, the ventilator settings must relieve patient symptoms. The approach that is generally recommended for long-term NIV is the low-high approach with gradual increase in support. A backup rate sufficiently high to control breathing nocturnally can rest the respiratory muscles and prevent apnea, especially in patients with neuromuscular disease. NIV can be provided both intermittently and continuously. There has been an increase in the continuous use of NIV, especially in patients with neuromuscular disorders. This has resulted in prolonging survival in these patients.

Monitoring of Patients with Long-Term Noninvasive Ventilation

Monitoring patients who are on long-term NIV requires an assessment of their respiratory function. Pulse oximeters are useful in detecting hypoxemia especially during sleep. End-tidal CO_2 monitors are only used in the clinic or hospital. Treatment of sleep-disordered breathing improves the quality of life and may prolong survival. Polysomnography may be required to document sleep disorders but is more expensive than nocturnal pulse oximetry. If a patient has bulbar weakness or severe obesity, there may be obstruction of the upper airway or obstructive sleep apnea in addition to sleep hypoventilation. Both problems may be treated with nocturnal ventilation.

Negative-Pressure Ventilation

Design and Modes of Negative-Pressure Ventilators

All negative-pressure ventilators have a chamber in which subatmospheric pressure is generated and a pump which generates this pressure. The chamber may cover only the chest and

the upper abdomen (cuirass) or all of the extracranial portions of the body (tank respirator, isolette, or a body suit). The tank respirator has both the chamber and the pump in one unit. In all other cases the two units are separate. The cuirass can be prefabricated or custom designed to fit the contours of the chest. Custom-designed cuirasses are especially useful in patients with skeletal or spinal deformities. All body suits fit over a hard shell similar to the cuirass placed over the chest and the upper abdomen. Most negative pressure pumps in use today are pressure cycled. Some volume-cycled pumps have been used but their use has been limited because the pump cannot compensate for the variable amounts of air leak. Additionally, some ventilators provide an inspiratory assist mode. At the present time, there are four modes of negative pressure application: (1) cyclical negative pressure, (2) negative/positive pressure, (3) continuous negative extrathoracic pressure (CNEP), and (4) negative pressure/CNEP. *Cyclical negative-pressure ventilation* refers to a mode where the ventilator generates the preset subatmospheric pressure during inspiration while expiration is passive. Negative/positive-pressure ventilation refers to a mode which is a combination of negative pressure during inspiration with positive pressure during expiration. *CNEP* refers to a mode in which a constant subatmospheric pressure is provided throughout the respiratory cycle and the patient breathes spontaneously. Negative pressure/CNEP refers to a mode where negative pressure inspiratory cycles are superimposed on CNEP.

Clinical Applications

Box 50-6 shows the indications, advantages, disadvantages, contraindications, and clinical side effects of negative-pressure ventilation. In 1965, Stahlman et al.[74] first reported on the use of a tank respirator to treat neonates with respiratory distress syndrome. Vidyasagar and Chernick,[10] in 1971, were the first to show that CNEP improved oxygenation in neonatal respiratory distress syndrome. In the 1970s, several controlled and uncontrolled studies showed that negative-pressure ventilation was effective in the management of neonatal respiratory syndrome.[75-77] However, the utility of this technique was limited because of problems such as upper airway obstruction, difficulties in achieving access to patients, difficulties in achieving an adequate seal, sores from the neck seal, and inability to maintain an adequate neutral thermal environment. Negative-pressure ventilation has been reintroduced in the treatment of neonatal respiratory distress syndrome. A recent randomized control study showed that application of CNEP was associated with fewer intubations and decreased the total duration of oxygen therapy.[78] However, CNEP was associated with a slightly higher (not statistically significant) mortality rate, cranial ultrasound abnormalities, and pneumothoraces. Further studies are warranted to assess the utility and safety of negative-pressure ventilation in neonatal respiratory distress syndrome.

Respiratory Dysfunction and Failure

During the polio epidemics in the 1930s and 1940s, negative-pressure tank ventilators reduced mortality in patients with spinal polio.[79-81] There has been a resurgent interest in negative-pressure ventilation in patients with neuromuscular diseases and skeletal deformities. In adults with kyphoscoliosis and neuromuscular disorders with chronic hypoventilation, intermittent use of negative-pressure ventilation, mostly nocturnal, decreased or reversed day time symptoms of hypoventilation and gas exchange abnormalities.[82,83] These studies show that negative-pressure ventilation is useful in acute or chronic respiratory failure associated with skeletal or neuromuscular

Box 50–6 Indications, Advantages, Disadvantages, and Contraindications of Negative Pressure Ventilation

Indications

1. Parenchymal lung disease
   - Respiratory distress of the newborn
   - Interstitial pneumonias
   - Acute respiratory distress syndrome
   - Acute pulmonary edema
2. Respiratory pump failure
   - Poliomyelitis
   - Neuromuscular diseases
   - Skeletal deformities
   - Persistent flail chest deformity
3. Cardiovascular disorders
   - After Fontan-type operations
   - Repair of total cavopulmonary connection
   - Tetralogy of Fallot
   - Phrenic nerve palsy after pediatric cardiac surgery

Advantages

1. Avoids intubation or tracheostomy
2. Preserves physiologic functions such as speech, cough, swallowing, and feeding
3. Allows fiberoptic bronchoscopy to be performed without disconnection from the ventilator
4. Promotes venous return by creating negative intrathoracic pressure.

Disadvantages

1. Noisy
2. Access to patient is difficult
3. Tank ventilators produce abdominal pooling of blood resulting in hypotension (tank shock)
4. Regulation of inspiratory-expiratory ratio is difficult (more recent ventilators such as the Hayek negative-pressure ventilator allows for regulation of inspiratory/expiratory ratio and application of negative end-expiratory pressure)
5. Difficult to sterilize
6. Lack of protection of the upper airway, especially in unconscious patients or those with bulbar dysfunction
7. Upper airway obstruction can be minimized with an oral airway
8. Difficulty in achieving an adequate seal
9. Discomfort

Contraindications

1. Gastrointestinal bleeding
2. Rib fracture
3. Recent abdominal surgery
4. Uncooperative patients
5. Sleep apnea syndrome
6. Neurologic disorders with bulbar syndrome

Clinical Side Effects

1. Tiredness
2. Musculoskeletal pain or tightness
3. Esophagitis
4. Rib fractures and pneumothorax
5. Impaired sleep quality
6. Poor compliance

disorders. Isolated case reports in adults have been published about using CNEP in adult respiratory distress syndrome and in persistent flail chest deformity.[84-87] CNEP has been used to assist ventilation in children with diffuse alveolar disease and progressive respiratory failure.[88-90] In 1975, Sanyal et al.[89] published a case series of five children with progressive respiratory failure from *Pneumocystis carinii* pneumonitis. Three patients improved with CNP and survived, whereas the other two continued to worsen and died. Sanyal et al.,[90] in 1977, published a larger series where CNEP was used to assist ventilation in 14 children who had progressive respiratory insufficiency caused by diffuse bilateral alveolar disease. Within 6 hours after therapy was started, oxygenation improved. The improvement was sustained and within 24 hours permitted a decrease in fractional concentration inspired oxygen. There was a concomitant decrease in intrapulmonary right-to-left shunt and a decrease in respiratory rate. Four of the 14 patients developed pneumothorax that was successfully decompressed. Ten patients survived. These observations establish CNEP therapy as an effective means of improving arterial oxygenation in spontaneously breathing older children, avoiding endotracheal intubation and prolonged use of muscle relaxants and sedatives.

Cardiovascular Disorders

Raine et al.[91] in 1992 published a pilot study in 10 children with respiratory failure and found the CNEP, introduced either in conjunction with intermittent positive-pressure ventilation or alone, did not produce large changes in cardiac output. In patients with Fontan-type operations, pulmonary blood flow and cardiac output increases with spontaneous inspiration and positive-pressure ventilation decreases antegrade pulmonary blood flow and may increase pulmonary valvular incompetence in patients with restrictive right heart physiology after repair of tetralogy of Fallot.[92] In children after repair of total cavopulmonary connection and tetralogy of Fallot and after Fontan-type procedures, negative-pressure ventilation provided using a Hayek external high-frequency oscillator improved cardiac output by 42% to 46% almost entirely by an increase in stroke volume with improvement in mixed venous oxygen saturation.[93] Systemic and pulmonary vascular resistances decreased significantly as well. A similar finding was observed in children after transcatheter occlusion of an asymptomatic patent ductus arteriosus and after open heart surgery.[94] Raine et al.[95] in 1992 reported in an uncontrolled study that negative-pressure ventilation using either CNEP or intermittent negative-pressure ventilation was a viable alternative to positive-pressure ventilation in patients with phrenic nerve palsy after pediatric cardiac surgery, reduced the need for diaphragmatic plication, and facilitated weaning from positive-pressure ventilation. These studies show that negative-pressure ventilation is a useful technique in selected patients after cardiac surgery where positive-pressure ventilation is not desirable or results in unwanted hemodynamic effects.

Summary

NIV is a viable alternative to invasive mechanical ventilation in selected children. NIV can be used both to meet short-term and long-term needs. Selection of patients is crucial to ensure success with NIV.

References are available online at http://www.expertconsult.com.

Ventilator-Induced Lung Injury

Jean-Damien Ricard, Didier Dreyfuss, Alexandre T. Rotta, and Georges Saumon

PEARLS

- Although essential to the support of patients with respiratory failure, mechanical ventilation can be associated with the development of pulmonary tissue injury, termed ventilator-induced lung injury (VILI).
- The concept of VILI has been elegantly tested in the research laboratory in both normal and diseased lungs, where the individual contribution of various factors, such as tidal volume, positive end-expiratory pressure, and overall state of lung distension can be determined. Lung volume at the end of inspiration (i.e., the overall degree of lung distension) probably is the main determinant of VILI severity.
- One must take the magnitude of the loss of aerated lung volume and alterations in lung mechanics into account to assess the risk of VILI.
- Experimental and clinical data support the idea that reasoned tidal volume reduction designed to prevent volutrauma can be advantageous in the management of these patients.

Mechanical ventilation is essential to life support of patients with respiratory failure. Several potential drawbacks to mechanical ventilation were identified early in its history.[1] More recent experimental studies have showed that certain ventilation modalities may produce subtle tissue damage similar to that seen in early acute respiratory distress syndrome (ARDS) and termed ventilator-induced lung injury (VILI). This issue has recently received much attention in the clinical field.[2,3] The purpose of this chapter is to describe pathophysiological events leading to VILI and to place these observations into a clinical perspective of ventilatory management of patients with ARDS.

Evidence for Ventilator-Induced Lung Injury

Ventilation of Intact Lungs

High Lung Volume Ventilator-Induced Lung Injury

Webb and Tierney[4] found that pulmonary edema rapidly developed in rats subjected to 45 cm H_2O peak airway pressure ventilation, whereas it did not develop in rats undergoing ventilation for a longer time with 14 cm H_2O peak airway pressure. Edema severity and rate of development increased with peak airway pressure magnitude. It was later confirmed that such a ventilation modality produces endothelial and epithelial cell damage and lung capillary permeability changes that result in nonhydrostatic pulmonary edema.[5] This edema formation is now generally believed to be the hallmark of VILI.

The respective roles of increased airway pressure and increased lung volume in this injury were clarified when mechanical ventilation at high and low tidal volume (V_T) were compared at identical (45 cm H_2O) peak airway pressures.[6] The injury was found only in rats subjected to high V_T and not in those undergoing ventilation at high airway pressure in which lung distention was limited by thoracoabdominal strapping (Figure 51-1).[6] Furthermore, in animals undergoing ventilation at high V_T by negative external distending pressure, pulmonary edema still developed, confirming that excessive airway pressure is not the causal factor of this type of injury.[6] This VILI that depends mostly on end-inspiratory volume has been called volutrauma.[7,8] The alveolar pressure corresponding to end-inspiratory volume is the "plateau" airway pressure (measured at no-flow), and its clinical importance has been emphasized in a Consensus Conference on mechanical ventilation.[9] Several investigators reached the same conclusions in other species using different protocols.[10-12]

Taken together, these experimental studies have shown that large tidal volumes are more critical than high intrathoracic pressures in the genesis of ventilator-induced lung edema in intact animals.

Low Lung Volume Ventilator-Induced Lung Injury

Unlike volutrauma, ventilation at low lung volumes does not seem to injure healthy lungs. Intact animals tolerate mechanical ventilation with physiologic V_T and low levels of positive end-expiratory pressure (PEEP) for prolonged periods of time without any apparent damage. Taskar and colleagues[13] have shown that the repetitive collapse and reopening of terminal units during 1 hour of mechanical ventilation does not result in appreciable lung damage, although it does alter gas exchange and reduce compliance, as does spontaneous (low V_T) ventilation under deep anesthesia.

Ventilation of Damaged Lungs

High-Volume Lung Injury

Several investigators have evaluated the effect of overdistension on damaged lungs. These studies consistently demonstrated the increased susceptibility of diseased lungs to the detrimental effects of some modalities of mechanical ventilation.

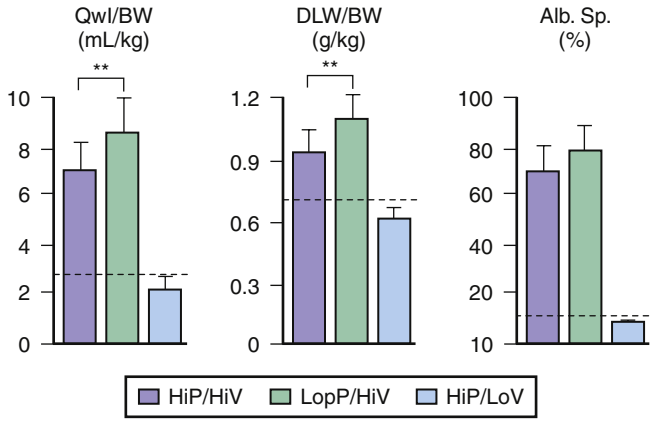

Figure 51–1. Comparisons of the effects of high-pressure–high-volume ventilation *(HiP-HiV)* with those of negative inspiratory airway pressure high tidal volume ventilation (iron lung ventilation, *LoP-HiV)* and of high-pressure–low-volume ventilation (thoracoabdominal strapping, *HiP-LoV). Dotted lines* represent the upper 95% confidence limit for control values. See Figure 51-3 for details on edema indices. Permeability edema occurred in both groups receiving high tidal volume ventilation. Animals undergoing ventilation with a high peak pressure and a normal tidal volume had no edema. *BW,* Body weight; *DLW,* dry lung weight; *Qwl,* extravascular lung water. *(From Dreyfuss D, Soler P, Basset G et al: High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure,* Am Rev Respir Dis *137:1159-1164, 1988.)*

The first studies were performed on isolated lungs. Bowton and Kong[14] showed that isolated perfused rabbit lungs injured by oleic acid gained significantly more weight when ventilated with 18 mL/kg V_T than with 6 mL/kg V_T. Hernandez and colleagues[15] compared the effects of oleic acid alone, mechanical ventilation alone, and their combination on lung capillary filtration coefficient and wet-to-dry weight ratio (which reflects lung protein accumulation) in young rabbits. Filtration coefficient and wet-to-dry weight were not significantly affected by low doses of oleic acid or by mechanical ventilation at a peak inspiratory pressure of 25 cm H_2O for 15 minutes. However, the filtration coefficient increased significantly when oleic acid injury was followed by mechanical ventilation at these pressures. Wet-to-dry weight ratio was also significantly higher than in lungs subjected to oleic acid injury or ventilation alone. The same team also showed that inactivating surfactant with dioctyl-succinate aggravates the filtration coefficient increase produced by ventilating isolated blood-perfused rabbit lungs at 30 to 45 cm H_2O peak pressure.[16] Whereas light microscope examination showed only minor abnormalities (minimal hemorrhage and vascular congestion) in the lungs of animals subjected to ventilation or surfactant inactivation alone, their combination caused severe damage (edema and flooding, hyaline membranes, and extensive alveolar hemorrhage).

These results suggested that ventilation at high volume and pressure might favor VILI in abnormal isolated lungs and that it might occur at lower airway pressure than in the normal lung. Whether this could also occur in lungs in situ was investigated by comparing the effects of different modalities of mechanical ventilation in rats with α-naphthylthiourea (ANTU)-injured lungs[17] (Figure 51-2). ANTU infusion alone caused moderate permeability pulmonary edema. Mechanical ventilation alone resulted in a permeability edema of severity related to magnitude of V_T. It was thus possible to calculate the theoretical amount

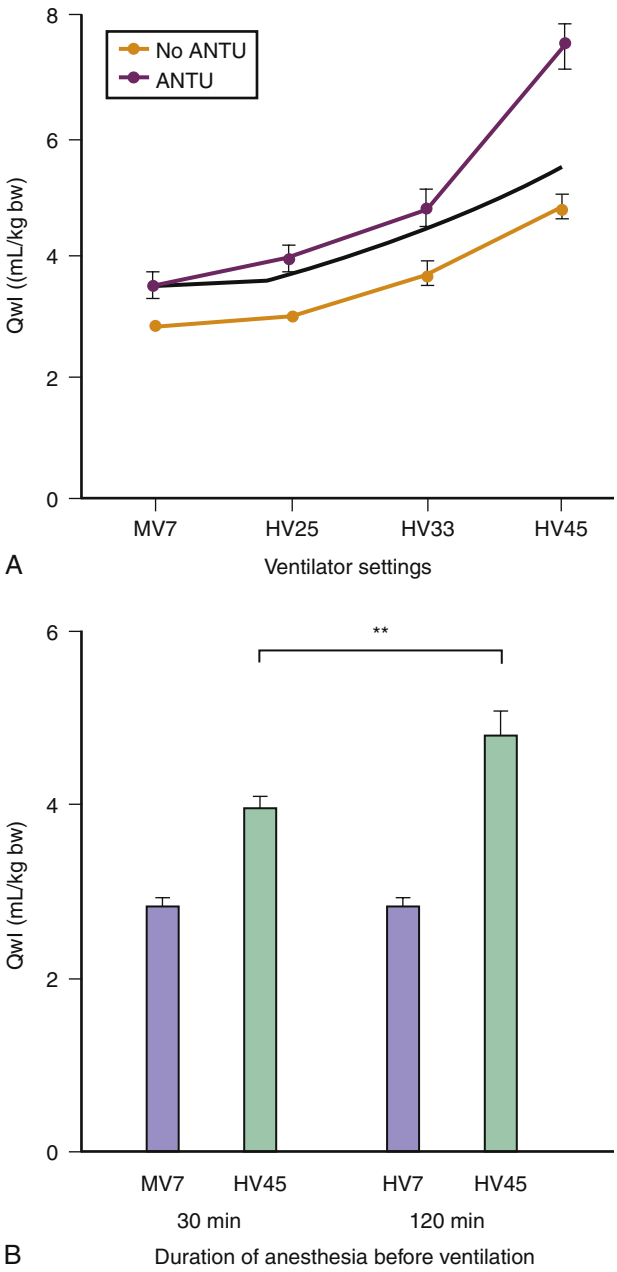

Figure 51–2. Interaction between previous lung alterations and mechanical ventilation on pulmonary edema. **A,** Effect of previous toxic lung injury. Extravascular lung water *(Qwl)* after mechanical ventilation in normal rats *(orange circles)* and in rats with mild lung injury produced by α-naphthylthiourea (ANTU) *(purple circles).* Tidal volume (V_T) varied from 7 to 45 mL/kg body weight *(bw). Black line* represents the Qwl value expected for the aggravating effect of ANTU on ventilation edema assuming additivity. ANTU did not potentiate the effect of ventilation with V_T up to 33 mL/kg bw. In contrast, ventilation at 45 mL/kg bw V_T resulted in an increase in edema that greatly exceeded additivity, indicating synergy between the two insults. **B,** Effect of lung functional alteration by prolonged anesthesia. Intact rats were anesthetized and breathed spontaneously for 30 or 120 minutes prior to mechanical ventilation with 7 mL/kg bw *(open bars)* or 45 mL/kg bw *(shaded bars)* V_T in intact rats. Qwl of animals that underwent ventilation with a high V_T was significantly higher than in those that underwent ventilation with a normal V_T. Qwl was not affected by the duration of anesthesia in animals that underwent ventilation with a normal V_T. In contrast, 120 minutes of anesthesia before high V_T ventilation resulted in a larger increase in Qwl than did 30 minutes of anesthesia. $^{**}P < .01$. *(From Dreyfuss D, Soler P, Saumon GL: Mechanical ventilation-induced pulmonary edema. Interaction with previous lung alterations,* Am J Respir Crit Care Med *151:1568-1575, 1995.)*

of edema that would result from ventilating ANTU-diseased lungs with a given V_T by summing up the separate effect of mechanical ventilation and ANTU. However, lungs of animals injured by ANTU had more edema than predicted when they underwent ventilation with a high V_T (45 mL/kg body weight), indicating that the two insults acted in synergy. Even slight lung alterations, such as those produced by spontaneous ventilation during prolonged anesthesia (which inactivates surfactant and promotes focal atelectasis[18,19]), are sufficient to exacerbate the harmful effects of high-volume ventilation.[17] The extent to which lung mechanical properties are altered prior to ventilation is a key factor in this synergy. The amount of pulmonary edema produced by high-volume mechanical ventilation in animals given ANTU, or after prolonged anesthesia, was inversely proportional to respiratory system compliance measured at the very beginning of high-volume mechanical ventilation.[17] Thus the more severe the lung abnormalities were before ventilation, the more severe was the VILI.

The reason for this synergy requires clarification. The presence of zones of alveolar edema in animals given this harmful ventilation was the most evident difference from those that underwent ventilation with lower, less harmful V_T.[17] Because alveolar flooding reduced the number of alveoli available for ventilation, they were more prone to overinflation, more vulnerable, and at greater risk of alveolar flooding. This in turn would further reduce aerated lung volume and result in positive feedback. The same reasoning applies to prolonged anesthesia, during which aerated lung volume was probably gradually reduced by atelectasis.[17] Both flooding and atelectasis decrease lung compliance by a "baby lung" effect, a reduction in the volume of lung available for ventilation. It is not surprising that the lower the compliance before ventilation, the more severe were the lung alterations induced by high-volume ventilation.[17] Thus uneven distribution of ventilation during acute lung injury[20] favors regional overinflation and injury. To substantiate this phenomenon, rats underwent ventilation with V_T of up to 33 mL/kg after alveolar flooding by instillation of saline solution into the trachea. Flooding with saline solution did not significantly affect microvascular permeability when V_T was low. As expected, capillary permeability alterations were more important in animals that experienced alveolar flooding than in intact animals that underwent ventilation at high V_T. Correlations also were found between end-inspiratory (plateau) airway pressure, the pressure at the "lower inflection point" on the pressure-volume (PV) curve, and the capillary permeability changes found in animals that experienced alveolar flooding and underwent ventilation with at high V_T (Figure 51-3).[21] Thus the changes in capillary permeability caused by lung overinflation are more severe in poorly recruitable (and less compliant) lungs.

Low-Volume Lung Injury

An increase in trapped-gas volume during pulmonary edema and acute lung injury probably occurs because of airway closure and is worsened by impaired surfactant function.[22] Under such conditions, the slope of the inspiratory limb of the respiratory system PV curve often displays a sharp increase at low lung volume. This change reflects the sudden and massive opening of units previously excluded from ventilation and has been termed the "lower inflection point." This phenomenon often has a dramatic effect on arterial oxygenation, because

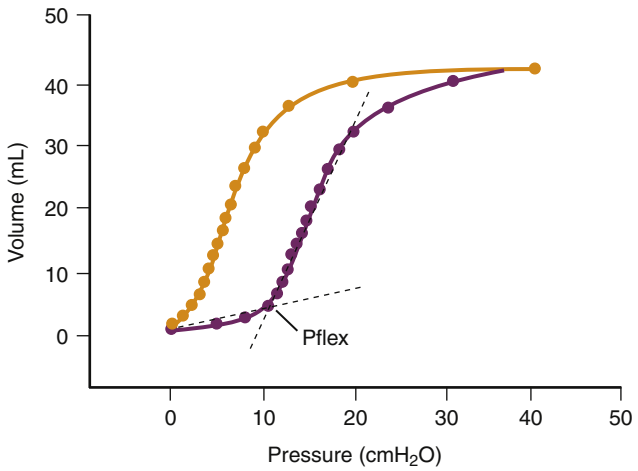

Figure 51–3. Static volume-pressure relationship for the total respiratory system of a surfactant-depleted juvenile rabbit. *Pflex* indicates the lower inflexion point.

setting PEEP above the pressure at this inflection point often decreases shunt and increases PaO_2.[23-26]

The possibility that pulmonary dysfunction may be aggravated if this inflection point lies within the V_T has been a recent focus of attention. Experimental evidence for this possibility initially was provided by studies comparing conventional mechanical ventilation with high-frequency oscillatory ventilation in premature or surfactant-depleted lungs. Studies performed on such lungs ventilated at various levels of PEEP suggest that repeated closure and reopening of terminal units can cause lung injury.[27-29] Argiras and colleagues[27] and Sandhar and associates[28] studied this issue in rabbits with surfactant-depleted lungs. During volume-controlled ventilation, peak inspiratory pressure was initially 15 mm Hg but increased to 25 mm Hg 5 hours later because lung compliance fell. PEEP was then adjusted to be either above (8 to 12 mm Hg) or below (1 to 2 mm Hg) the lower inflection point of the inspiratory limb of the PV curve. Mortality rates in the two groups were identical, but arterial PaO_2 was better preserved and less hyaline membrane formation occurred in the high-PEEP group.[27,28] This lessening of pathologic alterations was observed even when inspiratory/expiratory time ratios were adjusted so that mean airway pressures were the same in the low-PEEP and high-PEEP groups.[28] Muscedere and colleagues[30] reported similar results in isolated, unperfused rabbit lungs lavaged with saline solution and ventilated with a low (5 to 6 mL/kg) V_T and with a PEEP set below or above the inflection point. However, Sohma and colleagues[29] did not find this injury in vivo in rabbits whose lungs had been injured with hydrochloric acid.[29]

It often is argued that the lower inflection point on the PV curve reflects the recruitment of collapsed zones that are found predominantly in dependent areas[31,32] and that this recruitment persists during further lung expansion. Recently Martynowicz and coworkers[33] have questioned the existence of the repetitive collapse-reexpansion phenomenon during tidal ventilation and have reevaluated the significance of the lower inflection point on the PV curve. They studied the regional expansion of oleic acid–injured lungs using the parenchymal marker technique in dogs. They found that the gravitational distribution of volume at functional residual capacity was not

affected and not associated with a decreased parenchymal volume of the dependent regions. In addition, they found that the between-region asynchrony of tidal expansion was not influenced by oleic acid injury. Their findings therefore did not support the hypothesis that a more important gravitational gradient during VILI produces atelectasis by compression of the dependent lung, cyclic recruitment and collapse, and ultimately shear stress injury.[33] They propose that the displacement of air-liquid interfaces along the tracheobronchial tree causes the lower inflection point on the PV curve and conclude that this knee on the curve reflects the mechanics of partially fluid-filled alveoli with constant surface tension and not the abrupt opening of airways or atelectatic parenchyma.[34] It therefore remains unsettled whether injury caused by the repetitive reopening of collapsed terminal units and the protective effect of PEEP is restricted to the peculiar situation of surfactant depletion by bronchoalveolar lavage. In the clinical arena, the recent negative results of the ALVEOLI trial[35] and the two other more recent randomized controlled trials[36,37] cast doubt on the clinical existence of repetitive opening and closing lung injury.[38]

Roles of Tidal Volume, Positive End-Expiratory Pressure, and Overall Lung Distention

The influence of PEEP on acute lung injury (and more specifically on ventilator-induced pulmonary edema) must be studied in the context of the level of V_T. Indeed, PEEP increases functional residual capacity (FRC) and recruits the lung but also increases end-inspiratory volume when V_T is kept constant, thus possibly favoring overinflation. PEEP application also may depress hemodynamics and affect lung fluid balance. Therefore close analysis of the numerous studies that have been done to clarify the relationships between PEEP, oxygenation, and extravascular lung water accumulation during hydrostatic or permeability type edema must take into account the experimental approach used, that is, intact animals or isolated lungs (for which lung water content will differ), and whether or not V_T is reduced (thus increasing or not increasing end-inspiratory lung volume).

Effects of Positive End-Expiratory Pressure When Tidal Volume Is Kept Constant

Application of PEEP may result in lung overinflation if it is followed by a significant change in FRC because of the increase in end-inspiratory volume. Overinflation will affect preferentially the more distensible areas that receive the bulk of ventilation, which may explain the lack of reduction or even the worsening of edema reported following PEEP application in most experiments.[39] PEEP does not affect the severity of hydrostatic[40] or permeability[40,41] edema in intact animals, although it improves oxygenation[40] because of the recruitment of flooded alveoli (Figure 51-4). In isolated ventilated-perfused lungs, PEEP rather aggravates edema fluid accumulation[42] (Figure 51-5). Thus when V_T is left unchanged, increasing FRC with PEEP affects edema differently in isolated lungs or in intact animals. In the latter, the lack of effect of PEEP depends on the balance between PEEP-induced increase in end-inspiratory lung volume, which decreases interstitial pressure and increases filtration pressure in extra-alveolar vessels, and the hemodynamic depression due to elevated intrathoracic pressure that, in the opposite, decreases filtration pressure. In contrast, preservation of perfusion rate in isolated-perfused lungs favors edema formation.[42]

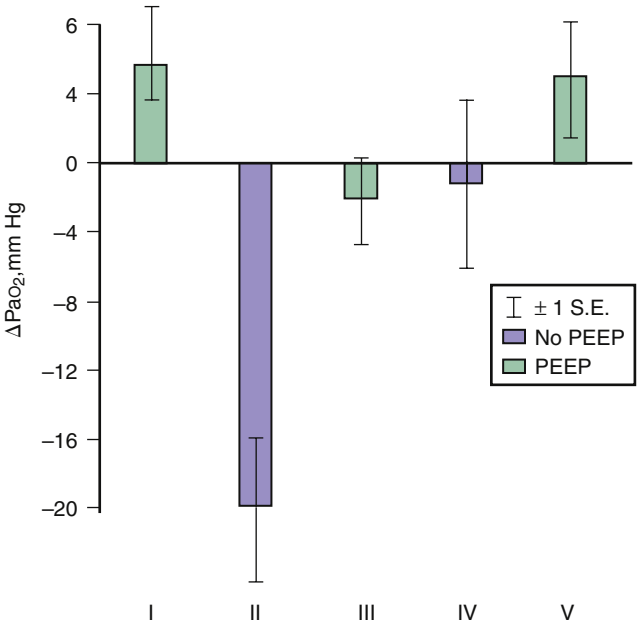

Figure 51–4. Change in arterial oxygen tension (ΔPaO_2, mm Hg) during 1-hour period between the initial and final measurements for groups I (control), II, and III (severe hydrostatic pulmonary edema, without and with positive end-expiratory pressure [PEEP], respectively), and IV and V (moderate pulmonary edema, without and with PEEP, respectively). The difference between ΔPaO_2 for groups II and III is significant ($P < .01$). *(From Hopewell PC, Murray JF: Effects of continuous positive-pressure ventilation in experimental pulmonary edema,* J Appl Physiol *40:568-574, 1976.)*

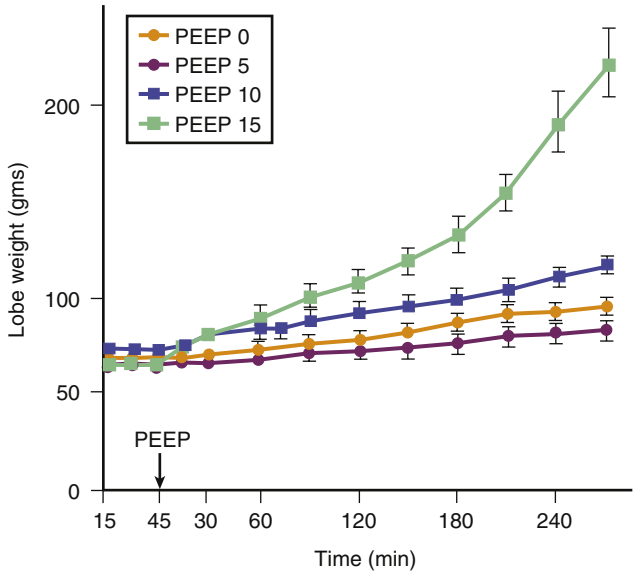

Figure 51–5. Effect of three levels of positive end-expiratory pressure (PEEP) on water accumulation in hydrochloric acid–injured ventilated-perfused dog pulmonary lobes. The highest PEEP resulted in a further increase in pulmonary edema. *(From Toung T, Saharia P, Permutt S, et al: Aspiration pneumonia: beneficial and harmful effects of positive end-expiratory pressure,* Surgery *82:279-283, 1977.)*

Effects of Positive End-Expiratory Pressure when Tidal Volume Is Reduced

Edema is less severe during high-volume ventilation (even though FRC is increased by PEEP) when end-inspiratory lung volume is kept constant by decreasing V_T (Figure 51-6). Webb and Tierney[4] showed that less edema developed during ventilation with 45 cm H_2O peak airway pressure when 10 cm H_2O PEEP was applied. The authors attributed this beneficial effect of PEEP to the preservation of surfactant activity. It was later shown that, although PEEP decreased the amount of edema, it did not prevent alteration of capillary permeability.[6] However, animals undergoing ventilation with PEEP had no alveolar damage in contrast with those that underwent ventilation without PEEP. The only cellular alterations found in animals that underwent ventilation with PEEP consisted of capillary endothelial blebs.[6] No satisfactory explanation has been found for this preservation of the epithelial layer. It may be that PEEP prevented fluid movement in terminal units, thereby decreasing shear stress at this level. Similar observations have been made by other investigators in intact animals[43,44] and in isolated perfused canine lobes.[45] The hemodynamic alterations induced by PEEP probably play an important role in lessening the severity of edema. Application of PEEP produces an increase in mean intrathoracic pressure that adversely affects cardiac output.[46,47] For example, in rats subjected to high peak airway pressure and 10 cm H_2O PEEP, edema was more severe when the hemodynamic alterations induced by PEEP were corrected with dopamine infusion.[48] The amount of extravascular lung water was correlated with systemic blood pressure, suggesting that restoration of cardiac output increased filtration pressure and was responsible for aggravation of edema. The reduction of edema and of the severity of cellular damage by PEEP during ventilation-induced pulmonary edema may be linked to reduced tissue stress by decreasing volume-pressure excursion, movement of foam in distal airways, preservation of surfactant activity, and a decrease in capillary filtration.

Importance of Overall Lung Distention

Lung volume at the end of inspiration (i.e., the overall degree of lung distention) is probably the main determinant of the severity of VILI. Pulmonary edema developed in rats that underwent ventilation with a low V_T and 15 cm H_2O PEEP, whereas it did not develop in rats that underwent ventilation with the same V_T but with 10 cm H_2O PEEP.[48] Similarly, doubling this V_T in the presence of 10 cm H_2O PEEP produced pulmonary edema, whereas it did not produce pulmonary edema in animals that underwent ventilation without PEEP. Thus the safety of a given V_T depends on how much FRC is increased.

In conclusion, permeability edema and VILI occur when a threshold degree of lung overinflation is reached. This situation can occur when V_T is increased from a given level of end-expiratory pressure. In contrast, when PEEP is increased at constant end-inspiratory pressure, it slows the development of edema and diminishes the severity of tissue injury but does not prevent altered microvascular permeability.[6,48] Finally, when the application of PEEP increases the end-inspiratory (plateau) pressure, it increases the risk of edema formation.[48]

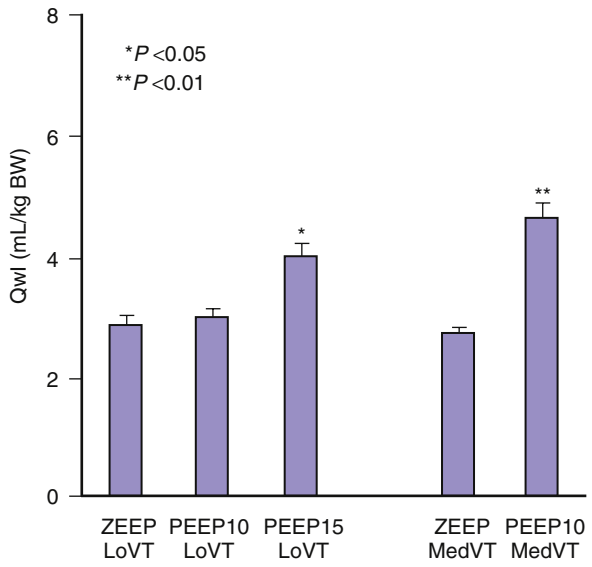

Figure 51–6. Effect of increasing positive end-expiratory pressure (PEEP) from 0 to 15 cmH_2O during ventilation with two different tidal volume (V_T) values (7 mL/kg body weight *[BW]*: LoV_T and 14 mL/kg BW: $MedV_T$). Pulmonary edema (as evaluated by increases in extravascular lung water [Qwl]) occurred when PEEP was increased. PEEP required to produce edema varied with V_T: 15 cmH_2O PEEP during ventilation with low V_T and 10 cmH_2O PEEP during ventilation with moderately increased V_T. $*P < .05$; $**P < .01$ vs. zero end-expiratory pressure (ZEEP) and the same V_T. *(From Dreyfuss D, Saumon G: Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation,* Am Rev Respir Dis *148:1194-1203, 1993.)*

Possible Mechanisms of Ventilator-Induced Lung Injury

It is now clear that ventilation-induced pulmonary edema is essentially the result of severe changes in the permeability of the alveolar-capillary barrier. Small increases in filtration pressure may combine with altered permeability to aggravate edema.

Ventilation may damage lungs by two different mechanisms, and the severity of damage depends on both intensity and duration of the insult. A rapidly occurring and severe permeability pulmonary edema may be produced in small animals as a consequence of acute lung stretch. This edema does not appear to require the involvement of inflammatory cells or secretion of mediators and can occur within a few minutes. Edema develops more slowly in larger animals for the same plateau pressure, rendering the situation more complex. A low lung volume injury may contribute its own effects to high end-inspiratory volume damage. Further, ventilation without PEEP may reduce aerated lung volume and gradually worsen mechanical nonuniformity. This lung inhomogeneity will in turn promote overinflation of the more compliant and probably healthier zones, leading to positive feedback aggravation. In addition, when lung lesions develop slowly, inflammatory pathways have enough time to be activated and may participate in tissue injury (Figure 51-7).

Mechanisms of Increased Vascular Transmural Pressure

Increased fluid filtration may occur at both extraalveolar[49,50] and alveolar[51-53] sites during mechanical ventilation. Increased transmural pressure in extraalveolar vessels results from the increase in lung volume, and the decrease in

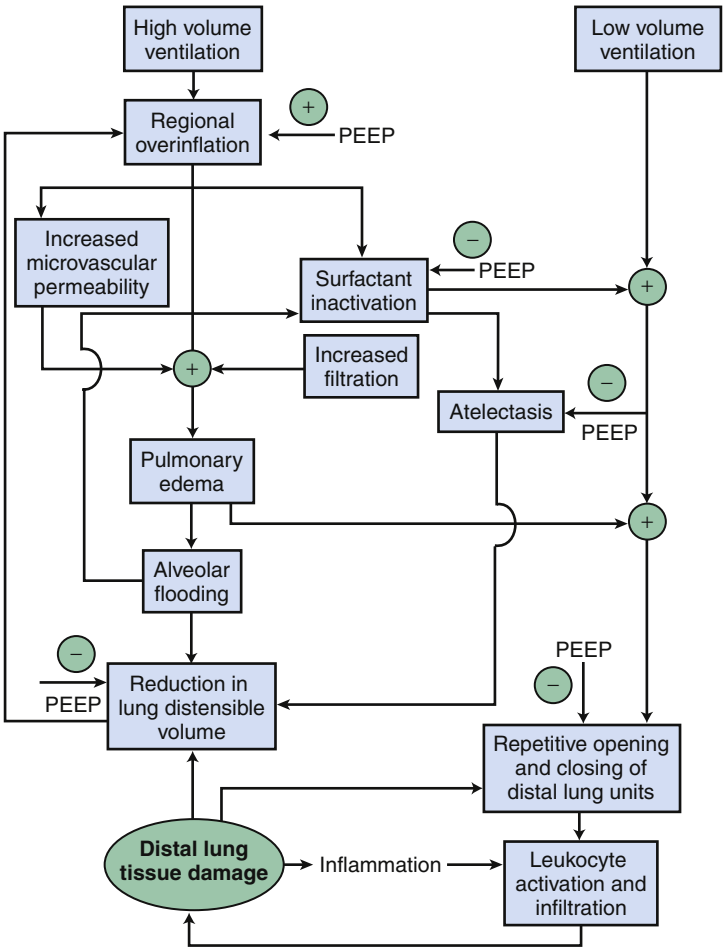

Figure 51–7. Flow diagram summarizing the contributors to mechanical ventilation–induced lung injury. Positive end-expiratory pressure (PEEP) generally opposes injury or edema formation *(minus sign)* except when it contributes to overinflation *(plus sign). (From Dreyfuss D, Saumon G: Ventilator-induced lung injury: lessons from experimental studies,* Am J Respir Crit Care Med *157:294-323, 1998.)*

perivascular interstitial pressure is the consequence of lung stretch.[46,54,55] Increased filtration across alveolar microvessels also may be promoted by the surfactant inactivation[4,53] that accompanies ventilation at high V_T or because of the presence of plasma proteins (such as fibrinogen and albumin) in airspaces.

Mechanisms of Altered Permeability

While capillary permeability alterations are obvious and may be severe during ventilator-induced edema, the underlying mechanisms are not fully understood and may vary according to the extent and duration of lung overdistension.

Effects of Surfactant Inactivation

In addition to its effects on fluid filtration, surfactant inactivation and elevated alveolar surface tension may increase alveolar epithelial permeability to small solutes. Surfactant inactivation by detergent aerosolization increases diethylenetriaminepentaacetic acid (DTPA) clearance in rabbits[56] and dogs.[57] This effect has been ascribed to the ventilation inhomogeneities and regional overexpansion that result from uneven inactivation of surfactant and maldistribution of lung mechanical properties rather than to the elimination of peculiar barrier properties of surfactant.[57] The effects of surfactant inactivation and large V_T ventilation on alveolocapillary permeability (as assessed by pulmonary DTPA clearance) are additive.[58] Endothelial permeability may be altered because the increased surface tension due to surfactant inactivation augments radial traction on pulmonary microvessels.[53]

Participation of Inflammatory Cells and Mediators

Role of Inflammatory Cells. The endothelial cell disruption observed during overinflation edema in small animals may allow direct contact between polymorphonuclear cells and the basement membrane. This contact may promote leukocyte sequestration. A striking feature of the VILI that occurs after several hours is the infiltration of inflammatory cells into the interstitial and alveolar spaces. In one of the earliest studies on this subject, Woo and Hedley-White[59] observed that overinflation produced edema in open-chest dogs and that leukocytes accumulated in the vasculature and macrophages in the alveoli. Further studies have confirmed these results[60] and have shown that high transpulmonary pressure increased the transit time of leukocytes in the lungs of rabbits.[61] Conversely, when animals are depleted in neutrophils, high-volume pulmonary edema is less severe than in nondepleted animals.[62] Protracted ventilation in small mammals also recruits leukocytes in lungs that may contribute to VILI.[63]

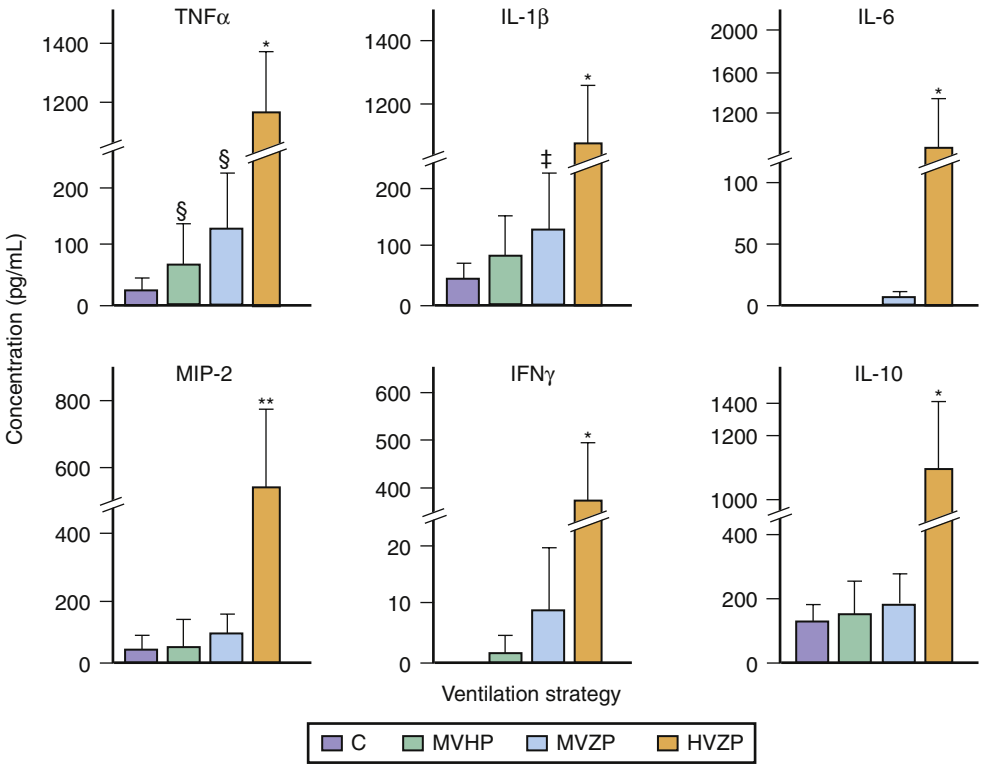

Figure 51–8. Effect of different ventilatory strategies on cytokine concentrations in lung lavage of isolated unperfused rat lungs. Four ventilator settings were used: controls (*C,* normal tidal volume [V_T]), moderate V_T + high positive end-expiratory pressure (PEEP) *(MVHP),* moderate V_T + zero PEEP *(MVZP),* and high V_T + zero PEEP *(HVZP)* resulting in the same end-inspiratory distension as MVHP. Major increases in cytokine concentrations were observed with HVZP. *IFN,* Interferon; *IL,* interleukin; *MIP,* macrophage inflammatory protein; *TNF,* tumor necrosis factor. *(From Tremblay L, Valenza F, Ribeiro SP et al: Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model,* J Clin Invest *99:944-952, 1997.)*

Role of Inflammatory Mediators. The role of inflammatory cytokines in the course of VILI has been the subject of recent studies and is a matter of debate.[64,65] Tremblay and colleagues[66] examined the effects of different ventilatory strategies on the level of several cytokines in bronchoalveolar lavage fluid of isolated rat lungs ventilated with different end-expiratory pressures and V_T. High V_T ventilation (40 mL/kg) with zero end-expiratory pressure resulted in considerable increases in tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, and macrophage inflammatory protein (MIP)-2 (Figure 51-8). Unfortunately, results from this study have not been replicated by another group using the same ex vivo lung model (Figure 51-9).[67] It is worth noting that stretching in vitro human alveolar macrophages[68] or A549 epithelial cells[69] led to no TNF-α release but to release of IL-8. In vivo studies of intact animals show that high-volume mechanical ventilation that produces a very severe pulmonary edema does not induce the release of TNF-α.[67,70] Studies on TNF-α messenger ribonucleic acid (mRNA) also yield conflicting results. Takata and coworkers[71] showed large increases in TNF-α mRNA in the intraalveolar cells of surfactant-depleted rabbits after 1 hour of conventional mechanical ventilation with peak inspiratory and end-expiratory pressures of 28 and 5 cm H_2O (resulting in a mean airway pressure of 13 cm H_2O), whereas Imanaka and colleagues[71a] showed no increase in lung tissue TNF-α mRNA of rats that underwent ventilation at high pressure (45 cm H_2O of peak inspiratory pressure[71]).

The only mediator that is constantly found in the different experimental studies is MIP-2 (or IL-8, pending on the

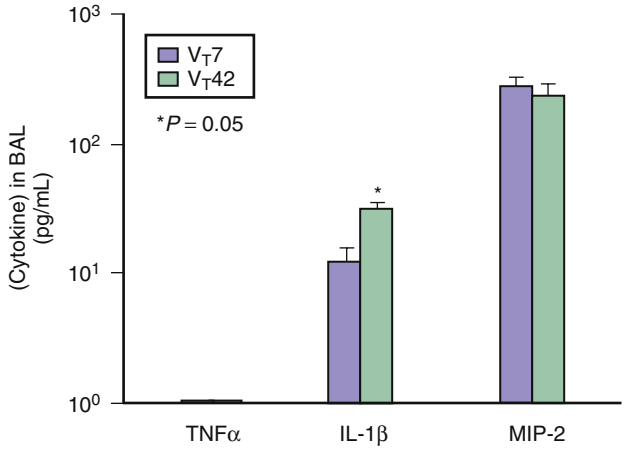

Figure 51–9. Effect of different ventilatory strategies on cytokine concentrations in lung lavage. Tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and macrophage inflammatory protein (MIP)-2 concentrations in bronchoalveolar lavage fluid (BALF) of rats ventilated for 2 hours with 7 mL/kg tidal volume (V_T) and 3 cm H_2O positive end-expiratory pressure (PEEP) (V_T7) and 42 mL/kg V_T and PEEP (V_T42). TNF-α was undetectable whatever the ventilation strategy. IL-1β and MIP-2 were found in small amounts. IL-1β was slightly higher (*P = .05) in BALF of rats ventilated with the larger V_T. (Note that 100 signifies a value below the detection threshold). *(From Ricard J-D, Dreyfuss D, Saumon G: Production of inflammatory cytokines in ventilator-induced lung injury: a reappraisal,* Am J Respir Crit Care Med *163:1176-1180, 2001.)*

experimental model). The presence of this neutrophil chemoattractant mediator in lungs subjected to high-volume ventilation is in agreement with the well-documented recruitment of neutrophils that occurs after long-term ventilation.[59,72-74] In vivo inhibition of MIP-2 ligand interactions led to a marked reduction in neutrophil sequestration and lung injury in mice subjected to high-volume ventilation for 6 hours.[63]

In addition to increasing the amount of cytokines in the lung, it has been suspected that overinflation during mechanical ventilation may promote the release of cytokines[75,76] or bacteria[77,78] into the blood, thus giving a causative role for mechanical ventilation in multiorgan dysfunction.[79,80] However, this hypothesis remains to be proven.[81]

New Insights in Ventilator-Induced Lung Injury

Cellular Response to Mechanical Strain

Interest is growing in the cellular response to mechanical strain, and related issues recently have been reviewed.[82] Parker and colleagues[83] studied the different signal transduction pathways that may be involved in the microvascular permeability increases observed during experimental VILI. They found that gadolinium (which blocks stretch-activated nonselective cation channels) annulled the increases in vascular permeability induced by high airway pressure.[84] The authors concluded that stretch-activated cation channels might initiate the increase in permeability induced by mechanical ventilation through increases in intracellular Ca^{2+} concentration. To further explore the involvement of this pathway, the same team showed that Ca^{2+}/calmodulin–myosin light chain kinase inhibitors significantly attenuate the vascular permeability increase induced by high-pressure mechanical ventilation in an isolated perfused rat model.[85] High-volume ventilation of isolated rat lungs leads to the release of reactive nitrogen species.[86] Nitric oxide participates in the control of endothelial permeability, and nitric oxide overproduction results in increases in endothelial permeability and blebs at the ultrastructural level very similar to those observed after periods of high-volume ventilation.[87]

Taken together, these results suggest that the increase in microvascular permeability may not simply be a passive physical phenomenon (a "stress failure"[88,89]) but may at least in part be the result of biochemical reactions. Maintenance of plasma membrane integrity is essential in response to mechanical stress. Recently Vlahakis and colleagues reported a heretofore-undescribed response of alveolar epithelial cells to deformation.[90] They labeled membrane lipids to study deformation-induced lipid trafficking and observed cell responses to deforming forces by laser confocal microscopy. A 25% stretch deformation resulted in lipid transport to the plasma membrane that ensured cell integrity and increased its surface area. This lipid trafficking occurred in all cells, in contrast with plasma breaks that were seen in only a small percentage of cells. The authors concluded that deformation-induced lipid trafficking serves in part to repair plasma breaks and that this could be viewed as a cytoprotective mechanism against plasma membrane stress failure seen during VILI.[6,89] Other investigators have focused on the relative importance of deformation frequency, duration, and amplitude in stress-induced cell injury.[91] Interestingly, authors found that limiting the deformation amplitude resulted in significant reductions in cell death at identical peak deformations (Figure 51-10). From these results, an analogy

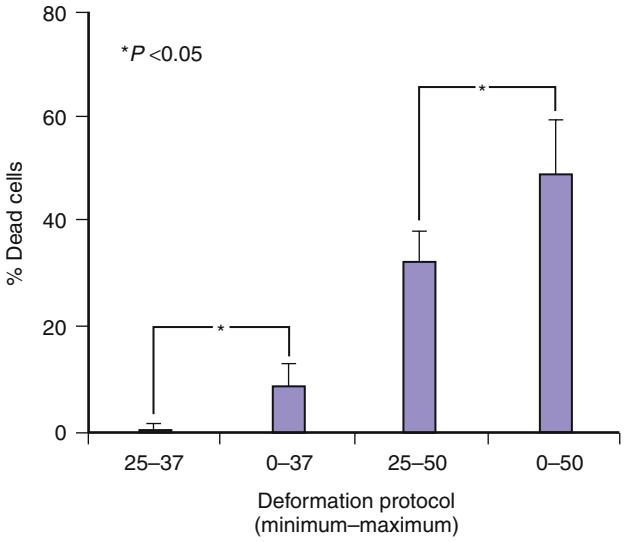

Figure 51–10. Relative importance of deformation magnitude and amplitude. Deformations were applied for 60 minutes at 15 cpm. Data are given as mean ± SD. Reducing the amplitude to 12% ΔSA or 25% ΔSA significantly reduced cell death when maximum deformation was held at 37% ΔSA or 50% ΔSA, respectively. *$P < .05$. *(From Tschumperlin DJ, Oswari J, Margulies SS: Deformation-induced injury of alveolar epithelial cells. Effect of frequency, duration, and amplitude,* Am J Respir Crit Care Med *162:357-362, 2000.)*

can be drawn with experiments that showed a decrease in lung injury when V_T was reduced with a constant PEEP level, thus reducing end-inspiratory lung volume.[48]

Influence of Carbon Dioxide Tension on Ventilator-Induced Lung Injury

Deleterious effects of hypocapnia have been extensively reviewed.[92] However, it is important to note that, in addition to detrimental effects of hypocapnia[93] and hypercapnia[94] on ischemia-reperfusion lung injury, experimental studies suggest that hypercapnia may protect from the acute increase in capillary permeability caused by overinflation[86] and from inflammation during VILI.[95]

Strategies to Reduce Ventilator-Induced Lung Injury: Use of the Pressure-Volume Curve

The ARDS network trial[2] has undisputedly shown that reducing V_T from 12 mL/kg to 6 mL/kg resulted in a 22% reduction in mortality rate (Figure 51-11). By protocol, the same reduction of V_T was applied to all patients allocated to the low V_T group. However, it has repeatedly been shown that pressures and the volumes considered safe for some patients with ARDS may cause lung overdistension in others.[31,32,96,97] Conversely, arbitrary settings may result in an unnecessary reduction in V_T, which a recent meta-analysis has suggested as being potentially harmful.[3]

It has been suggested that information from the inspiratory PV curve of the respiratory system could be used to tailor ventilator settings. For instance, the presence of an opening pressure (lower inflection point) could be used to adjust the PEEP.[23-25] It has been proposed that the V_T be adjusted according to PV curve analysis by limiting end-inspiratory pressures to the pressure at which a decrease in slope is seen at high

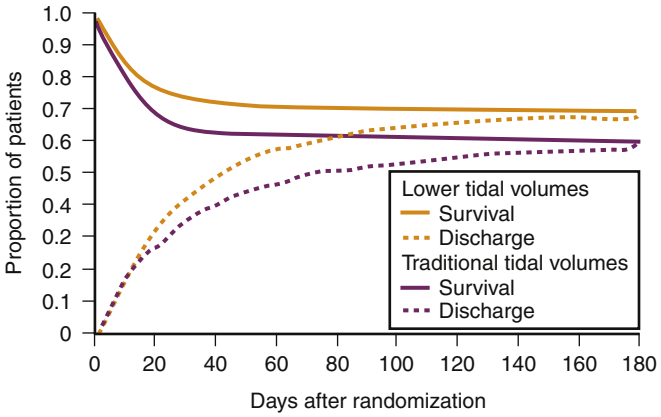

Figure 51–11. Probability of survival and of being discharged home and breathing without assistance during the first 180 days after randomization in patients with acute lung injury and acute respiratory distress syndrome. *(From The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome,* N Engl J Med *342:1301-1308, 2000.)*

pressure/volume (the upper inflection point [UIP]).[96,97,100] The UIP often seen in patients with ARDS has been ascribed to overinflation[96,97] or to the end of recruitment[101,102] during lung expansion. However, whether ventilator settings that would result in pressure/volume excursions above the UIP are deleterious remains unsettled and has never been assessed experimentally. The impact of pulmonary edema and the resulting decrease in ventilatable lung volume on the inspiratory limb of the respiratory system PV curve has not yet been evaluated. A better understanding of its significance is required before the UIP can be used to set V_T in patients. A recent experimental study[103] found that the reduction in ventilatable lung volume (the baby lung effect) not only decreases the compliance of the lung[31,104] but also affects the position of the UIP. It also was noted that the development of edema altered the PV curve by causing distal airway obstruction and that individual characteristics of the PV curve reflected the susceptibility of the lungs to the deleterious effects of high-volume ventilation. The authors found that the higher the compliance and the volume of the UIP were before ventilation, the less severe edema there was after overinflation. Taken together, these results suggest that the position of the UIP is a marker of ventilatable lung volume and is both influenced by and predictive of the development of edema during mechanical ventilation. Because the UIP is less influenced by ventilatory mechanics than is respiratory system compliance, it may be of greater clinical value.

Imaging Ventilator-Induced Lung Injury

Alveolar epithelial and pulmonary microvascular permeability to proteins was evaluated using a two-way protein flux scintigraphic study in rats during lung inflation.[105] Two tracers were used, ^{99m}Tc-albumin (in the alveolar instillate) and ^{111}In-transferrin (in the blood). Alveolar epithelial permeability was estimated from the rate at which ^{99m}Tc-albumin left the lungs. Microvascular permeability was simultaneously estimated measuring the accumulation of ^{111}In-transferrin in the lungs. Increasing lung tissue stretch by ventilation at high airway pressure immediately increased microvascular but also alveolar epithelial permeability to proteins. The same end-inspiratory pressure threshold (between 20 and 25 cmH_2O) was observed for epithelial and endothelial permeability changes.[103] In a subsequent study,[104] the same authors instilled a ^{99m}Tc-labeled albumin solution in a distal airway to produce a zone of alveolar flooding. The instillation protocol produced a zone of alveolar flooding that stayed localized during conventional mechanical ventilation or spontaneous breathing. High-volume ventilation dispersed alveolar liquid in the lungs. This dispersion was prevented by PEEP even when VT was the same and thus the end-inspiratory pressure was higher. High-volume ventilation resulted in the leakage of instilled ^{99m}Tc-albumin from the lungs. This increase in alveolar albumin permeability was reduced by PEEP.[104] Finally, the effect of two routes of administration (intratracheal and intraperitoneal) of terbutaline on VILI was evaluated.[105] High-volume ventilation resulted in immediate leakage of ^{99m}Tc-albumin from alveolar spaces and increased pulmonary uptake of systemic ^{111}Intransferrin. Terbutaline in the instilled solution and PEEP lessened alveolar ^{99m}Tc-albumin leakage and pulmonary ^{111}In-transferrin uptake due to high-volume ventilation, whereas terbutaline given intra-peritoneally only lessened ^{111}In-transferrin uptake. Terbutaline in the instilled solution also lessened the increase in lung wet-to-dry weight ratio due to high-volume ventilation.[105] Taken together, these results indicate that simple noninvasive imaging techniques can be used to noninvasively study the changes in lung microvascular and alveolar permeability to proteins in vivo and the movement of fluids in the lungs during mechanical ventilation. Continuously and simultaneously monitoring such variables might be of great interest in experimental research on VILI because it allows the assessment of physiologic or pharmacologic interventions.

Conclusion and Clinical Applications

The experimental concept of VILI is undeniably relevant to clinical practice.[2] High-volume injury contributes to mortality of patients with ARDS and may be reduced by decreasing V_T and plateau pressure. On the other hand, the concept of low lung volume injury that should benefit from high levels of PEEP has not received the same convincing clinical confirmation, given the negative survival data from three randomized controlled trials comparing two levels of PEEP.[35-37] Thus the ideal ventilatory strategy has yet to be determined. For the time being and until further evidence is obtained, one may put forward the following conclusions:

- Drastic V_T reduction may not be justified for every patient with ARDS.
- Reasoned V_T reduction designed to avoid volutrauma may be guided by mechanical lung properties provided by respiratory system PV curves to avoid excessive or insufficient V_T reduction.
- Although use of PEEP remains the cornerstone of management of hypoxemia during ARDS, to date, generalized use of high levels of PEEP is not justified.
- Ventilatory management of ARDS is not yet deeply supported by evidence, but basic physiologic principles remain helpful to clinicians.[38,65,106,107]

References are available online at http://www.expertconsult.com.

III

Chapter 52

Acute Respiratory Distress Syndrome in Children

Stéphane Dauger, Philippe Durand, Etienne Javouey, and Jean-Christophe Mercier

PEARLS

- The incidence of acute lung injury and acute respiratory distress syndrome is quite low in children.
- Insults leading to acute lung injury and acute respiratory distress syndrome are similar to those observed in adults, that is, direct lung injury including pneumonia, gastric content aspiration, lung contusion, hydrocarbon ingestion, smoke inhalation, and sickle cell disease; or indirect injury including near-drowning, multiple emergent transfusions, and sepsis.
- Endothelial and epithelial injury is critical to diffuse alveolar damage and pulmonary edema.
- Acute lung injury resolution may be hastened by strategies that activate apical ENaC type channels and basal Na^+/K^+-ATPase channels, including β-adrenergic agents.
- Ventilator-induced lung injury is now known to play a major role in the outcome, Ventilator strategies using both limited tidal volume (V_T) less than 6 to 8 mL/kg and inspiratory plauteau pressure less than 25 to 30 cm H_2O with permissive hypercarbia, and sufficient levels of positive end-expiratory pressure to decrease inspired fraction of oxygen are widely used.
- No adjunct therapies including high-frequency oscillatory ventilation, prone positioning, surfactant replacement, and inhaled nitric oxide therapy have demonstrated significant benefits. Despite a lack of conclusive trials, extracorporeal life support is used in some centers as a last resort.
- Noninvasive ventilation may be valuable in the management of respiratory failure in immunocompromised children, given the high mortality observed when tracheal intubation and mechanical ventilation are required.
- Although no conclusive data have emerged from appropriately designed trials, there is some evidence to suggest that steroids used at the late fibrosing stage of acute respiratory distress syndrome may be of benefit.

The acute respiratory distress syndrome is a common and devastating clinical syndrome of acute lung injury that affects both medical and surgical patients. In 1967, Ashbaugh et al. described 12 adults with the acute onset of tachypnea and cyanosis refractory to oxygen therapy, diffuse infiltrates on the chest x-ray, and decreased lung compliance.[1] Initially called the "adult" respiratory distress syndrome, this entity has now been coined the "acute" respiratory distress syndrome (ARDS), since it does also occur in children[2-5] and in newborns.[6] However, ARDS is rare in children, and its incidence is estimated to be from 1% to 5% of the children hospitalized in the PICU.[7-10]

Because the initial definition lacked specific diagnostic criteria, there was controversy over the incidence and natural history of the syndrome. Some investigators attempted to exclude cardiogenic causes of pulmonary edema by requiring a "normal" pulmonary capillary wedge pressure, and specified values range from 12 mm Hg or less,[11] to less than 18 mm Hg.[12] In 1988, an expanded definition was proposed that quantified the respiratory impairment through a four-point lung-injury scoring system that was based on the degree of infiltration evident on the chest radiograph, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), the level of positive end-expiratory pressure (PEEP), and the decrease in the static lung compliance.[13] Mild-to-moderate acute lung injury (ALI) was defined by a lung injury score less than 2.5, and severe lung injury (ARDS) by a score higher than 2.5. Although the lung injury scoring system has been widely used to quantify the severity of lung injury in clinical trials, it cannot be used to predict the outcome during the first 24 to 72 hours after the onset of ARDS. In contrast, when used at 4 to 7 days after the onset of the syndrome, scores greater than 2.5 may be predictive of a complicated course and the need for prolonged mechanical ventilation.

Furthermore, the direct (e.g., aspiration, fat embolism, drug ingestion, toxic gas inhalation, infectious pneumonia) or indirect (e.g., sepsis, acute pancreatitis, multiple blood transfusions, disseminated intravascular coagulation) cause of the acute lung injury was thought to influence the outcome, as well as the presence or absence of nonpulmonary organ dysfunction. However, the former concept was later challenged.[14]

In 1994, the American-European Consensus Conference Committee proposed a new definition (Table 52-1).[15] The consensus definition had two advantages. Firstly, it recognized that the severity of clinical lung injury varies: patients with less severe hypoxemia (as defined by PaO_2/FiO_2 ratio ≥200 and ≤300) were considered to have ALI, and those with more

Table 52–1 The American-European Consensus Conference Definitions of ALI and ARDS

Criteria	Timing	PaO_2/FiO_2	Chest Radiograph	Pulmonary Wedge Pressure
ALI	Acute onset	≤300	Bilateral infiltrates	≤18 mm Hg or the absence of clinical evidence of left atrial hypertension
ARDS	Acute onset	≤200*	Bilateral infiltrates	≤18 mm Hg or the absence of clinical evidence of left atrial hypertension

Many authors now advocate reevaluating the PaO_2/FiO_2 ratio after 1 day of optimized care, after 30 minutes of FiO_2 = 1.0, and with PEEP = 5 cm H_2O.

severe hypoxemia (as defined by PaO_2/FiO_2 ratio <200) were considered to have ARDS. Earlier recognition of patients with ALI was supposed to facilitate earlier enrollment of patients in clinical trials. Secondly, the definition was simple to apply in the clinical setting, where measurement of static compliance had been largely abandoned. However, the new definition did not take into account other important factors that influence the outcome,[16] such as the optimization of ventilation including PEEP level,[17,18] a significant improvement in blood gas exchange within the first 24 hours,[19] the underlying cause, and whether other organ systems were affected.[20] Nevertheless, the widespread acceptance of both the 1988 lung injury scoring system and the 1994 consensus definition has improved the standardization of clinical research and trials.[21] Using the 1994 definition, the radiographic diagnosis of ARDS showed a large interobserver variability in adults[22] and in children.[23] Also, diffuse alveolar damage with the involvement of the four lung quadrants is seen in less than half of the patients, and is not well-correlated to defined histological changes.[24] Thus the evaluation of PaO_2/FiO_2 or SpO_2/FiO_2 ratios[25] on the second day of optimized care has been introduced in order to better identify different degrees of lung injury of divergent outcome.[26]

Pathogenesis

Endothelial and Epithelial Injury

The alveolar-capillary barrier is formed of two separate cellular linear barriers, the vascular endothelium and the alveolar epithelium.[27] The acute phase of ALI and ARDS is characterized by the influx of protein-rich edema fluid into the air spaces as a consequence of increased permeability of the alveolar-capillary barrier.[28] The importance of endothelial injury and increased vascular permeability to the formation of pulmonary edema that characterizes the early phase of ARDS has been well established.

The critical role of epithelial injury to both the development of and recovery from ARDS has been more recently recognized.[29] The loss of epithelial integrity has numerous consequences. First, the diffuse alveolar damage contributes to alveolar flooding. Second, epithelial injury disrupts normal epithelial fluid transport, and impedes the removal of edema fluid from the alveolar space. Alveolar fluid clearance has been found to be impaired in the majority of patients with ALI and ARDS.[30] Third, alveolar type II cell injury impedes surfactant production and turnover, contributing to the characteristic surfactant abnormalities.[31] Finally, the inflammatory cascade is activated with the release of numerous mediators. Activated macrophages secrete proinflammatory cytokines including tumor necrosis factor-α (TNF-α), and interleukins (IL-1, IL-6, IL-8) that act locally to stimulate chemotaxis and activate neutrophils.[32] Neutrophils adhere to the injured capillary endothelium and marginate through the interstitium into the airspace. Neutrophils can, in turn, release oxidants, proteases, leukotrienes, and many other proinflammatory molecules (Figure 52-1).[33]

Role of Cytokines

A complex network of cytokines and other proinflammatory compounds is thought to initiate and amplify the inflammatory response in ALI and ARDS.[34] The regulation of cytokine production may be influenced by extrapulmonary factors including microbial products, lipopolysaccharide endotoxins, and macrophage inhibitory factor, which has been found in high concentrations in the bronchoalveolar lavage fluid of patients with this syndrome.[35]

Not only the production of proinflammatory cytokines is important, but also the balance between the proinflammatory and antiinflammatory mediators.[36] Several endogenous inhibitors of proinflammatory cytokines have been described, including soluble tumor necrosis factor receptor, interleukin-1 receptor antagonist, and antiinflammatory cytokines such as interleukin-10 and -11. The critical role of cytokines in acute lung injury and ventilator-induced lung injury has been, however, recently challenged.[37]

Role of Ventilator-Induced Lung Injury

While high fractions of inspired oxygen have long been considered potentially toxic to the lung, experimental evidence has recently accumulated that high volumes and pressures can injure the lung, causing increased permeability edema in the uninjured lung,[38] and enhanced edema in the injured lung.[39] Initial theories focused on capillary stress failure due to alveolar distension.[40] More recently, alveolar distension associated with the repeated collapse and reopening of alveoli was shown to initiate a cascade of proinflammatory cytokines.[41] As most patients with acute lung injury who die do so from multisystem organ failure, it has been postulated that ventilator-induced lung injury plays a key role in determining the negative clinical outcome of patients exposed to mechanical ventilation.[42] The term *cellular biotrauma* has been coined to describe the process by which mechanical stress produced by mechanical ventilation leads to the upregulation of an inflammatory response.[43] Thus cells are required to sense mechanical forces and activate opposite intracellular signaling pathways: (1) able to release growth factors and surfactant when forces are physiologic (e.g., fetal or postnatal lung breathing), and (2) proinflammatory cytokines when forces are pathologic (e.g., barotrauma or volutrauma due to either excessive inspiratory positive pressures

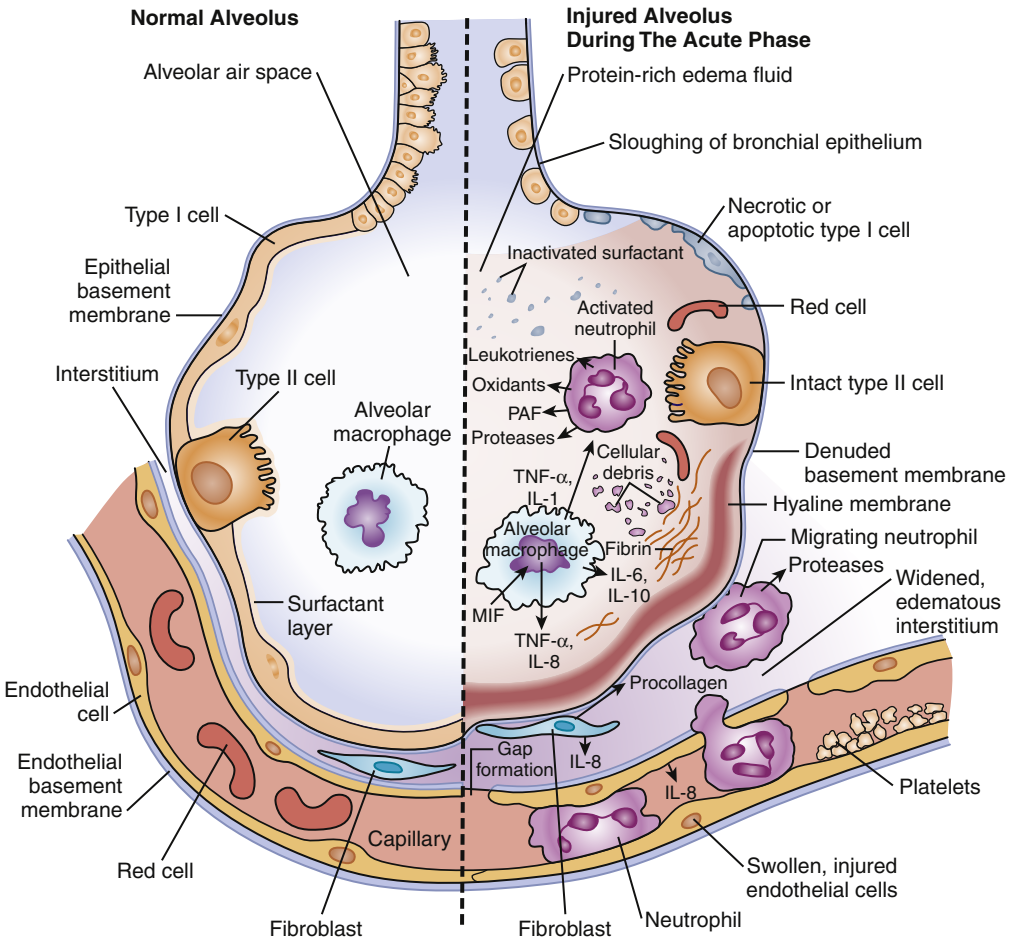

Figure 52–1. The normal alveolus (*left side*) and the injured alveolus in the acute phase of acute lung injury and the acute respiratory distress syndrome. In the acute phase of the syndrome (*right side*), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines, interleukin-1, 6, 8, and 10, (IL-1, 6, 8, and 10) and tumor necrosis factor a (*TNF-a*), which act locally to stimulate chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including interleukin-1, 6, and 10. Interleukin-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (*PAF*). A number of antiinflammatory mediators are also present in the alveolar milieu, including interleukin-1–receptor antagonist, soluble tumor necrosis factor receptor, autoantibodies against interleukin-8, and cytokines such as interleukin-10 and 11 (not shown). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant. *MIF,* Macrophage inhibitory factor. *(Modified from Ware LB, Matthay MA:* N Engl J Med *342:1334-1349, 2000, with permission of the publisher.)*

or tidal volumes).[44] Multiple other pathways can perpetuate or inhibit lung injury. Abnormalities of the coagulation system along with impaired fibrinolysis leads to alveolar fibrin formation,[45] and occlusion of small pulmonary vessels by platelet-fibrin thrombi contributes to pulmonary vascular remodeling and pulmonary hypertension.[46-48] Abnormalities in the production, composition, and function of the surfactant contribute also to alveolar collapse and gas exchange anomalies.[49]

Resolution of Lung Injury

Prognosis appears dependent on resolution of the pathologic processes. Alveolar edema is resolved by the active transport of sodium and perhaps chloride from the distal air spaces into the lung interstitium (Fig. 52-2).[50,51] Apical ENaC type channels and basal Na^+,K^+ ATPase channels appeared to be highly regulated by beta-adrenergic agents, whereas amiloride-sensitive sodium transport is modulated by basal nitric oxide.[52] Water follows passively through transcellular water channels, the aquaporins, located primarily on type I cells.[53] Lung fluid clearance is impaired in the majority of patients with ALI and ARDS, but maximal alveolar fluid clearance has been found to be associated with significantly lower mortality and a shorter duration of mechanical ventilation.[54] The removal of insoluble protein is also particularly important, since hyaline membranes provide a framework for the growth of fibrous tissue.[55] Insoluble protein appear to be removed by endocytosis and transcytosis, by alveolar epithelial cells, and by phagocytosis by macrophages.[56] Type II cells proliferate to cover the denuded basement membrane and then differentiate into type I cells, restoring the normal alveolar architecture and the fluid-transport function of the alveolar epithelium. This proliferation is controlled by epithelial growth factors, including keratinocyte and hepatocyte growth factors.[57] New blood vessels are formed mostly as a result of

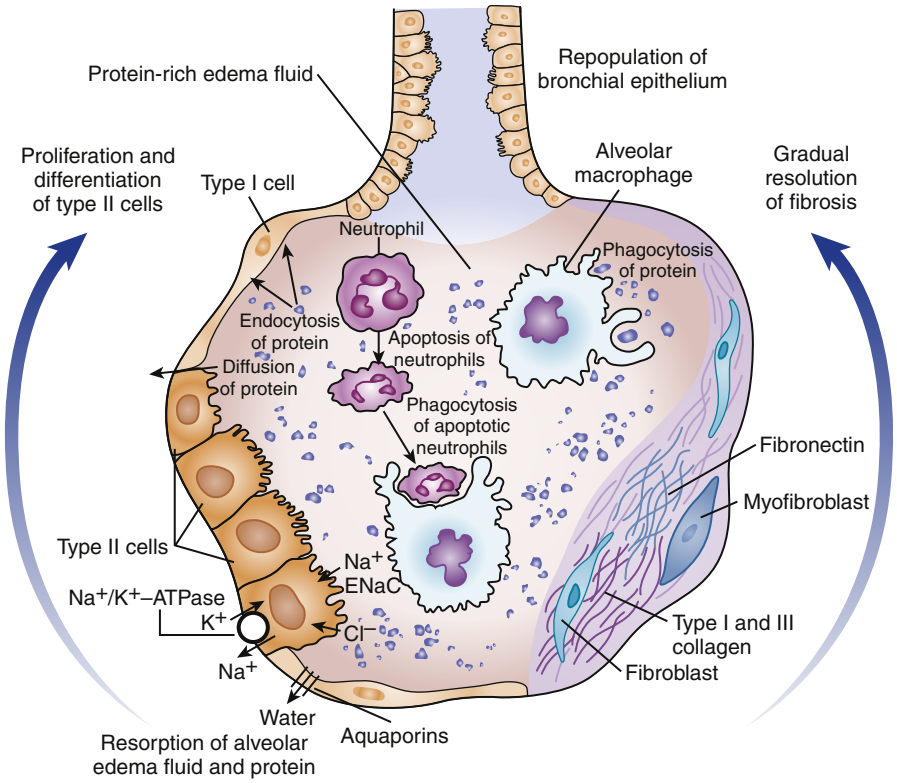

Figure 52–2. Mechanisms important in the resolution of acute lung injury and the acute respiratory distress syndrome. On the left side of the alveolus, the alveolar epithelium is being repopulated by the proliferation and differentiation of alveolar type II cells. Resorption of alveolar edema fluid is shown at the base of the alveolus, with sodium and chloride being transported through the apical membrane of type II cells. Sodium is taken up by the epithelial sodium channel (*ENaC*) and through the basolateral membrane of type II cells by the sodium pump (Na^+/K^+*-ATPase*). The relevant pathways for chloride transport are unclear. Water is shown moving through water channels, the aquaporins, located primarily on type I cells. Some water may also cross by a paracellular route. Soluble protein is probably cleared primarily by paracellular diffusion and secondarily by endocytosis by alveolar epithelial cells. Macrophages remove insoluble protein and apoptotic neutrophils by phagocytosis. On the right side of the alveolus, the gradual remodeling and resolution of intraalveolar and interstitial granulation tissue and fibrosis are shown. *(Modified from Ware LB, Matthay MA:* N Engl J Med *342:1334-1349, 2000, with permission of the publisher.)*

the vascular endothelium growth factor, and contribute to the normalization of the blood gas exchange.[58] Potential application of mesenchymal stem cells in acute lung injury has been explored in various in vivo models.[59]

Fibrosing Lung Injury

After the initial phase of acute lung injury and the acute respiratory distress syndrome, progression to fibrotic lung injury usually occur by 5 to 10 days after the onset of the disorder. The alveolar space becomes filled with fibroblasts and procollagen III peptide, of which the early appearance in the alveolar space has been associated with an increased risk of death.[60] The finding of marked fibrosing alveolitis on lung biopsy (or autopsy) correlates with an increased risk of death.[61] The mechanisms underlying the resolution of the inflammatory-cell infiltrates and fibrosis are unclear. Apoptosis is thought to play a major role for the clearance of neutrophils from the injured lung, as high concentrations of the markers of apoptosis have been shown in the bronchoalveolar lavage fluid taken from patients with the acute respiratory distress syndrome.[62,63] Antiinflammatory cytokines and proteases are also likely to play a major role. Mechanisms of repair and remodeling in acute lung injury have been recently reviewed.[64] It has become apparent that the process of fibrosing alveolitis begins early in the course of ARDS.[65] Determinants of persistent injury and abnormal repair and remodeling may be profoundly affected by both environmental and genetic factors. Recently, Chang et al.[66] performed proteomic and computational analyses on bronchoalveolar lavage fluid in patients with ARDS to identify proteins enriched and interactions that might be important for pathogenesis of lung injury, but no clear profile has emerged yet.

Clinical Features

Incidence and Etiology

The incidence of acute lung injury and acute respiratory distress syndrome is from 1% to 5% of pediatric intensive care admissions.[67-72] However, ARDS nowadays appears to be a relatively rare disease in children, perhaps because of more strict definitions or changing diagnostic criteria over the years. Within a 6-month period in nine large pediatric intensive care units across North America, 1096 (17.1%) of a total of 6403 admissions required mechanical ventilator support for a minimum of 24 hours. Of these, 701 (64%) met other criteria than primary respiratory failure for requiring mechanical support, including 13.5% upper airway obstruction, 11.5% cyanotic congenital heart disease, 9.7% life support restriction, and 5.5% chronically ventilated. In the 395 children who were eligible for respiratory failure studies, 62.4% had an acute primary diagnosis

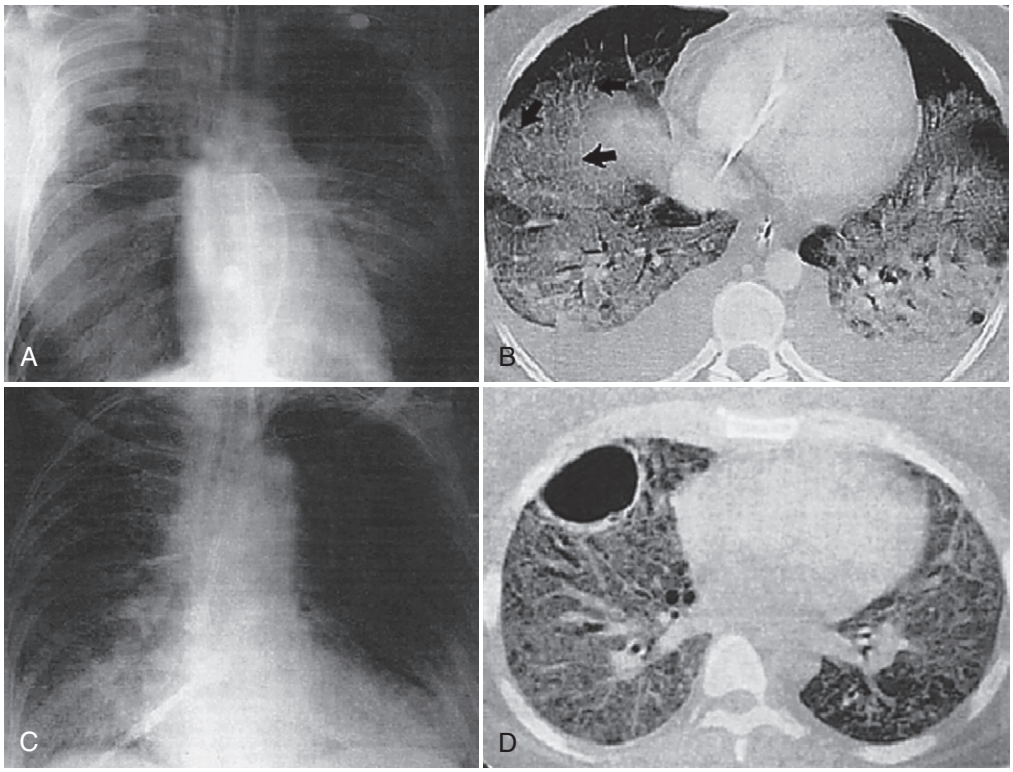

Figure 52–3. Radiograph and computed tomographic (CT) findings in the acute exudative phase (Panels **A** and **C**) and the fibrosing-alveolitis phase (Panels **B** and **D**) of acute lung injury and the acute respiratory distress syndrome. The *arrow* indicates thickened interlobular septa, consistent with pulmonary edema. *(From Goodman LR:* Radiol Clin North Am *34:33-46, 1996.)*

of pulmonary disease, 14.2% neurological disease, and 8.9% cardiac disease. Chronic underlying conditions were present in 43.2% of the patients. The most common acute diagnosis was bronchiolitis in infants (43.6%), and pneumonia in children 1 year old and older (24.5%). ARDS was identified in only 9 (5.7%) and 14 (9.7%) of the children with primary lung disease younger than 1 year and older than 1 year, respectively. Thus ARDS actually occurred in 23 children out of 6403 admissions, for a true incidence of 0.36%.[73,74]

Insults causing ALI or ARDS may either directly or indirectly injure the lung. Causes of direct lung injury include pneumonia, gastric contents aspiration, lung contusion, hydrocarbon ingestion, smoke inhalation, and sickle cell disease. Near-drowning, multiple emergent transfusions, and sepsis lead to ALI as part of multiorgan failure. Sepsis is the more common and lethal predisposing condition associated with ARDS, whether it is related to community-acquired infection (e.g., severe meningococcal shock), nosocomial infection (e.g., ventilator-associated pneumonia),[75] or serious underlying conditions (e.g., immunocompromised states).[76]

Clinical Course

The clinical course of ALI and ARDS parallels the histopathological abnormalities. Clinical changes that first occur are tachypnea, dyspnea, agitation, and hypoxemia. These findings usually develop rapidly during a period of hours, but can evolve over 1 to 5 days.[77] As the lung become edematous and consolidated, tachypnea and hypoxemia are caused by progressive restrictive lung disease and respiratory muscle fatigue. Chest radiographs show diffuse bilateral alveolar opacities, sometimes accompanied by small pleural effusion (Figure 52-3). However, CT scans reveal juxtaposition of abnormal dense lung regions and more functional lucent regions. Dense lung regions often develop in the dependent regions of the lung, reflecting collapse of the edematous lung with secondary atelectasis, whereas aerated regions usually prevail in nondependent areas.[78] Lung function measurements show a reduced functional residual capacity. Total lung compliance is reduced, but compliance of the small regions of functional lung is normal. Hypoxemia results from intrapulmonary shunting and the regions with low ventilation-perfusion relationships. These regions can be recruited in response to PEEP, thereby improving oxygenation.[79]

During the fibroproliferative phase, lung compliance is reduced by progressive lung fibrosis, and the effects of PEEP on oxygenation are less impressive. Lung parenchyma becomes better aerated despite accentuated interstitial markings indicative of fibrosis. At this stage, carbon dioxide retention is not uncommon. The requirement for mechanical ventilation may be prolonged for weeks, and clinical recovery usually requires a few months in children.[80] Although pediatric survivors of acute hypoxemic respiratory failure perceive no limitation in lifestyle, significant abnormalities in lung function, including bronchoreactivity, have been found.[81] Likewise, adult survivors of ARDS have persistent functional disability 1 year after discharge from the intensive care unit. Most patients have extrapulmonary conditions, with muscle wasting and weakness being most prominent.[82]

Oxygenation and Ventilator Strategy

Most patients with ALI and ARDS require supplemental oxygen and mechanical ventilation. These interventions can, however, themselves produce lung injury and worsen the acute respiratory distress syndrome.

Cellular toxicity of oxygen has been well established in both animals and human beings.[83] However, high levels of oxygen appear to be surprisingly well-tolerated in patients with acute respiratory failure, even for several days.[84] The reasons for this phenomenon are unclear. Antioxidant defense mechanisms have been found to be more efficient in primates than in rats.[85] Furthermore, prior lung exposure to endotoxin or cytokines (i.e., tolerance phenomenon) has been shown to protect animals exposed to 100% oxygen for several days, as compared to naive animals, who died rapidly.[86]

Ventilator-induced lung injury has recently been the subject of intensive experimental and human research (see Chapter 51). Traditionally, mechanical ventilation was delivered in an effort to normalize arterial blood gases. Tidal volumes of 10 to 15 mL/kg of body weight were used to normalize $PaCO_2$ values. After numerous experimental studies clearly demonstrated that excessive tidal volume traumatized lung structures, particularly when functioning lung volume is reduced to an aerated "baby lung" surrounded by extensive consolidated areas,[87] an international conference addressed factors likely responsible for ventilator-induced lung injury.[88] Several clinical trials evaluated lower ventilator settings as a means to minimize ventilator-induced lung injury and pulmonary fibrosis, even at the expense of normal blood-gas exchange, with little success apart from one preliminary study.[89-92] The culmination of this research, the ARDS Network trial, ultimately reported convincing improved clinical outcomes with a lung-protection ventilator strategy, compared with standard treatment for ARDS, in 861 adults.[93] The study group received 4 to 6 mL/kg of predicted body weight tidal volume and positive plateau pressure of less than 30 cm H_2O, compared with an 11 to 12 mL/kg tidal volume and positive plateau pressure of less than 50 cm H_2O in the control group. PEEP was adjusted to minimize FiO_2 but maintain oxygen saturation between 88% and 95%. $PaCO_2$ values were allowed to rise, but pH was maintained higher than 7.15. Adult patients receiving a lung protection strategy had a significantly reduced mortality rate (31% vs. 40%), fewer hospital days with extrapulmonary organ failure, and increased ventilator-free days (55% vs. 66%) over the first 28 hospital days compared with the control group). However, the marked improvement in the significant outcomes was later criticized when it appeared that the control group may have received higher than normal tidal volume on purpose.[94] Indeed, the lack of difference in significant outcomes observed in all previous trials but one may have been related to the relatively limited tidal volume (~10 mL/kg) used in the control group. A fierce debate ensued and was summarized in two successive commentaries.[95,96] Nevertheless, this paradigm is now also applied in children.[97]

PEEP maximizes alveolar recruitment, improves oxygenation insufficiency, and minimizes the need for oxygen supplementation, thereby minimizing iatrogenic oxygen toxicity. Early use of PEEP does not prevent the development or progression of ARDS.[98] In animal models of ALI, tidal volumes delivered without PEEP increase the shear stress between interfacing normal and injured regions, creating neutrophilic inflammation and cytokine release similar to ARDS.[99] However, PEEP can also overdistend the normal lung and compromise hemodynamic function (Figure 52-4).[100] Intensivists have therefore searched for the "best" PEEP, which maximizes lung compliance and oxygenation efficiency yet minimizes overdistension and reduced cardiac output.[101] For years, the issue of how to set up optimal PEEP remained controversial, when recently a new trial of the ARDS Network demonstrated that in patients with ALI and ARDS who received a tidal volume of 6 mL/kg of predicted body weight and an end-inspiratory plateau-pressure limit of 30 cm H_2O, clinical outcomes were similar whether lower (8.3 ± 3.2 cm H_2O) or higher (13.2 ± 3.5 cm H_2O) PEEP was used throughout days 1 to 4.[102] Two other trials of higher PEEP in adult patients receiving lung-protective ventilation failed to demonstrate a mortality difference but were safe and showed benefits that advocates will find reassuring.[103,104] Practical guidelines for ventilator settings in ALI or ARDS are provided in Table 52-2.[105]

Prone positioning is another way to recruit atelectatic dependent zones of the lung. Several mechanisms have been proposed to account for this effect, including an increase in end-expiratory lung volume, better ventilation/perfusion matching, and regional changes in ventilation associated with alterations in chest wall mechanics.[106] Prone positioning was shown to improve overall oxygenation in most patients including children with acute respiratory failure.[107,108] However, although it improved oxygenation, prone positioning did not improve survival in a multicenter randomized trial, in either adult or pediatric patients with ALI or ARDS.[109,110] Since then, three meta-analyses reached remarkably similar conclusions: that there was neither an observed effect on mortality nor on duration of mechanical ventilation.[111-113]

Permissive Hypercapnia

Permissive hypercapnia is a well accepted consequence of lung protection strategies of ventilator support. Goals of management are to allow gradual increase in $PaCO_2$, that is, no more than 5 mm Hg increase per hour, and to avoid acute severe acidosis.[114] $PaCO_2$ values of 65 to 85 mm Hg are well tolerated in most patients, although additional sedation may be necessary to reduce air hunger and dyspnea. Permissive hypercapnia is contraindicated in children with suspected increased intracranial pressure and in those with sickle cell disease.

High-frequency oscillatory ventilation (HFOV) reflects the extreme form of reduced tidal volume delivery, providing 1 to 2 mL/kg inspiratory volumes at frequencies of 5 to 15 Hz. Amplitudes of oscillation are set to minimize hypercapnia (HFOV is often very efficient in normalizing hypercapnia), whereas mean airway pressure is set to maximize lung inflation and oxygen efficiency. In a prospective, randomized, crossover study involving 70 children with diffuse alveolar disease and/or airleak syndrome, children receiving HFOV alone had better survival (94% vs. 60%), fewer days with supplemental oxygen, and chronic lung disease less often (11% vs. 30%) compared with the control group.[115] Fifty-eight percent of children who did not respond to conventional ventilation crossed over to HFOV and survived, whereas 18% of those crossing over to conventional ventilation because of persistent respiratory failure survived. Parallel to the emerging consensus that ventilator-induced lung injury was preventable, the

use of high-frequency oscillatory ventilators has significantly increased in severe pediatric respiratory failure. Recently, a multicenter randomized trial compared HFOV to conventional ventilation in 148 adults with ARDS. Although an early but not sustained improvement in PaO_2/FiO_2 ratio was observed in the HFOV group, no other significant differences were seen in oxygenation failure, ventilation failure, barotraumatism, and survival at day 30.[116]

Adjunct Therapies

Adjunct therapies aim at improving lung function and minimizing the risks of ventilator support.

Surfactant replacement therapy aims to reinflate a collapsed area of the lung, improve compliance, and reduce intrapulmonary shunting, thereby leading to reductions in morbidity and mortality. Surfactant not only is decreased in quantity but also is functionally abnormal in patients with ARDS.[117] Thus, on the basis of the similarities with neonatal respiratory distress syndrome, several anecdotal case reports, and then phase II trials, were encouraging. However, a multicenter randomized trial of 725 adult patients with sepsis-induced ARDS who received continuous aerosolization of a synthetic surfactant (Exosurf, GlaxoSmithKline, London, UK) for up to 5 days showed no significant effect on 30-day survival, length of stay in the intensive care unit, duration of mechanical ventilation, or physiologic function.[118] The lack of effect was attributed perhaps to the low level alveolar deposition and an absence of surfactant protein. Natural surfactant was therefore tested in a limited number of children with severe ARDS, and led to sustained improvement in the oxygenation in the subgroup of children without pneumonia and with PaO_2/FiO_2 ratio higher than 65.[119] Recently, in two international combined randomized double-blind trials involving 448 adult patients with ARDS from various causes, up to four intratracheal doses of a recombinant surfactant protein C–based surfactant given within a period of 24 hours failed to improve survival.[120] However, patients who received surfactant had a greater improvement in gas exchange during the 24-hour treatment period than patients who received standard therapy alone, suggesting the potential benefit of a longer treatment course.

Fluid management and hemodynamic support[121] are critical in the management of ALI and ARDS both of which are associated with sepsis.[122] Assessment of vascular volume status is not easy,[123] and its management is particularly difficult when large amounts of fluid must be administered to treat septic shock at the same time that capillary leak promotes accumulation of extravascular lung water. Although there was no effect on 28-day mortality, a low-fluid regimen significantly decreased the overall duration of mechanical ventilation in adult patients.[124] Fluid-refractory shock clearly affects the outcome of ARDS, since the need for vasopressors was found to be associated with increased mortality in adult patients with ARDS.[125,126] Both pulmonary hypertension associated with ARDS, and excessive airway pressures may significantly increase right ventricular afterload.[127] Despite their inherent shortcomings, transthoracic or transesophageal echocardiography are probably the most useful techniques to assess cardiac function in patients mechanically ventilated for ARDS.[128] Right ventricular dysfunction may be improved by cautiously decreasing PEEP, or limiting inadvertent PEEP by reducing the respiratory rate and adjusting the inspiratory: expiratory ratio. Persistent cor pulmonale should lead one to consider the use of specific pulmonary vasodilators such as inhaled nitric oxide and/or systemic vasopressors such as norepinephrine, since right ventricular function critically depends on right coronary perfusion pressure.[129]

Inhaled nitric oxide (INO) at 1 to 20 ppm relaxes pulmonary vascular smooth muscle. INO clinically reduces elevated pulmonary artery pressures and improves arterial oxygenation by increasing the blood flow to the lung regions that remained functional, thereby improving matching of perfusion to ventilation.[130,131] Effective doses in adults with ARDS varied from a few ppm to efficiently reduce pulmonary hypertension to a few ppb to significantly improve oxygenation.[132] Responsiveness to such low doses of NO suggests that tracheal intubation inadvertently creates an NO deficiency state by preventing autoinhalation of NO from the upper respiratory airways.[133] However, efficient doses appeared to be higher (5 to 20 ppm) in children and neonates.[134] Although INO may also benefit alveolar neutrophil function and cytokine release,[135] several clinical trials enrolling adults with ARDS from various causes were unable to demonstrate any significant improvement in survival.[136-140] Likewise, in children with severe hypoxemic respiratory failure, although INO at 20 ppm acutely improved oxygenation and lowered mean pulmonary artery pressure,[141] there was no clear effect on survival.[142] As 35% of children who initially did not respond to INO did so after lung volumes were increased by HFOV, combined use of HFOV and INO may provide more predictable improvement in children with ARDS.[143]

Extracorporeal life support (ECLS) provides both gas exchange and circulatory support for patients with life-threatening ALI and ARDS, and allows the lung to rest from mechanical ventilation. ECLS can be provided by venoarterial or venovenous bypass techniques, using artificial membranes or hollow fibers to provide oxygen and remove carbon dioxide and intravascular fluid. In a retrospective case-cohort study of 331 children with respiratory failure, 53 children who received ECLS were compared to 53 diagnosis- and risk-matched children who did not receive ECLS. The ECLS patients had a 26% mortality rate, whereas those who were treated in a standard fashion had a mortality rate of 49%.[144] In 84 adults with ARDS, ECLS was used in an algorithm of care when patients worsened despite a ventilator-protective strategy, prone positioning, and INO therapy.[145] Eighty-five percent of patients did not require ECLS with 83% survival. Of the 13 patients who had ECLS, 62% survived. Overall survival was 80%, suggesting that a combination of treatments can improve ARDS-related survival.

Ventilator-acquired pneumonia is the most common late complication of ALI and ARDS. Prolonged intubation, frequent suctioning, and suboptimal nutritional status all contribute to ventilator-associated pneumonia.[146] This infection is frequently polymicrobial, and commonly includes *Streptococcus pneumoniae*, *Staphylococcus* spp., and *Pseudomonas aeruginosa* or other multiresistant gram-negative rods that are frequently encountered in ICUs not having a restrictive antibiotic policy. Diagnosis of ventilator-acquired pneumonia is difficult, and is often based on fever, purulent aspect of the sputum, new infiltrates, and blood gas exchange worsening. Identification of the responsible germs usually requires the use of protected brush or bronchoalveolar lavage under fibroscopic guidance,[147] but these procedures are not easy in small

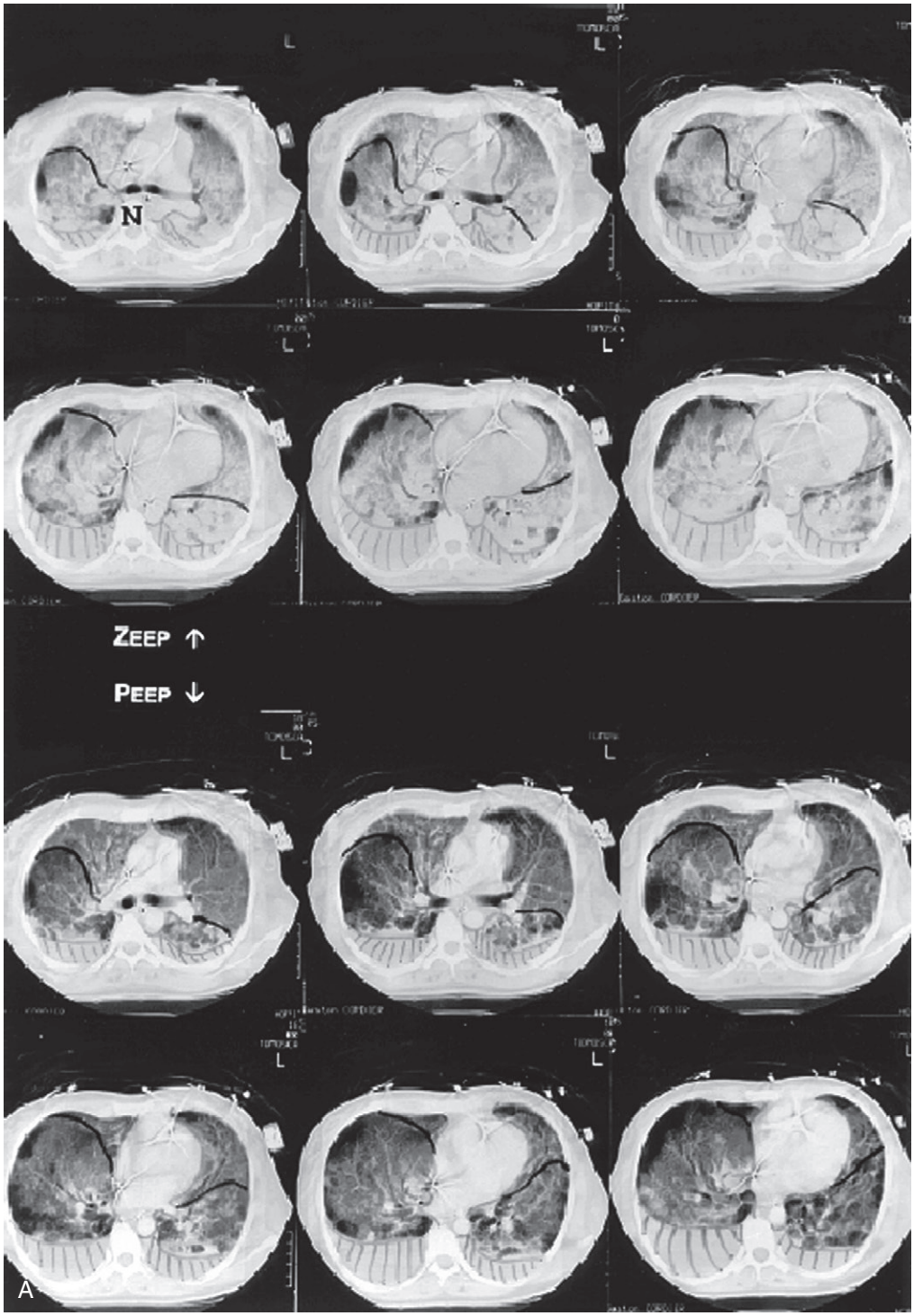

Figure 52–4. Divergent effects of positive end-expiratory pressure (*PEEP; lower panels*) as compared to zero end-expiratory pressure (*ZEEP; upper panels*) on regional lung recruitment assessed by computed tomography. **A,** In the acute diffuse form of acute respiratory distress syndrome (*left panels*), and **B**, the 'lobar' form (*right panels*), PEEP induced a marked lung recruitment of the edematous zones, but a marked overdistension of aerated zones in pneumonia (the *black line* shows the scissura and the *hatched area* the pleural effusion). *(From Puybasset L, et al:* Am J Respir Crit Care Med *159:1644-1655, 1998.)*

children. Recently, 8 and 15 days of appropriate antibiotic therapy have been found equally effective treatment of ventilator-associated pneumonia.[148] Mortality from nosocomial pneumonia in these patients is reported to be as high as 80%.

Corticosteroids are extensively used in acute respiratory failure,[149] including the most serious forms of ALI or acute respiratory distress syndrome.[150] In a first study, Meduri et al. treated 9 adult patients with ARDS of 7 days duration with 2 mg/kg methylprednisolone four times daily, then with stepwise decreased doses; eight patients improved after the fifth day of treatment, and six survived.[151] In a second study, the authors have treated 25 new patients similar to the eight

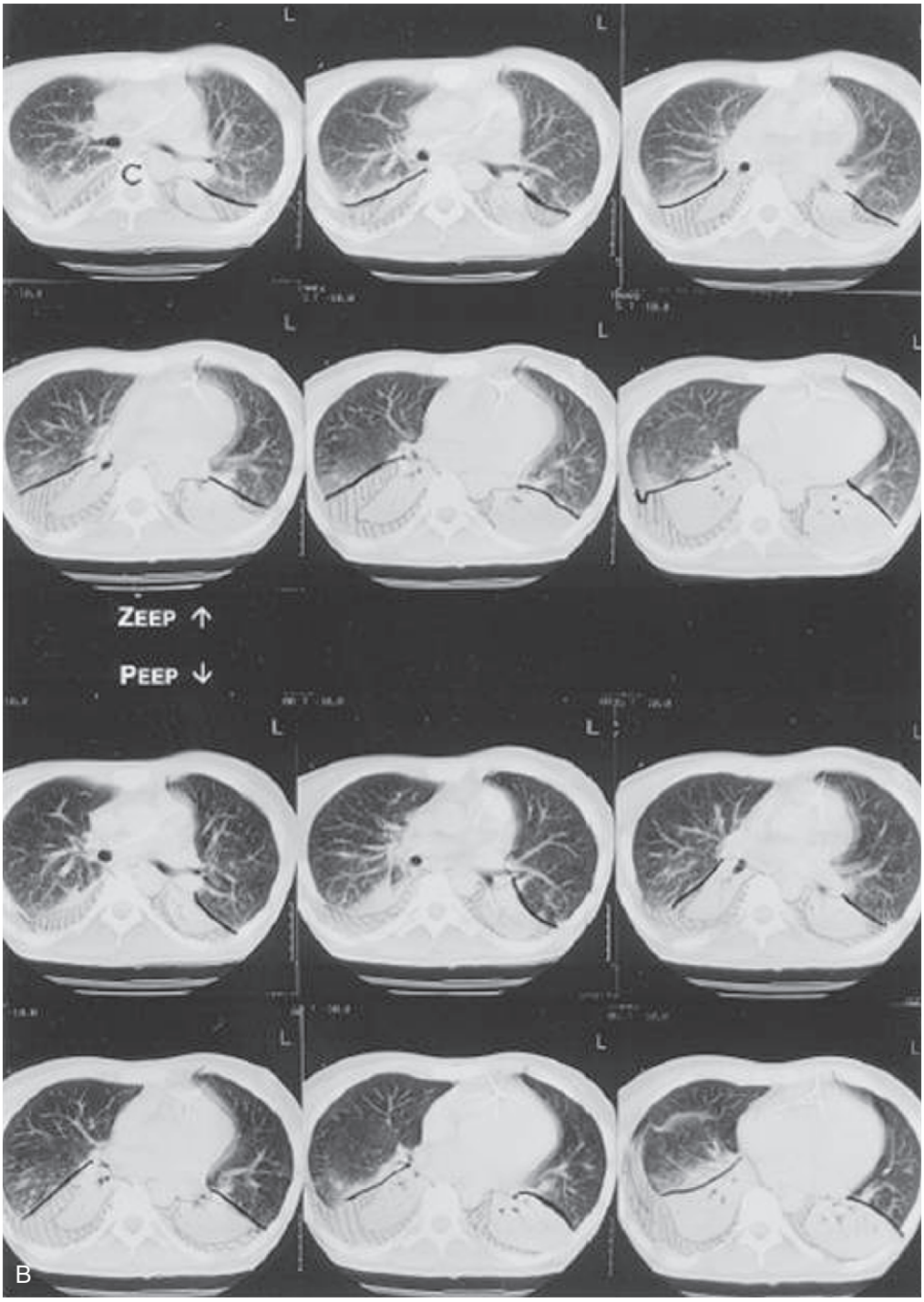

Figure 52–4.—cont'd

previous ones.[152] Steroids were initiated on the fifteenth day of mechanical ventilation at 2 mg/kg four times per day, with slow weaning over 6 weeks. After 1 week, blood gas exchange improved and survival was 76%. Interestingly, survival was 86% in the 21 responders compared with 25% in the four nonresponders. Then, in a small randomized trial of adult patients with severe ARDS who did not improve after the seventh day of mechanical ventilation, improvement in lung injury and multiple organ dysfunction scores as well as reduced mortality were observed after prolonged methylprednisolone treatment.[153] The efficacy and safety of corticosteroid therapy at the fibrosing stage of ARDS was proven in a large randomized trial by the ARDS network.[154]

Noninvasive Ventilation

The pulmonary complications of solid organ and hematopoietic stem cell transplantation have been recently reviewed.[155] Paramount among these are pulmonary complications, which arise as a consequence of the immunosuppressed status of

Table 52–2 Recommendations for Ventilator Settings in ARDS

CONVENTIONAL MECHANICAL VENTILATION		
Mode		Volume- or pressure-controlled "Airway pressure release ventilation" preferred when preservation of spontaneous ventilation is desired
Tidal volume	6–10 mL/kg	Permissive hypercapnia (increase <5 mm Hg/h) $PaCO_2$ 65–85 mm Hg well tolerated unless increased ICP Arterial pH >7.15
End-inspiratory plateau pressure	<30 cm H_2O	Above this limit, increased risks of barotrauma and air leaks
Positive end-expiratory pressure	10–15 cm H_2O	Lower PEEP levels, if heterogeneous lung injury Higher PEEP levels, if diffuse lung injury Consider early prone positioning (6–12 h)
Respiratory rate	20-60 bpm	Adjusted to age; higher than normal may limit hypercapnia
Inspiratory/expiratory ratio	1:2 to 1:1	Check for inadvertent PEEP
FiO_2	<60%–80%	Depends on how the diseased lung may be recruited PaO_2 40–60 mm Hg, SpO_2 85%–95%
HIGH-FREQUENCY OSCILLATORY VENTILATION		
Amplitude pressure	30–50 cm H_2O	To achieve visible chest vibrations
Mean airway pressure	15–30 cm H_2O	To achieve adequate chest recruitment (7 to 9 ribs)
Respiratory rate	3–10 Hz	Decrease to increase tidal volume (usually not measured)
Inspiratory/expiratory ratio	1:3 to 1:1	1:1 more appropriate in diffuse lung injury
FiO_2	<60%–80%	Depends on whether the lung may be recruited

ICP, Intracranial pressure.

the recipient as well as from such factors as the initial surgical insult of organ transplantation, the chemotherapy and radiation conditioning regimens that precede hematopoietic stem cell transplantation, and alloimmune mechanisms mediating host-versus-graft and graft-versus-host responses. Worsening of the respiratory status by a bacterial or viral process is often indistinguishable from ALI or ARDS. Thus, sepsis work-up should encompass blood cultures, tracheal fluid aspirates at intubation, bronchoalveolar lavage, viral tests by immunofluorescence or PCR in the blood, the urine, the stools, the tracheal aspirates, or bronchoalveolar fluid. *Pneumocystis* pneumonia is frequently seen in this context, and it is important to rapidly isolate the organism, usually by bronchoalveolar lavage, since the association of prolonged trimethoprim-sulfamethoxazole and short-term steroids is regularly efficacious.[156] Otherwise, the prognosis of the immunocompromised patients with ALI or ARDS severe enough to require tracheal intubation and mechanical ventilation is poor in all the series.

Avoiding intubation and mechanical ventilation is therefore a major goal in the management of respiratory failure in immunocompromised patients. A prospective, randomized trial of intermittent noninvasive ventilation, as compared with standard treatment with supplemental oxygen and no ventilatory support was conducted in 52 immunocompromised adult patients with pulmonary infiltrates, fever, and an early stage of hypoxemic respiratory failure.[157] Periods of noninvasive ventilation set in the pressure support mode delivering 7 to 10 mL/kg tidal volume at a respiratory rate of fewer than 25 breaths/min and PEEP stepwise increased by 2 cm H_2O up to a level of 10 cm H_2O through a face mask lasted at least 45 minutes and alternated every 3 hours with periods of spontaneous breathing. Each group of 26 adult patients included 15 patients with hematologic cancer and neutropenia. Fewer patients in the noninvasive ventilation group than in the standard-treatment group required tracheal intubation (12 vs. 20, $P = .03$), died in the intensive care unit (10 vs. 18, $P = .03$), or died in the hospital (13 vs. 21, $P = .02$).

In immunocompetent patients, after initially rather negative results,[158] there has been a renewal of interest in noninvasive ventilation in the early stages of ALI and ARDS. In a small randomized trial, 20 (62%) of 32 patients in the noninvasive-ventilation group and 15 (47%) of 32 in the conventional-ventilation group had an improved PaO_2/FiO_2 ratio within the first hour of ventilation.[159] Ten patients in the noninvasive-ventilation group subsequently required tracheal intubation. Twenty-three patients in the noninvasive-ventilation group (72%) and 17 in the conventional-ventilation group (53%) survived their stay in the intensive care unit (odds ratio, 0.4; 95% confidence interval, 0.1 to 1.4; $P = .19$), and 22 and 16 were discharged from the hospital, respectively. In a larger trial, 105 patients with severe acute hypoxemic respiratory failure were allocated to noninvasive ventilation (n = 51) or high-concentration oxygen therapy (n = 54).[160] Compared with oxygen therapy, noninvasive ventilation decreased the need for intubation (25% vs. 39%; $P = .028$), and increased the cumulative 90-day survival ($P = .025$). Multivariate analysis showed that noninvasive ventilation was independently associated with decreased risks of intubation, reduced risks of septic shock, and improved 90-day survival. Likewise, the same beneficial effect of noninvasive ventilation was confirmed in another trial not yet fully published.[161] However, in a recent preliminary study in 93 children with diverse causes of acute respiratory failure treated either initially or during weaning, the use of noninvasive positive pressure ventilation appeared

to reduce the rate of endotracheal intubation, except in the nine children with ARDS.[162] Moreover, several adult intensivists, experts in that field, recently cautioned that noninvasive positive pressure ventilation might actually delay the timing of endotracheal intubation which may become more hazardous in a hypoxic patient.

The success of noninvasive ventilation, however, critically depends upon several factors, including the choice of face masks,[163] the replacement of the filter-humidifier by a heated humidifier,[164] the removal of any device adding any extra dead space, and the use of a ventilator having a sensitive inspiratory trigger and a built-in algorithm to correct for leaks.[165] The most frequently used ventilatory mode is pressure support ventilation in combination with the necessary level of PEEP to recruit the lung, but the "airway pressure release ventilation" mode is increasingly used.

Conclusion

Substantial progress has been made in the understanding of ALI and ARDS. Significant actions have been made in recent years to reduce the aggressiveness of mechanical ventilation: reduction of tidal volume to a safer margin of 6 to 10 mL/kg, maintenance of a end-inspiratory plateau pressure less than 30 cm H_2O, acceptance of permissive hypercapnia, and use of a reasonable level of PEEP that allows a decrease in FiO_2 to safe margins. When respiratory failure worsens despite these measures, prone positioning and HFOV to optimize lung recruitment, INO therapy to reduce pulmonary hypertension and prevent cor pulmonale, and ECLS may all be helpful to buy time for the underlying pathology to recover. Mortality remains high, particularly when there is associated sepsis and evolving multiple organ dysfunction.[166] Further research is, therefore, needed to better understand the genetic polymorphisms that favor the occurrence of ALI and ARDS, and the mechanisms of alveolar fluid clearance and lung healing that may hasten recovery from ALI.

References are available online at http://www.expertconsult.com.

Extracorporeal Life Support

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PEARLS

- Venoarterial access for extracorporeal membrane oxygenation (ECMO) has been the most common cannulation technique because it provides both respiratory and cardiac support.
- Venovenous cannulation for ECMO is currently preferred for patients with adequate cardiac function.
- In venoarterial ECMO, desaturated venous blood is drained from the body and reinfused into a large artery after being oxygenated in the ECMO circuit.
- Venovenous ECMO differs from venoarterial ECMO in that blood is both withdrawn and returned into the venous circulation of the patient.
- The use of ECMO in patients with neonatal respiratory failure has decreased as new methods of support, such as inhaled nitric oxide, surfactant, and high-frequency oscillation, have been developed.
- As experience with ECMO support in older patients has grown, expansion to clinical situations such as cancer, sepsis, burns, and trauma has occurred.
- The largest area of growth of extracorporeal support is in patients with cardiogenic shock or following repair of congenital heart defects.
- One quickly expanding area of extracorporeal support is as a means of resuscitation in cardiac arrest. One third of the patient survived extracorporeal cardiopulmonary resuscitation, with two thirds of the survivors having good neurologic outcomes.
- Improvements in extracorporeal pumps, cannula, circuitry, and oxygenators are making ECMO safer and easier to use.
- A recent study of a trial of ECMO in adults with respiratory failure noted 63% survival in the ECMO group versus 43% in the conventional ventilation group at 6 months.

Aided by the discovery of heparin in 1916[1] and by advances in the technology of membrane oxygenators, extracorporeal life support has changed dramatically since the early 1950s, when John Gibbon first used a machine of his own design to provide extracorporeal life support for a cat whose pulmonary artery was occluded with a clamp.[2] Early experiences with the use of cardiopulmonary bypass for operations on the heart were mixed, but as experience and technology have continued to advance, the field of cardiopulmonary bypass has expanded at a rapid rate.[3-5] Today the dreams of clinicians like Gibbon have been realized, and extracorporeal support for the heart and lungs is used daily throughout the world. Nowhere is the impact of cardiopulmonary bypass seen more clearly than in pediatrics, where increasingly intricate intracardiac repairs of once-lethal congenital heart defects are performed every day with the aid of cardiopulmonary bypass.

As experience with bypass techniques in the operating suite grew, investigation of the use of extracorporeal support of patients with cardiopulmonary failure outside the operating room began.[6,7] Infants with severe respiratory disease or pulmonary hypertension were among the groups for whom use of a temporary cardiopulmonary bypass system seemed appropriate. This technique of modified cardiopulmonary bypass came to be known as "extracorporeal membrane oxygenation" (ECMO).[8] Although premature infants had an unacceptably high incidence of intracranial hemorrhage as a result of the systemic heparinization, infants of more than 35 weeks' gestation with respiratory failure were successfully supported with ECMO.[9,10] An abandoned infant with severe hypoxemia named "Esperanza" (hope) by her caregivers was among the first to be treated with ECMO by Bartlett in 1976.[10a] Today, Esperanza is a grown woman with children of her own. Efforts to organize and collate data on patients treated with ECMO resulted in the formation of the Extracorporeal Life Support Organization (ELSO). In 2009, ELSO celebrated its 20th anniversary. This largely volunteer network of physicians, surgeons, nurses, respiratory therapists, and all those with an interest in extracorporeal life support comprises more than 100 centers and contains data on more than 40,000 patients treated with extracorporeal life support throughout the world.[11]

As more patients have been treated and techniques have been refined, ECMO procedures and management of patients have evolved to the point that ECMO now can be offered to patient groups previously excluded from consideration.[12-14] Despite multiple attempts to define specific selection criteria for ECMO candidates, no well-defined and universally applied criteria exist. The decision regarding when a patient should be treated with ECMO remains empirical and based on experience. Similarly, although there is little complete standardization of ECMO circuit design, cannulation technique, and patient management, the general principles are fairly constant. Guidelines for ECMO center training, equipment selection, and patient selection and management recently have been developed by expert consensus and are posted on the ELSO Web site. Although the guidelines are fairly general, it is hoped that they will enable more standardization of practice

in the future. The information in this chapter represents general practice, the authors' experience, and a review of the literature. For more detailed information regarding extracorporeal life support, the reader is directed to the excellent text regarding this subject published by the ELSO organization.[10a]

Materials and Methods

Cannulation Techniques

Several modes of ECMO, or extracorporeal life support (ECLS), as it is also known, have been developed that differ according to cannulation site and minor physiologic principles. However, the basic circuit is similar for all modes. Cannulation is achieved either by the venoarterial or venovenous mode. Venoarterial access has been used most commonly and will be discussed first.

Venoarterial Extracorporeal Membrane Oxygenation

Venous Access. In venoarterial ECMO, desaturated systemic venous blood is drained from the body and reinfused into a large artery after being oxygenated in the ECMO circuit (Figure 53-1). The right atrium is the usual site accessed for ECMO cannulation. The internal jugular (IJ) vein is a large vessel with a fairly short, straight course to the right atrium and thus is preferred during cervical cannulation. To augment cerebral venous drainage in patients who undergo cannulation via the right IJ vein, some centers also place a smaller cannula retrograde in the vessel to the level of the jugular venous bulb at the base of the skull. This catheter can facilitate cerebral venous drainage and provide a means of monitoring jugular venous oxygen saturation. Some clinicians believe that monitoring jugular venous saturation provides information on adequacy of oxygen delivery to the brain and that it is valuable during ECMO, although this practice is relatively controversial. Reports of an increase in venous drainage via the retrograde cannula of up to one third have been noted in some centers.[15] The retrograde catheter is connected by a Y-adapter into the larger venous drainage line.[16,17]

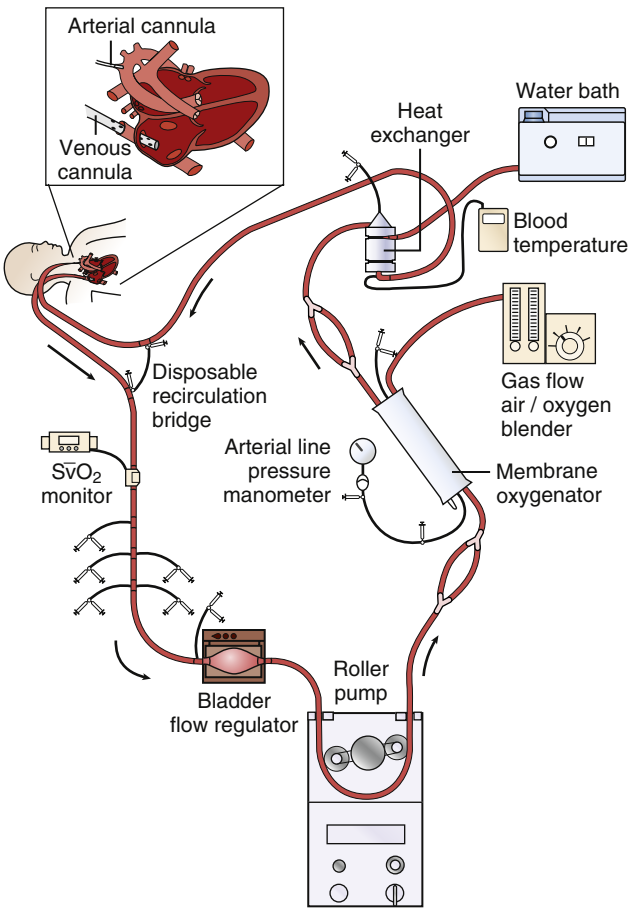

Figure 53–1. Venoarterial extracorporeal life support via cervical cannulation. Svo_2, Venous oxygen saturation. *(M. Dowhy, with permission. Courtesy Children's Hospital, Pittsburgh, Pa.)*

In older children and adults, the femoral vessels can be used for cannulation.[18] Venous access is obtained from the saphenous or femoral vein into the inferior vena cava (IVC), or the cannula can be advanced further up the IVC to the right atrial/IVC junction. Although femoral vein cannulation diverts less venous return to the pump than a catheter positioned in the right atrium, the amount of blood drained is often adequate to meet the needs of the patient. Femoral cannulation is generally restricted by age and size to adolescents or adults. Some surgeons suggest that if the child is old enough to walk and run, the femoral vessels are of adequate size to consider femoral cannulation. One author (H.J.D.) has successfully used femoral vessels in a 13-kg 6-year-old child without difficulty. For patients with femoral venous access who exhibit venous stasis or obstruction of the extremity distal to the cannula, a similar catheter to that used for jugular venous drainage can be placed down the leg via the saphenous or femoral vein to augment decompression of the leg and augment venous return. This catheter is then connected by a Y adapter into the venous drainage line of the ECLS circuit. Compartment syndrome from venous stasis in femoral venous cannulation has been described, and thus careful monitoring of the extremity is mandatory.[19]

In patients who undergo cannulation via the mediastinum, the venous cannula is often placed directly into the right atrial appendage.[20] Although other vessels, such as the subclavian vein or left IJ vein, have been used for ECLS, they have been associated with limb perfusion abnormalities or difficulties with adequate blood flow.

Arterial Access. Arterial access is obtained for cervical venoarterial ECMO by cannulating the right carotid artery and advancing the cannula to the arch of the aorta. Care must be taken not to direct the end of the cannula toward the aortic valve, because this position may result in aortic insufficiency induced by the high-velocity blood flow returning from the ECMO circuit and being directed toward the aortic valve leaflets. Alternatively, if the arterial cannula is advanced too far down the aortic arch, it can occlude blood flow to the left carotid artery and the brain. Concern over use of the carotid artery for cervical ECMO cannulation and the potential for neurologic abnormalities or stroke later in life is a predominant reason why cervical venoarterial ECMO may be less desirable than venovenous support.

The femoral artery also can be used for access during venoarterial ECMO. If a long femoral artery cannula that reaches the thorax is used, good oxygenation to the upper body is assured, but resistance to flow will be elevated.[21] If a short femoral

artery cannula is used, it normally sits in the iliac vessels. The amount of arterial return reaching the upper body, heart, and brain in this mode of ECMO is dependent on antegrade flow out of the native left heart and the retrograde flow from the ECMO arterial return. In patients with severe cardiac dysfunction, arterial return from the ECMO circuit flows further up the aorta and may predominate. In patients with good cardiac function, the majority of upper body arterial flow may be from native left heart ejection. Arterial flow from low-lying ECMO cannulas with good native heart function may thus preferentially flow to the lower body. This arterial flow will mix with venous return from the lower body before the oxygenated blood flows through the cardiopulmonary circuit and out the aorta. In patients with impaired gas exchange, the amount of venous mixing prior to reaching the ascending aorta reduces the amount of oxygen that is delivered to the upper body (heart and brain). Thus the PaO_2 and arterial oxygen saturations in the upper body may be lower than that obtained with cervical venoarterial ECMO. Concern over limited oxygen delivery to the brain has resulted in slow acceptance of venoarterial ECMO with a low-lying femoral arterial cannula. Successful use of ECMO has been achieved, however, with this mode. Monitoring obtained oxygenation with a pulse oximeter on the right hand, ear, or nose of the patient is a good safety precaution to assess the amount of oxygenated flow getting to the head during this mode of ECMO. Echocardiography often can determine the extent of retrograde aortic flow versus native heart ejection. Femoral arterial cannulation also can be associated with impaired flow to the distal limb and resultant ischemia. A small "feeder" cannula can be directed distally down the leg artery and then connected by a Y adapter into the arterial cannula to improve perfusion. Additionally, placement of a 14-gauge catheter into the posterior tibial artery that is then connected by a Y adapter into the arterial side of the ECMO circuit also can provide distal limb perfusion. Ischemia and the need for amputation with femoral artery cannulation has been reported, and thus meticulous attention to limb perfusion is required to prevent this complication.

In mediastinal cannulation, the arterial return cannula is usually placed into the aortic arch under direct vision.[22] During mediastinal cannulation, patients with severe left ventricular dysfunction who cannot open the aortic valve to eject blood often have a left atrial venting catheter inserted to allow decompression of the left heart. This technique prevents pulmonary venous hypertension, which can lead to severe pulmonary edema or hemorrhage. This catheter can be connected by a Y adapter into the venous drainage of the ECLS circuit to provide adequate left heart decompression. Patients with intact sternums who require left atrial decompression often are taken to the cardiac catheterization suite for a blade atrial septostomy that then allows the left heart to decompress into the right atrium and the blood to be drained into the venous ECMO cannula.[23]

Other arterial access sites such as the subclavian also have been used but have resulted in difficulty with limb perfusion. One recent report described the successful use of the axillary artery by means of a Gore-Tex graft placed into the side of the vessel for venoarterial support in adult lung transplant patients supported by ECMO.[24]

The primary modality to verify proper cannula position has traditionally been chest radiography. In a recent report comparing echocardiography and chest radiographs for evaluation of cannula placement during pediatric ECMO, 12% of patients had an abnormal cannula position noted with ECHO that was not identified on a chest radiograph. An additional 7% of patients were noted to have an abnormal cannula position during incidental echocardiography for other reasons. Any concerns with cannula position should be clarified by an echocardiographic examination.[25]

Venovenous Extracorporeal Membrane Oxygenation

Venovenous ECMO differs from venoarterial ECMO in that blood is both withdrawn and reinfused into the patient's venous circulation (Figure 53-2). Cannulation can be introduced via either the cervical or femoral vessels.[26] Currently several types of multiple lumen, single cannulas exist. One such cannula, manufactured by Origen Inc (Austin, Tex.), is available in sizes from 12 to 18 Fr and can support patients weighing up to 12 kg. This cannula is placed into the right IJ vein and requires only one surgical site. The drainage and infusion lumens in this cannula are separated by a distance of a few centimeters. Careful placement and orientation of the cannula can reduce recirculation of reinfused blood from the ECMO circuit, although some amount of recirculation (which will be discussed later in further detail) always occurs. A new venovenous cannula manufactured by Avalon Inc also has become available in sizes from 13 to 31 Fr and is able to obtain flow rates to support even large adult patients. This cannula has two drainage lumens, one of which is positioned in the IVC and one in the superior vena cava. A reinfusion port that sits between the two lumens is directed at the tricuspid valve. Placement of this cannula requires meticulous assessment with echocardiography or fluoroscopy for optimal performance. Although experience with the Avalon cannula is not very extensive at this time, it has the advantage of reducing the need for multiple venous cannulation sites. Time will tell if the advantages of this cannula outweigh its increased cost. Preliminary results are encouraging.

Venovenous ECMO also can be provided via two (or more) separate access sites. The right IJ and femoral vein provide access in the majority of patients. Patients with venovenous cannulation may have venous blood drained from the right atrium via the IJ vein or from the IVC via the femoral vein. Although more venous drainage usually can be obtained from a cervical cannula (which is usually shorter and larger than a cannula that can be placed into the femoral vein), the femoral site often may prove adequate. Older children and adults also may undergo bilateral saphenous or femoral cannulations, with one cannula placed into the high IVC and the other ending in the low IVC or iliac vessels[27] (Figure 53-3).

Several features unique to venovenous cannulation are important to understand. First, because blood is both withdrawn and reinfused into the venous circulation, adequate native cardiac function must exist to provide the "pumping" of oxygenated ECMO return to the patient's systemic circulation. One factor that may influence cardiac function during venovenous ECMO is that well-oxygenated blood returning from the ECMO circuit will enter the right heart. This highly oxygenated blood may reduce pulmonary artery pressure by reducing pulmonary vascular resistance, which may in turn improve right heart function.[28] Likewise, highly saturated blood ejected from the left ventricle to the coronary arteries may improve myocardial blood flow and improve cardiac

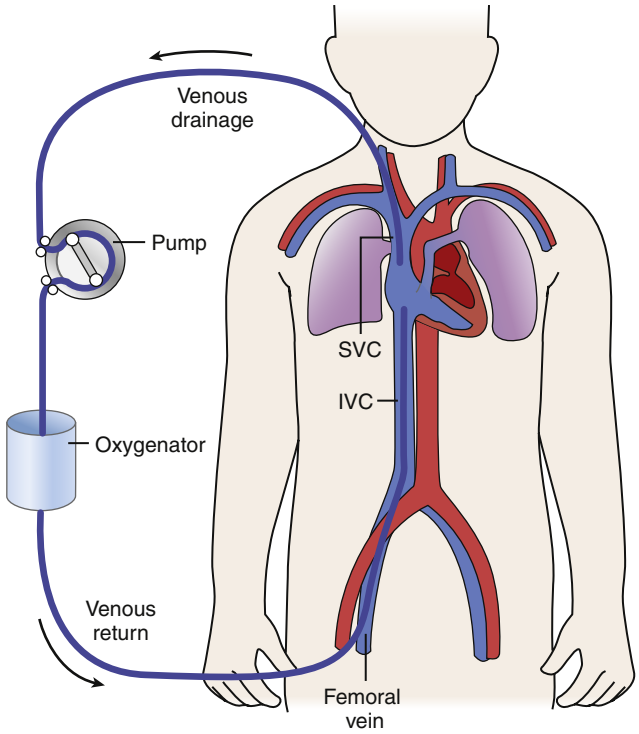

Figure 53–2. Venovenous extracorporeal life support. Note superior vena cava (SVC) to right atrium as venous outflow tract and femoral vein to inferior vena cava (IVC) as inflow tract. Outflow and inflow drainage and reinfusion directions can be reversed.

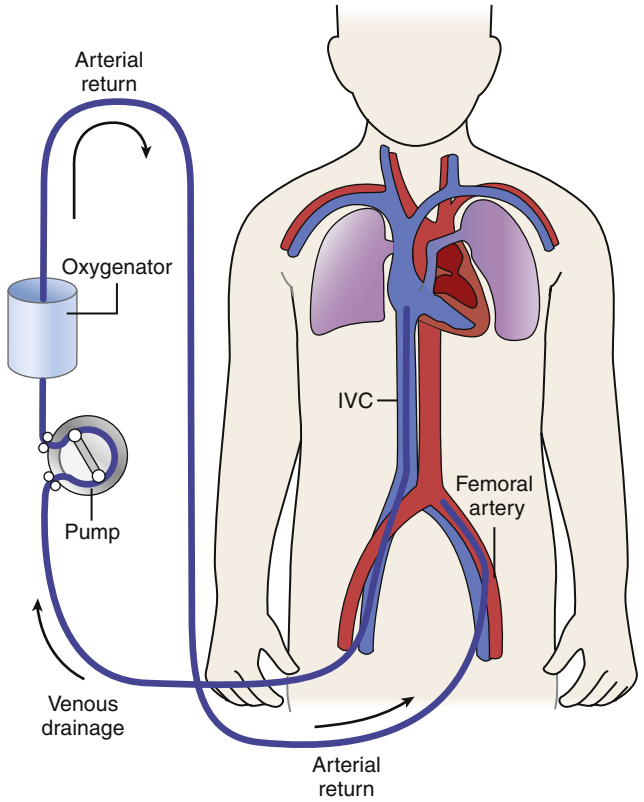

Figure 53–3. Modified venoarterial extracorporeal membrane oxygenation circuit. Bilateral femoral venous and arterial cannulation for extracorporeal life support. *IVC,* Inferior vena cava.

performance. For these reasons, some clinicians will initiate venovenous ECMO even in patients with cardiac dysfunction and transition to venoarterial ECMO if support is inadequate. Other clinicians prefer to use venoarterial ECMO preferentially if cardiac dysfunction exists.

Another feature of venovenous ECMO is that because blood is withdrawn and reinfused into the venous side of the circulation, some of the return coming from the ECMO circuit will be drained by the venous drainage cannula before it goes through the patient's heart into the systemic circulation. This phenomenon is known as "recirculation," and it can be a major limiting factor in providing adequate patient support with venovenous ECMO.[29] With double-lumen cannulas placed via the right IJ vein to the right atrium, careful orientation of the inflow lumen toward the tricuspid valve may limit recirculation. The larger separation of drainage and inflow lumens with the Avalon device seems to be associated with fewer recirculation difficulties.

With two-site venous cannulation, recirculation can be limited to some degree by ensuring that some distance separates the end tips of the drainage and infusion cannulas in the body. Recirculation also can be reduced by draining from the femoral vein cannula and reinfusing into the right IJ vein cannula. The extent of recirculation can be estimated by following the venous saturation in the ECLS circuit; high levels of recirculation will elevate the displayed venous saturation on the drainage line because some of the highly saturated return from the ECLS circuit is immediately drawn out by the drainage cannula. Whether venovenous cannulation will provide adequate capture of the patient's cardiac output for ECMO support depends on how large the cannulas are, where they lie in the vessel, and how much overall ECMO support the patient requires.[30]

Percutaneous Cannulation

Although the historical approach to vessel access has been via an open procedure with placement of cannulas under direct vision, kits for percutaneous placement now exist in many sizes. These kits use a modified Seldinger technique with obturators increasing in size to dilate the vessel. Once the appropriate size is reached, the cannula is passed into the vessel over the largest obturator.[31]

Percutaneous cannulation carries with it the inherent risks of potentially tearing a large vessel during cannulation. Although percutaneous cannulation in some centers is performed by nonsurgical personnel, surgical backup to perform an immediate cutdown for control of bleeding from a disrupted vessel may be needed. Despite the obvious fear of vessel disruption, this complication occurs infrequently. In one early series of 21 patients who underwent cannulation percutaneously, only 18% required any purse-string suturing around the cannulation site for bleeding, and none experienced vessel disruption.[32] Percutaneous cannulation avoids the need for an open surgical site, thus decreasing surgical site bleeding and risk of infection.

Decannulation

Decannulation involves removal of surgically placed cannulas and repair of the operative site, with or without vessel repair. Vessels used in traditional, open venotomy or arteriotomy ECMO often can be repaired at decannulation, although this approach is not used universally. Whether avoiding ligation or repairing cannulated vessels results in long-term improvement in blood flow or reduced risk of stroke from thrombosis or infarct is unknown.[33-37] The longest follow-up study of repaired carotid vessels found restenosis or occlusion in 24%. Patients with reconstructed vessels had fewer neuroradiologic abnormalities and a smaller incidence of cerebral palsy than did unrepaired historical control subjects, although these data represent a small, single-center report and are not the result of a randomized study.[38] Femoral vessels are sometimes accessed via a Gore-Tex or similar graft sewn into the side of the vessel. This graft is tied off at decannulation.

Percutaneously placed cannulas are merely withdrawn at decannulation while gentle pressure is applied to the site until hemostasis is obtained. Vessels accessed percutaneously are not usually ligated either at initiation or decannulation from ECMO. Femoral artery repair often is performed to ensure continued integrity of the vessel and limb perfusion.

Heparin is discontinued at decannulation, and normalization of coagulation usually occurs within a few hours. Protamine can be used for the reversal of heparin-induced coagulation effects if desired, although the risk-benefit ratio of this approach must be considered. Venous thrombosis may develop after ECLS has been discontinued, especially if femoral cannulation is used, which may be an additional reason why heparinization should not be reversed.

Venous Reservoir and Venous Saturation Monitor

Following cannulation, venous ECMO blood flows by gravity through the attached tubing to a reservoir called the "bladder." The bladder historically is a 30- to 50-mL oblong device that sits at the lowest point of the ECMO circuit and allows blood to collect and be drawn from it to the pump-head. It also acts as an air trap and normally has access ports to allow aspiration of any air collected in the bladder chamber. The output of the ECMO circuit is determined primarily by the amount of venous blood that can be withdrawn from the patient to enter the circuit. The venous drainage to the bladder is gravity dependent, generated by the pressure difference between the column of blood in the venous cannula and the reservoir. Thus the siphon effect of venous return is augmented by elevating the patient higher above the venous reservoir.[39] Because the venous cannula can drain only as much blood as is available at the cannulation site, adequate systemic venous return must be maintained. In addition to systemic hypovolemia, any process that limits right atrial filling, such as pneumothorax or pneumopericardium, will also impede drainage to the ECMO circuit.[40] Changes in venous and arterial tone also may alter right atrial and venous filling pressures and affect the amount of venous drainage that can be obtained. The bladder can be used as a servoregulating device that helps to match forward flow to venous return. Advancement in bladder technology has resulted in the Better Bladder (Circulatory Technology Inc, Oyster Bay, NY), which is a piece of collapsible tubing encased in a hard shell. Changes in venous return cause contraction of the tubing, which is registered as a change in negative venous pressure in the circuit. This device provides servoregulation of flow. The vertical orientation of the bladder reduces clotting compared with older oblong, horizontal devices. Servoregulation by monitoring of direct negative and positive pressure within the ECMO circuit has eliminated the use of the bladder in some centers, although most still incorporate some sort of "bladder" within the circuit.

Most centers use a venous saturation monitoring device along the venous drainage line. Monitoring venous saturation over time gives information regarding the balance of oxygen delivery and extraction. Especially in patients receiving ECLS for cardiac support and who have minimal lung injury, care must be taken in interpretation of the observed venous saturation. The presence of left atrial drains or left-to-right intracardiac shunts will increase the observed venous saturation in the ECLS drainage line but may not reflect overall venous saturation in the body. Measuring venous saturation as an index of oxygen delivery and consumption balance from another site not involved with the ECLS circuit is recommended in this circumstance.

Types of Pumps and Oxygenators

Roller-Head Pumps

The majority of ECMO centers use a roller-head pump during extracorporeal support. This device contains steel roller heads enclosed in a box (the pump housing) (Figure 53-4). The heads rotate and push against the ECMO circuit tubing, which is threaded through the box. The piece of tubing in contact with the roller heads is called the raceway and is generally composed of a special material called super-Tygon, which is less likely to rupture under the wear and tear induced by the roller heads. Blood contained in the tubing is advanced forward by the motion of the roller heads. The amount of blood advanced from the raceway is dependent on the number of revolutions of the roller heads, the tubing size, and the

occlusion between the heads and the tubing. Too little contact between the roller heads and the tubing (loose occlusion) will decrease the amount of blood advanced, while excessive pressure of the roller heads against the tubing (tight occlusion) will obstruct blood from moving forward and cause excessive wear on the tubing, which may result in rupture. The correct occlusion is set by measuring the displacement of fluid during roller-head rotation during setup of the ECMO circuit. Newer pumps used for ECMO now often incorporate flow probes that display the actual amount of blood flowing through the ECMO circuit. Transonic probes also can be attached to the outside surface of the ECMO tubing to monitor flow.

Loss of venous return with continuous rotation of the roller heads results in generation of high negative pressure in the ECMO tubing that can lead to hemolysis and cavitation as air is drawn out of solution.[41] The collapse of the tubing and cannula that can be induced by high negative pressure also can lead to damage of the endothelium of the vessel or the right atrium. To protect the patient as venous return is lost and the bladder starts to collapse, a signal is sent to the pump head that causes it to slow down or stop until adequate venous return is achieved and the bladder is once again full. Older versions of the servoregulation system stop the pump whenever venous return diminishes and then restart it when venous return is adequate. This on/off action of servoregulation has been shown to result in acute changes in cerebral blood flow in patients who have undergone cannulation via the cervical route, which may be harmful.[42] Newer circuit and pump designs have eliminated the traditional "bladder box" in favor of the Better Bladder previously described, which performs a similar servoregulating function. The elimination of the bladder reduces the potential for clot formation. It also removes a potential site for air trapping, however, which was easily accomplished with the older cylindrical bladder design. In the new systems, as venous return to the ECMO circuit diminishes, the collapsible tubing signals the roller heads to slow down and then speed up again once adequate venous return is obtained. This mechanism may decrease the on/off action of the roller-head pump and potentially limit the acute changes in blood flow noted with the older style of servoregulation. Newer pumps also may be able to provide pulsatile flow, which may be useful in maintaining normal perfusion patterns to the body. The nonpulsatile nature of venoarterial ECMO flow has been implicated in the renal dysfunction sometimes noted in patients treated with venoarterial ECMO. The pulsatile flow of the newer pumps has yet to be effectively linked to native heart ejection, although this link is a goal in the future.

Roller pumps generate high pressure in the circuit distal to the raceway/roller heads. Thus acute interruption to forward flow as may occur with kinking of the arterial cannula or elevated resistance to blood flow on the high-pressure side of the circuit can result in immediate and potentially lethal circuit rupture. Monitoring of the high pressure side of the ECMO circuit is universal, with critical high limits for arterial line pressure determined based on tubing size and pump flow. Pressures below 300 to 350 mm Hg are desired. Newer pump systems provide safety mechanisms to stop the ECMO pump if line pressure limits are exceeded. Some centers use filters in the ECMO circuit prior to blood return to the patient, which can help detect air bubbles or trap debris. While using a filter seems practical, in reality these devices may be so sensitive that they result in many episodes of stopping ECMO to check alarms or maintain the filters. This stoppage of ECMO may harm the patient and is one reason that air detectors or filters are not used universally.

Centrifugal Pumps

Centrifugal pumps also are used for ECMO support (Figure 53-5). Advanced technology in this area has resulted in many centers changing from roller-head to centrifugal pumps. Some centrifugal pump heads contain a spinning rotor that is controlled by magnets within and without the cone.[43,44] Blood enters the cone at the apex and is propelled tangentially to the base of the pump head, where it is expelled. The longer blood sits in the centrifugal head and the faster the head spins, the more hemolysis will be created. It is also postulated that as blood clots develop in the membrane oxygenator over time and increase outflow resistance, this scenario may also increase hemolysis within the rotor head. Hemolysis has limited the use of centrifugal pumps. Newer pump designs have small heads that require little priming volume and technical advancements in generating the "spinning" motion, which may be associated with less hemolysis than in the past. Use of low-resistance hollow fiber oxygenators

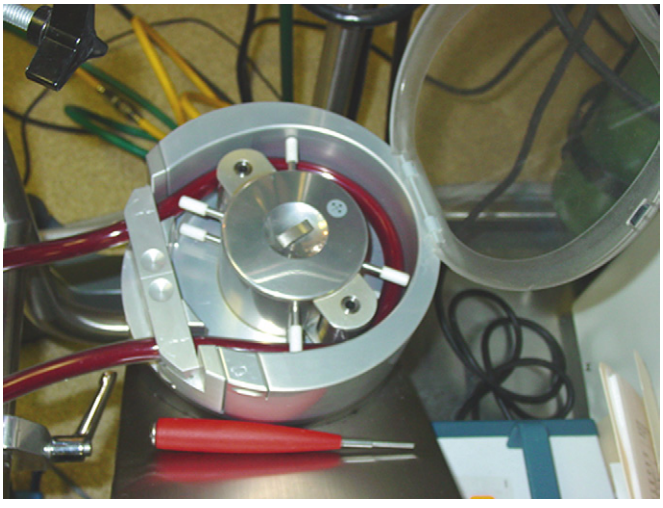

Figure 53–4. Roller (occlusive) pump.

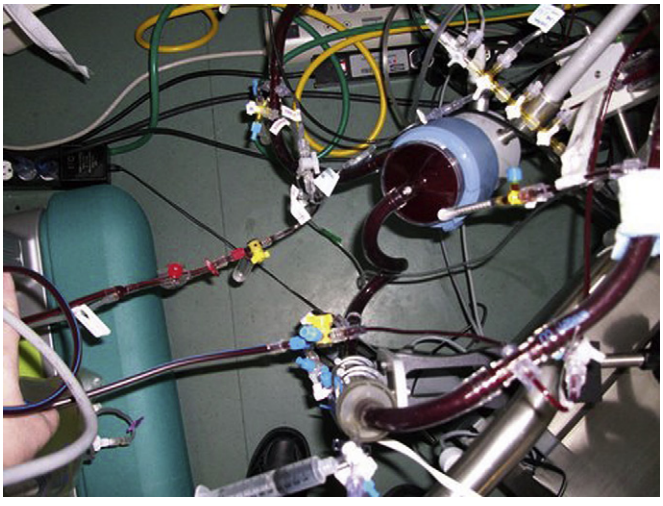

Figure 53–5. Centrifugal pump.

also may reduce hemolysis and make centrifugal pumps even more efficient.

Blood flow to the centrifugal head is augmented by the "suction" effect of the spinning pump head and thus is not as dependent on gravity drainage as are roller-head pumps. Thus centrifugal pumps can be placed at any level relative to the patient, which makes transporting the patient who is being treated with ECMO easier than with roller-head devices. The active suction effect of centrifugal heads can create levels of negative pressures as high as −200 to −700 within the venous inlet tubing. High amounts of negative pressure generated by centrifugal pumps can result in hemolysis, endothelial damage of cannulated vessels, or cavitation of air. Monitoring of venous pressure with alarm limits to signal when excessive negative pressure is occurring is common in most centers. Monitoring venous return and understanding the function of centrifugal pumps are keys to safe and appropriate use of this form of support.[45,46] Another advantage of centrifugal pumping devices is that air and debris are trapped within the vortex of the pump head and may be less likely to embolize to the patient than with roller-head circuits. This advantage is countered by some reports that centrifugal pumps generate more microbubbles than do roller-head devices. A recent publication examining causes of hemolysis noted that the direct interaction of blood with air and high negative pressure (such as occurs with cardiotomy suction during bypass surgery) resulted in the greatest amount of hemolysis.[47] Centrifugal circuits contain a flow probe that displays how much blood is being returned to the patient. Servoregulation occurs by the same method as with roller pumps, in that venous and arterial pressure limits and goals are set and the pump (or the specialist) adjusts flow to maintain set goals. Another advantage of centrifugal pumps is that if there is occlusion of the circuit past the centrifugal head, no high back pressure is exerted to result in rupture of the circuit. Obstruction to forward flow, however, will result in increased hemolysis from the blood trapped in the centrifugal head. The components of ECMO circuits used with centrifugal pumps can be completely coated with heparin, which may limit bleeding or the need for exogenous heparin. Although centrifugal pumps are easy to set up and operate, lack of familiarity with them compared with roller-head pumps requires that close attention to patient physiology and pump interaction be maintained. The newer designs of centrifugal systems allow miniaturization such that transport systems can be more compact and much less cumbersome than in years past.

Advances in ACLS will likely be drawn from continuing work with artificial heart or ventricular support devices. One intriguing report from Japan noted successful use of a self-regulating ECMO device that contained two sac-type blood pumps that are placed in parallel and use compressed air to eject blood. This pump is completely self-regulated and provides pulsatile ECMO return. Three neonatal patients with respiratory failure were successfully supported in Japan with use of this device.[48]

Whether by semiocclusive contact between pump roller heads and ECMO tubing or by advancement through a centrifugal head, blood moves past the pumping device to the membrane oxygenator, where gas exchange occurs. Oxygenated blood then flows through a heat exchanger, where it is rewarmed or cooled depending on the clinical situation, and then it returns to the patient.

Membrane Oxygenator

Until recently, the predominant membrane oxygenator was a silicone membrane envelope (with a plastic spacer screen inside) wound in a spiral fashion around a polycarbonate spool. Gas flows within the interior of the envelope, and blood flows between the turns in the membrane envelope. Blood flow to the membrane lung is controlled by the pump setting.

Gas exchange in the membrane oxygenator is determined by the permeability of the membrane to oxygen and carbon dioxide (their diffusion coefficients), the available membrane surface area, the pressure gradient for oxygen or carbon dioxide between the gas compartment and the blood, and the amount of time gas and blood interface across the membrane.[49] Viscosity, temperature, and pH of the blood also can influence the amount of oxygen binding to the blood as it passes through the oxygenator. Each membrane has a predetermined maximum blood flow above which the thickness of the blood film will limit oxygenation. Blood or gas flow in excess of the manufacturer's specifications may generate high pressure within the membrane oxygenator, which may cause it to rupture. If the blood side of the envelope ruptures, blood will escape into the gas side of the envelope and will drip out through the gas exit port at the bottom of the oxygenator (colloquially called a *nosebleed*). Small breaks in the integrity of the blood/gas barrier with little bleeding can be tolerated because the small tear will usually clot off. More vigorous bleeding often requires an emergent oxygenator change. Rupture of the gas side of the envelope from excessive gas pressure can result in air being transferred to the blood phase of the membrane. This scenario is a true emergency that requires immediate stopping of ECMO and replacement of the oxygenator. Although it is an uncommon complication, a massive air embolus and death can occur in this scenario.

Countercurrent gas and blood flows in the oxygenator provide optimal gas exchange by maintaining the pressure gradient for oxygen transfer from gas to blood along the entire length of the membrane surface. The gravitational gas flow through the membrane also helps remove the condensation that forms when warm blood flows by cooler gas in the membrane. Water droplets are expelled from the membrane surface via the gas exhaust port. Membrane failure can be characterized by a decrease in the capacity to remove carbon dioxide or to oxygenate blood. Membrane failure may result from clot formation on the membrane, which decreases the available surface area for gas exchange; excess condensation in the membrane lung ("pulmonary edema"); or technical defects in the membrane itself. A difference of greater than 100 torr between the estimated PAo_2 in membrane gas and that in blood leaving the oxygenator may indicate early membrane failure. Membrane failure also can be predicted when the pressure drop between blood entering the membrane and leaving it increases and becomes >100 torr. This situation may indicate clotting in the membrane oxygenator with restriction to blood flow. Initially, increasing the partial pressure of oxygen (PO_2) in the membrane gas may augment diffusion of oxygen across the available surface area into the blood and maintain adequate oxygenation. Increasing the flow rate of gas across the membrane also may help remove condensation and improve gas diffusion. When these methods fail or the pressure difference between entry and exit of blood in the oxygenator continues to rise, the oxygenator may need to be

replaced. Although the exact timing for membrane oxygenator failure varies, generally they are not rated for use beyond 7 days. Replacement of the oxygenator is usually a quick and uncomplicated process.

Hollow-Fiber Oxygenator

Hollow-fiber oxygenators are becoming more available for ECMO use and are quickly replacing the silicone oxygenator. These devices are microporous and have long, thin fibers. Blood flows either between the inside or the outside of the fibers. These devices have a lower resistance to blood flow and a lower priming volume than the traditional silicone membrane lung, which makes them faster and easier to prime.[50] Early versions of these oxygenators were plagued by plasma leakage difficulties that resulted in very short life spans for the oxygenator and limited their use. Newer versions hold promise as in vivo studies have shown excellent gas exchange, little hemolysis, and durability of days to weeks without failure from plasma leakage. European versions of hollow-fiber oxygenators, now available in the United States, last for weeks at a time.

In one survey, 80 of 103 North American ECMO centers listed in the ELSO directory as neonatal centers (78%) responded to a survey regarding use of different ECMO devices. Of the responding centers, 82.5% routinely used roller pumps for neonatal ECMO, and the remaining 17.5% used centrifugal pumps. Silicone membrane oxygenators were used by 67% of the respondents, whereas 19% used microporous hollow-fiber oxygenators, and 14% used polymethylpentene hollow-fiber oxygenators. A bladder was used by 85% of the centers, and 4% of these used a mechanical bladder box for servoregulation; the remaining 96% used pressure servoregulation. An air bubble detector was used by 88% of the responding centers. A surface coating was used by 44% of the centers on all their neonatal patients treated with ECMO. Thirty-one percent of the centers use an activated clotting time of 180 to 220 seconds.[51] It is likely that a survey done today would find an increasing number of centrifugal pumps and hollow-fiber oxygenators being used in many centers.

Other advances in oxygenator development have allowed adequate oxygenation without an intercurrent pump to be incorporated. One device, the Novalung, takes arterial blood from the femoral artery and directs it through a hollow-fiber device for oxygenation and carbon dioxide removal, and then reinfused blood is directed into the femoral vein.[52] Experience with this device is growing, and multiple reports of bridging to lung transplantation or to resolution of lung injury can be found in the literature. In addition, an implantable artificial lung is close to being ready for clinical trial.

Other Points

One recent concern with ECMO circuitry is the potential for high levels of Di(2-ethylhexyl)phthalate (DEHP) to be leeched from the polyvinyl tubing over time and thus increase the exposure of the patient to this chemical. One neonatal ECMO circuit evaluation noted that high levels of DHEP were found with routine roller head use over time.[53] High levels of DHEP have been shown to cause sterility and endocrine abnormalities in rats. A recent follow-up report of 22 neonatal patients treated with ECMO who are now 14 to 16 years of age found no abnormalities in observed genital development, sex hormone levels, or thyroid, renal, or hepatic function.[54] Another study found no accumulation of DEHP in the circulating fluid of ECMO circuits that were pre-primed for up to 30 days prior to clinical use.[55]

Work with heparin-bonded tubing also has resulted in several commercially available products. Although none has been proved to effectively reduce the need for systemic heparin administration on a long-term basis, short periods (<24 hours) of support without heparin have been achieved without clotting of the circuit or observable thrombosis in the patient. Complete heparin-bonded ECMO circuits that include a hollow-fiber oxygenator are now available and are used especially in situations where bleeding is expected (in postoperative patients, for example) to lessen or avoid the need for anticoagulation. Research into other ways to prevent circuit clotting such as altering platelet aggregation with agents such as nitric oxide also holds promise for the future.[56]

Patient Populations Treated with Extracorporeal Life Support

The demographics of patients who have received ECMO support over time is shown in Table 53-1.

Neonatal Cardiopulmonary Failure

Most patients treated with ECMO have been neonates with severe respiratory failure with an overall survival rate of 75%. Common diagnoses include meconium aspiration syndrome, respiratory distress syndrome, sepsis, and persistent

Table 53–1 Total Numbers of Extracorporeal Life Support Patients

Group	Total Cases	Survive to Discharge or Transfer	%
NEONATAL			
Respiratory	23,191	17,478	75
Cardiac	3749	1454	39
Extracorporeal cardiopulmonary resuscitation	492	184	37
PEDIATRIC			
Respiratory	4188	2325	56
Cardiac	4564	2121	46
Extracorporeal cardiopulmonary resuscitation	908	348	38
ADULT			
Respiratory	1663	853	51
Cardiac	1059	360	34
Extracorporeal cardiopulmonary resuscitation	381	102	27
TOTAL	**40,195**	**25,225**	**63**

Modified from Extracorporeal Life Support Organization: *International ECMO registry report of the Extracorporeal Life Support Organization,* Ann Arbor, MI, 2009, Extracorporeal Life Support Organization.

pulmonary hypertension of the newborn (PPHN). With the exception of the last group, most of these infants experience a combination of pulmonary parenchymal and vascular dysfunction that leads to impaired gas exchange.[57] The diagnosis, outcome, and mode of ECMO applied in neonatal patients are shown in Table 53-2.

Because vasodilation in the pulmonary circuit depends on alveolar oxygen tension (PAo_2) and pH, any process that results in hypoxia or acidosis can cause persistently high pulmonary vascular resistance, failure of the foramen ovale and ductus arteriosus to close, right-to-left shunting, and profound cyanosis. Obstruction to pulmonary venous drainage or abnormalities in the pulmonary vascular circuit also can result in pulmonary hypertension. Whatever the cause, the resulting systemic arterial desaturation may depress myocardial performance, worsen acidosis, and perpetuate the dysfunctional circulation. The impact of parenchymal lung disease and PPHN varies among infants, but the circulatory contribution to hypoxia of PPHN is commonly very important.

When medical therapies fail to relieve hypoxia and pulmonary hypertension in an infant, ECMO may be an effective means of support. ECMO provides adequate gas exchange and circulatory support without further exposure to high oxygen concentrations or high airway pressures, thus fostering healing of the damaged lungs. The circulatory changes that result from initiation of ECMO also lower pulmonary vascular resistance. Draining right atrial blood reduces right atrial pressure and promotes closure of the foramen ovale. In addition, the reduced blood flow to the pulmonary vascular bed decreases pulmonary flow, reduces pulmonary artery pressure, and relieves right-to-left shunting through the patent ductus arteriosus. Well-oxygenated blood flowing left –to right through the patent ductus arteriosus promotes its closure. By relieving hypoxia, hypercapnia, and acidosis, ECMO promotes relaxation of pulmonary vascular tone. The amount and extent of pulmonary arteriolar smooth muscle begins to regress.[58] These changes allow the transition to a mature circulation. The infant continues to receive ECMO until the parenchymal lung disease heals sufficiently to allow adequate gas exchange. However, pulmonary function tests indicate that commonly infants are weaned from ECMO with only moderate improvement in mechanical lung function.[59] These observations support the impression that circulatory abnormalities contribute importantly to neonatal "respiratory" failure and may partially explain the dramatic difference in outcome between neonates and older patients treated with ECMO.

Infants with congenital diaphragmatic hernia comprise a special subgroup of patients treated with ECMO for severe pulmonary hypertension and respiratory failure.[60,61] Severe pulmonary hypertension or lung hypoplasia leads to about 50% mortality even with ECMO support.[62] Morphologic examination, better understanding of the pathophysiology of this lesion, and stabilization with ECMO as needed preoperatively has improved the survival rate in some centers in this challenging group of patients.[63-66]

As alternative support methods such as high-frequency ventilation (HFV), surfactant, and inhaled nitric oxide (iNO) have been developed and have gained acceptance, the need for ECMO support of neonates has declined.[67] Annual neonatal ECMO cases now number around 800 per year, down from the peak of 1500 cases in the early 1990s. Survival rates also have decreased in the neonatal population during the last few years, which is speculated to be related to delays in institution of ECMO while other less invasive therapies are attempted. Infants for whom all other therapies fail and who require ECMO may thus be sicker than in years past when ECMO was the only "rescue" therapy available. While this explanation seems logical, in an evaluation of the ELSO registry data, there was no difference in outcome between infants who received treatment with iNO, HFV, or both prior to ECMO and those who did not (H. J. Dalton and P. Rycus, unpublished data, 2002). Similarly, there was no statistical difference in measures of respiratory severity such as the arterio-alveolar oxygen tension difference ($AaDO_2$) or oxygenation index in the past few years. An alternative explanation is that use of ECMO has expanded from "simple" neonates with respiratory failure to include a variety of neonates with comorbidities that also may influence survival.

Table 53–2 Neonatal Extracorporeal Life Support for Respiratory Failure

Primary Diagnosis	Total Cases	No. Surviving	% Surviving
NEONATAL CASES BY DIAGNOSIS			
CDH	5821	2982	51
MAS	7513	7036	94
PPHN/PFC	3793	2949	78
Infant RDS	1474	1244	84
Sepsis	2600	1944	75
Other	1856	1169	63
NEONATAL MODE OF EXTRACORPOREAL LIFE SUPPORT			
VA	15,860	11,458	72
VV	349	271	78
VVDL	4624	3945	85
VA (+V)	1317	962	73
VV → VA	675	430	64
VVDL + V	585	477	82

Modified from Extracorporeal Life Support Organization: *International ECMO registry report of the Extracorporeal Life Support Organization,* Ann Arbor, MI, 2009, Extracorporeal Life Support Organization.

CDH, Congenital diaphragmatic hernia; *MAS,* meconium aspiration syndrome; *PPHN/PFC,* persistent pulmonary hypertension/persistent fetal circulation; *RDS,* respiratory distress syndrome; *V,* venous; *VA,* venoarterial; *VV,* venovenous; *VVDL,* venovenous double lumen.

Pediatric and Adult Patients

Approximately 250 nonneonatal pediatric patients undergo ECMO each year for severe respiratory failure, with an overall survival rate of 53% (Table 53-3).[68] Most of these patients have severe hypoxia, hypercapnia, or intractable air leaks. Pulmonary dysfunction resulting from bacterial or viral pneumonia, aspiration syndromes, intrapulmonary hemorrhage, acute respiratory distress syndrome, and other poorly defined disorders have been treated successfully with ECMO. The uncertainties accompanying the use of ECMO in neonates, who compose a homogeneous group relative to other age groups, are compounded in older children. The enormously heterogeneous older pediatric population spans nearly two

Table 53–3 Extracorporeal Life Support for Pediatric Respiratory Failure

Primary Diagnosis	Total Cases	No. Surviving	% Surviving
PEDIATRIC CASES BY DIAGNOSIS			
Bacterial pneumonia	478	271	57
Viral pneumonia	926	587	63
Aspiration pneumonia	200	132	66
ARDS	475	259	54
ARF, non-ARDS	741	370	50
Other	1413	722	51
PEDIATRIC MODE OF EXTRACORPOREAL LIFE SUPPORT			
VA	2356	1193	51
VV	743	473	64
VVDL	523	358	68
VA (+V)	176	81	46
VV → VA	253	117	46
VVDL + V	112	76	68

Modified from Extracorporeal Life Support Organization: *International ECMO registry report of the Extracorporeal Life Support Organization,* Ann Arbor, MI, 2009, Extracorporeal Life Support Organization.
V, Venous; *VA,* venoarterial; *VV,* venovenous; *VVDL,* venovenous double lumen.

decades of physiologic development, and cardiorespiratory failure develops as a result of a multitude of different disorders. Furthermore, many patients have varying degrees of multiple organ failure along with respiratory disease at the time ECMO is instituted. Resolution of both lung disease and secondary organ dysfunction must occur to achieve survival. These factors result in lower survival rates in older patients treated with ECMO than that achieved with the neonatal patient population.[69]

One small subgroup of persons receiving ECLS support are patients with status asthmaticus. In a recent study comparing results with patients who had asthma and that of the ELSO database, the center reported 13 patients who underwent ECLS between 1986 and 2007.[70] The median time from intubation to ECLS was 14 hours (range, 1 to 34 hours). The mean arterial pH was 6.93 (range, 6.78 to 7.03), and $Paco_2$ was greater than 130 prior to institution of ECLS. Four of the thirteen patients (31%) had a cardiorespiratory arrest in the intensive care unit (ICU) prior to institution of ECLS. Use of medical therapies prior to ECLS included intravenous β-agonist in 100%, ketamine infusion in 92%, administration of magnesium sulfate in 69%, helium/oxygen in 69%, and use of an anesthetic inhalational agent in 62%. The mean duration of ECLS was 95 hours (range, 42 to 395 hours). The survival rate was 100%, with no neurologic sequelae noted. Venovenous cannulation was done in 95% of the patients. A second asthma group can be found in the ELSO database, with a total of 64 patients supported by ECLS over the same time frame (including the aforementioned 13 patients). There was little difference in the pre-ECLS variables of age, $Paco_2$, and pH between the groups. The mean duration of ECMO was 94 hours, and 94% of the patients survived. Venovenous cannulation was done in 86% of patients.[70]

Despite attempts to define predictive models for ECMO candidacy and institution, none have proved universally applicable. The clinician still most often relies on clinical judgment at the bedside when determining when conventional medical therapy has failed. Perhaps the largest change in nonneonatal ECMO in the past few years is the variety of patients to whom it has been applied. Patients with recent trauma, tracheal injury requiring reconstruction, burns, smoke inhalation, and severe sepsis, along with those who are immunocompromised, and those who have had a toxic ingestion with cardiopulmonary collapse, are but a few of the types of patients who might have been excluded from ECMO support a few years ago but have now received successful ECMO therapy.[71-74] The multiple exclusion criteria used in the early days of ECMO have now been fairly well eliminated, and each potential patient is generally considered on a case-by-case basis. Even patients with known bleeding disorders such as hemophilia have successfully received ECMO support.[75]

Perhaps one group in which ECMO is still cautiously avoided or rarely applied is patients with malignancy and bone marrow transplant. The continued high mortality in these patients when respiratory failure develops, however, has recently caused several clinicians to advocate for application of ECMO at an early point in the disease to see if outcomes can be improved.

In a recent review of the ELSO data registry, 107 patients with malignancy and respiratory and/or cardiac failure were analyzed. Seventy percent of patients had hematologic disease and 30% had solid tumor malignancy; 80% of the patients required ECLS primarily for pulmonary support. Forty-two percent of patients were weaned off ECLS support, with 35% surviving to hospital discharge. Risk factors for death in the pre-ECMO period were a lower Pao_2, higher oxygenation index, and a higher level of positive end-expiratory pressure (PEEP). Development of renal or cardiopulmonary complications during ECMO also was associated with poor outcome. Deaths were attributed to irreversible organ failure (34%), diagnosis incompatible with life (10%), hemorrhage (5%), and family request to withdraw support (7%). No difference in outcomes was noted in patients with either hematologic malignancies or solid tumors.[76]

This article also commented on the response to a questionnaire by 118 ECMO centers, which noted that 95% of responding sites would consider use of ECMO in a patient with malignancy. This response demonstrates the change in attitude among many clinicians with regard to patients with cancer, which has been a contraindication to ECMO in the past.

Although initiation of ECMO support prior to the development of multiple organ system failure is desired, many patients present with established organ failure already in progress. ECMO may provide an optimal environment for organ recovery in such patients, not just providing respiratory or cardiac support. Further, the ability to add adjunctive devices such as hemofiltration or dialysis (Figure 53-6) to augment renal function and allow use of plasmapheresis or plasma exchange or hepatic support devices is another aspect of ECMO support that may facilitate patient care and organ recovery. Implementation of ECMO during multiple organ systems failure now occurs under a variety of conditions, with resolution of organ

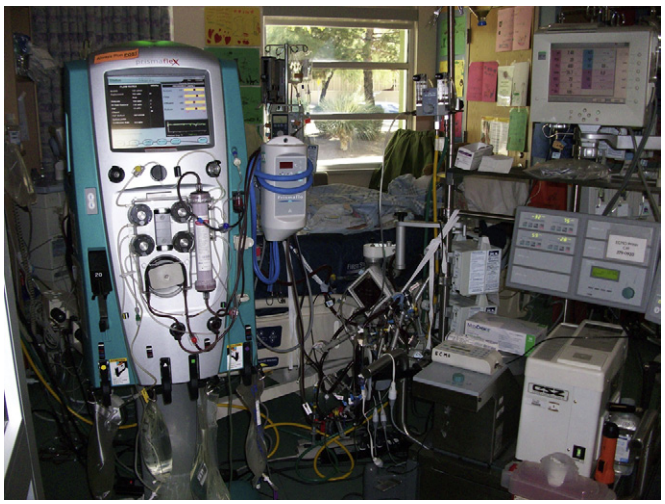

Figure 53–6. Continuous renal replacement therapy in use with extracorporeal membrane oxygenation circuit.

Table 53–4 Extracorporeal Life Support for Adult Respiratory Failure

Primary Diagnosis	Total Cases	No. Surviving	% Surviving
ADULT CASES BY DIAGNOSIS			
Bacterial pneumonia	332	184	55
Viral pneumonia	93	59	63
Aspiration pneumonia	46	28	61
ARDS, postoperative/ trauma	175	91	52
ARDS, not postoperative/ trauma	287	133	46
ARF, non-ARDS	85	49	58
Other	691	326	47

Modified from Extracorporeal Life Support Organization: *International ECMO registry report of the Extracorporeal Life Support Organization,* Ann Arbor, MI, 2009, Extracorporeal Life Support Organization.

dysfunction and good outcome often obtained.[77] Furthermore, because it avoids the circulatory derangements that often result from extreme forms of mechanical ventilation and provides systemic perfusion without the need for high-dose levels of inotropic agents, ECMO also may prevent damage to other systems.

Extracorporeal Membrane Oxygenation in Adults

ECMO support in adults has been limited (Table 53-4). Early randomized trials of ECMO use in adults did not show benefit of ECMO, and this has closed the door for ECMO consideration for adults in many clinician's eyes.[78] However, these studies had design and procedure flaws that may have affected results. Patients were maintained on high levels of ventilator support, despite ECMO, and bleeding complications were excessive when compared with today's standards. Many reports of successful use of ECMO in adults exist.[79,80] Recently a randomized trial of venovenous ECMO compared with conventional mechanical ventilation in adults with respiratory failure in the United Kingdom was completed and published (the Conventional ventilation or ECMO for Severe Adult Respiratory failure [CESAR] study). A total of 180 patients were enrolled and randomly allocated to receive treatment by ECMO (n = 90) at the single ECMO center in the United Kingdom or to receive conventional management ventilation (CMV) (n = 90) at a designated CMV center. Randomization criteria included a Murray score of >3 or severe respiratory acidosis with pH <7.20. Study results noted that 63% of patients allocated to "consideration for treatment by ECMO" survived to 6 months without disability compared with 47% of those allocated to conventional management (P = .03; risk ratio, 0.69; 95% confidence interval 0.05 to 0.97). Of note, however, 17 of 90 patients randomly assigned to "consideration for treatment by ECMO" who were treated within the ECMO center with a "gentle ventilation" (low tidal volume, limited pressure) strategy were not treated with ECMO and 14 survived. Whether this finding represents the beneficial effects of increased expertise within centers that support patients with severe respiratory failure with ECMO availability or other factors is unknown. Early transfer of patients with potentially reversible respiratory failure who meet similar criteria as those in the CESAR study may be recommended. This study also found a cost/benefit ratio in terms of quality of life and economics that was favorable in the ECMO group.[81]

In another report of ECMO in 255 adults with severe respiratory failure, 68% were weaned off ECMO support and 53% survived to discharge. Multivariate analysis noted that age, gender, pH less than 7.10, the number of pre-ECMO days in which a ventilator was used, and the pre-ECMO Pao_2/Fio_2 ratio were associated with outcome.[82] Other reports of the successful use of ECMO for adult patients with burns, trauma, myocardial infarct with arrest, and a variety of other disease processes exist in the literature. The recent H1N1 flu epidemic reports from Australia, Canada, and the United States in which ECMO use in adults resulted in a 50% to 70% survival rate has caused a sudden increase in the willingness of many adult clinicians to consider use of ECMO. Whether the current surge of centers that are supporting adults with ECMO or that are quickly developing adult ECMO programs will continue or fade as the flu pandemic dissipates is unknown.

The availability of new, large, percutaneous cannulas for venovenous ECMO support, along with small centrifugal pumps and less cumbersome total ECMO systems, are all advantageous to the adult population. Alternative support techniques such as pumpless extracorporeal support and the implantable artificial lung are additional clinical modalities for adult respiratory failure.[83-85]

Extracorporeal Membrane Oxygenation for Myocardial Dysfunction

Perhaps the largest expansion in application of ECMO has been in patients with cardiogenic shock or following repair of congenital heart defects.[86-88] The International ELSO Registry lists more than 9000 patients who have received ECMO for cardiac failure, predominantly following surgical repair of congenital heart defects (Table 53-5).[89] Outcome of neonatal and pediatric patients notes that 60% are successfully weaned from ECMO and 43% survive to be discharged from the hospital. Adult cardiac patients have slightly worse survival rates, with 48% weaned off ECMO and 34% discharged from the hospital.

Table 53–5 Extracorporeal Life Support for Cardiac Failure: Cardiac Runs by Diagnosis

Age Group	Total Runs	Survived	% Survived
0–30 DAYS			
Congenital defect	3436	1274	37
Cardiac arrest	47	12	26
Cardiogenic shock	46	19	41
Cardiomyopathy	97	61	63
Myocarditis	46	24	52
Other	308	125	41
31 DAYS TO <1 YEAR			
Congenital defect	1972	842	43
Cardiac arrest	53	25	47
Cardiogenic shock	29	11	38
Cardiomyopathy	121	65	54
Myocarditis	57	39	68
Other	295	137	46
1 YEAR TO <16 YEAR			
Congenital defect	1029	453	44
Cardiac arrest	77	30	39
Cardiogenic shock	62	27	44
Cardiomyopathy	337	197	58
Myocarditis	161	107	66
Other	465	225	48
≥16 YEAR			
Congenital defect	104	33	32
Cardiac arrest	60	16	27
Cardiogenic shock	153	60	39
Cardiomyopathy	159	60	38
Myocarditis	44	28	64
Other	683	221	32

Modified from Extracorporeal Life Support Organization: *International ECMO registry report of the Extracorporeal Life Support Organization,* Ann Arbor, MI, 2009, Extracorporeal Life Support Organization.

Although center-specific factors separating patients with myocardial dysfunction who will die from those who will recover adequate function without such invasive support have been put forth in the literature, none have proved to be universally accepted.[90-93] Patients with evidence of low cardiac output and shock (including low urine output, poor perfusion, hypotension, elevated cardiac filling pressures, and low mixed venous oxygen saturation) despite maximal respiratory and pharmacologic support are candidates for ECMO rescue. The absence of clear criteria for using ECMO and the reluctance to initiate such invasive support often delays use until cardiac arrest has occurred. As a result, a significant number of patients treated with ECMO have recovered myocardial function only to die of hypoxic/ischemic encephalopathy that was experienced before ECMO was begun.

One seeming trend in cardiac patients is to consider ECMO earlier in the course of dysfunction. Availability of ECMO is now a mandatory piece of many cardiac surgical programs. As newer and smaller cardiac assist devices are developed for pediatric patients, the need for ECMO support in this population may wane, but at this time ECMO provides the most readily available support technique over a wide range of patient ages and sizes for cardiac failure.[94,95]

Most patients requiring ECMO for circulatory support have undergone venoarterial ECMO because of its capacity to provide both respiratory and circulatory support. Whereas for many patients cannulation is achieved through the carotid and jugular vessels, transthoracic cannulation is performed frequently in postoperative patients via a reopened sternotomy. Use of the femoral vessels is also feasible in larger patients. Patients with severe left ventricular failure may require a left atrial vent or atrial septostomy to decompress the left ventricle and prevent pulmonary hemorrhage from pulmonary venous congestion. After evidence of myocardial recovery on ECMO, patients are tested with progressively lower flows, with assessment of myocardial function by echocardiography and observation of systemic blood pressure, perfusion, blood gas tensions, and mixed venous oxygen saturation. When a patient exhibits good ventricular function and adequate systemic circulation at low flow, ECMO is discontinued and conventional therapy is resumed. The majority of survivors recover myocardial function within 72 hours of ECMO support, although patients with myocarditis or cardiomyopathy can have good survival rates even after prolonged ECMO support. In most reports, patients whose myocardial function has not improved substantially within 24 to 72 hours of rest on ECMO are not likely to recover cardiac function sufficient to support life.[96,97] Transplantation may be an option in these patients if their underlying cardiac anatomy and general clinical condition make them appropriate candidates.[98] Patients who fail to improve often are evaluated by cardiac catheterization during ECMO to identify residual lesions (if postoperative) or abnormalities that may be amenable to further surgical repair or catheterization laboratory interventions. Cardiac patients with good respiratory function may not routinely require ventilator support. Such patients may require only low levels of ventilator support or be extubated during ECMO, which may alleviate the need for heavy sedation to maintain endotracheal tube position.

Myocarditis and cardiomyopathy are two categories of nonsurgical cardiac failure that have increasingly received ECLS support. While it may be difficult acutely to differentiate unknown cardiomyopathy from viral myocarditis, both diseases may benefit from mechanical support with ECMO or ventricular assist devices that creates a stable hemodynamic milieu where the heart can "rest" and recover. One review of the ELSO registry noted a 61% survival rate in 255 children with myocarditis. Seven patients received cardiac transplantation, with six surviving to discharge. The average duration of ECLS in nontransplant patients was 168 hours, with a range of 145 to 226 hours. Multivariate analysis showed that female gender, arrhythmia while undergoing ECMO, and renal failure requiring dialysis were associated with increased inhospital mortality.[99]

One analysis of a single institution's experience of ECLS following cardiac surgery in children spanning a 17-year period found that 38% of cardiac patients survived to discharge. One third of the children had single ventricle cardiac pathology. Cannulation occurred in the operating room in 46%

of patients, and 51% of cannulations took place in the ICU. Complications included reexploration for bleeding (56%), neurologic complications such as ischemic brain injury or intracranial hemorrhage (17%), renal dysfunction (10%), and pulmonary hemorrhage (5%). Factors associated with mortality were renal failure, neurologic complications, longer ECLS duration, and need for recurrent ECMO support. Mortality also may have been affected by the lack of a cardiac transplant program for patients not recovering myocardial function.[100]

In another recent review of 58 patients receiving ECMO following congenital heart defect repair (January 2003 through June 2008), 67% of patients were weaned off ECMO support and 41% survived to hospital discharge. Single ventricle repair was noted in 53% of patients. When analyzed for factors associated with outcome, ECMO duration longer than 10 days (odds ratio [OR], 6.1), urine output less than 2 mL/kg/h in the first 24 hours (OR, 15), renal failure (OR, 9.4), and pH less than 7.35 after 24 hours of ECMO (OR, 82.3) were all found to be independent predictors of failure to wean from ECMO. Independent predictors of failure of hospital discharge in spite of successful decannulation were: ECMO time of 10 or more days (OR, 11.5), a red blood cell transfusion volume greater than 1000 mL/kg during the entire period of ECMO course (OR, 11.5), and sepsis. Patients who underwent single ventricle repair were at higher risk of hospital mortality (OR, 4.9). This study also developed a probability of weaning from ECMO table based on the four previously mentioned predictors. For example, a patient with an ECMO duration of more than 10 days who had renal failure and poor urine output and pH at 24 hours of ECMO would have a predicted mortality rate of 100%. Similar evaluations in larger series of patients to validate such assessments should be performed to refine ECMO care and improve family counseling regarding prognosis.[101]

To obtain more detailed information on cardiac surgical patients who receive ECLS, an addendum to the general ELSO registry data form was developed several years ago. Data analysis from this subgroup of ECLS patients is under way and should be published soon.

Extracorporeal Membrane Oxygenation for Resuscitation

Perhaps the fastest expansion of the use of ECLS is in support of patients with refractory cardiac arrest. This type of support is termed extracorporeal cardiopulmonary resuscitation (ECPR), or ECMO during cardiac arrest. Designed as a resuscitative tool for patients in cardiac arrest, ECPR has been reported in more than 2000 neonates, children, and adults, with an overall survival to discharge rate of 34%. To facilitate expedient access to ECMO support for ECPR, in situations of acute deterioration or whenever there is insufficient time or personnel for routine ECMO, many centers maintain a "rapid deployment" ECMO circuit setup that is either preprimed with a crystalloid solution or can be primed within a very short period. Other centers use a portable, centrifugal bypass perfusion system that also is easily set up within 10 to 20 minutes. Both methods often use a hollow-fiber membrane oxygenator, which is less difficult and faster to prime for use than a traditional silicone-coated membrane lung.

In a recently published metaanalysis of ECPR, 288 patients were identified, with 40% surviving to hospital discharge. Venoarterial ECMO was used in 99% of patients, and 63% underwent cannulation through an open chest. Median length of stay on ECMO was 4.3 days. The overall occurrence of complications was high (59%). The most commonly occurring complications were neurologic (27%), renal (25%), sepsis (17%), bleeding (7%), and multisystem organ failure (9%).[102]

Another review from the National Registry of CPR found 199 pediatric patients who were treated with ECMO during arrest with an overall survival rate of 44%. In 59 survivors who had their neurologic outcome recorded, 95% had favorable outcomes based on Pediatric Cerebral Performance Scores. By multivariate analysis, renal insufficiency, metabolic or electrolyte abnormality at the time of arrest, and use of sodium bicarbonate or tromethamine were associated with decreased rates of survival. Underlying cardiac illness was associated with an increased rate of survival to discharge.[103]

No definitive criteria exist for patient selection and management for ECPR. One cautionary note is that cardiac patients often are reported to have improved outcomes when compared with noncardiac patients. Whether this finding represents disparity in access to ECPR between cardiac and noncardiac patients, underlying pathophysiology, or other factors requires ongoing study. An addendum to the ELSO registry that has been specifically designed for patients experiencing cardiac arrest may provide more detailed information to answer ongoing questions.[104,105]

Trauma Patients

Trauma patients, particularly those with multiple injuries, are at risk of respiratory failure. Trauma remains the leading cause of death in young adults. Common pathophysiological mechanisms include direct chest injury causing pulmonary contusion, long bone or pelvic fractures causing fat embolization, or as an inflammatory-mediated event following systemic injury known as acute respiratory distress syndrome. Extracorporeal membrane oxygenation provides "lung rest" by permitting reduced ventilator settings and limiting further barotrauma while maintaining tissue perfusion and oxygenation. In this study comprising 28 adult patients treated with ECMO because of trauma-related respiratory failure, 20 patients were successfully weaned off ECMO and discharged. Eight patients died as a result of overwhelming sepsis and irreversible cardiogenic shock.[106] Good outcomes in pediatric patients undergoing ECMO following trauma also have been reported.

A newly funded National Institutes of Health trial of penetrating trauma resuscitation by means of an extracorporeal life support variant holds interest for the future. This protocol involves placement of a femoral arterial cannula in the descending aorta, above which a balloon is inflated and a cold flush solution is delivered to the upper body (heart/brain). This procedure results in a state of suspended animation, allowing the patient to be taken to the operating suite for definitive repair of injuries; bypass then allows rewarming and recovery.

Other applications of ECMO include management of patients with extreme hypothermia who require gradual extracorporeal rewarming. Trauma patients with massive hemorrhage and ongoing coagulopathy from transfusion-related hypothermia also have received short-term extracorporeal support with bypass to facilitate rewarming to temperatures

that help normalize the coagulation process. Once rewarming is achieved, cannulas are withdrawn.

Patient Selection Criteria

Various mortality prediction criteria have been put forth as indicators of when ECMO rescue is best applied, although many of these criteria have been derived from small series of historical data for patients with respiratory failure or were extrapolated from neonatal respiratory failure data.[107-110] Attempts to provide universally accepted criteria for institution of ECMO have proved difficult.

The predominant listed criteria for treating a pediatric patient with ECMO remains "failure to respond." Although no strict definition of what failure to respond entails exists, the basic premise may be interpreted as a determination by the clinician who is caring for the patient that current support is insufficient and death is imminent without ECMO rescue. More than 50% of pediatric patients treated with ECMO who were reported to the ELSO registry have failure to respond as the major criteria for initiation of ECMO.

For the majority of patients who undergo ECMO, less invasive methods of respiratory support have failed.Such methods of support often include conventional mechanical ventilation in pressure control or pressure-regulated volume control modes, high PEEP, HFV, surfactant, or iNO. An evaluation of the ELSO registry noted that in pediatric patients who underwent ECMO, use of both iNO and high-frequency oscillatory ventilation prior to ECMO was associated with poorer outcome than in patients who received neither or only one of these modalities prior to ECMO (H.J. Dalton and P. Rycus, unpublished data, 2004). Examples of selection criteria used for ECLS in the past include the following:

1. Requirement for Fio_2 greater than 60% to maintain arterial oxygen saturation more than 85% to 90% despite high PEEP
2. Mean airway pressures higher than 20 cm H_2O on conventional mechanical ventilation
3. Mean airway pressures higher than 25 to 35 cmH_2O on HFV
4. Evidence of ongoing barotrauma in the form of air leak or pulmonary interstitial edema
5. An oxygenation index (OI) of greater than 40, where OI = (100 × [Mean airway pressure × Fio_2])/Pao_2
6. Mechanical ventilation less than 7 to 14 days
7. Lack of an underlying irreversible illness
8. Lack of known significant neurologic damage
9. Lack of an ongoing bleeding diathesis
10. Inability to ventilate

Concern has been expressed that respiratory severity indices reported in the past are not applicable to patients of today who experience respiratory failure, although few recent reports compare past severity indices to outcome in the current era. One recent report examined the current utility of respiratory severity indices used in the past for potential ECMO eligibility in 118 children with acute hypoxemic respiratory failure.[99] Indices examined included the $AaDO_2$, OI, Pao_2/Fio_2, ventilation index, and mean airway pressure (Paw), as well as individual ventilator settings and arterial blood gas values. When risk of mortality based on respiratory severity indices predictions were compared with actual mortality observed in these 118 children, survival was much better than would have been predicted based on historical data.[111] As an example, an OI greater than 40 has been associated with more than 80% risk of death in the past. Although only 15 patients reached an OI greater than 40 in this study, the positive predictive risk of mortality in these patients was 40%, significantly lower than predicted by past reports. An $AaDO_2$ greater than 450 for 24 hours, Paw higher than 23, or $AaDO_2$ higher than 420 had positive predictive value for mortality rate of 32% to 40%. Using logistic regression, no respiratory parameter ($AaDO_2$, OI, Paw, ventilator settings, or blood gas values) was independently correlated with death. All deaths were associated with multiorgan system failure, coincident pathology, or perceived treatment futility, leading to limitation or withdrawal of care. The overall mortality rate of these 118 children was 22%, with no previously healthy child dying from respiratory failure. Nonconventional therapies applied included HFV in 25 (21%) of 119 (64% survival), surfactant administration in 15 (13%) of 119 (73% survival), iNO in 38 (32%) of 119 (69% survival), and ECMO in 4 (3%) of 119 (75% survival) of patients.

In another review of factors associated with death in children with severe respiratory failure, the peak oxygenation index and pediatric risk of mortality (PRISM) score were found to be independent predictors of outcome, although no definitive OI cutoff that predicted death could be identified.[112] Using this parameter as a tool to serially assess the severity of hypoxemic respiratory failure is useful.

Gas Exchange and Oxygen Delivery

Oxygenation

The difference between the PO_2 in the gas supplied to the oxygenator and that in the patient's systemic venous blood provides the "driving pressure" across the membrane lung. As an example, 30% oxygen blended into the gas entering the oxygenator will result in an estimated PAo_2 about 228 torr at sea level. The PO_2 of venous blood entering the oxygenator depends on the difference between oxygen delivery and consumption in the patient, but is usually about 40 torr. The driving pressure for oxygen diffusion into the blood thus would be approximately 188 torr (228 torr – 40 torr = 188 torr), which is usually adequate to achieve 100% saturation of hemoglobin. Higher oxygen concentrations in the gas phase may be necessary to compensate for loss of membrane surface area over time to maintain hemoglobin saturation. At post-oxygenator oxygen saturations greater than 95%, increasing the oxygen concentration of the sweep gas has little incremental effect on blood oxygen content. For this reason, oxygen concentration in sweep gas usually is adjusted to maintain an oxygen saturation of approximately 95% in postoxygenator blood.

Carbon Dioxide Exchange

The pressure gradient for carbon dioxide between blood and gas is less than that for oxygen. The partial pressure of carbon dioxide in the body is usually low (the venous partial pressure of carbon dioxide, $Pvco_2$, is 45 to 55 torr), so that the pressure difference between the blood and gas phase in the oxygenator is much less than it is for oxygen. Despite the small pressure difference, the membrane's high diffusion coefficient for carbon dioxide (at least six times that for oxygen) allows excellent carbon dioxide removal, even at low flow rates.

To eliminate more carbon dioxide, the gas flow in the membrane must be increased, much as alveolar ventilation must increase to eliminate carbon dioxide from the body under physiologic conditions. Carbon dioxide removal is also limited by the surface area across which gas exchange can occur. Thus increased carbon dioxide clearance may be obtained by using larger oxygenators or using more than one oxygenator in parallel in the circuit. Conversely, to prevent excessive CO_2 removal and hypocapnia in small infants and neonates, carbon dioxide may be blended into the gas mixture to further reduce the partial pressure difference between blood and gas and maintain normocarbia.

Oxygen Delivery

During venoarterial ECMO, both increasing oxygen delivery and increasing the patient's Pao_2 and arterial saturation can be accomplished by increasing the ECMO flow rate. This strategy diverts more of the systemic venous return into the ECMO circuit for oxygenation while at the same time proportionally decreasing the amount of venous blood that enters the diseased pulmonary circuit. The result of increasing ECMO flow, then, will be an increase in oxygen delivery provided by the circuit and an elevation in measured systemic arterial saturation and Pao_2. Another means to change the proportion of native blood flow to that from the ECMO circuit is to decrease the overall blood volume in the patient. During cardiopulmonary bypass, filling pressures and overall blood volume can be adjusted by removal of blood volume into the bypass circuit. Circulating volume is also frequently decreased by modified ultrafiltration. During ECMO, these same principles can be followed: excessively high filling pressures can be lowered by simple removal of blood volume from the circuit, and diuretics and renal replacement strategies can be used to control fluid balance. Care must be taken, however, to avoid decreasing circulating volume excessively, because this may in turn cause tissue hypoperfusion or an increase in oxygen extraction.

Systemic oxygen delivery is defined as the product of cardiac output and arterial oxygen content.[113] By altering the amount of cardiac output diverted from the patient to the ECMO circuit, venoarterial ECMO can be "complete" or "partial." In the patient undergoing complete venoarterial ECMO, the cardiopulmonary circuit is almost totally bypassed and oxygen delivery is determined by the product of pump flow and the oxygen content of blood leaving the oxygenator. Most centers use partial venoarterial ECMO because adequate systemic oxygenation can be achieved by diverting 60% or more of cardiac output to the ECMO circuit. Studies have suggested that complete bypass of the pulmonary circuit may lead to pulmonary alkalosis or ischemia and cause direct damage of the pulmonary capillary bed.[114] Microsphere studies have shown that the majority of coronary artery perfusion comes from native left heart ejection during ECMO, which is another reason to avoid total bypass.[115] Monitoring of adequate oxygen delivery is aided by following venous saturation.[116] Most ECMO circuits contain a sensor along the venous return line that measures and displays venous saturation. Other centers use an in-dwelling blood gas monitor for the same purpose. Low venous saturation and other markers such as elevated lactate, poor perfusion, decreased urine output, and mental status changes may indicate the need for improved oxygen delivery. If ECMO flow cannot be increased to provide adequate support, an additional drainage cannula to augment ECMO flow and allow increased support may be needed.

In patients who undergo cannulation via the venovenous route, reduced systemic oxygenation will be observed compared with patients with venoarterial ECMO. This reduced systemic oxygenation is a result of the lower amount of native cardiac output that can be processed by the oxygenator and recirculation effects that limit the return of oxygenated blood to the patient from the ECMO circuit. Persistent signs of inadequate oxygen delivery or continued hemodynamic instability with venovenous ECMO may require conversion to venoarterial ECMO. Patients receiving venovenous ECMO support or who have a left atrial communication to the ECMO circuit may have artificially high measured venous saturations because of mixing of well-oxygenated blood with systemic venous return. Monitoring venous saturations from another site in the body may be helpful to monitor adequacy of support in this circumstance.

One novel means of improving oxygenation to the head and upper body in patients who have undergone cannulation through the bilateral femoral veins is to add an additional venous cannula via the right IJ vein to the right atrium. Connecting this cannula to the inflow return side of the ECMO circuit will increase the amount of oxygenated bypass directly returning to the right heart. This procedure may improve overall oxygen delivery to the patient while still avoiding the need for arterial vessel cannulation.

Loose occlusion of the roller heads against the raceway tubing also can lead to less blood being propelled forward through the ECMO circuit and reduce systemic oxygen delivery. In centrifugal pumps, low head revolutions also can result in inadequate forward flow of blood to the patient, and if the patient's arterial blood pressure is higher than that generated within the centrifugal circuit, arterial blood can flow from the patient into the centrifugal circuit. Increasing the revolutions per minute in the pump head will reverse this problem. Persistent vasodilation, which occurs in patients with sepsis, may require the administration of low levels of vasoconstricting agents to maintain adequate central venous pressures and adequate pump return without massive fluid administration

Patient Management

Screening

Infants who are candidates for ECMO undergo routine cranial ultrasonography to identify existing intracranial hemorrhage.[117,118] The presence of hemorrhage greater than that confined to the germinal matrix (grade I) is a contraindication to ECMO, because heparinization may cause additional bleeding. Older patients also may have evaluation of intracranial bleeding by ultrasound if an open fontanelle is present. Computed tomography also can be useful if the patient is stable enough to undergo such an examination. Frequently, however, older patients are not stable enough to undergo a computed tomography scan, and a clinical neurologic evaluation may be hampered by sedation or neuromuscular blockade prior to ECMO. The decision to treat a patient with ECMO thus is made on the best assessment of neurologic function. Echocardiography is usually performed prior to institution of ECMO to determine if hypoxia is a result of structural defects in the heart, which may be better served by surgical repair

than by ECMO support. Echocardiography also can identify ventricular dysfunction, pulmonary hypertension, and pericardial effusions; all these data are useful to properly manage the patient and to select the optimal form of ECMO or even to avoid it if less invasive procedures can be undertaken. ECHO also is used to detect the presence and direction of central shunts within the cardiac system.[119,120]

Interhospital transport of patients either for ECMO consideration or those for whom ECMO was initiated at a non-ECMO facility is a challenge. Transporting patients undergoing ECMO can be technically challenging and expensive. At present in the United States only three facilities routinely provide this service. One single center report found no statistical difference in survival rates for patients for whom ECMO was initiated in their center compared with patients who underwent cannulation at an outside facility and were brought to their center while receiving ECMO support. The logistics involved with such endeavors require meticulous planning. The transport team consisted typically of an ECMO coordinator, pediatric cardiac surgeon, surgical assistant, and intensivist. The predominant mode of transport was by helicopter (75%). No patient died during transport. Whether increased use of ECLS will occur and the need for ECMO transport capabilities throughout the United States will increase is unknown at this time. This is one area where regionalization of such services might prove practical.[121]

Cannulation and Initiation of Extracorporeal Life Support

A guideline for selection of cannula size and circuit components based on patient weight is shown in Table 53-6 (cardiac and respiratory failure patients).

Cannulation is usually performed at the bedside, with the patient receiving a combination of local anesthetics and intravenous analgesics, sedatives, and neuromuscular blocking drugs. An initial bolus of heparin (usually 50 to 100 units per kg) and continued heparin infusion ensures systemic anticoagulation for the duration of ECMO. Activated clotting time, measured at the bedside, provides a gauge for adjusting the heparin dose to avoid either catastrophic clotting in the circuit or bleeding complications.[122] The ECMO flow is initially begun at 50 mL/kg/min and is increased in 50- to 100-mL increments. In infants, a rate of 100 to 200 mL/kg/min usually provides adequate perfusion and oxygenation, although patients in a state of high cardiac output, such as sepsis, may require a higher rate. Use of high-flow ECMO also is recommended in patients with single ventricle physiology and a systemic-to-pulmonary artery shunt to provide adequate circulation for both systemic and pulmonary organs.[123] Pediatric patients usually require about 90 mL/kg/min of ECMO flow to maintain adequate oxygen delivery, and adult patients require rates of 50 to 70 mL/kg/min. Estimates of flow needs also can be predicted by using cardiac index data based on body surface area (BSA). One caution in estimating ECMO flow in this manner is that patients with sepsis or multiple organ dysfunction may require flows that are much higher than predicted. These factors must be taken into account when selecting cannula size, because larger cannulas than that predicted by BSA may be required. Patients with sepsis or critical illness may require flows that are higher than that predicted from BSA algorithms. In venoarterial ECMO, the arterial waveform provides a rough estimation of the degree of bypass provided by the ECMO circuit. Because ECMO flow is nonpulsatile, increasing flow and decreasing left ventricular output will result in a flattening of the arterial wave contour and a narrowing of the pulse pressure. Severe myocardial dysfunction also may cause a flattened wave contour because left ventricular output may be minimal. This effect must be kept in mind when waveform contour is used to monitor the extent of bypass.

Priming

Priming of the ECMO circuit prior to initiation is accomplished with a crystalloid solution that is then replaced with blood. Because required blood usually has been citrated and stored, it may be acidotic, depleted of calcium, and have a high potassium level. Calcium (usually as calcium chloride), bicarbonate or tromethamine, and heparin are added during the priming procedure. Electrolytes should be measured in the priming blood before bypass is begun, because disturbances of cardiac rhythm or frank cardiac arrest can occur upon initiation of ECMO.[124] Hyperkalemia exists almost universally in the ECMO primed circuit despite buffering by calcium and bicarbonate. The potassium level rarely causes systemic effects once the ECMO prime is diluted with the patient's intrinsic blood volume. As an example, if a neonatal patient with a

Table 53–6 Sample Component Requirements Based on Weight for Extracorporeal Life Support (Respiratory and Cardiac Support: Roller-Head Pump)

	Weight (kg)					
Material	**2.5–6**	**6–12**	**12–25**	**25–40**	**40–70**	**70+**
Tubing pack (inches)	¼	¼	⅜	⅜	½	½
Raceway (inches)	¼– 3/8	⅜	⅜–½	½	½	½
Oxygenator	0800	1500	1–2500	1–3500	1–4500	1–4500 ×2
Venous cannula (French)	10–15	14–19	17–19	19–21	19–23	19–29
Chest venous cannula (French)	16	20	22	24–28	28–32	32–36
Arterial cannula (French)	8–12	12–15	14–17	17–21	17–21	19–23
Blood prime (units of packed red blood cells)	1	1–2	2–3	3–4	4	4–5

Modified from University of Michigan, Ann Arbor, MI, and Children's National Medical Center, Washington, DC.

blood volume similar to that of the ECMO circuit has a potassium level of three and the ECMO prime has a potassium level of seven, the circulating potassium level may be around five upon ECMO initiation. This scenario is unlikely to cause systemic or cardiac effects. Larger patients with blood volumes proportionally much greater than that of the ECMO circuit will have less risk of hyperkalemia or hypocalcemia. Use of the freshest blood available also may lessen the degree of hyperkalemia in the primed circuit. Rarely, hyperkalemia may be of such concern that blood must be washed prior to ECMO use or the primed ECMO circuit cannot be used until the potassium level is reduced. In this circumstance, blood in the circuit is replaced with fresh frozen plasma or albumin to lower the circulating potassium concentration in the prime.

Patient Management During Extracorporeal Life Support

Hypovolemia causes low central venous pressures and results in decreased venous return to the circuit. This situation can be corrected easily with fluid administration. Increased oxygen delivery also can be accomplished by increasing the pump flow rate, which increases blood diverted into the ECMO circuit for oxygenation. Anemia can be corrected with transfusion of blood products. Maintenance of hemoglobin is needed to sustain adequate oxygen content.[125,126] Although clinicians disagree about the level of hemoglobin needed during ECMO, all clinicians agree that transfusion up to a hemoglobin level of 14 to 15 g/dL gives the greatest amount of support. Patients who have a hemoglobin level much lower (10 g/dL) also may do well. The needs of the patient and the risks of transfusion are a balance that the clinical team assesses on an ongoing basis. Treatment of sepsis requires identification of the responsible organisms and initiation of antibiotic therapy.

Intermittent administration of packed red blood cells to maintain adequate blood volume and hematocrit will be required.[127-129] Fresh frozen plasma also may be given intermittently to provide adequate clotting factors and help prevent excessive bleeding.[130] Platelet sequestration in the ECMO circuit is a constant problem. Historically, platelet counts of 80,000 to 100,000/mm^3 have been maintained routinely for patients undergoing ECMO to deter bleeding, but multiple examples now exist of patients undergoing ECMO with thrombocytopenia of 30,000/mm^3 or lower and in whom massive bleeding was not a problem. Although patients often require frequent platelet transfusions, the capacity of transfusions to increase platelet counts to high levels may be limited in some patients, such as those with cancer. In such patients, lower platelet counts may be allowed and careful monitoring for bleeding is maintained.

Another recently identified problem with ECMO, especially for prolonged runs, is heparin-induced thrombocytopenia (HIT). HIT should be suspected in any patient receiving heparin when a drop in platelet count occurs that is unresponsive to platelet transfusion or when the platelet count continues to fall without an identified reason. Although HIT usually develops 5 to 15 days after the initial exposure to heparin, it can occur immediately in patients with previous exposure to heparin, such as patients who have undergone cardiac surgery. HIT associated with immune response to heparin can result in severe thrombocytopenia. The only "cure" is to stop the patient from being exposed to heparin. During ECMO, stopping exposure to heparin necessitates the use of other anticoagulation methods. Currently, lepirudin and Argatroban are the two alternatives that have been commented upon with regard to ECMO, although neither is widely used in the pediatric population in general.[131-133]

Lepirudin is a derivative of the leech anticoagulant hirudin. Two reports of its use during ECMO noted no bleeding or clotting complications. It works rapidly and has a relatively short half-life of 1.3 hours, and the dosage is determined on the basis of weight. In one pediatric report a 0.1 mg/kg bolus was administered followed by an infusion of 0.12 mg/kg/h and the patient was monitored to maintain the activated partial thromboplastin time at two times the control level. Use of lepirudin is relatively contraindicated in patients with renal failure.

Argatroban is also a direct thrombin inhibitor approved for use in patients with HIT. It is metabolized predominantly by the liver but excreted normally even in patients with severe renal failure. In one report of two infants with congenital diaphragmatic hernia and HIT who were treated with Argatroban at a dose of 0.5 to 10 μg/kg/min to maintain activated clotting time around 200 seconds, the infants had no associated bleeding or thrombotic complications. Another report of thrombin production in ECMO circuits comparing heparin-prepared circuits with Argatroban-primed circuits found that the circuits primed with Argatroban had less thrombin generation.[134] Thrombocytopenia due to platelet antibodies also has been described.

Adequate nutrition is essential for healing and is provided as total parenteral nutrition, enteral feeding, or a combination of both. The old concern of lipids potentially causing either platelet malfunction (bleeding) or increased lung damage from metabolism of arachidonic acid seems to have died away. Anecdotally lipids have been associated with shortened circuit lifespan and with the development of cracks in stopcocks used to connect the lipid infusion line to the ECMO circuit. [135] Use of lipids also may be associated with a shortened lifespan of hollow-fiber oxygenators. Enteral feeding has been shown to be safe and effective during ECMO and may limit the need for total parenteral nutrition with its associated complications.[136,137]

Currently, maintaining strict fluid balance in critically ill patients is popular, and patients undergoing ECMO are no exception. The use of diuretics, concentrated drug infusions, and hemofiltration in patients with renal insufficiency are other important aspects of patient care.[138,139] Renal failure, hypervolemia, and fluid overload are frequently seen in patients undergoing ECMO. Use of continuous renal replacement therapies (CRRTs) has become commonplace during ECMO, both to maintain fluid balance, support failing kidneys, and potentially clear "bad humours" from the blood. One of the proposed mechanisms for development of acute renal failure (ARF) in patients undergoing ECMO is a reduction in the pulsatile character of renal perfusion. Circuit-associated hemolysis in patients receiving CRRT also can perpetuate ARF. The most widely used technique for providing CRRT is to connect a hemofiltration filter into the ECMO circuit and to control the ultrafiltrate volume using an intravenous infusion pump.[140]

A study that examined acute renal failure in patients who were undergoing ECMO and required CRRT noted that ARF was present in 70% of patients and CRRT was initiated in 58% of patients. The study concluded that the odds of developing

ARF increased with duration of ECMO support. Patients undergoing ECMO in whom ARF developed had a 4.7-fold increase in the odds of inhospital mortality.[141]

One recent abstract noted that CRRT with continuous venovenous hemofiltration (CVVH) was used in 27 (32%) of 84 pediatric patients undergoing ECMO, usually to maintain fluid balance. Overall survival was 75% for patients with respiratory failure. Of these 84 patients, 27 were matched for age, diagnosis, and PRISM III score with patients undergoing ECMO who did not receive CVVH. Improved fluid balance over time, less use of diuretics, and the tendency to reaching caloric-intake goals more quickly were noted in patients undergoing renal replacement. No difference was found in survival (67% CVVH, 82% non-CVVH, $P = .352$), duration of ventilation after ECMO, or the need for potassium supplementation between groups.[142] Data from the ELSO registry shows that about 30% of pediatric and adult patients undergoing ECMO undergo renal replacement either by hemofiltration or dialysis, although elevations of creatinine greater than 1.5 were reported in only 15% of pediatric patients. Other adjunct extracorporeal therapies such as plasmapheresis or liver support systems also have been used successfully during ECMO.

The optimal ventilatory management for patients undergoing ECMO is not known, and each center may have its own preference for how to treat the lungs during ECMO. Minimizing further barotrauma or oxygen toxicity and providing an environment that promotes lung healing are basic goals. For neonatal patients undergoing venoarterial ECMO, most centers use ventilator settings with low peak inspiratory pressure (PIP) (25 to 30 cm H_2O), PEEP (5 cm H_2O), intermittent mandatory ventilation rate (6 to 12 breaths/min), and fraction of inspired oxygen (Fio_2, 0.21). Lung volume decreases dramatically with such settings in most patients undergoing ECMO, resulting in generalized opacification on the chest radiograph. Maintaining lung expansion and functional residual capacity with higher levels of PEEP (10 to 15 cmH_2O) was associated with shorter ECMO durations in one neonatal study, and this approach is used frequently at many centers.[143] Given the recent evidence supporting the role of atelectasis in ongoing cytokine production, maintaining some lung distention with PEEP even during ECMO seems prudent. In older patients, use of PEEP with reduced peak airway pressures, low ventilator rates, and low concentrations of inspired oxygen is also the predominant method of support. Commonly, PEEP levels in the range of 5 to 15 cm H_2O, PIP less than 30 cm H_2O, and breath rates of 10 to 12 with inspired oxygen concentrations between 30% and 40% are reported in the pediatric and adult ECMO literature.

Patients with barotrauma and persistent air leaks even at low distending airway pressures on ECMO may benefit from a period of total apnea to allow the lungs to rest.[144] The technique of allowing airway pressure to equilibrate with atmospheric pressure has been used successfully to promote healing of ruptured parenchyma within 48 to 72 hours. Reinflation is accomplished by lavage to remove accumulated secretions, hand ventilation to begin recruiting collapsed alveoli, and then resumption of mechanical ventilation to complete alveolar reexpansion. Use of HFV to improve lung recruitment, bronchoscopy to remove inspissated secretions, and prone positioning to improve lung mechanics have all been used successfully in patients undergoing ECMO. Surfactant also has been given to improve oxygenation and lung mechanics, although data on its effectiveness during ECMO is lacking.

At high flow rates in patients undergoing venoarterial ECMO, a minimal amount of blood is entering the pulmonary circuit. Manipulating ventilator settings, especially in patients with diseased lungs with impaired gas exchange, has little effect on blood gas tensions. Oxygenation and carbon dioxide elimination depend on the function of the ECMO circuit. With venovenous cannulation, less overall bypass is obtained, and the systemic oxygenation provided by ECLS is less than with venoarterial access. Arterial oxygen saturations are thus lower with venovenous support. While the majority of patients do well with saturations in the 80s, monitoring of adequate oxygen delivery by following lactate, venous saturation, urine output, metabolic acid-base balance, and mental status is recommended with these patients.

Increasing oxygenation over time may herald recovery of native pulmonary function. As the lungs heal, compliance and tidal volume increase.[145] The radiograph of the lung fields gradually improves from atelectatic opacification to increasing lung aeration. Increasing concentration and absolute volume of expired carbon dioxide also heralds improved alveolar/capillary gas exchange. These changes, along with evidence of decreasing pulmonary artery pressure (indicated by resolution of right-to-left intracardiac shunting), may signal that the patient is ready to be weaned from ECMO.[146]

Maintaining patient comfort during ECMO can be a challenge, especially in prolonged ECMO runs. Sedation and analgesia are provided by routine medications such as morphine, fentanyl, midazolam, lorazepam, and other agents. If lorazepam infusions are used, intermittent osmolality and the osmol gap should be calculated to prevent propylene glycol toxicity.[147] Medications may be absorbed by the membrane oxygenator, and patients can become tolerant to them over time.[148] The extraordinary amount of medications some patients require has led some centers to use anesthesia gas in the membrane oxygenator, although a protocol for appropriate scavenging of these gases must be developed for use. European centers are facile in maintaining patients in a "normal" awake state in which they can play games, read books, and even eat during their ECMO course. Nursing and family support play a major role in the success of providing ECMO with little sedation.

Weaning from Extracorporeal Membrane Oxygenation

A patient can be weaned from ECMO in several ways. The most common mode involves reducing the ECMO flow rate in increments every 1 to 2 hours, provided that arterial and mixed venous oxygen saturations remain adequate. Once ECMO flow is reduced to provide only about two thirds of cardiac output, ventilator support is increased (PIP 20 to 30 cm H_2O, intermittent mechanical ventilation 20-30, PEEP 5 cm H_2O, and Fio_2 30% to 40%). Weaning continues to an ECMO flow of 50 to 100 mL/min in infants or an estimated 10% of cardiac output. If the patient remains physiologically stable with acceptable blood gas tensions at this low flow, the ECMO cannulas are clamped and the infant is observed while off ECMO support for a short time. If respiration and circulation remain stable during the trial, the cannulas are removed and conventional therapy is resumed. Quicker weaning

methods involve decreasing ECMO flow in larger increments over shorter periods, similar to the way it is performed during cardiopulmonary bypass in the operating room.[149]

Complications

Complications that occur during ECMO can be mechanical or related to the particular patient. The most common adverse events reported to the ELSO Registry are shown in Table 53-7 (patients with respiratory failure) and Table 53-8 (cardiac patients).

Table 53–7 Mechanical and Patient-Related Complications for Respiratory Population

Complication	Neonatal Respiratory n (%)	Pediatric Respiratory n (%)	Adult Respiratory n (%)
MECHANICAL			
Oxygenator failure	5.9 (53)	13.3 (44)	19.3 (43)
Tubing rupture	0.6 (72)	2.7 (47)	2.5 (30)
Pump malfunction	1.7 (67)	2.8 (46)	3.0 (33)
Cannula problems	11.5 (68)	15.3 (50)	9.1 (39)
PATIENT-RELATED			
Gastrointestinal hemorrhage	1.7 (45)	4.2 (25)	4.2 (21)
Cannula site bleeding	6.9 (65)	14.4 (51)	14.9 (44)
Surgical site bleeding	6.2 (45)	14.7 (46)	19.8 (36)
Hemolysis	11.1 (65)	9.3 (43)	7.1 (27)
Brain death	1.0 (0)	5.7 (0)	4.2 (0)
Seizures: clinically determined	9.9 (61)	6.2 (35)	1.5 (36)

Modified from Extracorporeal Life Support Organization: *International ECMO registry report of the Extracorporeal Life Support Organization,* Ann Arbor, MI, 2009, Extracorporeal Life Support Organization.

Bleeding

Bleeding as a result of the systemic heparinization required with ECMO is the major complication associated with ECMO.[150] Whereas bleeding occurs predominately from cannulation or surgical sites, intracranial hemorrhage is the most dreaded site for bleeding to occur. Intracranial bleeding occurs in approximately 11% of patients overall, with the rate highest in the neonatal patient and lowest in the adult population. Bleeding that occurs outside the head that cannot be controlled with medical means requires surgical investigation. Although obvious risks accompany surgical intervention in a bleeding patient who has undergone systemic anticoagulation, many operative repairs have been accomplished during ECMO support.[151] Initial attempts to control bleeding focus on decreasing the rate of heparin infusion and lowering activated clotting time levels. Limitation of heparin may put the circuit at risk for increased clotting, especially at lower flow levels. This risk must be balanced against the bleeding risk.

Medications to help prevent clot breakdown in the patient also are used. Historically, aminocaproic acid, also known by the trade name Amicar, has been the predominant medication used during ECMO.[152] An antifibrinolytic amino acid, Amicar displaces plasminogen from fibrin and inhibits clot breakdown. Although a recent survey found that a wide range of doses are used, one common algorithm follows a dosage scheme of 100 mg/kg as a load followed by an infusion of 25 to 50 mg/kg/h. Although it has been used in ECMO centers for many years, a recent randomized controlled trial of Amicar versus placebo in neonates found no difference between groups in the need for transfusion or the need for circuit changes due to thrombosis. More recently, aprotinin was a favored agent in many centers.[153] A serine protease inhibitor, aprotinin is an anti-fibrinolytic agent that inhibits protein C and factors Va and VIIIa in the extrinsic coagulation pathway and inhibits the intrinsic pathway as well. It also preserves platelet function, reduces vascular permeability, and has been suggested to decrease the inflammatory response to cardiopulmonary bypass. Aprotinin has not been compared

Table 53–8 Mechanical and Patient-Related Complications for the Cardiac Population

Complication	0-30 Days n (%)	31 Days to <1 Year n (%)	1 Year to <16 Years n (%)	≥16 Years n (%)
MECHANICAL				
Oxygenator failure	7.5 (22)	8.4 (27)	9.2 (40)	20.0 (30)
Tubing rupture	0.7 (27)	0.8 (20)	1.4 (31)	0.6 (29)
Pump malfunction	1.6 (29)	2.1 (34)	2.3 (37)	1.2 (21)
Cannula problems	6.3 (35)	5.7 (38)	7.0 (41)	5.8 (30)
PATIENT-RELATED				
Gastrointestinal hemorrhage	1.0(8)	2.0 (14)	2.9 (27)	3.5 (17)
Cannula site bleeding	9.8 (27)	10.6 (38)	16.1 (49)	19.5 (35)
Surgical site bleeding	32.0 (29)	34.5 (37)	30.0 (45)	29.3 (30)
Hemolysis	10.8 (28)	9.4 (34)	8.3 (41)	12.0 (28)
Brain death	1.2 (0)	3.9 (0)	7.9 (0)	7.5 (0)
Seizures: clinically determined	7.8 (29)	9.6 (26)	5.2 (22)	3.2 (15)

Modified from Extracorporeal Life Support Organization: *International ECMO registry report of the Extracorporeal Life Support Organization,* Ann Arbor, MI, 2009, Extracorporeal Life Support Organization.

in a randomized fashion to Amicar or placebo during ECMO. Aprotinin is administered as a loading dose of 10,000 units/kg and continued at an infusion rate of 10,000 units/kg/h. Reports in adult patients of an increase in renal failure and poor outcome in cardiac patients receiving aprotinin during bypass surgery has caused it to be removed from the market at this time. Circuit thromboses may be noted with use of Amicar or aprotinin.

Several recent reports of intractable bleeding on ECMO have commented on the benefits of factor VIIa, although the data regarding this medication are still too sparse to recommend it without further investigation.[154] In a recent study, use of R factor VIIa was noted to be effective in decreasing chest tube bleeding from 47 to 10 mL/kg/h in four patients with refractory hemorrhage. Each patient received two doses of R factor VIIa (dose, 90 to 120 μg/kg) 4 hours apart.[155]

In another report, 92% of patients undergoing ECMO with bleeding responded to R factor VIIa therapy. A significant reduction in chest tube bleeding was noted, along with a significant reduction in the administration of blood products. Major thrombosis was noted in two of the patient who received R factor VIIa therapy.[156]

Other centers have reported decreased bleeding with lower doses of R factor VIIa administration; they have administered 40 μg/kg and then increasing the dose to 90 μg if bleeding continued. Anecdotal reports of thrombosis with factor VIIa are more frequent than those found in the literature, and thus careful assessment of risks and benefits should be undertaken prior to factor VIIa use.

Discontinuation of heparin to help control intractable bleeding also can be beneficial and has been used for variable periods, up to 36 hours or more, without significant clotting in the ECMO circuit.[157] Larger patients with faster ECMO flow rates are more likely to tolerate discontinuation of heparin without significant clotting. However, it is wise to have a backup circuit readily available if clotting does occur and the ECMO system requires an emergent replacement.

Infection

Infection is another potential complication of ECMO.[158] Colonization of indwelling catheters, selective adherence of bacteria to polyurethane surfaces, sequestration of bacteria from the body's normal antibody and phagocytic defense mechanisms, and the patient's prior debilitated state are all factors that may increase the risk of infection.[159,160] Successful therapy may be difficult without eliminating invasive equipment, most significantly the ECMO catheters. Viral infection from blood transfusions may occur rarely. The risk may be limited by minimizing the exposure to blood products from multiple donors with multi-aliquoted, sequentially dispensed units of packed red cells. Although sepsis (which was either preexisting or developed as the patient underwent ECMO) was once seen as a reason to exclude patients from ECMO support, several reports have demonstrated that sepsis can be cleared and septic patients can be treated successfully with ECMO. In fact, the most recent guidelines for hemodynamic support of pediatric patients with septic shock note that ECMO should be considered in patients with refractory catecholamine-resistant shock.[161] Although some debate still occurs about whether patients in a state of high-cardiac output shock will obtain any benefit from augmenting cardiac output further with ECMO, such patients have been treated successfully with ECMO support.[162]

Long-Term Outcome

Patients undergoing ECMO are at risk of neurologic damage from hypoxia, acidosis, hypotension, induced alkalosis prior to ECMO, and hemorrhage or ischemia related to systemic heparinization and alterations in cerebral blood flow following ligation of the carotid artery and internal jugular vein.[163-168] Nevertheless, two thirds of neonates who survive respiratory failure appear to have a normal neurodevelopmental outcome. The remaining third experience mild to severe deficits in motor or cognitive function. Sensorineural hearing loss has been noted in 23% of patients, an incidence comparable with that in infants with persistent pulmonary hypertension who are treated conventionally. The long-term effects of carotid artery and jugular vein ligation are unknown.

Severe chronic respiratory disease in patients treated with ECMO is uncommon.[169] Most reports relate an incidence of bronchopulmonary dysplasia (defined as the need for oxygen beyond the first month of life) from 4% to 27%. Most cases occurred in patients who had required extreme ventilator settings for more than 7 days before ECMO rescue. A follow-up report of neonates treated with ECMO who were evaluated at 10 to 15 years after ECMO found that although they had some diminished lung function by pulmonary function testing, they had similar aerobic capacity and were able to reach anaerobic exercise goals similar to those of age-matched healthy control subjects.[170]

Of 4000 pediatric respiratory ECMO patients listed in the Registry through July 2009, 9% had intracranial infarct or hemorrhage found on computed tomography examination. Brain death occurred in 6% of the patients, and 6% of patients had reported seizures. Long-term neurologic outcome data are sorely missing in the pediatric population. Few centers maintain regular follow-up clinics, and patients often are referred for ECMO from distant sites, which makes follow-up difficult as well. In one report of 15 pediatric and four adult patients, 58% survived to discharge. Patients were evaluated with use of the Pediatric Cerebral Performance Category (which measures cognitive impairment) and the Pediatric Overall Performance Category (which measures functional morbidity). Overall, 64% of survivors had normal Pediatric Cerebral Performance Category scores, 27% had mild disabilities, and 9% had moderate cognitive disability. Functional morbidity was normal in 27%, while 45% had mild disability, 18% had moderate disability, and 9% were severely disabled.[171] In another small series of 26 patients monitored 1 to 3 years after ECMO, 38% of preschool-age children were described as normal and 31% had observed abnormalities. Four patients (31%) who had prior neurologic dysfunction remained at baseline following ECMO. Among children who were school-age, 77% were described as normal by parental report.[172] More specific neurologic follow-up in the pediatric age groups is needed.

Neurologic complications in cardiac patients who undergo ECMO parallel that of patients who have respiratory failure. Brain death occurred in 4% of patients, 3% had intracranial infarct, and 6% had intracranial hemorrhage. Because many cardiac patients are in a state of prolonged low cardiac output or sudden cardiac arrest prior to ECMO, the ability to assess neurologic function once ECMO is instituted is vitally

important. Paralysis and sedation should be minimized until a neurologic examination can occur. This information is especially important in patients who are being listed for transplantation to avoid transplanting a viable organ into an inappropriate recipient.

A recent study that sought to identify risk factors for acute neurologic injury in children undergoing ECPR found that 22% patients had acute neurologic injury, which they defined as occurrence of brain death, brain infarction, or intracranial hemorrhage identified by ultrasound or computerized tomography imaging. Brain death occurred in 11%, cerebral infarction in 7%, and intracranial hemorrhage in 7%. The inhospital mortality rate in patients with acute neurologic injury was 89%.

During ECMO, neurologic injury was associated with ECMO complications including pulmonary hemorrhage, dialysis use, and CPR during ECMO. Pre-ECMO factors including cardiac disease and pH greater than 6.8 were associated with decreased odds of neurologic injuries.[173]

In a recent study of 2-year survival, mental, and motor outcomes after cardiac extracorporeal life support in patients younger than 5 years, 46% of patients survived to discharge, with 41% of patients alive at 2-year assessment. Neurodevelopmental concerns were identified in most survivors, with a mean mental score of 73 ± 16, mental delay in 50% of survivors, and motor or sensory disability in 12%.[174]

This study outlines the need for more intricate and intensive follow-up of patients undergoing ECMO to identify residual neurologic damage that may be improved with early intervention.

Another report of 64 cardiac patients undergoing ECMO found that 28 (44%) had neurologic complications.[175] Seizures occurred in 18 patients (28%), 3 patients (5%) had an embolus or thrombus, 9 patients (14%) had an intraventricular hemorrhage higher than grade 2, and 13 patients (20%) had anoxic encephalopathy. In 68% of patients with neurologic complications, hemodynamic compromise had occurred prior to ECMO. Five patients had evidence of neurologic complication prior to ECMO, 30% of patients with neurologic complications had received cardiopulmonary resuscitation prior to ECMO, and 14% had several hours of low cardiac output prior to ECMO. Sixty-nine percent of patients who were electively removed from ECMO had neurologic and/or multisystems organ failure.

The long-term follow-up of children with cardiac disease who required mechanical circulatory support during a decade of experience at Children's Hospital in Boston was recently analyzed.[176] Thirty-seven children (26 who survived ECMO and 11 who survived treatment with a ventricular assist device) were monitored for an average of more than 4 years. Only a single patient died in either group, for an overall long-term survival rate of 95%. Eighty percent of the patients in both groups were described as exhibiting good to excellent general health. Both low weight at the time that support was originally instituted and a long duration of hypothermic circulatory arrest in operative patients were associated with poor neurologic outcome. The majority of patients with these characteristics were supported with ECMO. Neurologic impairment of a moderate to severe degree was noted in more than 60% of the patients who underwent ECMO and in 20% of ventricular assist device survivors. Adverse neurologic outcomes were not associated with presupport cardiac arrest, carotid cannulation, or carotid reconstruction. Other series have noted neurologic complications in 20% to 30% of cardiac patients undergoing ECMO. Survivors generally are described as "normal" neurologically, although the extent of examination or radiologic assessment of the brain is unknown.

Another study of neonatal ECMO found sensorineural hearing loss in 26% of patients. Of those affected neonates, 72% had progressive sensorineural hearing loss, with 48% having a delayed onset of hearing loss identified. Factors identified with increased risk for sensorineural hearing loss were a primary diagnosis of congenital diaphragmatic hernia, duration of ECMO therapy longer than 7 days, and the total number of days the children received aminoglycoside antibiotics.[177]

Longer term evaluation of patients surviving ECLS and comparison with patients who had a similar disease severity and diagnosis are imperative to adequately interpret neurologic outcome.[178]

The Future

The use of ECMO in the neonatal patients with respiratory failure has been accepted medical practice for many years, although improved care and management of these patients has reduced the need for ECMO in this population. The current extension of ECLS systems to older pediatric and adult patients in a variety of clinical settings highlights the changes that have occurred in the ECLS environment. Progress in renal replacement, liver support, and plasmapheresis and the development of new cardiac support devices applicable to pediatrics also may expand the use of ECMO or related techniques overall. Additionally, the development of small, portable systems for cardiopulmonary resuscitation may herald a new age of extracorporeal support. Technical advances in ECLS equipment continue to make such support safer and more efficient. Venovenous ECMO techniques have been refined and used successfully in patients from neonatal to adult age groups. Single-cannula, double-lumen catheters for venovenous ECMO may obviate the risks of arterial cannulation and offer the benefit of requiring only one surgical site for venous access. Heparin-bonded circuits may decrease the need for systemic anticoagulation and the risk of hemorrhagic complications. Until the day when medical science may make the need for extracorporeal life support obsolete, research into ways to make it safer and more efficient should continue.

References are available online at http://www.expertconsult.com.

Pediatric Neurocritical Care

Michael J. Bell

PEARLS

The nine steps that must be accomplished when building a successful critical care program include:

- Planning and organization
- Training basic nursing/physician skills
- Building and equipping the unit
- Opening the unit
- Developing special standards and protocols
- Training nonphysician personnel
- Continuing education of nurses/physicians
- Developing full-time coverage
- Developing research programs

Efforts have been made in recent years to develop programs to care for children with critical neurologic conditions with the use of teams of dedicated specialists, generally pediatric intensivists and neurologists. These programs, termed *pediatric neurocritical care* at present, depend upon the ability of dedicated staff to focus much (if not all) of their clinical and research endeavors toward common or uncommon neurologic conditions in order to improve outcomes for this vulnerable population of children. This chapter will describe the evolution of pediatric neurocritical care as a care paradigm from a historical perspective, outline several rationales for embarking on this new organization of clinical care, and describe challenges for the future development of these programs. Throughout this chapter and for the sake of simplicity, the phrase "neurocritical care program" is used to describe critical care programs developed to treat adults (and more recently children) with neurologic disorders. This chapter does *not* review neurocritical care disorders or pathophysiological principles, such as status epilepticus or management of intracranial pressure, because these disorders and principles are comprehensively reviewed in other chapters of this book. However, studies of neurocritical care disorders that serve to argue for the further development of a neurocritical care focus in pediatric critical care will be discussed.

Historical Context

Advances in medical care have either emerged as a result of tectonic shifts of the mantle of the health care system or by incremental shifts of the landscape. As an example, military conflicts have contributed to cataclysmic changes in health care, from the development of life-saving trauma surgical techniques (from the U.S. Civil War to current conflicts) to the development of effective triage systems for evacuating and treating wounded soldiers (culminating in improved systems developed during World War II through the Korean and Vietnam conflicts).[1] As a specialty, Critical Care Medicine was a product of yet another seismic blast to the health care system—the polio epidemics that raged throughout Europe and the United States in the late 1940s and early 1950s. Advances in ventilation allowed patients to survive this debilitating affliction, culminating in the organization of the first intensive care unit (ICU) at the Baltimore City Hospital in 1961 that was staffed by in-house physicians.[2] The director of this first multidisciplinary ICU was Dr. Peter Safar, a founding father of cerebral protection from cardiac arrest who advanced the field of neuroprotection during his long, storied career.

The subspecialty of neurological critical care has evolved in a more gradual fashion compared with the overall specialty. Dr. D.W. Dandy is credited with developing the first three-bed neurosurgical ICU at the Johns Hopkins Hospital in Baltimore in 1929, while the first fully staffed, large-scale neurocritical care unit was formed in 1969 at the University of Colorado by Dr. Michael Earnest.[3] Gradually, similar neurological critical care units were established in many universities and tertiary care centers, paralleling the development of other subspecialty ICUs for coronary, cardiovascular, surgical, pulmonary, and other conditions. Currently neurological critical care units can be further subdivided in many centers into neurotrauma, neurovascular, neurosurgical, and others. In 2002, several dozen practicing neurointensivists formed the Neurocritical Care Society (with membership now numbering greater than 800) and held its first annual meeting in February 2003. And in 2007, the United Council on Neurological Subspecialties offered the first examination in neurocritical care and accredited fellowship programs across the United States.

For pediatrics, caring for neurologically injured children was always at the forefront in establishing critical care programs. In their landmark paper from 1975, Downes and Raphaely[4] begin by writing, "The major objective of intensive care is to provide maximum surveillance and support of vital systems in patients with acute, but reversible life-threatening disease. In pediatric patients, the reversal of life threatening conditions and preservation of essential functions, **especially those of the brain**, may result in many years of useful life." During this time, Reye's syndrome epidemics were commonly afflicting previously healthy children and intensive

neuroprotective measures were used with increasing success to restore full neurologic function.[5]

These early years of pediatric critical care led to many advances, including: (1) management of respiratory failure (e.g., the advent of exogenous surfactant for respiratory distress syndrome,[6,7] high-frequency oscillatory ventilation,[8] permissive hypercapnia, inhaled nitric oxide,[9] and extracorporeal membrane oxygenation[10]); (2) surgical correction of congenital heart diseases (e.g., palliative surgery—Blalock-Taussig shunts,[11] the Norwood procedure,[12] definitive repair—arterial switch procedure for Transposition of the Great Vessels, the Fontan procedure,[14] supportive care—cardiopulmonary bypass,[15,16] and ventricular-assist devices[17,18]); (3) therapies for sepsis (e.g., goal-directed resuscitation therapy[19] and development of new antibiotics); and (4) supportive therapies for failing organs (e.g., hemofiltration, hemodialysis, continuous renal replacement therapy, plasmapheresis/plasma exchange, and organ transplantation). The culmination of these and many other clinical advances have led to decreases in mortality rates in most pediatric critical care units to between 3% to 5%.

With this impressive reduction in mortality, the necessary next step in improving clinical care for critically ill children is to minimize morbidity. It is in this context that pediatric neurocritical care has emerged, because neurologic morbidity was seen as one of the greatest challenges to future advancement of the field. In 2000, Robert Tasker[20] was among the first to write about a conceptual framework of multiple neurologic conditions that might benefit from particular expertise within pediatric neurocritical care when he provided an evidence-based summary of three important neurologic conditions of critically ill children: the management of severe head injury, use of benzodiazepines to treat status epilepticus, and the emergence of new forms of encephalopathies in children. In the intervening years, various groups have argued for the introduction of pediatric neurocritical care within the specialty of pediatric critical care medicine. The remainder of this chapter will examine the various rationales for advancing pediatric neurocritical care programs and possible future directions for this effort.

Rationales for Development of Pediatric Neurocritical Care

Rationale 1

The first rationale for advancing pediatric neurocritical care programs is that sufficient numbers of children with critical neurologic conditions exist to justify the establishment of a new service specifically for this population of children.

An important question for the development of pediatric neurocritical care programs involves an assessment of whether there are enough patients to justify the formation of this type of clinical service. As stated earlier, adult neurocritical care units and programs have been in existence for years and have therefore answered this question in the affirmative. During their early period, Bleck and colleagues[21] surveyed admissions to their 14-bed general medical ICU and found that only 92 of 1850 admissions were related directly to neurologic conditions, mostly stroke and intracerebral hemorrhages. However, they found that 217 patients experienced neurologic complications during the admission, including hypoxic/ischemic encephalopathy, seizures, metabolic encephalopathy, and stroke. A more recent analysis demonstrated that brain tumors, strokes, and subarachnoid hemorrhages accounted for more than 50% of admissions to neurocritical care units[22] but failed to provide an absolute number of admissions. In the intervening years, thrombolytic therapy for ischemic stroke, neurovascular procedures for aneurysmal subarachnoid hemorrhage, and the advent of comprehensive traumatic brain injury and stroke teams have increased the need for intensive care for adults. The evidence that adult neurocritical care is a viable program in many centers largely rests with its widespread implementation. Although the absolute number of neurocritical care units has not been collated, the United Council of Neurological Subspecialties has certified 25 programs in the United States and 215 diplomates in Neurocritical Care (see http://www neurocriticalcare.org/files/public/NCS. neurocriticalcare.org/files/public/NCS Volume4Number4).

The only pediatric experience in subspecialty critical care program development comes from pediatric cardiac intensive care programs. Large pediatric institutions—for example, Children's Hospital of Boston, Children's Hospital of Philadelphia, and The Hospital for Sick Children in Toronto—have long histories of cardiac intensive care programs.[23] These programs are based on the philosophy that a multidisciplinary team of cardiac intensivists, cardiologists, cardiac surgeons, anesthesiologists, neonatologists, and specially trained nursing and ancillary staffs can most effectively treat the unique pathophysiology encountered in correction of congenital heart disease. The viability of these programs is generally related to the volume of congenital heart surgery cases referred to the institution, and patients admitted to the hospital on this service generally are located in a unique space outside of the general pediatric intensive care unit (PICU). As of 2004, there were 132 pediatric cardiac intensive care programs and 250 members of the Pediatric Cardiac Intensive Care Society (http://www.pcics.org/), indicating that these types of programs have certainly been viable for many institutions.

At the time of this writing, limited information exists regarding the number of patients receiving care in pediatric neurocritical care programs. LaRovere and Riviello[24] summarized their experience in developing a pediatric neurocritical care service at Children's Hospital of Boston. They reported that 557 neurocritical care consultations were obtained over a multiyear period. Because little information is provided about the disorders treated and the role of the pediatric neurocritical care team in patient management, it is difficult to discern the precise difference between this effort and an active neurologic consulting service. At Children's National Medical Center, a neurocritical care consulting service consisting of an intensivist, two neurologists, and neurosurgical staff was formed within the framework of the PICU.[25] This service was designed to improve collaboration between the services and implement evidence-based guidelines for care of children with traumatic brain injury, stroke, status epilepticus, and other neurologic disorders. In a 14-month period, 373 neurocritical care consults were obtained from 1423 patient admissions. Approximately two thirds of the consultations were obtained in children with primary neurological diagnoses at PICU admission, but a substantial portion (34.1%) of the consultations were obtained among children admitted with other medical/surgical conditions (Table 54-1). The wide variety of diagnoses observed argued strongly that at least the three main specialties (intensivist, neurologist, and neurosurgeon) were required to make a comprehensive clinical team. Weaknesses

Table 54–1 Admission Diagnoses for Children Who Had a Pediatric Neurocritical Care Medicine Consultation

Primary Neurologic Diagnosis	No. (%)	Primary Medical Diagnosis	No. (%)
Status epilepticus	70 (18.9)		
TBI	53 (14.2)	Respiratory failure	41 (11.0)
Tumor	48 (12.8)	Cardiovascular, non-CNS	27 (7.2)
Neurosurgical procedure, other	24 (6.4)	Shock	22 (5.9)
Hydrocephalus	17 (4.6)	Cardiac arrest	14 (3.8)
SAH/ICH	13 (3.5)	Coma, unknown cause	14 (3.8)
Stroke	7 (1.9)	Ingestion	5 (1.3)
Meningitis	5 (1.3)	DKA	5 (1.3)
Other	2 (0.5)	Other	6 (1.6)
Totals	239 (64.1)		134 (35.9)

CNS, Central nervous system; *DKA,* abnormal neurologic findings associated with diabetic ketoacidosis; *meningitis,* inclusive of meningitis and meningoencephalitis disorders; *SAH/ICH,* atraumatic subarachnoid hemorrhage or intraventricular hemorrhage; *stroke,* all arterial ischemic strokes and cerebral sinovenous thromboses; *TBI,* traumatic brain injury.

of this study included the inability to determine if the consulting service led to improved outcomes for patients and lack of analysis on the financial viability of this model of care. Most recently, a fully independent primary pediatric neurocritical care service staffed by intensivists with extensive neurological experience has begun at the Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center. This service has seen 297 patients in the first 9 months, and a full description of the patient composition and viability of the program is currently under review. Other pediatric neurocritical care programs are currently active at several institutions, including at Children's Memorial Hospital (Northwestern University), St. Louis Children's Hospital (Washington University in St. Louis), and Weill-Cornell Medical Center.

Rationale 2

The second rationale for advancing pediatric neurocritical care programs is that the development of pediatric neurocritical care programs will improve the overall outcome of children under their care.

Any successful new program in critical care must lead to improved patient outcomes to justify changing existing approaches. At its basic level, improvements in mortality would provide the ultimate justification for such efforts, with concomitant decreases in neuropsychological and neurological morbidity also being important. Seminal work has indicated that adult or pediatric intensivist–led clinical teams are associated with improved outcome[26-29] and serve as a model for future innovations in changes in care teams.

Adult neurocritical care programs have demonstrated an association between their services and outcomes in a variety of ways and for several medical disorders. In 2001, Mirski and colleagues[30] demonstrated that admission to a "Neuroscience Intensive Care Unit" in a single institution was associated with improved outcome (decreased mortality and decreased length of stay) when compared with the similar institution prior to formation of this new ICU. On a larger scale, Diringer and Edwards[31] analyzed more than 1000 admissions of patients with intracerebral hemorrhage from hospitals with and without neurocritical care programs. They found that patients admitted to hospitals without neurointensivists had a 3.4-fold increased risk of inhospital mortality (odds ratio, 3.4; confidence interval, 1.65 to 7.6) after controlling for patient demographics, severity of intracranial hemorrhage, and hospital size. Varelas and colleagues[32] demonstrated that patients with stroke also benefited from neurocritical care programs. Specifically, in prospectively studying a total of 433 stroke patients (174 admitted prior to development of the neurocritical care unit and 259 admitted after development of the unit), they found no difference in mortality between the groups but decreased length of stay across all stroke subgroups. Lastly, Josephson and colleagues[33] demonstrated that patients with subarachnoid hemorrhage treated in a neurocritical care setting had decreased length of ICU stay (12.4 days vs. 10.9 days) and decreased need for cerebral spinal fluid diversion (23.0% vs. 11.5%) but no change in hospital mortality.

Presently no studies have assessed the utility of pediatric neurocritical care programs for improving mortality or other important outcome parameters, which is not surprising considering the dearth of studies outlining these programs in the literature. Nor does the literature contain any studies demonstrating improved mortality or morbidity after the institution of pediatric cardiac intensive care programs, despite their significantly longer history compared with pediatric neurocritical care programs. In moving forward it will be important to demonstrate improvements in outcomes, but this task will be particularly challenging because of the variety of developmental stages of childhood. In assessing mortality it will be important to avoid the limitations in the adult neurocritical care studies (i.e., comparison to historical control subjects) and utilize expected mortality measured by standardized severity of illness measures (such as PRISM or other scoring systems).

Rationale 3

The third rationale for advancing pediatric neurocritical care programs is that advances in care, either technologic or experimental, will be integrated more effectively with a pediatric neurocritical care program compared with the standard approach.

Advances in the delivery of neurological-specific care, based either on new technologies or on standardized guidelines based on new evidence, continue at an increasing rate, and some persons have argued that these advances justify a dedicated team of clinicians to provide such care. As outlined in other chapters within this textbook, the number of monitoring devices and technical advances for children with neurological injuries continues to grow. Digitally acquired electroencephalograms and electronic interpretations that can be gleaned at the bedside in real time, brain tissue oxygen catheters that provide second-to-second assessments of local cerebral oxygen tension, and noninvasive measures of regional brain saturations by near-infrared spectroscopy devices are now in routine use for children. Other techniques, including cerebral microdialysis and cerebral blood flow (CBF) devices (either catheters to assess local CBF or imaging studies to determine global CBF), are poised to be used in the coming years. Determining the correct combination of monitoring systems and implementing protocols to maximize their potential benefit and minimize possible harm is a daunting challenge that will be faced by all practitioners in the coming years. This argument was proposed by Suarez[34] as a justification for widespread adoption of adult neurocritical services and by Chang[35] to support development of pediatric cardiac intensive care programs.

Evidence-based guidelines covering several neurologic disorders of children continue to emerge, and effective integration of these guidelines, along with technological advances, into clinical practice in critically ill children will be an important challenge for clinicians. Consider the following examples: (1) in 2003 the Brain Trauma Foundation published guidelines (currently being revised) for management of children after traumatic brain injury[36]; (2) the American Heart Association has published guidelines for caring for children after stroke (including the use of antithrombotic therapies)[37]; (3) the American Academy of Neurology published a practice parameter to recommend treatment guidelines for children with status epilepticus[38]; and (4) the American Heart Association published guidelines on cardiopulmonary resuscitation and emergency cardiovascular care for children and neonates that also includes opinions regarding the neuroprotective strategy of hypothermia.[39-41] All of these general guidelines have important consequences for caring for the critically ill child, and successful incorporation of these recommendations into clinical protocols within the ICU will be an important step in optimizing care.

Several recent clinical studies also outline the importance of rigorously controlled neuroprotective strategies and argue for specialists who might improve the chances of successful implementation. First, in one of the most significant studies in the past decade in pediatric critical care, Hutchison and colleagues from the Canadian Critical Care Trials Group tested if early institution of hypothermia—basically the only neuroprotective strategy currently available for testing—would improve outcome after severe traumatic brain injury in children.[42] In a trial involving 225 children, a strong trend toward worse outcome in the treated group was noted, including both death and poor neurologic outcome. However, significant methodological problems with the trial were discerned by the authors, including an increased number of children with hypotension in the treatment group, an increased incidence of the necessary use of vasoactive agents during the rewarming phase, and administration of an incomplete dose of hypothermia (approximately 16 hours based on data within the manuscript compared with 24 hours in the proposed protocol). In a smaller study of a single center, Fink and colleagues[43] found that children undergoing hypothermia for cardiac arrest had the same mortality rate compared with those remaining in normothermia in an uncontrolled audit of a single center. More importantly, they found that overshooting of the target temperature was common (10% with a rectal temperature of <30° C) in this nonprotocol-driven care plan. Both of these studies argue that careful control of neuroprotective strategies is essential for the safety of clinical trials and ultimately for clinical care. In the future, if neuroprotective strategies are used for any of a number of neurological conditions, it may be the role of the pediatric neurointensivist to effectively implement the strategy.

Future of Pediatric Neurocritical Care

As described throughout this chapter, pediatric neurocritical care is a new concept, and currently more questions than answers exist regarding its implementation. A basic question of staffing and leadership of this effort remains in question. Models including pediatric intensivist–led programs (Children's National Medical Center, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, and St. Louis Children's Hospital) and pediatric neurologist–led programs (Children's Hospital of Boston, Children's Memorial Hospital, and Texas Children's Hospital) exist currently. At this juncture it seems likely that an integrative approach with both of these services and neurosurgery will be required for the foreseeable future, because it is as unlikely that an intensivist-trained neurocritical care specialist will feel completely comfortable reading electroencephalograms as it is for a neurologist-trained specialist to feel comfortable managing a critical airway. Scher[44] argues that the approach of "cross-disciplinary training" may be the most effective means to achieve this cross-pollination of skills.

The overall organization of pediatric neurocritical care programs in the future and the scope of their missions is yet to be determined. The Neurocritical Care Society has formed a Pediatric Neurocritical Care Subcommittee (whose Chair is James Riviello of Baylor College of Medicine) to explore the incorporation of pediatric topics into the mission of the Neurocritical Care Society. An independent, pediatric-based administrative approach was proposed in September 2008 when a pediatric neurocritical care investigators meeting was convened in Chicago (Northwestern University; Mark Wainwright, Chair). The focus of this international group (more than 50 attendees) was "to bring together bench and clinical investigators with interests related to pediatric CNS injuries including stroke, traumatic brain injury, seizures and neurologic complications of critical illness, with a goal of beginning to identify research priorities, and approaches to management in pediatric neurocritical care common to all these disorders." Yet another approach is being proposed by the Pediatric Acute Lung Injury and Sepsis Investigators, who convened a Pediatric Neurocritical Care subgroup in March 2009. This group advocates for national efforts to spur research into neurocritical care topics for children with the anticipation that these efforts will lead to improvements in care.

In summary, enthusiasm for the practice of pediatric neurocritical care continues to grow across the United States and abroad. At this time, University-affiliated pediatric critical

care and neurology divisions have started clinical services in pediatric neurocritical care. In going forward, it is important to determine if these clinical programs effect important outcomes for children and which team structure allows for the best results. In their landmark paper, Safar and Grenvik[2] argue that a sequence of nine steps must be accomplished when building a successful critical care program: (1) planning and organization, (2) training in basic nursing/physician skills, (3) building and equipping the unit, (4) opening the unit, (5) developing special standards and protocols, (6) training nonphysician personnel, (7) continuing education of nurses/physicians, (8) developing full-time coverage, and (9) developing research programs. At present, step 3 may be omitted, because there is little ongoing effort to build self-standing neurocritical care units for children at this time. Nevertheless, it seems that many programs have accomplished a number of the eight remaining steps with some success. It remains to be seen how implementation of these programs will fare in the coming years and what advances in care and outcome may be obtained.

References are available online at http://www.expertconsult.com.

IV

Chapter 55

Pediatric Neurologic Assessment and Monitoring

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PEARLS

- The examiner should focus both on localization of a neurologic deficit and identifying mechanism(s) of injury (or potential injury) as a means to adjusting therapy.
- Communication between team members, serial examinations, and early recognition of changes in the examination or other monitoring parameters are essential.
- Metabolic monitoring methods, including partial pressure of oxygen and microdialysis, have great potential to advance the detection of, and therapy for, secondary neurologic injury in pediatric acute brain injury. The application of these tools to neurocritical care and demonstration of their efficacy in improving outcomes will require advances in data collection, bioinformatics, and methods of data analysis.

Overview and Basic Principles of Pediatric Intensive Care Unit Neurology

The approach to the neurologic assessment of the patient in the pediatric intensive care unit (PICU) requires an interdisciplinary approach using bedside neurologic examination and laboratory testing combined with invasive and noninvasive monitoring.[1] While this approach to patients with neurologic disorders recapitulates elements of the approach to differential diagnosis used in the outpatient setting and non-ICU inpatient care, there are important fundamental differences that are specific to the practice of critical care neurology.[2,3] In general, these differences involve the need to obtain testing (imaging, neurophysiology, laboratory) on patients who may appear neurologically intact, the need to intervene before a specific neurologic diagnosis has been obtained, and the challenge of determining whether such interventions affect long-term outcome. Thus, the cardinal features of the practice of neurology in the PICU are the need for serial neurologic examinations, the importance of communication between nurses and physicians and between multiple medical services, the need for early recognition of changes in the neurologic exam, and the anticipatory management of patients with the potential for progressive neurologic deterioration. The confounding effects of sedation and/or postoperative anesthesia on neurologic functioning pose an additional set of challenges to the assessment of these patients. Nevertheless, a logical approach to the neurologic examination is possible by using the standard structure of a neurologic examination, combining this exam with attention to the mechanisms of injury (present or potential), and thereby developing a plan for ongoing monitoring and management. Last, it is prudent to regard every patient in the PICU as having the potential for neurologic complications of his or her illness. These patients, whose primary diagnoses range from neurologic complications of solid organ transplant to liver failure to congenital heart disease, may suffer neurologic injury from any combination of hypoxic, ischemic, inflammatory, or metabolic cerebral insults.

Recognition of Neurologic Complications in the PICU Patient

Children who develop neurologic complications of critical illness deserve a specific mention. This is likely an underrecognized population in many PICUs, not least because of the prevalence of nonconvulsive seizures[4] (NCS) or ICU-acquired paresis.[5] In these cases, the recognition of new neurologic deficit(s) relies on the ability of the PICU team to recognize changes in the neurologic exam. In general, interventions to treat or attenuate neurologic insults, whether seizures, ischemia, or increasing intracranial pressure (ICP), are more likely to be successful if initiated early in the process of injury. This means that effective neurologic monitoring in the PICU does not rely solely on the availability of a neurologist, electroencephalogram (EEG), or neuroimaging. Rather, the prerequisite to using these monitoring tools is a high index of suspicion for new neurologic injury on the part of the medical team for patients who do not have primary neurologic injuries.

In addition to the physical exam, there are a number of modalities that can be used for the monitoring of neurologic function in critically ill children and adults.[6,7] This includes continuous EEG monitoring, which is well-established as a modality essential for the detection of NCS in the adult and PICU populations,[8,9] ICP monitoring, transcranial Doppler,[10] and metabolic[11] and tissue oxygen monitoring.[6,12] Thresholds for detection of cerebral ischemic injury have been proposed for brain oxygen tension[13] and near-infrared spectroscopy (NIRS).[14] With respect to pediatric neuromonitoring, as yet

there is no consensus on normal values or the age-dependence of these endpoints.

Establishing a Baseline Neurologic Examination and Anticipatory Planning for New Deficits

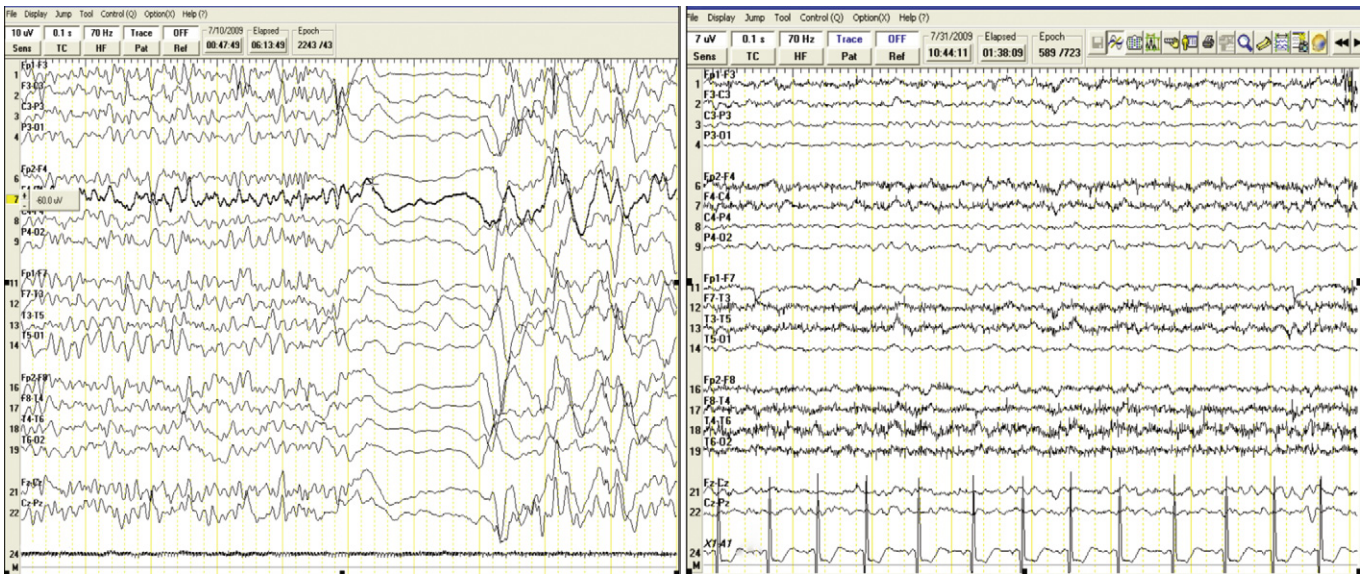
The examiner should discuss the findings with the bedside nurse and other members of the medical team. If possible, abnormal findings should be demonstrated to the members of the team. There should be a consensus on the key findings and the approach to be taken for evaluation and management if the neurologic exam changes. Important features of the approach to the neurologic examination of the child in the PICU include the need for serial examinations and the need to establish a plan to manage any changes in this exam before they occur. This is the most important message of this chapter.

History and Assessment of Risk Factors

For children in the PICU, the medical history may provide essential information about the mechanisms and timing of neurologic insult. This information is needed for the interpretation of the neurologic exam and assessment of potential mechanisms of neurologic injury. These data are then used to assess the risk for progression of neurologic injury, to prioritize therapeutic interventions, and to determine the need for, and timing of, additional evaluations, including imaging, EEG, and laboratory studies. In many cases, the decisions to treat (or not treat) a neurologic injury in the PICU will have to be empiric and based on a careful assessment of risk factors and potential mechanisms of injury as well as a weighing of the risks and benefits of such intervention. For example, the approach to evaluation of altered mental status presenting to the PICU will be different with children with an established complex partial seizure disorder, sickle cell disease, or a stem cell transplant recipient on immunosuppressant drugs. Before examining the patient, knowledge of salient details of the medical history allows the examiner to begin to formulate a diagnostic approach and to prepare the early steps in management. The patient with a history of epilepsy in the example above would likely require an emergent EEG to rule out NCS, while the patient with sickle cell disease and risk factors of vascular injury with the same symptoms may require an imaging study, and the immunosuppressed patient a lumbar puncture. The presenting neurologic symptoms may be similar, but the history dictates the assessment based on the likely mechanisms producing the deficits found on neurologic examination.

Iatrogenic Complications of Pharmacotherapy

It is not uncommon to overlook the side effects of drugs in the PICU. A review of medications should be part of the neurologic assessment of any patient with new neurologic symptoms. The initial assessment of the patient should include attention to medications that cross the blood-brain barrier, or that may interfere with the renal or hepatic metabolism of centrally active drugs. In patients in renal or liver failure, or requiring dialysis, the side effects of a centrally acting drug must be considered in the differential diagnosis for any neurologic symptom. This may occur even in the presence of "normal" doses of drugs or levels of anticonvulsants, as off-target drug toxicities may be due to metabolites, not the drug itself. An example is shown of a child with a mild static encephalopathy and spasticity, on dialysis as the sequela of perinatal renal injury, who developed progressive encephalopathy (Figure 55-1). Treatment with flumazenil with immediate improvement in mental status, confirmed that the accumulation of baclofen in this dialysis-dependent patient was the source of a waxing and waning encephalopathy. Common examples in the PICU include immunophilin-associated



A B

Figure 55–1. Bipolar EEG montage (**A**) of a child with a mild static encephalopathy and spasticity, on dialysis as the sequela of perinatal renal injury, who developed progressive encephalopathy with high-amplitude epileptiform discharges. Treatment with flumazenil resulted in immediate improvement in mental status and sustained improvement in the EEG (**B**), confirming that the accumulation of baclofen in this dialysis-dependent patient was the source of a waxing and waning encephalopathy.

seizures, encephalopathy, hypertension; oculogyric crisis, delirium during reduction of sedation, and persistent paralysis from prolonged neuromuscular blockade. In many cases, the attribution of the symptoms to a drug side effect (excess level, too-rapid withdrawal, idiosyncratic reaction, impairment of clearance) will be a diagnosis of exclusion. Nevertheless, a review of medications and recent changes should be a routine component of the neurologic assessment.

Approach to the Physical Exam

Vital Signs

Therapies that target specific mechanisms of cell injury for acute CNS disease are lacking in adult and pediatric neurocritical care. Nevertheless, one simple intervention, the prevention of hyperthermia, may significantly reduce neurologic injury after stroke or traumatic brain injury (TBI). The neuroprotective benefit of induced hypothermia remains to be proven for pediatric TBI.[15-17] While hypothermia may remain as yet an unproven therapy for neurologic insults, the prevention of hyperthermia can be regarded as a safe, and probably effective, intervention.[18] Therefore, as a general principal for ICU neurology in patients with known or suspected central nervous system (CNS) injury, the neurologic exam should first include vital signs and fever should be treated aggressively. The range of temperatures determined to be "normothermic" may vary but a consensus should be reached and temperatures above the accepted range treated quickly.

In contrast to adults, there are limited data on the optimum ranges for blood pressure, ICP, and cerebral perfusion pressure (CPP) for children. In adults, there are goal-directed protocols aimed at improving outcome following TBI. The targets of ICP less than 20 mm Hg and CPP above 60 mm Hg are based on a number of studies.[19-23] In contrast, very limited data exist for children with TBI.[24,25] Guidelines suggest an ICP threshold of 20 mm Hg for all ages and a CPP threshold of 40 to 65 mm Hg as an "age-related continuum."[26] In children younger than 15 years of age, a mean CPP less than 40 mm Hg during the first 48 hours following injury has been associated with increased mortality.[27] Although children with TBI younger than 2 years of age have a high mortality rate compared with older children, no thresholds for ICP or CPP have been established for this age group.[28] Accordingly, blood pressure, temperatures, and oxygenation must be interpreted in the context of the underlying neurologic insult or risk for further injury. As a general principle, hyperthermia with the attendant increase in cerebral metabolic demand should be treated aggressively whatever the primary injury.[29]

General Physical Exam

An essential component of the neurologic examination is obtaining an accurate head circumference. This may serve as a baseline for following the development of hydrocephalus in the at-risk infant. In older children, an abnormal (large or small) head circumference may be a previously overlooked sign of pathology. The fontanelle should be palpated and the findings on the exam agreed upon with the infant in a quiet, resting state. A bulging fontantelle is an important finding of meningeal irritation or increased ICP. Examination of skin for the cardinal features of the phakomatoses may identify café au lait spots characteristic of neurofibromatosis, or shagreen patches, hypopigmented macules, and angiomyofibromas characteristic of tuberous sclerosis. The physical findings associated with inflicted trauma deserve particular mention as these may be subtle[30]; they include unusual patterns of bruising, blood in the oropharynx, and burn or belt marks.

Importance of Observation in the Neurologic Exam

The elements of the neurologic examination in the PICU comprise the same features of the neurologic exam as for patients who are not critically ill. The assessment of mental status, cranial nerves, motor function, reflexes, sensation, and cerebellar function must be adapted to each patient, but the structure of the neurologic exam in the PICU is no different from the outpatient examination. If possible, sedating drugs and paralytic agents should be reduced prior to the exam. If this is not feasible, the exam must be interpreted in the context of these confounds.

The assessment of mental status begins with observation. The examiner should first confirm the drugs used for sedation if any, and recent changes in dosing. It is not possible to give precise dose ranges for typical sedating agents associated with a mental status exam. For commonly used agents in the PICU (midazolam, morphine, fentanyl, dexmedetomidine) the effects of the drug on arousal and responsiveness will vary with the age of the patient, duration of exposure, nature of the neurologic insult, effect of other drugs on metabolism, and genetically determined ability to clear these drugs. This complex set of interactions underscores the importance of experience in the examination of these patients to determine what is an acceptable level of arousal, as well as the need for serial neurologic examinations.

The observations of the nurses and parents should first be solicited. The examiner should enquire about evidence for changes in arousal or awareness, such as spontaneous eye-opening, evidence of a sleep-wake cycle, change in activity, or response to interventions such as suctioning. If family members are present, their observations of response to their presence or voice are important and may represent the first signs of awareness on the part of the patient. It is quite appropriate to have a family member carry out part of the exam, asking the patient to follow commands, as young children are more likely to respond to their family than to a stranger.

The pattern of breathing rate and rhythm should be observed. Specific patterns may help localize the site of neurologic dysfunction but not the mechanism involved (Table 55-1). The crescendo-decrescendo pattern alternating with periods of apnea, characteristic of Cheyne-Stokes respiration, may be due to dysfunction of the cerebral hemispheres, the thalamus, or the hypothalamus with preserved brainstem function, but can also be found in patients with congestive heart failure or primary respiratory disease. Similarly, the sustained, deep breathing pattern of central neurogenic hyperventilation may be due to either structural injury to the midbrain, sepsis, pulmonary disease, or compensated metabolic acidosis.

The conventional neurologic examination proceeds from mental status, cranial nerves, motor (bulk, tone, and strength), reflexes, and sensation to cerebellar exam and gait. In children and in the PICU in particular, the exam must be based on good observation and typically performed out of sequence. It is easier to assess tone and reflexes in the asleep, relaxed patient, before waking the patient up to assess mental status. While the exam is discussed in the standard order

Table 55–1 Approach to the ICU Neurologic Examination: Localization and Mechanism

Exam Finding	Structural-Vascular Insult	Toxic-Metabolic
Consciousness	Stays at same level or deteriorates	Waxes and wanes, milder impairment; toxins may cause progressive decline
Respiration	Cheyne-Stokes (crescendo-decrescendo alternating with apnea): loss of cerebral, thalamic, or hypothalamic control of breathing Neurogenic hyperventilation (sustained, rapid, deep breathing): midbrain disease Gasping respiration (irregularly irregular): dysfunction of lower brainstem or medulla	Cheyne-Stokes: congestive heart failure, primary respiratory disease Neurogenic hyperventilation, metabolic acidosis, sepsis, liver failure Gasping respiration, intoxication (opiates, barbiturate), hypothyroidism
Fundoscopy	Papilledema due to increased ICP	Papilledema does not occur except in hypertensive encephalopathy, lead intoxication, hypoparathyroidism
Eye position	Versive deviation Stroke ipsilateral to direction of deviation Retraction or convergence nystagmus Midbrain Ocular bobbing Pons Intranuclear opthalmoplegia Pons or midbrain Oculomotor nerve palsy Midbrain or herniation Skew gaze Brainstem	Versive deviation Seizure contralateral to direction of deviation No extraocular movement with preserved pupil reactivity Toxin
Pupil reactivity	Small reactive Thalamus, hypothalamus Midposition, fixed Midbrain Pinpoint, reactive Pons Small, combined with ptosis Horner syndrome, lateral medulla, sympathetic chain Large, fixed Oculomotor nerve, tectum	Small, reactive Large, fixed Botulism, opthalmic drops
Eye movements	If asymmetric, likely structural Oculomotor nerve palsy Midbrain or herniation syndrome Abducens nerve palsy Unreliable localization Internuclear ophthalmoplegia Midbrain or pons Dysconjugate or skew gaze Brainstem Absent vertical and retained horizontal movement Midbrain Absent horizontal and retained vertical movements Pons	Roving more common with metabolic derangements Absence of all movement with intact pupil light reflex
Adventitous movements	Posturing; sign of herniation Myoclonus following severe cerebral ischemia	Restlessness, tremor, spasm, myoclonus, chorea, akathisia
Muscle tone	Asymmetric; increased, normal, or decreased	Symmetric, normal, or decreased

below, it is often more informative to begin the hands-on part of the exam with assessment of tone and reflexes. Once awake and agitated, it may be difficult to elucidate subtle asymmetries of tone and reflexes, which may be key findings of the exam.

The state of arousal (awake, asleep), responsiveness, (interactive, verbal, nonresponsive), position (tone and asymmetry of limb position), movement (purposeful, spontaneous, dystonic, choreic, asymmetry of movement) can all be reliably assessed by observation. In a nonintubated, nonsedated patient the examiner may proceed directly with a standard mental status exam adjusted for age. In the young child who is able to cooperate, the specific cognitive and language skills expected for age can be assessed (Table 55-2).

Nonorganic Pathology in the Pediatric Intensive Care Unit

Not all neurologic deficits in the PICU are organic. Conversion disorders also occur in critically ill patients or result in patients being admitted to the PICU. In the latter case, this is most often associated with nonepileptiform seizures. These cases may

Table 55–2 Age-Dependent Motor and Language Patterns

Age (mo)	Motor	Language
15	Walks alone, crawls up stairs	Jargon; follows simple commands
18	Runs, sits on chair, walks up stairs with hand held	Knows 10 words, names pictures, identifies body parts
24	Runs well, walks up and down stairs	Uses three-word sentences
30	Jumps	Refers to self as "I"
36	Stands on one foot, goes up stairs with alternating feet	Knows age and gender, counts three objects
48	Hops on one foot, throws ball	Tells a story
60	Skips	Names four colors, repeats 10-syllable sentences

Modified from Behrman RE, Kliegman RM, Nelson WE, et al: *Nelson textbook of pediatrics*, ed 14, Philadelphia, 1992, WB Saunders, pp 18–104.

Table 55–3 Clinical Features of Seizures and Nonepileptic Spells

	Seizures	Nonepileptic Spells
Eyes	Open	Closed
Automatisms	Common	Rare
Stereotypical behavior	Common	Rare
Gradual onset	Rare	Common
Waxing and waning course	Rare	Common
Thrashing movements	Rare	Common

have been treated with anticonvulsants, resulting in respiratory depression requiring intubation or ICU monitoring. A number of features of the examination and history may help make this distinction (Table 55-3). Seizures are a common complication of critical illness in adults and children[31] and are also a common reason for neurologic consultation in the PICU. A high index of suspicion for seizures in the PICU is important in order to decrease the risk for secondary brain injury resulting from the metabolic stress imposed by seizures. In such cases, video EEG monitoring is the most efficient means of distinguishing ictal from nonictal events. While continuous EEG monitoring may be needed to determine whether such events are seizures or not, there are features of the physical exam that may aid in making this diagnosis. In general, and particularly in infants, the eyes are open during a seizure. In one series,[32] over 90% of cases with electrographically confirmed seizures occurred with eye opening. The eyes may look straight ahead, versively deviate to one side contralateral to the hemisphere from which the seizures originate, or exhibit only nystagmus. Seizures are typically a "positive" phenomenon and will have movement associated with them unless there has been injury to the corticospinal tracts resulting in a paretic limb. Other features of the exam or description of the spells including stereotypy, crescendo-decrescendo behavior, or the presence of automatisms may help to distinguish ictal and nonictal behavior. In most cases, video EEG monitoring is the most efficient means of distinguishing ictal from nonictal events.

Even in the PICU, the examiner should remember that functional deficits may occur, and a number of motor signs may help identify the origin of functional symptoms. Given the complex pathophysiology of many critically ill patients and the multiple potential mechanisms of neurologic injury, the diagnosis of a functional neurologic deficit should be made only after a thorough evaluation for organic causes. Although this is uncommon in the PICU, a functional etiology should not be overlooked and early identification may help to minimize diagnostic testing and unnecessary or high-risk treatment. There are a number of elements of the physical exam that may help distinguish between organic and functional neurologic deficits.[33] An inconsistent examination may be the first clue; for example, a patient with apparent weakness during bedside strength testing may be noted to change position during sleep or another may walk despite apparent paresis on bedside testing. These observations can often be very helpful in the assessment of children with weakness thought to be due to a neuromuscular disease. After first observing for inconsistency, the most useful test for functional weakness is the Hoover sign. This test relies on the principle that when flexing one's hip, the natural accompanying movement is to extend the contralateral hip.[33] With the patient supine, the examiner places one hand on the weak leg and the other hand under the ankle of the strong leg. The patient is then asked to perform a straight-leg raise of the healthy limb. In a functional pattern of weakness, the examiner will feel no downward pressure from the good leg since there is no effort being applied to raise the ostensibly weak leg. Other tests include the "arm-drop" in which a paretic or plegic arm is dropped over the patient's face (the patient with organic weakness is more likely to allow the arm to strike the face), or observation of exact splitting of sensory or vibration deficits in the midline. A number of functional gait disturbances are also characteristic, including a monoplegic dragging gait (the whole limb is dragged without the circumduction present in pyramidal hemiparesis), a "walking on ice" pattern, excessive slowness, or sudden buckling at the knees with recovery. Of these, none are definitively diagnostic of a functional pathology, and in children in particular must be interpreted with caution. Importantly, functional and organic deficits may coexist.

Assessment of Level of Consciousness and Mental Status

For children with depressed consciousness, the precise stimulus required to elicit a response and the nature of this response should be specified. It is not helpful to describe the patient as "lethargic" or "obtunded." First, the child is called by name to determine whether there is a response. If this is not effective, the examiner may ask a family member to speak to the child. Next, the stimulus is increased. It is most helpful to simply describe the patient's response to specific stimuli and to use the same stimuli for serial examinations. The Glasgow Coma Scale score, although of limited use in preverbal children, is a quantitative measure (Table 55-4). If the patient's eyes open to voice, the response to commands is next tested. This is discussed in more detail below, but the commands should be increased in complexity from one-step to two- or

Table 55–4 Glasgow Coma Scale

Activity	Best Response	Score
Eye opening	Spontaneous	4
	To command	3
	To pain	2
	None	1
Verbal	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Motor response	Obeys commands	6
	Localizes pain	5
	Withdraws to pain	4
	Abnormal flexion to pain	3
	Abnormal extension	2
	None	1
Total		3–15

three-step. If there is no response to voice, a painful stimulus is next applied. It should be noted that in patients with sensory deficits due to neuropathy, spinal cord, or CNS lesions or with focal limb weakness, the extremity or dermatome selected for testing should have intact sensory or motor function. In the sedated or severely impaired patient the response may comprise only increase in heart rate. It is important that the stimulus and the specific response, rather than vague descriptors ("lethargic, drowsy, sleepy") are documented, as this will be more helpful in assessing serial examinations. The rate of sedating drugs or recent administration of sedating drugs should be documented with this exam.

The assessment of higher cognitive function, and the early recognition of compromise of cognitive function, is a challenge at any time when evaluating young children. In the ICU, where the additional confounds of sedation, other organ dysfunction, sleep disturbance, and anxiety must be accounted for, this evaluation is somewhat more challenging. Of course, this is usually the most important component of the exam and the technologies used for neurologic monitoring in the ICU (imaging, EEG, NIRS, microdialysis, tissue oxygenation) all serve the same goal of the bedside exam, of detecting compromise of cerebral function to enable directed therapeutic intervention.

In the older, awake child a complete mental status exam can be performed. This must be adjusted for age (see Table 55-2) but should include assessment of language (fluency and comprehension): the ability to name, repeat, write, read, and respond to written commands. Simple mathematical problems should be adjusted to the child's age-dependent ability. Praxis can be assessed quickly even in the PICU by demonstration of learned behaviors, even in the young child (brush your teeth, brush your hair). Other components of the mental status exam, including memory, fund of knowledge, and reasoning can be assessed by holding a conversation with the patient.

Most importantly, the examiner needs to have an appropriate index of suspicion for these subtle neurologic deficits of attention, memory, praxis, language comprehension, and reading comprehension which may be the early sign of new neurologic injury. This is particularly true for patients with metabolic (often liver or renal failure), infectious, or iatrogenic (sedation, immunophilins) risk factors for CNS dysfunction and may easily be missed if not specifically investigated.

Fundoscopic Examination

Examination of the fundi may reveal hemorrhages or papilledema. Hemorrhages indicate either acute subarachnoid or subdural hemorrhage, cranial trauma from a direct blow or shaking injury, or malignant hypertension. Papilledema indicates raised ICP from any cause. Usually papilledema develops hours after the onset of the elevated ICP. Acute severe increases, however, as with subarachnoid hemorrhage (SAH) from a ruptured saccular aneurysm, can result in almost instantaneous papilledema. Sometimes papilledema never develops, despite prolonged severe elevations of ICP.

Cranial Nerve Examination

The pupillary reaction to light is abolished only by structural damage to the midbrain or third cranial nerve. Loss of the pupillary reflexes is always an ominous finding. Preservation of pupillary reflexes in the presence of deep coma suggests a metabolic-toxic cause. The interpretation of the patterns of pupil reactivity is summarized in Table 55-1.

Measurement of pupil size and light response is a quantifiable measure of brainstem and autonomic nervous system function, and absence of pupil reactivity is a poor prognostic sign after TBI or cardiac arrest. To provide a very precise measure of pupil size and speed of contraction and relaxation, a portable handheld device (pupillometer) is now available that illuminates the eye with an infrared light (850 nm) while acquiring 124 images for analysis. The data (pupil size, rate of contraction and relaxation) are stored on the device and can be downloaded to a computer. In a study of healthy volunteers and adult patients with TBI and ICP monitors in place, a discrepancy in pupil size of more than 0.5 mm appeared to be associated with ICP above 20 mm Hg.[34] Normal values for pediatrics have yet to be determined and the interpretation of these values in the setting of pediatric neurologic critical care is unclear. Nevertheless, as a quantitative, noninvasive adjunct to the neurologic exam, this technology holds promise.

Eye movements are assessed first by observation and then elicited in the patient with depressed mental status with doll's head maneuver (oculocephalic response) or cold caloric stimulation (oculovestibular response). The interpretation of eye movements and position is summarized in Table 55-1. In general, coma produced by metabolic dysfunction is initially associated with roving, dysconjugate movement and may progress to the cessation of movement. Cold caloric stimulation will produce nystagmus, with the rapid phase contralateral to the ear that has been stimulated. This rapid phase is the equivalent of saccadic eye movements and also indicates

intact functioning of the cerebral cortex. The ears are irrigated separately several minutes apart. In comatose patients the fast "corrective" phase of nystagmus is lost and the eyes are tonically deflected to the side irrigated with cold water or away from the side irrigated with warm water. These vestibuloocular responses are lost or disrupted in brainstem lesions. Versive eye deviation is a common finding suspicious for seizures. In this case, the eye deviation is contralateral to the hemisphere with the ictal focus. Alternatively, stroke in the ipsilateral hemisphere may also produce versive eye deviation toward the side of the stroke.

An abnormal corneal reflex may indicate either fifth nerve afferent disease (ipsilateral stimulation results in neither a direct nor consensual eye blink) or seventh nerve efferent disease (ipsilateral stimulation results in a brisk consensual but no direct response).

Unilateral weakness of eye closure, forehead movement, and mouth movement indicates peripheral seventh cranial nerve palsy, whereas failure to move only the mouth with preservation of upper face movements indicates a central corticospinal tract lesion rostral to the pons. Facial weakness may be noted during grimacing while responses to painful stimuli are evaluated. Voluntary pharyngeal and laryngeal control is tested by asking the patient to speak and say "ahh." In the absence of voluntary movement, a hypoactive gag indicates medullary or vagal dysfunction and a hyperactive gag indicates interruption of corticospinal inhibition to the medulla. In a comatose patient or one whose consciousness is rapidly deteriorating, one must quickly determine whether the patient is experiencing raised ICP. Papilledema or third cranial nerve palsy are strong evidence of elevated ICP.

Approach to the Motor Exam

In the comatose or obtunded patient, asymmetry of resting tone or spontaneous movement are simple signs of paresis that can be detected by first observing the patient. In children, this is particularly important, as a subtle weakness may not be apparent once the child is more awake and resisting cooperation with the exam. An externally rotated, partly flexed abducted leg may indicate an ipsilateral hemiparesis due to an upper motor neuron lesion. Facial weakness should also be first evaluated by observation before attempting formal testing (often impossible or unreliable in young, anxious, or sedated children). Signs of facial weakness at rest may include a widened palpebral fissure, diminished nasolabial fold, or flattened corner of the mouth. The examiner should next attend to the initial movement of the face, either spontaneously or in response to a noxious stimulus. Subtle weakness may be apparent only in a delayed response to these stimuli.

Weakness may be due to lesions at any level of the neuraxis. The goal of the examination of the weak patient is to identify the pattern of weakness as upper or lower motor neuron and thereby identify the most likely mechanisms. The upper motor neuron (UMN) comprises the corticospinal tract and its neurons. The corticospinal tract begins in the motor and premotor cortex anterior to the central sulcus, descends through the central white matter of the cerebral hemispheres, decussates in the lower medulla, and terminates on the anterior horn cells or interneurons closely associated with the anterior horn cells. The innervation of muscles that control movement of the jaw, pharynx, larynx, upper half of the face, neck, thorax, and abdomen is derived from both cerebral hemispheres. Consequently, unilateral cerebral lesions lead only to weakness of the contralateral limbs and lower face. The lower motor neuron (LMN) is comprised of the anterior horn cells, motor roots, peripheral nerves, pre- and postsynaptic components of the neuromuscular junction, and the muscles receiving this innervation. Stereotyped reflex movements may be present despite spinal cord injury, because these responses are coordinated by local spinal reflexes below the level of the lesion. In contrast, movement is absent following injury to the LMN because it is the final common pathway producing muscle activity. If the patient is not able to cooperate with a complete exam testing all muscle groups, in addition to observing for asymmetric posture, the observation of facial movement, testing for neck flexion, grip strength, pronator drift, and counting the duration (up to 10 seconds) that the patient can maintain a straight leg raise are efficient means of assessment.

A number of key findings on the pattern of weakness can distinguish between UMN and LMN injury, chronic and acute injury, neuropathy, and neuromuscular disorders including ICU-acquired paresis, myasthenia gravis, and Guillain-Barré syndrome (GBS). Acute UMN lesions result in a hypotonic or flaccid pattern of weakness, and in the legs may be associated with the Babinski sign. In contrast, chronic UMN injury results in a hypertonic limb with associated hyperreflexia. An LMN pattern of weakness is more likely to be associated with a decrease in muscle tone and bulk and decreased or absent reflexes. In general, proximal weakness suggests a myopathic process, while a distal pattern of weakness suggests a neuropathy. The precise incidence of critical illness neuropathy and myopathy (CIPMN) is uncertain in children.[5] Extensive data from adult studies have identified CIPMN, manifest as a variable combination of weakness, muscle atrophy, hyporeflexia, and sensory deficits, as a common cause of extubation failure with a high incidence of long-term morbidity. The contribution of the risk factors in adults, (sepsis, hyperosmolarity, neuromuscular blockage, prolonged ventilation, and corticosteroids) to pediatric CIPMN is not known. CIPMN is primarily a clinical diagnosis, although nerve conduction and electromyography studies may be confirmatory. Management, particularly in children, is empirical but this disorder should be suspected in any critically ill child with diminished reflexes and new weakness or difficulty with extubation.

The two most common neuromuscular disorders that require ICU level of care in children are GBS and myasthenia gravis (discussed in Chapter 64). A number of practical steps can aid in the diagnosis or recognition of progression of each disorder. For patients with known myasthenia admitted to the ICU in crisis, it is important to note the timing of anticholinesterase treatment and the timing in relation to each evaluation of strength. In general, testing should be performed at the nadir of weakness prior to each treatment. This is the only reliable way in which a decline in strength can be detected in these patients for whom one should have a very low threshold for intubation, particularly in the patients with bulbar involvement. In the case of GBS, patients who cannot walk unaided should be treated with intravenous immunoglobulin.[35] Neither GBS nor myasthenia should alter pupil reactivity. If the pupils are slow to react or do not react in a weak infant, the diagnosis of botulism should be considered.[36]

Posturing, due to increased ICP, should be distinguished from abnormal movements including chorea and dystonia.

Decorticate posturing consists of adduction and stiff extension of the legs, flexion and supination of the arms, and fisting of the hands. This occurs when the midbrain and red nucleus control body posture without inhibition by diencephalon, basal ganglia, and cerebral cortex. Decerebrate posturing consists of stiff extension of legs, arms, trunk, and head with hyperpronation of lower arms and plantar flexion of the feet. This indicates pontine and vestibular nucleus control of posture without inhibition from more rostral structures. Lesions below the level of vestibular nuclei lead to flaccidity and abolition of all postures and movements. These movements should be distinguished from dystonia or chorea, which may be seen as side effects of medications, or as the sequelae of basal ganglia injury, metabolic disorders, or neurotransmitter disorders.

Reflexes

In the PICU, reflexes may be absent, wax and wane during the course of the day, or be elicited by some examiners but not others. This variability can be diminished by taking time to elicit the reflex, performing the exam when the child is in a quiet, resting state, by experience, and by focusing on key reflexes. In general, the purpose of the exam is to determine whether there are changes in intensity (a reduction or increase) or symmetry or development of pathologic reflexes. It is common for upper extremity reflex testing to be limited by the presence of one or more armboards. Thus, the lower extremities are usually the most reliable site for evaluation of symmetry and intensity.

At a minimum, reflexes to be tested include the tendon jerks in the upper (if available) and lower extremities and the Babinski sign (dorsiflexion of the great toe, sometimes accompanied by fanning of the toes in response to stimulation of the lateral plantar aspect of the foot), as the cardinal screening test for intact functioning of the pyramidal system. If an extensor plantar reflex is present, this reflects injury along the corticospinal tract. The rest of the neurologic exam is then used to identify the level at which this injury is present. A number of other techniques (e.g., Chaddock, Oppenheim, Gordon, Strumpell, Moniz, Gonda-Allen) may be used[37] to elicit the extensor response but the Babinski is the most reliable.

In patients with decreased or altered mental status, frontal lobe release signs may be tested. These signs reflect diffuse cerebral dysfunction or injury. The grasp reflex involves the patient reflexively gripping the examiners finger or hand as the palm is brushed. The palmomental reflex is elicited by scratching the thenar eminence and observing for twitching of ispsilateral lower jaw muscles. The snout reflex is elicited by tapping on the mouth and producing puckering of the lips. To elicit the rooting reflex, the mouth is lightly scratched resulting in the patient turning to align the mouth with the finger. The glabellar reflex is elicited by tapping the forehead in the midline (this is done from above to head so as not to confuse the response with the reflex response to visual threat), and observing for repeated blinking each time the forehead above the bridge of the nose is tapped.

Cerebellar Function and Gait Evaluation

Normal coordination requires that both muscle strength and proprioception are intact. The interpretation of the cerebellar exam testing should be done with these systems already evaluated. Abnormal eye movements including dysmetria (overshoots of the target or a series of ratchet-like undershooting movements to reach the target when the eyes are rapidly brought from fixation on one object to another), gaze-evoked or downbeat nystagmus, or speech (slow, impaired prosody, distorted consonants or vowels, mutism) may be the only observable manifestations of cerebellar dysfunction in a patient who is sedated or too weak to cooperate with the remainder of the exam. Truncal ataxia can be detected by sitting the patient up in the bed. If possible, gait should be evaluated and observed for a widened base and the ability to perform rapid turns while maintaining normal balance.

Sensory Examination

Even in the alert patient, this component of the neurologic examination is the least reliable and the first to be discarded if necessary. This examination requires a cooperative patient. Of the components of this exam, vibration and joint position sense are the most sensitive. In the sedated patient or patient with depressed level of consciousness, sensation testing may need to be limited to noting withdrawal or flexion of the stimulated limb or an increase in heart rate. In the cooperative patient, temperature sensation can be evaluated using a tuning fork, that should feel cool. The examiner should be particularly alert to detecting a level at which sensation (pain, temperature, light touch) is lost or diminished in patients with spinal cord injury, TBI (with unrecognized cord injury), inflammatory (transverse myelitis) or demyelinating disorders of childhood (e.g., acute disseminated encephalomyelitis, multiple sclerosis), that may involve the spinal cord. In patients with cerebral injury, a lack of response to sensory testing should be distinguished from neglect.

Abnormal Movements or Altered Sensorium in the Child with Static Encephalopathy

This is a common issue in the PICU, often because of concern that the patient may be seizing, and may prompt obtaining additional imaging or EEGs since these children have primary neurologic disorders. A stepwise approach is helpful. These patients may have a limited behavioral repertoire but are at risk for multiple subtle medical problems including unrecognized pain, all of which may initially manifest with the same behavior. For a neurologist, this evaluation should also present an opportunity to revisit the diagnosis of "cerebral palsy" or "static encephalopathy," which may be obscuring a diagnosable (and perhaps treatable) disorder such as DOPA-responsive dystonia. In such cases, in addition to (often instead of) monitoring for neurologic injury evaluations, other etiologies should be considered, including unrecognized trauma, hip subluxation, long bone fractures, constipation, volvulus, inguinal hernia, gastric distension, or bowel adhesions.

Goals of the Neurologic Examination in the Pediatric Intensive Care Unit

At the conclusion of the neurologic examination in the PICU, the examiner should be able to identify the location(s) of neurologic dysfunction at the very least in terms of injury to grey (encephalopathy, seizures, neglect, aphasia) or white (weakness, spasticity) matter, posterior circulation (brainstem

dysfunction, cranial nerve palsy with contralateral weakness), spinal cord (sensory or motor level), peripheral nerve (decreased or absent reflexes), neuromuscular junction, or muscle, along with the presence of any signs of increased ICP. This should be established either as the baseline exam or compared to previous examinations and therefore assessed as progressing, improving, or stable. Next, the mechanism producing this injury should be assessed and ranked in order of likelihood. In general, this will involve either primary neurologic insult such as TBI, stroke, CNS infection, neurodegenerative disease, autoimmune or parainfectious processes, or the complications of other common pediatric disorders requiring ICU care including sepsis, congenital heart disease, liver failure, organ transplant, diabetic ketoacidosis, renal disease and dialysis, status epilepticus, or iatrogenic complications of commonly used drugs such as immunophilins or intrathecal chemotherapy.

The goal of the examiner is to combine data from the history, presenting signs, and physical examination (which may, of necessity, involve only observation of the patient) in order to develop a differential diagnosis for both the site of injury and mechanism. In general, these mechanisms will involve one or more common etiologies including: vascular (ischemia, hemorrhage, large or small vessel, arterial or venous, artery-to-artery, or cardioembolic); metabolic (either iatrogenic, often abnormalities of sodium, glucose, or ammonia; or the first presentation of a metabolic disorder); autoimmune (CNS lupus, autoimmune encephalopathies and epilepsies); parainfectious (e.g., acute disseminated encephalomyelitis); iatrogenic (sedation, neuromuscular blockade, immunophilins); toxic (drugs of abuse, drug metabolite accumulation in liver or renal failure); and infectious (systemic infection with CNS involvement, meningitis, or encephalitis, reactivation of a latent CNS infection in the immunosuppressed patient).

Based on the postulated location of the insult, the stability of the neurologic examination, the mechanism of injury, and the risk for progression of neurologic injury, the monitoring modalities can then be selected based on the need to either establish a diagnosis, monitor for secondary neurologic injury, or both.

Neuromonitoring

Neuroimaging

Computerized tomography (CT) and magnetic resonance imaging (MRI) each have specific advantages (Table 55-5) and should be selected for specific purposes (discussed in Chapter 56). CT measures x-ray density, is available easily, can be performed quickly, and is a sensitive means of detection of cerebral edema or blood. CT is relatively insensitive to acute ischemic injury and does not provide sufficient resolution in the posterior fossa, where lesions may be missed. Diagnostic CT scans should be performed first without contrast and then with contrast. Contraindications to contrast are renal failure, incipient renal failure, or a history of allergy to contrast media. White (dense) lesions on the noncontrast study are either hemorrhage or calcification. In most patients in the PICU, these white areas represent hemorrhage. Contrast enhancement indicates either local breakdown of the blood-brain barrier or excess vascularity and is associated with neoplasms, infections, inflammatory lesions, and subacute stroke.

The increasing availability of MRI is leading to greater use of it in the evaluation of acute brain injuries. MRI stimulates tissue with a specific radiofrequency pulse, after which the tissue returns to its preexcited state by processes known as T1 or T2 relaxation. In the T1 sequences, which measure T1 relaxation, cerebrospinal fluid appears dark, while it appears white in the T2 sequences. Gradient echo (GRE) sequences are most sensitive for detection of hemorrhage on MRI. In these sequences blood appears dark early (4 to 6 hours) after hemorrhage and remains dark in all later stages of hemorrhage. Small infarcts, infections, inflammatory areas, and demyelinating plaques are much more readily detected on MRI than on CT. Fluid-attenuated inversion recovery imaging uses T2-weighted sequences in which cerebrospinal fluid appears dark. For detection of ischemia, diffusion-weighted imaging (DWI) is more sensitive than CT scan in the visualization of acute cytotoxic edema. This sequence can identify acute ischemic strokes as bright lesions within minutes of their occurrence (Figure 55-2, *A*). Bright lesions on DWI indicate a restriction in the movement of water and thus are consistent with an increased water content of that region. The degree of water proton mobility is quantified by the apparent diffusion coefficient (ADC). On ADC maps, areas of restricted diffusion appear as hypointense (dark) (Figure 55-2, *B*). The reason for early decline in ADC is thought to be cytotoxic edema as a result of cellular energy failure causing a loss of ion homeostasis and a subsequent shift of water to the intracellular compartment. Not all restricted diffusion is ischemic in origin (Figure 55-2, *C* and *D*) and may instead be associated with inflammation (infection, demyelination) or metabolic derangement as in the case shown, an example of a metabolic

Table 55–5 Neuroimaging Advantages and Limitations

	Plain CT	MRI	CTA	MRA	Conventional Angiogram
Purpose	Detection of edema or blood	Higher anatomic resolution; DWI can detect early ischemic changes	Evaluate large cerebral arteries	Evaluate large cerebral arteries	Gold standard; obtain if CTA or MRA is negative and dissection or vasculitis is suspected
Advantage	Fast, widely available	DWI can detect acute ischemia	Better detection of intracranial stenosis and occlusion than MRA	Detects large-vessel arteriopathy	Most sensitive to small-vessel disease, dissection, vasculitis
Limitations	May not detect acute ischemia; insensitive to posterior fossa lesions	Less available on emergent basis; patient may need sedation	Large radiation dose	Not a measure of flow; not sensitive to small vessel disease	1% risk of complication

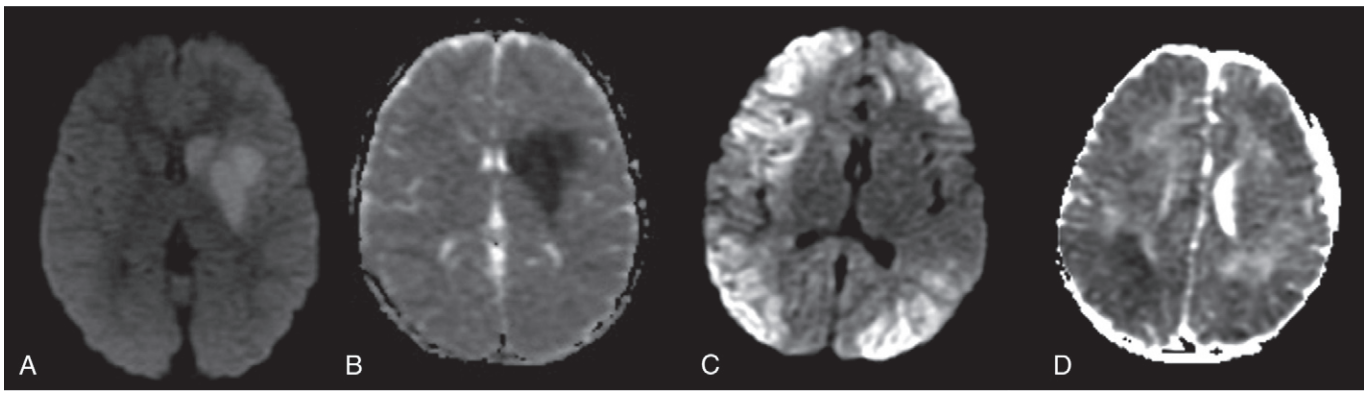


Figure 55–2. **A,** Restricted diffusion manifest as hyperintense signal in the left caudate, putamen, and globus pallidus in a 5-year-old girl with acute onset of right-sided weakness due to carotid dissection after a fall. **B,** Dark signal on the ADC map supports the mechanism as ischemic in this clinical context. **C,** Restricted diffusion in a watershed pattern in a previously healthy 1-year-old child with partial ornithine transcarbamylase deficiency and associated reduced signal in the corresponding ADC map (**D**). In this case, the mechanism is due to metabolic compromise, not ischemia.

stroke due to partial ornithine transcarbamylase deficiency mimicking a watershed stroke.

MR angiography (MRA) and MR venography (MRV) are used to detect vascular occlusions in large- and medium-size vessels in the head and neck, cerebral aneurysms larger than 5 mm and arterial dissection. As dissection is a relatively common cause of stroke in the young, MRA is a useful modality in the evaluation of pediatric stroke. This sequence detects the presence of methemoglobin in the false lumen within the vessel wall. CT angiography (CTA) is an alternative to MRA and is also noninvasive. MRA may be preferable to CTA because contrast agent is not required and the procedure does not use ionizing radiation. If MRA or CTA is negative and a dissection is suspected, conventional angiogram should be obtained. Similarly, if small vessel arteriopathy or vasculitis is suspected and MRA or CTA is negative, conventional angiography should also be obtained. Magnetic resonance spectroscopy (MRS) is used to measure the peak concentrations of certain brain metabolites such as *N*-acetylaspartate, creatine, lactate, and choline in defined areas of the brain. Measures of injury such as elevated lactate or reduction of *N*-acetylaspartate are not reliably specific to metabolic disease, metabolic stress, ischemia, demyelination, malignancy, or inflammation. When present, these measures may confirm cell injury but their absence does not rule out tissue damage.

For traumatic diffuse axonal injury (DAI) in particular following TBI, diffusion tensor imaging (DTI) has emerged as a promising means of detection of injury. DAI is thought to be a major contributor to cognitive dysfunction ranging from cognitive difficulty to coma following TBI,[38,39] but it is difficult to diagnose or characterize noninvasively. Advances in imaging technology using DTI MRI have allowed early detection of axonal injury in patients following TBI and have linked cognitive disability in these patients to white matter signal changes.[38,40] Animal studies of TBI comparing DTI findings to histopathological evidence of axonal injury show that this imaging modality is a sensitive tool to detect axonal injury.[41]

The effect of therapeutic hypothermia on the radiographic evolution of restricted diffusion on DWI in children following cerebral ischemia is not known. In practice, this means that as the use of hypothermia is extended from the asphyxiated newborn to children with cardiac arrest[42] and TBI, the results of DWI studies may potentially underestimate the degree of ischemia if obtained during or close to treatment with hypothermia. Transport of the critically ill child, the increased duration of the scan (compared with CT), and the availability of the scanner are important in the decision to obtain MRI. One approach is to streamline the use of MRI by only obtaining sequences specific to the insult being evaluated. Thus, for suspected ischemia only DWI and ADC sequences are obtained; for hemorrhage, GRE; for hydrocephalus, MR of the ventricles; for sinus thrombosis, MRV; for dissection or large vessel vasculitis, MRA; for metabolic disease, MRS; and for cortical dysplasia in epilepsy patients, standard MRI. This means that a patient admitted with suspected stroke can complete a study (MR ventricles and DWI) in a much shorter time than is otherwise required and the most important initial question (presence or absence of ischemia) can be addressed so that therapy can be adjusted.

Intracranial Pressure Monitoring

The most common indication for ICP monitoring in critically ill children is TBI (discussed in Chapter 61), in which the measurement of ICP serves to direct therapy with the goal of preventing the secondary complications of TBI resulting from cerebral hypoperfusion or metabolic stress. For children with severe TBI, a CPP between 40 and 65 mm Hg is recommended,[26] and CPP of 60 to 70 mm Hg for adolescents. Optimal CPP levels for children under 2 years of age have not been established. Nevertheless, it is possible that outcome from other neurologic insults resulting in cytotoxic or vasogenic cerebral edema may be improved by therapy optimized to maintain cerebral perfusion, as directed by monitoring of ICP. In pediatric acute liver failure, the main determinant of outcome is neurologic morbidity[43] with compromise of astrocyte metabolism postulated as a pivotal mechanism in the development of cerebral edema associated with hepatic encephalopathy.[44] ICP monitoring is used in approximately 7% of patients with meningitis,[45] and mortality is higher in patients with meningitis and mean CPP less than 50 mm Hg.[46] In the longer term, other indications for ICP monitoring may expand to include diabetic ketoacidosis, cardiac arrest, near-drowning, or refractory status epilepticus. At present, there is no consensus for

ICP monitoring other than following TBI, as there are no data to show any improvement in outcome and there are concerns that the risks outweigh the potential benefits.[47,48] It is important to keep in mind that, in children in particular, neuroimaging cannot be used as the definitive measure of the presence or absence of intracranial hypertension (Figure 55-3). Rather, the examiner must rely on a combination of assessment of risk factors, clinical examination, and changes in the examination, combined with imaging findings (which may be unremarkable).

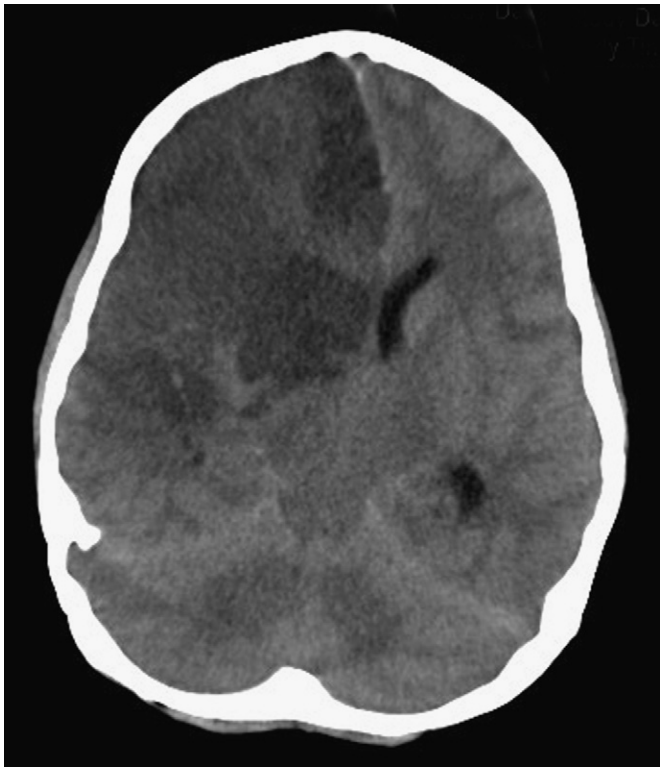


Figure 55–3. Cranial CT without contrast in a 9-year-old with acute onset of left-sided weakness, demonstrating extensive edema with midline shift in the right cerebral hemisphere, consistent with infarctions in the right anterior cerebral and middle cerebral artery distribution, sulcal effacement, and compression of the right lateral and third ventricle. This patient was still awake and following commands when this scan was obtained.

Brain Tissue Oxygen Monitoring

Maintaining adequate tissue oxygenation is a fundamental goal in management of any compromised organ in the critically ill patient. Accordingly, brain tissue oxygen ($PbtO_2$) monitors are now included in the treatment guidelines for management of TBI.[49] The Neurotrend system, using a colorimetric method with optical fluorescence, measures three variables: O_2, pH, and CO_2, but is rarely used in clinical practice in the United States and is currently not commercially available. The Licox system (Integra Neurosciences, Plainsboro, NJ) uses a Clark-type electrode with a catheter 7 mm in length and measures both $PbtO_2$ and temperature. The indications for placing the $PbtO_2$ monitor are the same as those for patients requiring ICP monitoring following TBI. Typically, the probe is placed in the white matter of the brain, because it is more metabolically stable than the gray matter. If the region of injury is to be monitored, the catheter is placed adjacent to, but not in the region of, the contusion or clot, the area of insult, or in the ischemic penumbra. While there have been no randomized trials evaluating $PbtO_2$ monitors, a retrospective analysis of 150 evaluable patients with severe TBI[50] found that brain hypoxia ($PbtO_2$ <10 mm Hg) was associated with worse outcome and mortality. Notably, the complication rate was less than 1%. There is debate as to whether the $PbtO_2$ monitor is measuring oxygen extraction or cerebral blood flow (CBF).[51] Animal studies suggest that the monitor is not simply measuring CBF,[52] consistent with data from human severe-TBI cases using a probe in the least-injured hemisphere, showing a significant relationship between $PbtO_2$ and the product of CBF and cerebral arteriovenous oxygen tension difference.[53] Taken together, these data indicate that this monitor detects both oxygen tension and CBF. The promise of this technology for pediatric neuromonitoring is considerable but a number of caveats remain. The threshold (10 to 15 mm Hg) for poor outcome is based on mostly adult data. The age dependence of this threshold, the dose dependence of an exposure to cerebral hypoxia, and the disease specificity (for insults other than TBI) of this endpoint remain to be determined.

Cerebral Microdialysis

Cerebral microdialysis, like $PbtO_2$ monitoring, is an invasive method for estimating cerebral metabolism. This technology uses the capillary technique to measure the concentration of key metabolites (glucose, pyruvate, lactate), excitotoxic amino acids (glutamate and aspartate), and membrane breakdown products (glycerol) in the brain parenchyma in order to detect evolution of primary injury and the development of secondary injury.[54] The microdialysis catheter is a fine tube, placed via a burr hole, within a semipermeable dialysis membrane that permits diffusion of molecules from the extracellular space along the catheter and into a vial. This vial is then placed in the microdialysis analyzer. In general, the catheter is placed via the same burr hole as the $PbtO_2$ and ICP monitors into the normal brain or the penumbra of the injured brain. The most common system is the CMA 600 microdialysis analyzer (CMA Microdialysis, Stockholm, Sweden). As with $PbtO_2$ monitoring, results will vary, depending on whether the probe is placed in healthy tissue, tissue adjacent to the primary site of injury (penumbra), or in the injured tissue. For adults with TBI or SAH requiring ICP monitoring, the use of microdialysis has been recommended, following a consensus meeting.[55] A number of adult studies have shown, in TBI and SAH cases, an association between metabolic stress (lactate/pyruvate ratio >40) and poor outcome.[11] In a retrospective analysis of 20 adult patients with severe brain injury, tight systemic glucose control was associated with reduced cerebral glucose and with corresponding evidence (increased lactate/pyruvate ratio) of compromised brain metabolism.[56] While prospective studies are needed to determine whether metabolism-directed therapy can improve outcome, as are data on age- and disease-specific values in children, and a consensus is needed on the indications for in pediatric neurocritical care, it is clear that the ability to monitor and react to compromised cerebral metabolism in the long term will be essential to improving neurologic outcome.

Near-Infrared Spectroscopy

NIRS measures tissue oxygen saturation by determining the difference in intensity between transmitted and received light delivered at specific wavelengths.[57] Commercial cerebral NIRS products measure oxygenation by using light between 700 and 1000 nm wavelength to measure transparency of tissue to light. Since hemoglobin absorbs near-infrared light depending on its oxygenation state, changes in hemoglobin oxygenation can be quantified using the modified Lambert-Beer law. In theory, NIRS may therefore serve as a noninvasive method for detection of cerebral or somatic hypoxia. In practice, the reliability of cerebral NIRS has been questioned in a study showing that in infants up to 190 days old, cerebral NIRS values were not reproducible.[58] In a study of adult human cadavers, the cerebral tissue oxygenation measured by NIRS in a third of these subjects was higher than the lowest value of normal controls.[59] While there remains controversy over the relationship between NIRS values, particularly for the CNS, the cumulative evidence from studies in congenital heart disease supports a role for NIRS in physiologic monitoring. In a study of postoperative congenital heart disease patients, cerebral and flank regional oxygen saturation were correlated with central venous oxygen saturation in both cyanotic or acyanotic patients and single-ventricle or two-ventricle physiology.[60] Change in arterial pressure of carbon dioxide was associated with change in cerebral, but not flank regional oxygen saturation, suggesting that cerebral NIRS is detecting changes in cerebral oxygenation. In patients with elevated ICP, cerebral regional oxygen saturation measured by NIRS was significantly reduced,[61] but this association was present only in cases of brain tumors and hydrocephalus. The cumulative evidence suggests that NIRS may ultimately prove useful both in the monitoring for neurologic complications following surgery for congenital heart disease[62] and in other neurologic disorders.

Electroencephalographic Monitoring

The importance of the EEG as a monitoring tool in the PICU is not only in its role in the detection of electrographic seizures but also, in doing so, as a means for detecting and treating secondary insults in the critically ill patient. The objective of neurologic monitoring in the ICU, from the bedside exam to ICP, is the early recognition of secondary insults to the brain, and the EEG is a noninvasive tool to include in this armamentarium. In a full montage, 20 scalp electrodes are placed over the skull and record the electrical activity of the surface of the brain. In general, the EEG is used to detect seizures, electrographic alone (NCS), epileptiform activity, and focal slowing or discharges. Criteria for the use of continuous EEG (cEEG) monitoring in the PICU have not been established and there is wide variation in the use of this technology.[63]

Importantly for ICU neurology, the EEG cannot be used to determine the etiology of abnormal patterns, discharges, or seizures. Seizures may be the presenting symptom of new ischemic (venous or arterial) or hemorrhagic injury in the critically ill patient. In the PICU, the detection of electrographic or clinical seizures should prompt investigation of common PICU causes of seizures such as metabolic derangement, drug reaction, vascular injury, or infection. Often, a change in EEG pattern (loss of complexity, slowing, new epileptiform discharges) in the absence of seizures may also reflect new neurologic insult. The import of these changes can only be interpreted in the context of each patient's risk factors for neurologic injury.

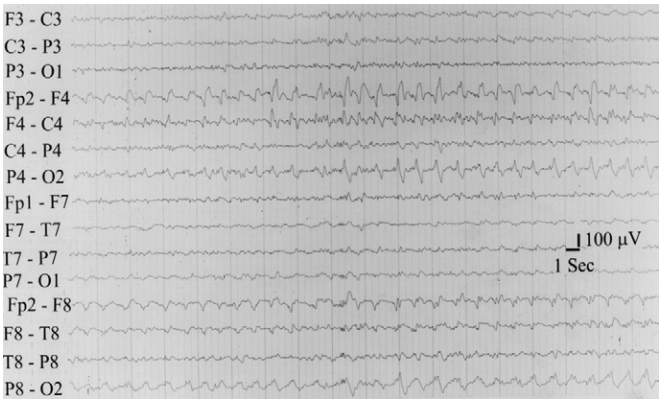


Figure 55–4. Bipolar EEG montage of an 11-year-old girl 4 weeks after umbilical cord transplant for acute myelocytic leukemia. Note the electrographic seizures at F4 and F8. This patient has had limbic encephalitis due to reactivation of latent human herpesvirus-6 infection. The only clinical manifestations of nonconvulsive seizures in this patient were loss of short-term memory and decreased sleep.

Status epilepticus and refractory status epilepticus are associated with a significant increase in mortality in adults and children (discussed in Chapter 60).[64-67] Since repetitive seizures become self-sustaining and pharmacoresistant after 15 minutes,[68] early recognition of clinical or electrographic seizures is an important factor in enhancing the efficacy of anticonvulsants to terminate seizures and reduce the additional metabolic stress seizures impose on the injured brain. However, NCS or status epilepticus may be difficult to diagnose. Both are often unrecognized in comatose patients.[69,70] Convulsive or nonconvulsive seizures have been detected in up to 50% of patients in an ICU when examined with cEEG monitoring.[71-73] Many of these patients are in electrographic nonconvulsive status epilepticus (NCSE).[74] Importantly, routine (r)EEG recording fails to detect NCS in approximately 50% of critically ill patients whose NCS were detected with cEEG monitoring.[73,75] In patients in whom NCS are suspected, cEEG monitoring for at least 12 hours is required to detect NCS,[4,31,73] since the majority of these seizures will be not be detected during the short duration of an EEG. An example of NCSE is shown in Figure 55-4 in a patient with limbic encephalitis following cord blood cell transplantation, whose only neurologic deficits were decreased sleep and loss of short-term memory. Thus cEEG monitoring rather than rEEG should be used in any comatose or obtunded patient in whom seizures are suspected. While cEEG is recommended over rEEG because of the greater sensitivity of NCS detection with prolonged monitoring, there are no established criteria to determine patients to select for such monitoring. Given the prevalence of NCS in adult and PICU studies (up to 50% of comatose ICU patients) a reasonable approach is to monitor any obtunded or comatose ICU patient with a primary neurologic injury or in whom neurologic complications of therapy or disease may occur.

In addition to the detection of NCS, EEG is used to guide therapy during induction of or withdrawal from burst suppression. This is most easily achieved using cEEG, but if this is not available serial rEEGs may serve the purpose. In the

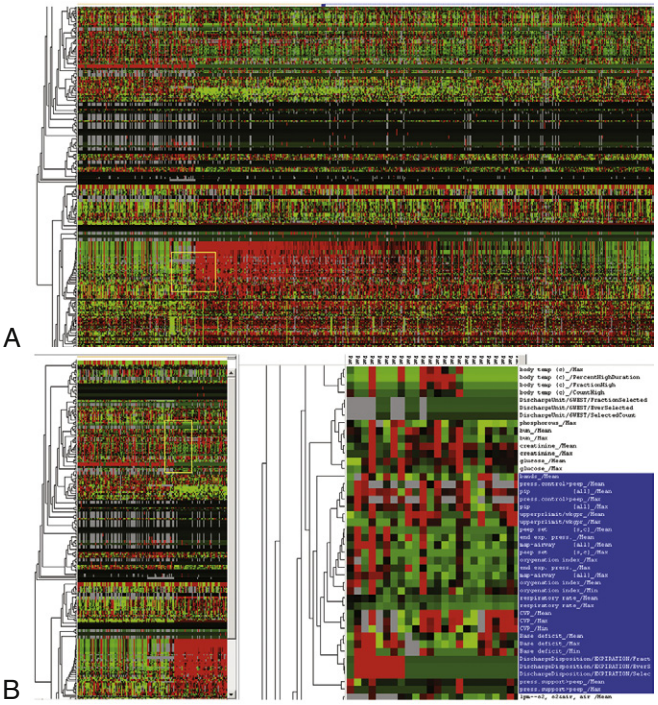


Figure 55–5. **A,** Master view of heat-map analysis of all PICU patients over a 5-year period, older than 1 year of age, who required mechanical ventilation. The differences between survivors (*left*) and nonsurvivors (*right*) can easily be seen. This analysis incorporated thousands of variables ranging from census tract data to laboratory results and ventilator settings. **B,** View of selected cluster of variables highlighting those associated with differences in outcome after ventilation. This approach is proof principle of the potential of data mining in the ICU to discover novel relationships and generate hypotheses.

PICU, careful attention should be paid to the integrity of the scalp as skin breakdown following prolonged exposure to the EEG electrodes may occur within 1 to 2 days and may limit the ability to perform serial monitoring studies.

Integrating Neurologic Monitoring Data

The growth in tools for invasive and noninvasive neuromonitoring in the ICU forces the issue of how to collect, integrate, and interpret these data.[76] It is clear that the use of physiologic thresholds to define "good" or "bad" values is oversimplified for pediatric neurocritical care in particular, and based on limited data with no well-established age-dependent parameters. This approach tends to interpret one variable in isolation from others and relies on the skill and experience of the clinician interpreting the data. Further, the volume of data generated on a minute-to-minute basis in the PICU places demands on the network used for storage of these data. The goal of "plug-and-play" for all devices (monitors, infusion pumps, ventilators), that generate potentially clinically important data has not yet been achieved in the PICU. Indeed, these devices typically do not have a common source for recording time, rendering even the interpretation of the timing of treatment, changes in ventilator parameters, laboratory results, or physiology open to question even if the obstacles to acquiring these data have been overcome. One approach may be to limit the acquisition of data to only those variables best validated for outcomes in TBI. This approach will likely miss unanticipated relationships that may emerge only using an unbiased non-hypothesis-driven analysis of multiple variables. An example of this approach from a retrospective analysis of PICU data is shown in Figure 55-5. Using a cluster analysis of all patients older than 1 year who required mechanical ventilation, the differences between survivors and nonsurvivors can easily be seen. This analysis incorporated thousands of variables ranging from census tract data to laboratory results and ventilator settings, and demonstrates the potential of the application of these tools to the array of data generated in the PICU. Therefore, in order to make use of the data generated by neuromonitoring, to interpret these data in relation to other physiologic and laboratory variables, and to develop new methods of analyses beyond thresholds and values at single time points rather than trends over time, it will be necessary to establish real-time data collection from all devices attached to the PICU patient, link these data (including waveforms) to laboratory and socioeconomic data, direct the flow of this information to new analysis tools, validate the data returning to the bedside, and iteratively develop and test predictive tools for the recognition of new cerebral or systemic injury. Thus progress in the application of neuromonitoring for management of children with brain injury is fundamentally linked to the development of improved (better integrated, higher granularity) data collection and tools for bedside analysis using the emerging methods of bioinformatics.

References are available online at http://www.expertconsult.com.

Neuroimaging

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PEARLS

- Multiple imaging modalities are available for evaluation of the brain, head, neck, and spine of the critically ill child. The most appropriate modality depends on consideration of patient pretest probability for the clinically suspected diagnosis, the modality sensitivity, and the patient's age and condition.
- When ordering radiographic studies, particularly computed tomography scans, keep in mind the radiation burden, especially for infants. When ordering magnetic resonance imaging for young children, one must keep in mind the risk related to sedation and general anesthesia.
- The ever-increasing complexity of imaging modalities and medical problems in the intensive care unit warrants liberal consultation with radiology colleagues to yield an appropriately tailored imaging protocol and a more relevant interpretation.
- In the pediatric population and especially in critically ill patients, noninvasive imaging modalities that are likely to answer the clinical question should carefully be considered as an alternative to a catheter angiogram, which is minimally invasive but has a real, non-zero risk of procedure-related complications.

Imaging Modality Overview

Multiple imaging modalities are available to investigate the neurologic status of children in the intensive care unit (ICU). Selection of the most appropriate examination requires weighing factors of modality sensitivity against the suspected pathology, having a degree of suspicion for a particular pathology, and considering the practicalities afforded by the complexity of the examination and the child's condition. In this chapter, available imaging modalities and the disease processes most likely to be subject to neuroimaging evaluation are reviewed.

Ultrasound

Standard cranial ultrasound has been a mainstay in the neonatal ICU. Ultrasound generates gray-scale digital images from components of an ultrasound beam reflected off tissue interfaces with no ionizing radiation, and with the added advantage that bedside imaging can be performed. However, cranial ultrasound has a restricted window through which to visualize the brain, primarily through an open anterior fontanelle, and therefore it is limited for the most part to the first few (4 to 6) months of life. Ultrasound is sensitive to some intracranial pathology, including the detection of germinal matrix hemorrhage, evaluation of ventricular size, and evaluation of severe white matter lesions in premature infants, including cystic periventricular leukomalacia (PVL). It is less sensitive for pathologies such as mild to moderate parenchymal ischemic changes, subarachnoid and punctate parenchymal hemorrhage, and subtle cerebral malformations. Extra-axial collections, especially those along the lateral cerebral convexities, also can be difficult to appreciate on ultrasound performed through a midline fontanelle.

Color Doppler with the standard ultrasound machine uses the shift in frequency associated with reflection of the sound beam off a moving interface (the "Doppler shift" phenomenon) to detect motion in the image field, most commonly from blood in vessels. Those pixels with movement are assigned a color to distinguish them from pixels without movement. The color assigned (most often red and blue) is different depending on whether movement is away from or toward the transducer, and the color assigned is arbitrary so that arteries and veins are not necessarily red and blue, respectively. Color Doppler allows for some investigation of the cerebral circulation, primarily through the open fontanelle. Transcranial Doppler (TCD) uses the same Doppler shift to produce waveforms that give information about flow velocity and direction. TCD has the advantage that it can be performed through the thinner portions of the skull, primarily the temporal squamosa, in older children and adults (Figure 56-1). TCD has been used in evaluation of cerebral perfusion in patients with sickle cell disease[1] and vasospasm secondary to subarachnoid hemorrhage.[2] TCD is generally sensitive to stenoses greater than 50% in the central cerebral circulation, with the highest sensitivity and specificity being in the middle cerebral artery (MCA).[3,4]

Computerized Tomography

Computerized tomographic (CT) scanning has higher sensitivity compared with ultrasound for many intracranial pathologies, including most neurosurgical emergencies, and is not limited by closing and closed fontanelles. Imaging on modern scanners with multiarray detectors can be performed very rapidly. CT, however, requires transporting the patient from the ICU (although some portable units are available) and uses ionizing radiation (x-rays) to produce digital computer–reconstructed images based on differences in tissue density

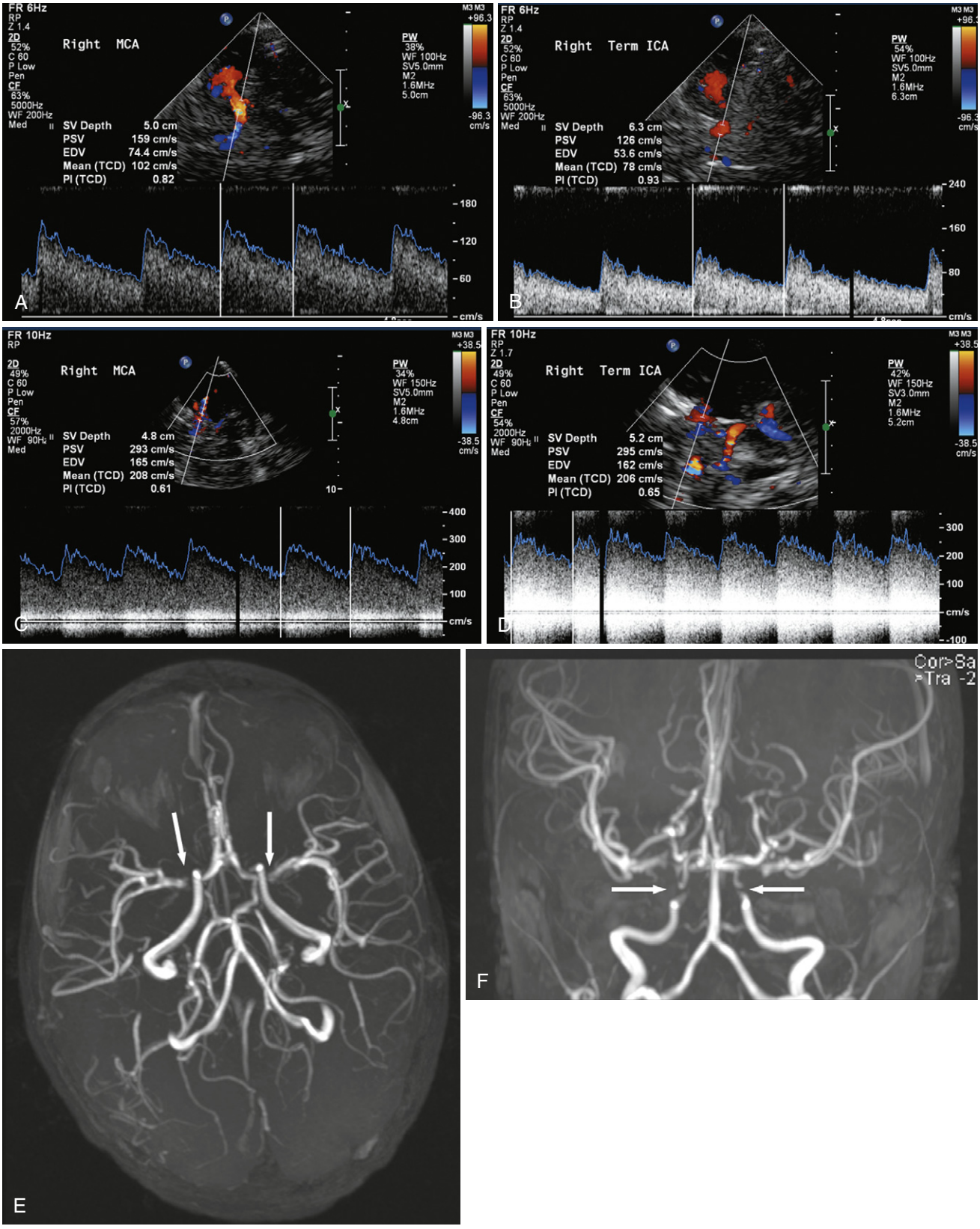

Figure 56–1. Transcranial Doppler ultrasound images. Color and spectral Doppler waveforms from (**A**) normal right MCA and (**B**) right terminal ICA. Abnormal right middle cerebral (**C**) and terminal internal carotid (**D**) waveforms in another patient with sickle cell disease and prior history of stroke. MR angiographic images (**E** and **F**) of this patient with abnormal Transcranial Doppler demonstrate narrowed proximal MCAs and terminal ICAs.

(which affects x-ray attenuation). The choice of radiation parameters, slice thickness, post-processing, and image viewing (window width and level) must be tailored to the particular clinical question to optimize the images. Bone and other calcifications have the highest density, and in decreasing density are (nonadipose) soft tissue (such as the brain), water (e.g., cerebrospinal fluid [CSF]), fat, and then air. The difference in density between bone and brain is great, whereas the difference between brain and fat is less. The density difference between gray and white matter is much smaller but is sufficient to be appreciated with the appropriate window and level. Generally, as edema develops in non-fatty tissue, there is a decrease in density. Acute blood (approximately between 12 and 72 hours old) is of higher density than brain, and CT is very sensitive in detection of acute (generally less than 1 week old) parenchymal and subarachnoid hemorrhage (SAH). CT is also useful in the evaluation of ventricular size and extra-axial collections.

Iodinated intravenous (IV) contrast can be used with CT to evaluate the integrity of the blood-brain barrier (BBB) and differences in tissue perfusion. With injection of IV contrast, vessels demonstrate a transient increase in density, with a variable rate of contrast leak into the tissues, depending on the local pathophysiology. The rate of equilibration of contrast concentration between vessels and parenchyma is much slower in the brain because of the intact BBB. Contrast then is especially useful in the brain, where disruption of the normal BBB can reveal underlying pathology. This increased density from contrast material is also used to image arteries and venous structures with CT angiography (CTA) and CT venography (CTV), respectively. With the appropriate software, post-processing of the data can produce three-dimensional (3D) images of the vessels.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) utilizes a high field strength magnet in combination with radiofrequency pulses to produce images based on the nuclear resonance of hydrogen protons in tissue, primarily in water and fat. MRI provides the most sensitive measure of most (but not all) central nervous system (CNS) pathologies, and unlike CT, imaging can be acquired in any plane (although state-of-the-art multidetector CT scanners can acquire volumetric data that can be reformatted in any plane). Imaging, however, requires patient transport to the scanner; increased examination complexity and potential safety concerns are primarily related to the high-field-strength magnet (typically 1.5 or 3.0 Tesla) and long imaging sequences (1 to 10 minutes). MRI provides the greatest tissue characterization, facilitated by several sequences obtained in a complete study. MRI is particularly useful in evaluation of the posterior fossa (brainstem and cerebellum) and spinal cord, where "beam-hardening" due to bone results in considerable artifact on CT, although this problem has become less of an issue with modern multidetector CT scanners.

To ensure safety, MRI-compatible monitoring and life support systems must be used. Patients need to be screened for any internal hardware or implants that would preclude scanning, such as MRI-incompatible aneurysm clips. Electronic devices such as pacemakers are rendered dysfunctional by the changing magnetic field occurring during MRI and hence patients with such devices generally should not undergo MRI (further details are available at http://www.mrisafety.com/). Injuries and deaths have been reported because of the failure to recognize these dangers. Most MRI sequences require imaging times in the range of minutes and are very susceptible to motion degradation. For patients who are unable to cooperate, deep sedation or anesthesia is often required. It also is important to screen the renal function of patients who might get an MRI because gadolinium-based contrast may need to be used. Gadolinium recently has been implicated in the development of nephrogenic systemic fibrosis in some patients with compromised renal function, which is not uncommon in the ICU setting.[5]

MRI exploits nuclear characteristics of hydrogen protons principally in tissue water, referred to as the T1 (longitudinal relaxation) and T2 (spin-spin relaxation) of the tissue. An imaging sequence includes both T1 and T2 components to create an image; however, an individual sequence can be formulated to be predominately one or the other, that is, T1 weighted or T2 weighted (often referred to as simply T1 or T2 sequences). Because most pathobiology results in some disturbance of water, these imaging parameters turn out to be quite sensitive to many pathologies. On T1-weighted images, water—such as CSF in the ventricles or vitreous in the globes—is dark. This water is bright on T2-weighted images. One point to be aware of is that for the most part the signal intensity of any tissue being imaged on MRI is relative (unlike the absolute density measure in CT). Hence the detection of pathology is dependent upon visualizing differences in intensity of one tissue relative to another.

Fluid-attenuated inversion recovery (FLAIR) is a variation of T2-weighted imaging where the CSF is specifically rendered dark or suppressed so as to enhance visibility of hyperintense pathology in parenchyma, especially adjacent to normal CSF spaces. Fat is hyperintense on T1-weighted sequences and is also fairly bright on fast T2-weighted sequences, which is possible with most modern-day scanners. In some situations it is advantageous to suppress the brightness of fat, which can be specifically done at the cost of increased scan time. Gradient-recalled echo (GRE) and susceptibility-weighted MRI sequences are often utilized for detection of hemorrhage, although these sequences generally also result in more artifacts. The appearance of acute blood on CT is fairly straightforward, appearing hyperdense initially (because of the extraction of serum), becoming isodense by about a week, and appearing hypodense thereafter. The appearance of blood on MRI is much more complex, and although generally it is detectable much longer, it can be difficult to appreciate hyperacute blood (approximately less than 12 hours old) with MRI, especially subarachnoid hemorrhage. Overall, the detection of calcium and hyperacute blood can be quite difficult by MRI, and CT is often better in this regard. IV contrast is also used in MRI, with similar application with CT. In this case the contrast is a gadolinium chelate that shortens the T1 relaxation time of nearby water. The result is that the water near gadolinium is hyperintense on T1-weighted images. This effect can be used to detect BBB disruption, which is seen in various pathologies including ischemia, inflammation/infection, and status epilepticus. Malignant and some benign brain tumors also demonstrate enhanced capillary permeability with enhancement following contrast. MRI with gadolinium is about an order of magnitude more sensitive than CT using iodinated contrast in detecting BBB disruption. Some areas of the brain lack the BBB, including the choroid plexus, pituitary gland, and the median eminence, and thus they enhance normally.

Diffusion-weighted imaging (DWI) has assumed an invaluable role, particularly in the intensive care setting. This sequence is now integrated into most brain MRI examinations and is particularly sensitive to areas where brain parenchyma has sustained acute cytotoxic injury, most commonly but not limited to ischemia. DWI is sensitive to the motion of water at the molecular level.[6] Detecting this molecular level motion requires strong fast gradients that have become standard on modern-day MRI scanners to allow sufficiently rapid scanning to effectively "freeze" the gross tissue motion that normally swamps this molecular level motion. Different cerebral pathologies produce different types of edema (e.g., cytotoxic, vasogenic, and interstitial). Evaluation of the molecular (Brownian) motion of water turns out to be a sensitive measure of some pathologic states, the most significant application currently being cytotoxic edema associated with the detection of ischemia.[7] Cytotoxic edema causes "restriction" of water diffusion with a decrease in the apparent diffusion coefficient (ADC). This is seen as hypointensity on the calculated ADC map image but is more easily appreciated as hyperintensity on the DWI "trace" image. In contrast to cytotoxic edema, vasogenic and interstitial edema result in "increased" water diffusion and therefore an increase in the ADC. Care must be taken in interpreting the DWI trace images because they have some T2 weighting, and "T2 shine-through" can result in a focus of increased signal on DWI trace images that does not represent true restricted diffusion. Review of the calculated ADC map images should show a corresponding darkening in a focus of cytotoxic edema to confirm restricted diffusion. Also, the hyperintensity on DWI trace images may "pseudo-normalize" for a period of time several days following the ictus because of the development of associated vasogenic edema. Restricted diffusion due to infarct will generally resolve over the course of 1 to 3 weeks and allows a new infarct to be distinguished from older lesions. It also should be noted that restricted diffusion is not limited to ischemia and can be seen in other acute cerebral pathologies.

Advanced Magnetic Resonance Imaging Techniques

Newer techniques in MRI such as MR perfusion, MR spectroscopy (MRS), and diffusion tensor imaging are providing new information that is being increasingly utilized in the management of critically ill patients.

Perfusion MR is used in the evaluation of cerebral perfusion. The most widely available techniques use rapid scanning associated with a bolus of IV gadolinium contrast to measure first-pass changes in signal intensity. These techniques give a relative measure of perfusion, but not quantitative flow. This relative measure can be used to detect diminished cerebral blood flow in one area compared with another. Newer noncontrast MRI techniques such as arterial spin labeling generally have lower signal to noise ratio (sensitivity) but are improving and potentially quantifiable. There is some early experience with arterial spin labeling in pediatric stroke resulting from sickle cell disease.[8,9]

Conventional MRI is based on the signal intensities derived from the hydrogen bonded to oxygen in water and, to a lesser extent, the hydrogen bonded to carbon in fat. With the appropriate software, MR can be used as a "probe" for hydrogen bonded to other molecules (termed *MR spectroscopy*). The sensitivity is sufficient to detect metabolite molecules in the millimolar range, although at a much lower resolution than that used to detect water for imaging. The non-water molecules are most commonly reported as ratios of signal peaks that correspond to one of several molecules. In the brain the most common metabolite peaks detected are N-acetyl aspartate, creatine, choline, and in some physiologic states, lactate. The MRS signal is either obtained from a single voxel (usually several mL in volume; voxel is the "volume element" of the image = pixel × depth) or multiple voxels (as small as 1 to 2 mL in volume). Multivoxel MRS can be used to make low-resolution images using a technique termed chemical shift imaging for some of the more prevalent metabolite peaks. The utility of MRS is still in evolution, and newer variants of MRS are constantly being evaluated. Detection of lactate to evaluate newborn ischemia and some metabolic diseases is one of the ongoing applications and areas of research. MRS also has a role in children with mitochondrial disorders.[10]

Magnetic Resonance Angiography

Fluid motion within tissues can be used by MRI to image flow in vessels and CSF. This imaging can be accomplished with and without contrast, although contrast techniques are generally more sensitive for vascular flow, with some newer contrast angiography sequences also providing temporal/flow information. The MR angiogram can be tailored for artery (MRA) or vein (MRV) visualization, primarily based on flow direction, and is usually most effective if the area of interest can be narrowed, for example, the circle of Willis, although newer techniques have greatly increased the area that can be covered in one scan. The maximum resolution of MRA of slightly under 1 mm is generally less than CTA, where maximum resolution can be under 0.25 mm.[11] In addition to the source images (the thin angiographic sections obtained during the scan), various reconstructed images can be obtained, including 3D rotational reformations derived from maximum intensity projection reconstructions (Figures 56-2 and 56-3) and surface renderings, which also can be viewed from multiple projections. Many clinical cerebral arterial questions are now answered with MRA, and MRV of the superficial and deep venous systems has largely replaced diagnostic catheter venograms.

Catheter Angiograms

Although significant inroads have been made in cerebral vascular evaluation with both CTA and MRA, when indicated, catheter angiography remains the gold standard for most vessel imaging. Catheter angiography also provides temporal/flow data, such as appreciation of early venous drainage with arteriovenous malformations. Angiography is basically a rapid series of radiographs obtained during injection of iodinated contrast directly into the arteries or veins being imaged. Most angiography units produce digital images using digital subtraction (hence the term "digital subtraction angiography"), that is, images where the background "mask" has been subtracted, leaving an image primarily of the contrast-filled vessels. High-end modern-day units utilize biplane technology that permits acquisition of digital angiographic images from multiple projections using a single contrast injection. This technology also can be used to derive 3D rotational angiograms, images from which can be further post-processed to obtain volume rendered and surface-shaded images.

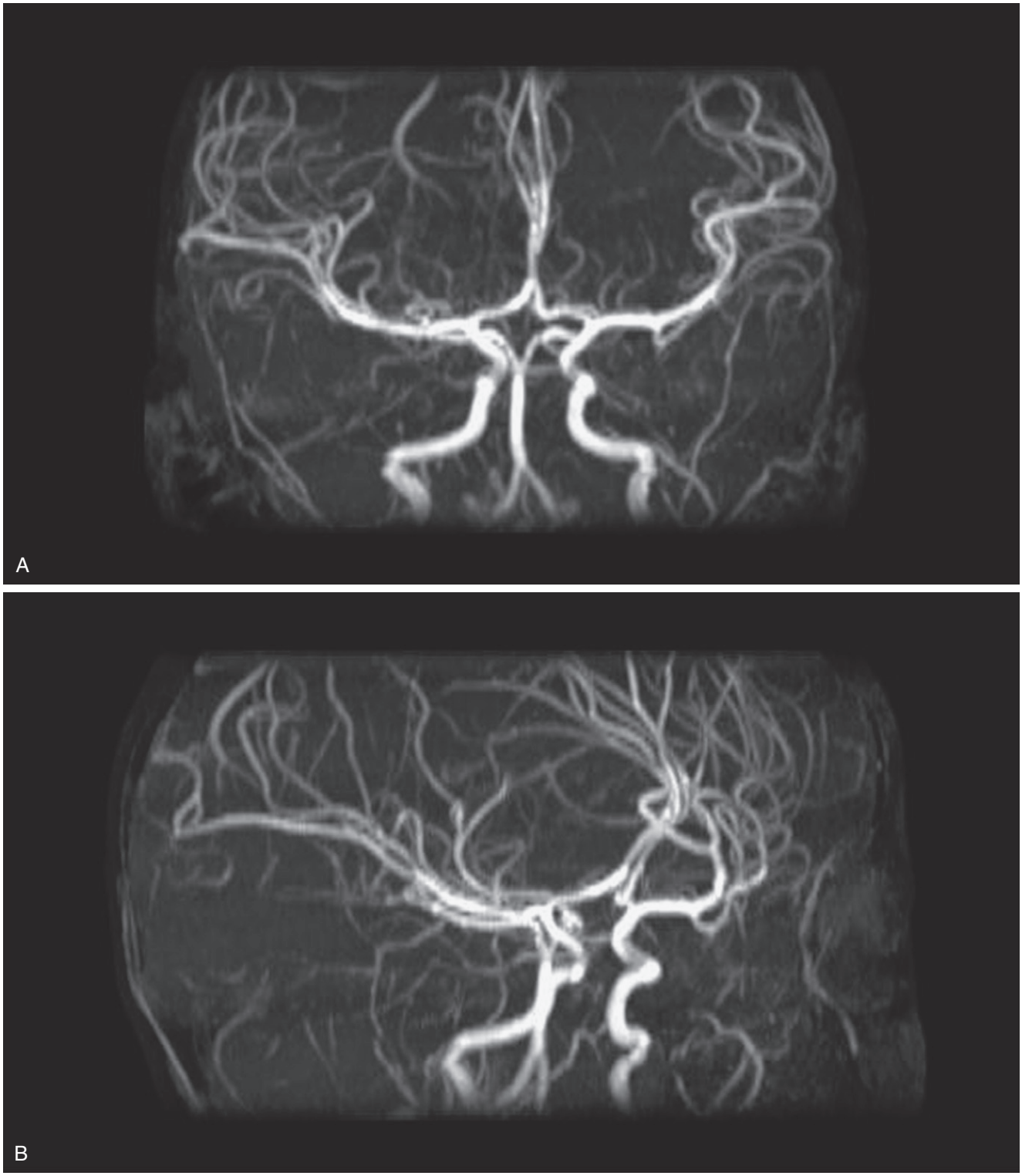

Figure 56–2. Normal MRA scans. Frontal (**A**) and oblique (**B**) maximum intensity projection images from an MRA demonstrate normal anterior and posterior circulations.

Catheter angiography requires transport to and patient support in the angiography suite. Vascular access for arterial studies is usually through the femoral artery and generally has a small but "non-zero" risk of vessel injury, including dissection and embolization. In very young patients, injury to the femoral artery is of greater concern, and although any acute risk to the limb is extremely uncommon, relative diminished leg growth in some cases has been documented. Risks of neurologic complication following cerebral angiography are small but do exist, with the reported incidence of permanent defects typically ranging from about 0.5% to 0.07%.[12,13] Therapeutic endovascular procedures carry higher risks but generally are

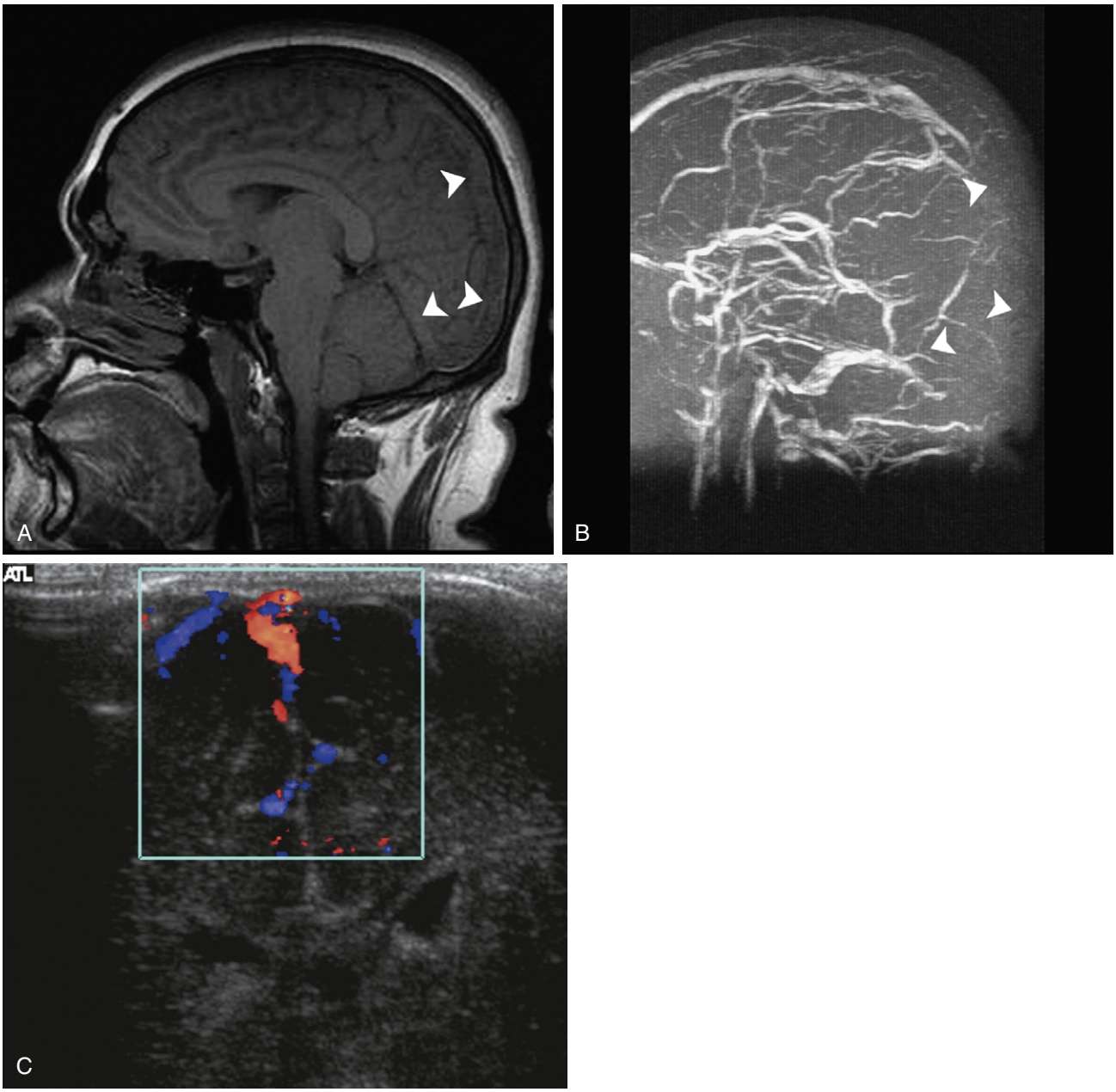

Figure 56–3. Superior sagittal sinus (*SSS*) thrombosis on MRV. Sagittal T1 magnetic resonance imaging (**A**) shows intermediate signal intensity in sagittal and straight sinuses (*arrowheads*). No flow is seen on MRV (**B**) in these vessels (*arrowheads*), which is consistent with thrombosis. Color Doppler evaluation (**C**) of the SSS in another 6-month-old patient with suspected thrombosis demonstrated a patent SSS with normal draining cortical veins (see color insert).

in lieu of riskier neurosurgical procedures or at times are the only avenue of treatment.

Myelography

Myelography involves radiographs and/or CT of the spine following opacification of the subarachnoid space by intrathecal injection of iodinated contrast, most commonly injected at the lumbar level. The myelogram has almost completely been replaced by MRI, especially in the pediatric population, because MRI can depict both extrathecal encroachment and intrathecal masses, as well as evaluate signal characteristics of the spinal cord itself and any mass. Exceptions include the inability to obtain an MRI either because of local field disruption, most commonly from ferromagnetic spinal rods, or because of MRI incompatibility due to safety issues (e.g., a pacemaker). CT provides better results than MRI in the evaluation of the bony spinal column, particularly in patients with trauma, whereas MRI is used in patients with trauma to evaluate soft tissues in the spinal column, most importantly the cord.

Nuclear Medicine

Most nuclear medicine studies involve injection of a very small amount of radioactively labeled substance (radiopharmaceutical tracer compound or radiotracer) and either follow

the physiologic uptake and metabolism of the radiotracer or the movement of the radiotracer with a gamma camera.

Technetium pertechnetate and technetium-diethylenetriamine pentaacetic acid are radiotracers used for radionuclide cerebral angiography to evaluate cerebral perfusion, thereby confirming a clinical diagnosis of brain death. Single photon emission computed tomography imaging using technetium-hexamethylpropyleneamine oxime as the radiotracer is used to monitor for cerebral perfusion defects in patients with subarachnoid hemorrhage who are at risk for vasospasm. With use of acetazolamide (Diamox), a carbonic anhydrase inhibitor, hexamethylpropyleneamine oxime single photon emission CT can be used to evaluate cerebral reserve in patients with stroke.

Ventriculoperitoneal (and ventriculoatrial) shunt function evaluation often includes a nuclear medicine shunt study. Flow in the shunt is assessed by injecting a small amount of radiotracer in the shunt reservoir and following the movement of the activity with a gamma camera.

Preterm and Term Neonate Imaging

In the premature infant, ultrasound remains the primary modality for detection and follow-up of germinal matrix hemorrhage and to detect intraventricular extension, and in the neonate, it remains the primary modality to evaluate for hydrocephalus (Figure 56-4). Furthermore, assessment can be made for white matter injury including periventricular leukomalacia, especially the cystic form, although MRI will be more sensitive for noncystic periventricular leukomalacia, and MRI in preemies performed at about the third week of life has been reported as predictive of outcome at term.[14] Routine screening cranial ultrasound has been recommended for all infants younger than 30 weeks' gestation between day 7 and 14, optimally repeated at 36 to 40 weeks' gestation.[15] Moderate to large parenchymal and extraaxial areas of bleeding also can be detected with ultrasound. As previously mentioned, smaller extraaxial collections, especially laterally along the cerebral convexities, can be missed with ultrasound, as can small parenchymal hemorrhages.

As noted in Chapters 57 and 62, understanding of hypoxic-ischemic encephalopathy (HIE) in children is complicated by the developmental status of the child. The pattern of injury seen is determined by the characteristics of the insult and the maturational state of the brain. Metabolic demands and regions of selective vulnerability evolve during development. Grayscale ultrasound, which is widely used for intracranial imaging in the neonate, is relatively insensitive to acute changes associated with HIE.[16] As edema develops, usually after several hours, increased echogenicity of brain parenchyma can be seen, but this measure is nonspecific and relative and often is difficult to appreciate. Blood associated with a hemorrhagic infarct also will appear as increased echogenicity. As mass effect develops secondary to edema, ventricular and sulcal effacement can be seen. Later, vascular and perivascular mineralization can result in linear thalamic and basal ganglia echogenicities (lenticulostriate vasculopathy or mineralizing angiopathy).[17] Ultrasound Doppler evaluation of newborn ischemia has shown some utility. Brain perfusion can be investigated by determining the resistive index (RI). RI in the normal neonate (0.75 ± 0.1) is higher than that seen in the older infant before (0.65 ± 0.5) and after (0.55 ± 0.5) fontanelle closure.[16] An increase in the RI with a decrease in the peak systolic velocity and end diastolic velocity in infants with HIE within the first 12 hours of life as measured in the anterior and middle cerebral arteries correlated with a poor prognosis at 1 year of life. A decrease in RI to less than 0.60 at 12 hours (anterior and middle cerebral arteries) and 24 hours (all insonated arteries, including basilar artery) after neonatal asphyxia, which is thought to be a result of the decreased vascular tone associated with loss of autoregulation, has been associated with a poorer outcome at 12 to 18 months of life.[18,19] Approximately half of these patients with low RI scores have normal grayscale images. There is a host of other reasons for low RI scores, however, including cardiac disease, extracorporeal membrane oxygenation, ongoing hypoxia, hypercapnia, and technical issues. It also should be noted that increased fontanelle pressure can increase the RI measure by 20%, hence there is considerable user dependence to this application. If hyperemia persists, and as HIE evolves, cytotoxic edema increases and leads to increased intracranial pressure and increased RI measurements. A high RI score on the first day of life with evidence of neonatal insult suggests an in-utero injury. Although some centers have continued to pursue use of ultrasound, much of this evaluation has been supplanted by MRI.

CT detection of acute ischemic injury also depends on edema resulting from the injury. Edema is seen as decreased attenuation and loss of gray-white differentiation, usually several hours post ictus.[20] Small or early infarcts can be missed with CT, and detection of ischemia in the newborn is made more difficult by the generally lower attenuation of the relatively "watery" unmyelinated newborn brain. For this reason, in some instances of neonatal ischemic injury, there may actually be an increase in the attenuation of this "watery" unmyelinated white matter because of an outpouring of serum proteins from damaged blood vessels. As brain swelling develops in the first few days, there can be a loss of CSF spaces seen as ventricular compression, sulcal effacement, and loss of perimesencephalic cisterns. Acute thrombotic stroke associated with arterial thrombosis can at times be appreciated acutely as a hyperdense artery, most commonly the middle cerebral artery on noncontrast CT. Acute hemorrhage, such as with hemorrhagic arterial (from reperfusion) or venous infarcts, will be hyperdense initially on CT, evolving to isodense over the first week.

Standard MR sequences exploiting T1 and T2 relaxation times also depend on the development of edema to appreciate acute ischemic injury, which results in hyperintensity on T2-weighted and FLAIR images and hypointensity on T1-weighted images. This change typically takes at least several hours to develop, and although generally more sensitive than CT in adults, evaluation of the newborn is again made somewhat difficult by the lack of myelination. As a result ischemia sometimes can be more conspicuous on CT than on T1- or T2-weighted MRI (Figure 56-5). The FLAIR sequence has proven to be more sensitive than T1 and T2 to ischemic changes in older myelinated children and adults. DWI is more sensitive than T2 and FLAIR sequences and correlates well with at least short-term neurologic outcome in neonates and infants.[21] These sequences, as previously discussed, have been shown to be acutely sensitive to the cytotoxic edema associated with ischemia.[7] This cytotoxic edema results in diminished diffusion of water in the affected area. DWI in experimental

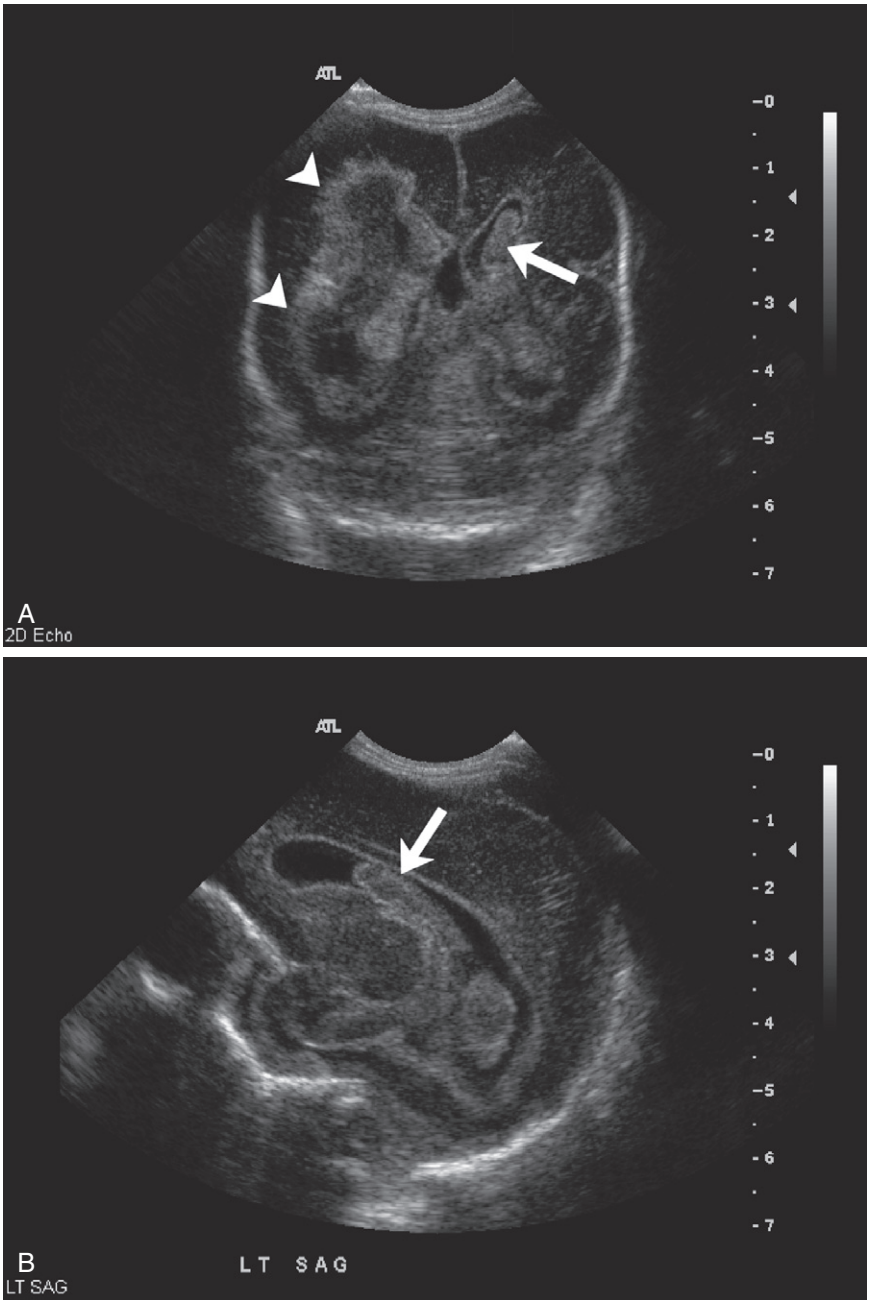

Figure 56–4. Germinal matrix hemorrhage in a premature infant. Coronal (**A**) and left parasagittal (**B**) ultrasound images through the anterior fontanelle demonstrate dilated lateral ventricles with intraventricular extension of clot on the left (*arrows*) and parenchymal extension on the right (*arrowheads*) consistent with a grade 3 bleed on the left and grade 4 bleed on the right (some radiologists would assign this hemorrhage an overall grade of 4).

models can detect ischemia in minutes after onset as a region of restricted diffusion.[22,23] These sequences have now become widely implemented in adult and pediatric neuroimaging, where differentiation of acute ischemic stroke from other neurologic disorders permits appropriate implementation of stroke therapies. The restricted diffusion associated with ischemia evolves over a 1- to 3-week period, at which time the diffusion image usually normalizes. If sufficient tissue destruction has occurred, the diffusion ultimately will increase because of the greater amount of free water following necrosis. This change in diffusion is also useful in distinguishing a new stroke (which will show decreased diffusion) from an older lesion (which will have increased diffusion), whereas both lesions may be of similar signal intensity on standard T1 and T2 imaging (Figure 56-6).

Timelines for relative T2 and diffusion changes have been shown to differ in neonates and infants versus older children and adults. Animal models have suggested that diffusion changes in neonates and infants with HIE do not necessarily precede T2 changes. This finding is presumably a result of age-dependent differences in brain water content and changes therein as a result of differences in vascular permeability in response to hypoxic-ischemic insult.[24,25] The initial diffusion abnormality may increase over the first day, and the extent of the diffusion abnormality can encompass both the core infarct as well as penumbra and hence potentially

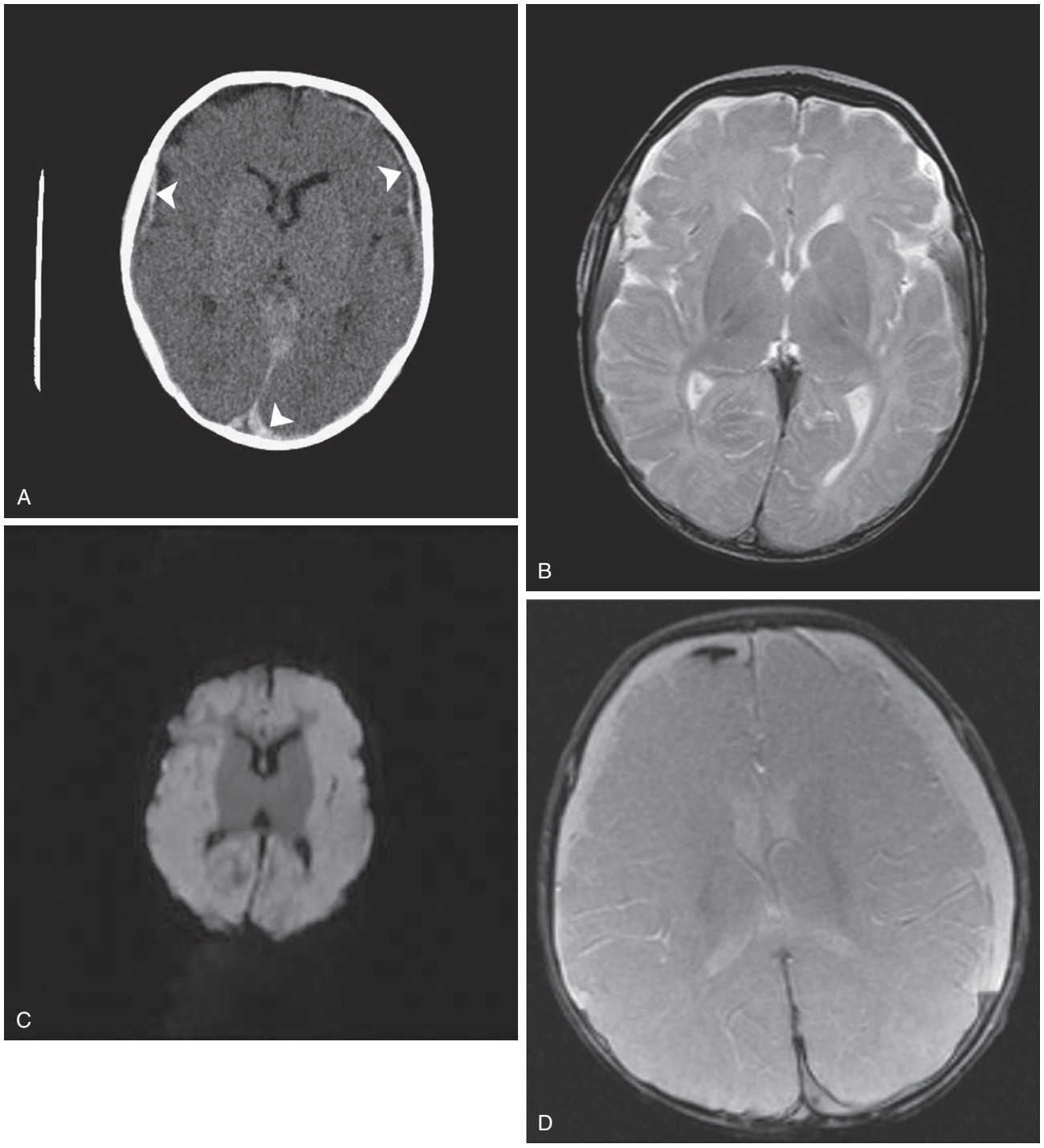

Figure 56–5. Nonaccidental trauma with diffuse cerebral ischemia. Axial noncontrast CT (**A**), axial T2-weighted (**B**), and diffusion-weighted MRI (**C**). **A,** CT shows a thin layer of acute subdural blood (*arrowheads*) and diffuse loss of gray-white demarcation in the cerebral hemispheres. **B,** Although the T2 image appears remarkably normal with appropriate lack of myelination in this 3-month-old child, the relative brightness of the cerebral hemispheres compared with the central gray on diffusion-weighted images (**C**) is consistent with a diffuse ischemic insult. **D,** Gradient-recalled echo MRI in another 4-month-old with nonaccidental trauma demonstrates dark, low signal areas in the right frontal subdural space and left posterior parafalcine regions, consistent with subdural hematomas.

overestimate the ultimate infarct. This potential overestimation could be an indication for MR perfusion, which can separate the areas of core infarction and penumbra.[26] The identification of lactate on MRS is also evolving as a useful tool that may serve as a predictor for the severity of perinatal asphyxia, although considerable complexity is involved in applying this technology. [22,27]

As previously mentioned, the pattern of hypoxic-ischemic injury varies with the etiology of the insult, as well as the developmental state of the brain. Early in-utero insults result in tissue resorption, without the ability to mount a gliotic response that is not seen until the third trimester. During early brain development, insults can result in congenital malformations. HIE or injury in the early to mid second trimester may result

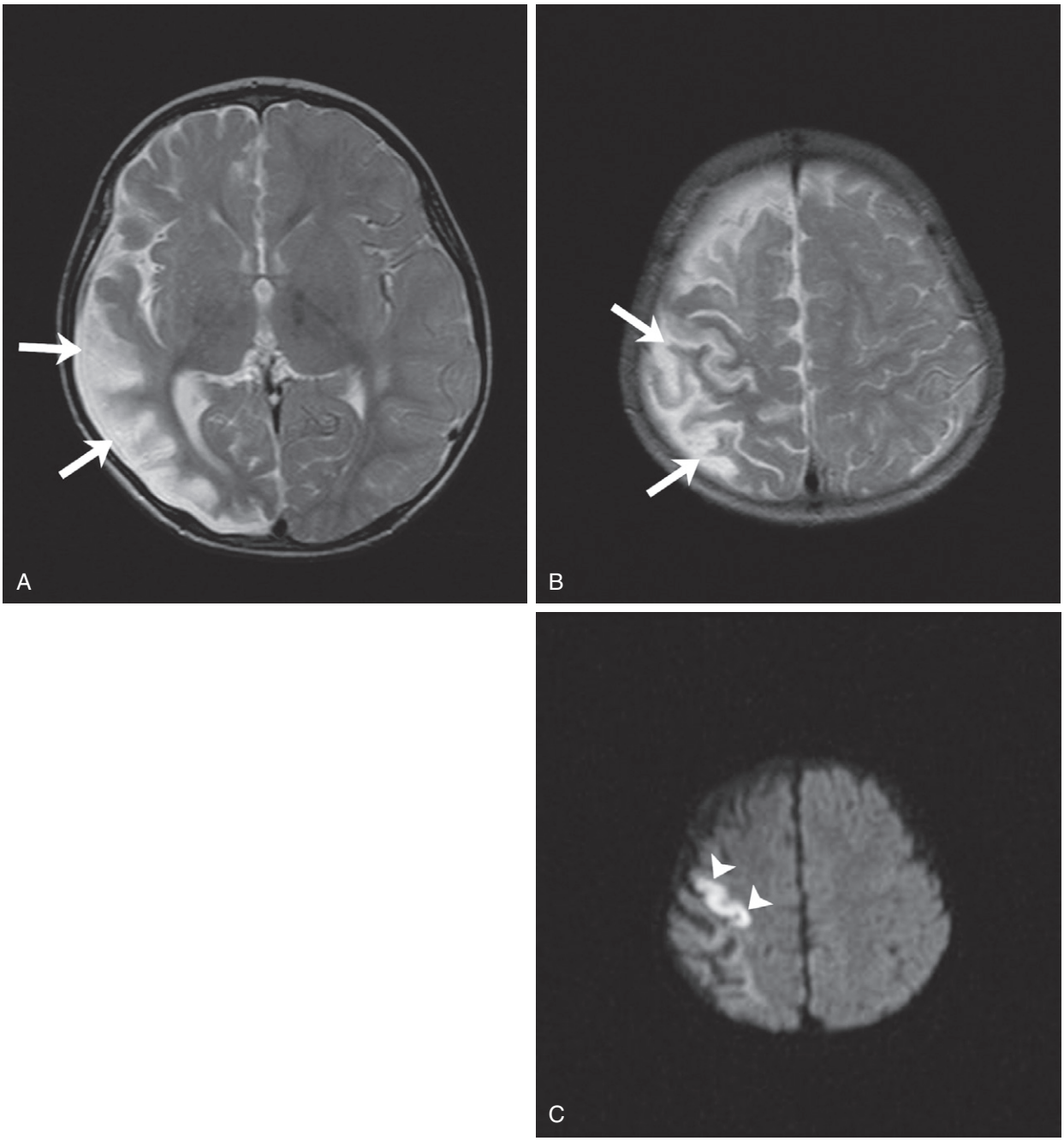

Figure 56–6. Remote and acute infarcts. Axial T2-weighted MRI (**A** and **B**) shows cerebral volume loss with encephalomalacia and gliosis (*arrows*) associated with an old stroke in this child with new onset of progressive left-sided weakness. Diffusion-weighted MRI (**C**) reveals a new area of infarct (*arrowheads*) at the edge of the remote abnormality.

in polymicrogyria. In the twenty-fourth to twenty-sixth week of gestation range, HIE can preferentially injure the deep gray matter nuclei in the setting of total asphyxia. PVL is the pattern of injury seen with prolonged partial hypoxia at 24 to 34 weeks. Typically with PVL on neonatal gray scale ultrasound there may be increased echogenicity in the periventricular white matter, an appearance that is indistinguishable at this stage from edema or from parenchymal hemorrhage, which also may be seen. As PVL progresses cystic change occurs that progresses to coalescent cavitation of the involved white matter, and collapse of these spaces results ultimately in the thinning and volume loss of the white matter, particularly in the posterior periventricular white matter. Although cranial ultrasound affords better resolution for the visualization of cystic change of early PVL in the premature neonate, MRI has overall greater sensitivity to white matter injury, especially in the more advanced stages of PVL, and demonstrates an undulating ventricular margin with associated periventricular T2/FLAIR signal abnormality with or without a paucity of white matter. However, it is not yet clear if this increased sensitivity is of significant prognostic value. Ischemic insults to the term child demonstrate different patterns of injury, determined by the specifics of the insult and the vulnerability of various areas. Profound hypoxia in the term infant results in injury

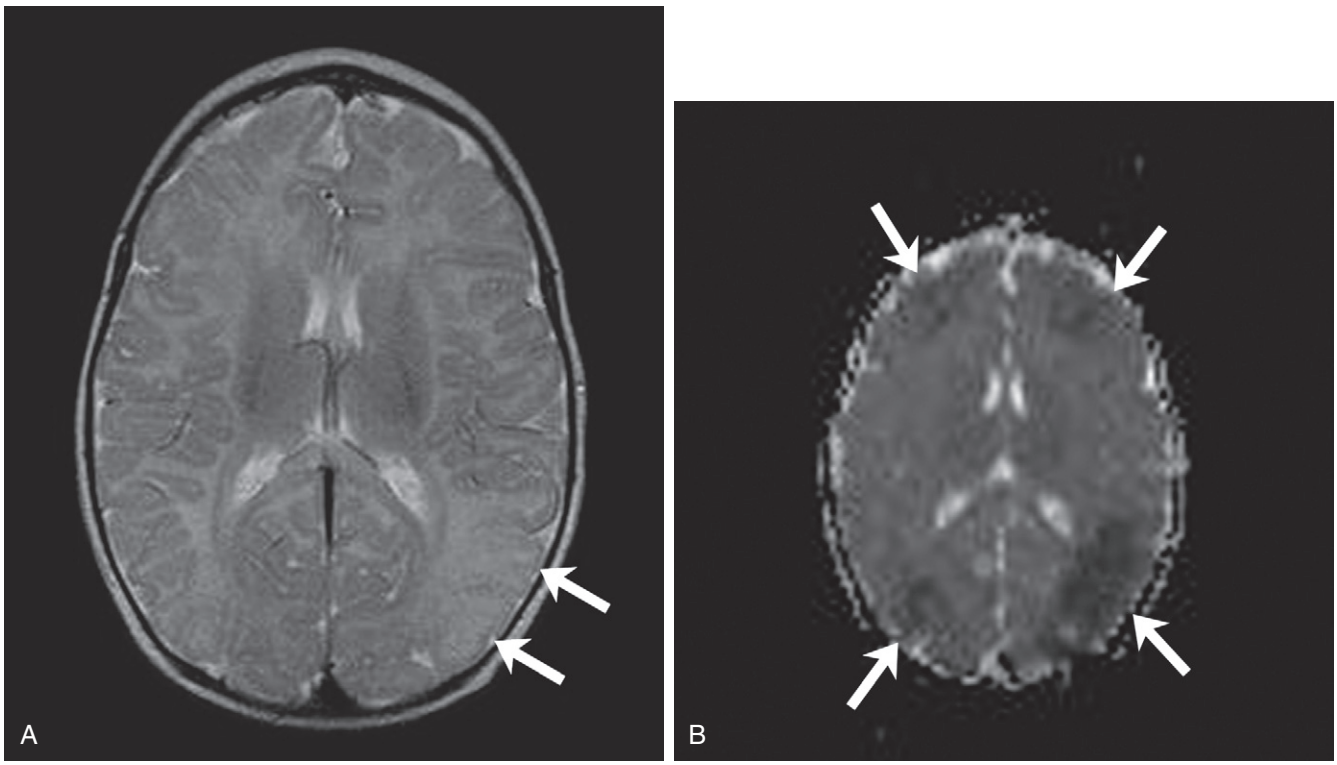

Figure 56–7. Watershed infarct. **A,** Axial T2-weighted MR image shows some loss of the gray-white interface on the left posteriorly (*arrows*). **B,** Diffusion-weighted image shows bilateral restricted diffusion consistent with ischemic injury in a watershed distribution (*arrows*).

largely to areas that are most actively myelinating, in particular the perirolandic white matter and the associated corticospinal tracts and the white matter tracts associated with the occipital cortex. In contrast, a watershed pattern of injury discussed in the next section develops with prolonged partial ischemia that is not sufficient to cause an infarct of the entire cerebrum. Current recommendations for the encephalopathic term infant have included early CT to assess for intracranial hemorrhage, with consideration for MRI with DWI and GRE sequences later in the first postnatal week to assess for extent of injury.[15]

Stroke in the Older Infant/Child

Although the imaging picture may not be specific, a diagnosis of acute stroke usually can be made in combination with the clinical history (as discussed in Chapter 63).[28] The imaging pattern can be of help in determining an etiology. A watershed distribution is consistent with a low flow/hypotensive cause (Figure 56-7). Specifically, changes of ischemic injury are seen at the boundary regions between the major cerebral distributions, that is, between anterior and middle cerebral territories and between middle and posterior cerebral arterial territories. Lesions involving multiple arterial distributions suggest a central thrombotic source, although other causes such as a vasculitis or demyelinating diseases also can have this multivessel or multifocal picture (Figure 56-8). Classically, embolic lesions will tend to be seen at the gray-white junction and most commonly in the MCA distribution. Individual variability of boundary regions[29] and pathology-induced alteration in flow limit the definitiveness of arterial distribution categorization following vascular insult.

As previously discussed, diffusion-weighted imaging also proves to be very useful in earlier imaging detection of cerebral infarcts (Figure 56-9) and separating recent infarcts from a background of abnormality, such as prior infarcts (see Figure 56-6). The area of restricted diffusion on DWI is generally thought to represent irreversible injury, especially when associated with T2/FLAIR signal abnormality, although there may be some cases in which the lesions are at least potentially reversible. In the setting of acute stroke, perfusion MRI may have a contributory role in demonstrating the total region of brain at risk (penumbra) and predicting the ultimate extent of infarct.[26] The area of perfusion abnormality beyond that of diffusion abnormality is thought to represent the penumbra and to be at risk but potentially salvageable. The presence of hemorrhage with a stroke can represent hemorrhagic conversion of a "bland" stroke or an underlying vascular lesion. A large recent study found an incidence of hemorrhagic stroke of 1.4 per 100,000 person years in those younger than 20 years of age. An underlying aneurysm was found in 13%, including 57% of those with pure subarachnoid hemorrhage, 2% of those with a pure parenchymal hemorrhage, and 5% of those with a mixed hemorrhage.[30]

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome results from a loss of autoregulation in the older infant and child as seen in hypertensive encephalopathy, cytotoxic and immunosuppressive drug neurotoxicity, and thrombotic thrombocytopenia purpura (see also Chapter 81). Typically posterior reversible encephalopathy syndrome preferentially involves a posterior

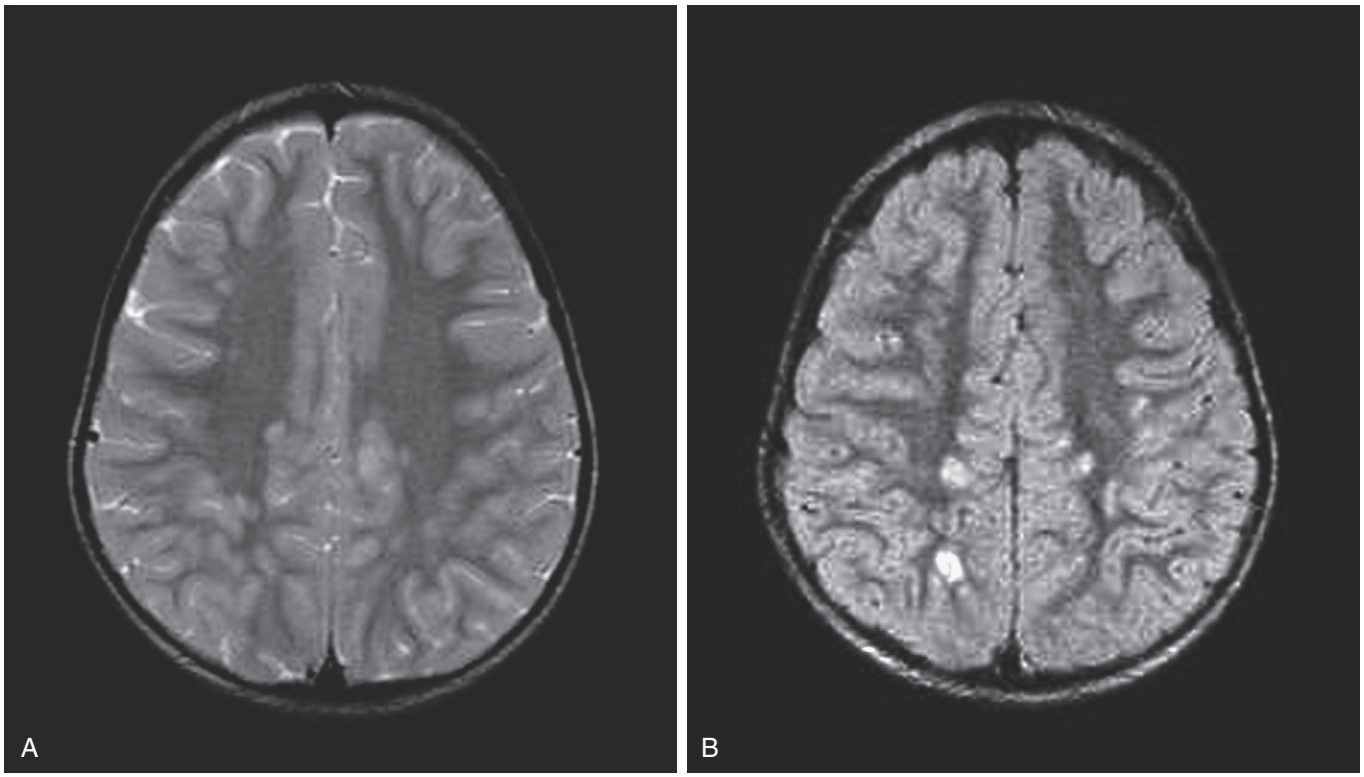

Figure 56–8. ADEM. T2-weighted (**A**) and FLAIR (**B**) images show multiple foci of hyperintensity. In addition to ADEM, vasculitis and multiple emboli could have this imaging appearance.

and parasagittal distribution of the brain with T2 and FLAIR hyperintensities and also less frequently can involve the frontal lobes and brainstem.[31-33] Lesions often are relatively symmetric with confluent lesions centered in the subcortical white matter that may demonstrate patchy enhancement (Figure 56-10). Frequently, because the underlying pathology causes only vasogenic edema, these lesions will not be restricted on DWI. However, ischemia can be triggered by a severe increase in blood pressure, resulting in superimposed cytotoxic edema and therefore diffusion-restricted lesions that usually result in infarctions, the severity of which often correlates with prognosis.

Venous Infarct

The presence of blood in an area of cerebral infarct raises consideration for a venous stroke, although an arterial-induced stroke occasionally can have associated hemorrhage (reperfusion injury). A nonarterial distribution infarct also raises suspicion of a venous stroke. In the setting of suspected venous stroke, evaluation of the cerebral venous system should be undertaken. Ultrasound has limited utility in this setting, although evaluation of superior sagittal sinus flow can be undertaken in the young infant with an open fontanelle (see Figure 56-3, *C*). CT evidence of a venous clot can be detected as hyperdense venous sinuses acutely on noncontrast scans and as the "empty delta sign" (lower density in area of clot surrounded by enhancing blood) in the superior sagittal sinus on contrast-enhanced scans. This assessment can be problematic in the newborn in whom the normal low-density unmyelinated brain and typically higher hematocrit makes the venous sinuses appear dense normally on CT. Classically, the venous phase of a catheter angiogram has been used to look for venous sinus thrombosis. Catheter evaluation of the venous sinuses, however, has been effectively replaced with MRV techniques. MRV uses flow-sensitive sequences that can delineate the major venous sinuses quite effectively (see Figure 56-3, *A* and *B*). A subacute clot in a venous sinus also can be evident on standard T1- and T2-weighted MRI as bright areas in the venous sinuses, although an acute clot can be more difficult to appreciate. On MRI, GRE sequences may demonstrate low signal, and T1 contrast-enhanced sequences may demonstrate areas of nonenhancement of thrombosed venous sinuses.

Etiologic workup of stroke in children includes a broad differential. Although catheter angiogram remains the gold standard and is necessary occasionally, ruling out a vascular lesion has evolved in recent years with greater use of MRA and CTA.

Arterial dissections can be diagnosed with MRI and MRA or with CTA. Visualization of methemoglobin in the false lumen with fat-saturated T1-weighted or proton density–weighted MRI sequences detects most dissections, although subtle lesions may still require catheter angiogram for diagnosis. On CTA, the false lumen is detected by the absent or diminished enhancement compared with the true lumen. Suspicion for dissection is raised in the setting of multiple apparent embolic strokes in a single carotid distribution or within the posterior circulation when there is a history of trauma, although spontaneous dissections are seen occasionally. As previously mentioned, the presence of emboli in multiple circulations raises the question of a more central etiology such as a heart valve vegetation.

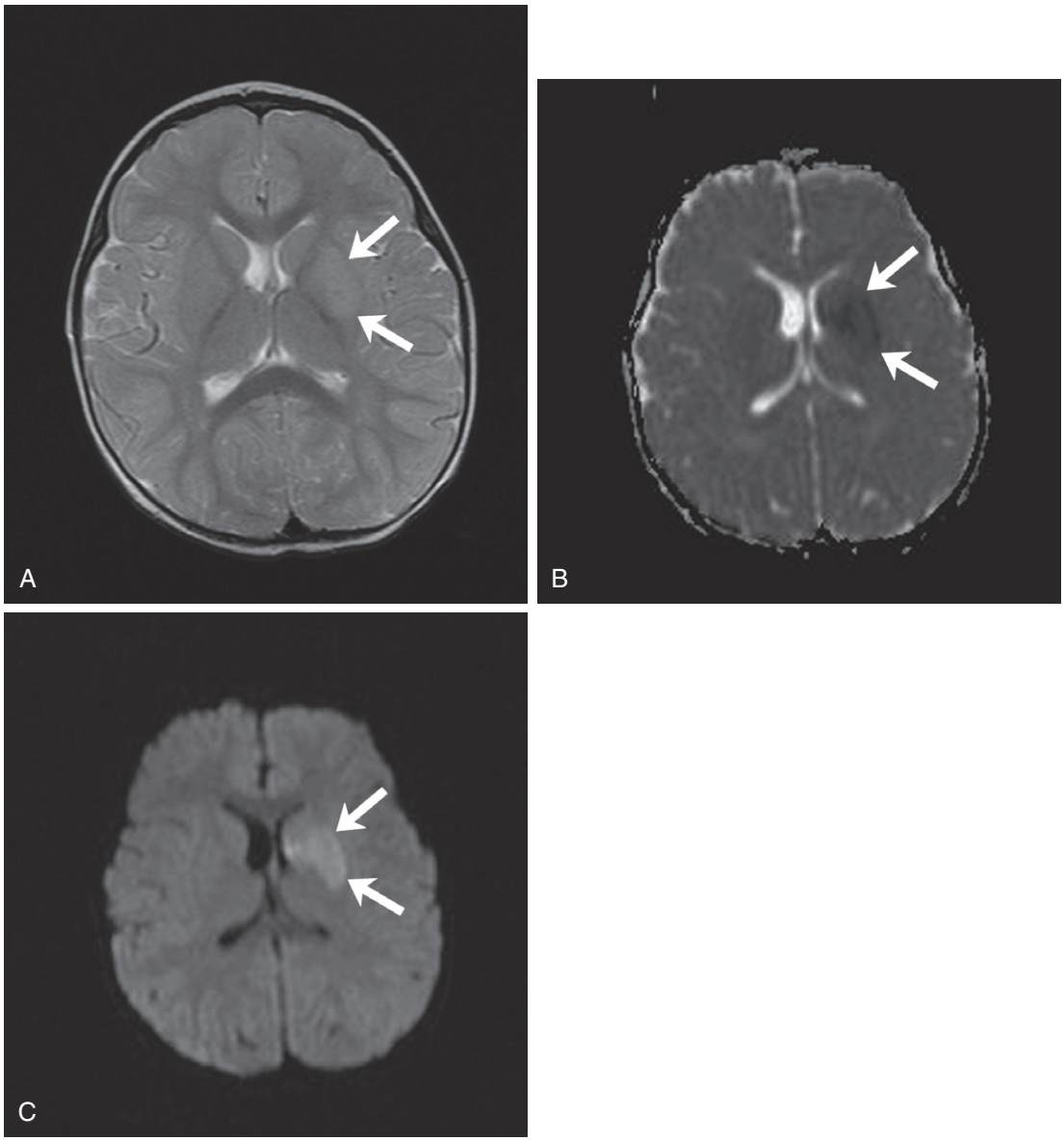

Figure 56–9. Basal ganglia acute infarct. Axial T2-weighted MR image (**A**) shows subtle increased T2 signal in left basal ganglia (*arrows*). More conspicuously shown on the apparent diffusion coefficient map (**B**) and diffusion-weighted images (**C**) is restricted diffusion (*arrows*) associated with an early infarct involving the left caudate and lentiform nuclei.

Vasculopathy/Vasculitis

Acquired vasculopathies can be a result of known infectious or noninfectious causes or of unknown pathophysiology such as in primary cerebral vasculitis, which tends to involve medium and small vessels, or moyamoya syndrome, which demonstrates greatest involvement of the central cerebral vessels. Vasculopathy involving large and medium-sized vessels can be seen on MRA, although more subtle irregularities and small vessel involvement still requires a catheter angiogram, which remains the gold standard imaging modality.

In acute hemiplegia of childhood, classically a basal ganglia infarct resulting from M1 MCA segment narrowing and occlusion of lenticulostriate vessels is seen, with cortical injury being less common. Narrowing typically of the terminal carotid and proximal M1 MCA segment of the affected side often can be delineated on MRA. A lack of well-developed collaterals also will be noted, as is typical of moyamoya syndrome, where the vessel occlusion has been more slowly progressive over a longer period. Moyamoya "syndrome" denotes the pattern of vessel involvement that can be associated with type 1 neurofibromatosis, radiation injury, or other pathology. When it is idiopathic, the term moyamoya "disease" is used. More commonly, moyamoya syndrome/disease will be bilateral and MRI will demonstrate evidence of chronic ischemic insult. The enlarged lenticulostriate collaterals generally will be appreciable on both a good MRA (with a "puff of smoke appearance" initially described with catheter arteriography) and as flow voids through the basal ganglia on MRI (Figure 56-11). These apparent flow voids need to be distinguished from enlarged perivascular spaces that also are seen in this region.

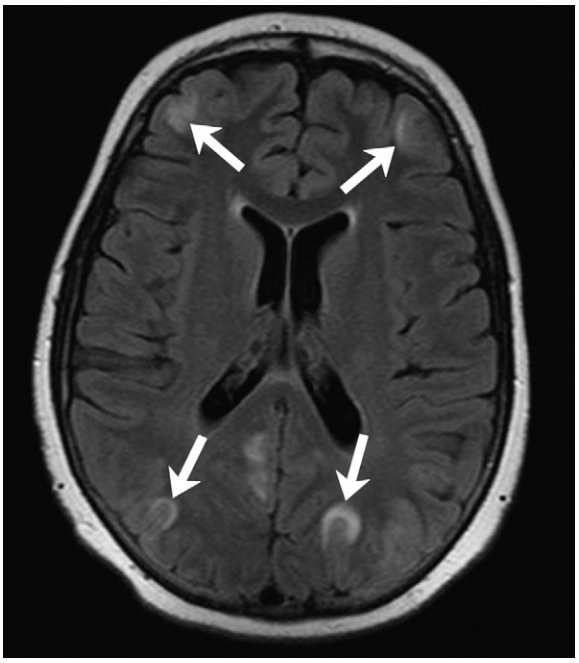

Figure 56–10. Posterior reversible encephalopathy syndrome. Axial FLAIR MRI showing subcortical foci of hyperintensity (*arrows*) associated with cyclosporin toxicity. Note that abnormalities may have a variable distribution and are frequently, but not always, posterior in location.

Vasculitic changes can accompany infections including meningitis, either through direct invasion of vessels or by an immune response to the particular pathogen. Parenchymal injury, if present, is mediated by ischemic changes. The pattern of involvement in the immune-mediated mechanism may be fairly symmetric, as can be seen in acute disseminated encephalomyelitis (ADEM) or some metabolic diseases. Noninfectious vasculitides, including those associated with systemic disease, for example, systemic lupus erythematosus and, in particular, primary CNS vasculitis, can be more problematic in diagnosis. Classically, a catheter angiogram and occasionally a brain biopsy have been used to evaluate the possibility of primary CNS vasculitis. Most cases of symptomatic vasculitis will demonstrate abnormality on standard MRI (T2, FLAIR, and DWI) sequences, and thus a completely normal MRI makes the likelihood of CNS vasculitis low. Occasionally, however, there can be a vasculitic process in the presence of a normal MRI.[34] Furthermore, cases have been reported of biopsy-proven CNS vasculitis in which the MRI was abnormal and results of a catheter angiogram were normal.[35] Because medium and small vessels often are involved in the setting of CNS vasculitis, to which MRA has less sensitivity, a catheter angiogram may be indicated in the setting of very strong concern for vasculitis with a normal MRA and occasionally even a normal MRI.

Vascular Malformations

Most arteriovenous malformations and aneurysms can be detected with a combination of MRI and MRA or CTA, although small lesions can be missed (Figure 56-12). Catheter angiogram remains the gold standard for arteriovenous malformation diagnosis, confirming flow dynamics and the presence of intranidal aneurysms, and generally will be required before surgical intervention. In the appropriate clinical setting such as a spontaneous SAH without etiology, a negative MRI, MRA, or CTA, however, should not exclude a catheter angiogram. Arterial aneurysms are much less common in children than in adults, with many of those seen likely being congenital or due to infection in contrast to the typical acquired berry aneurysms seen in adults. As in adults, all but the smallest aneurysms can be seen on MRA or CTA, with CTA sensitivity for berry aneurysms in adult series reported in the range of 80% to 97%.[11] These studies, though, need to be of optimum resolution, generally targeted to the high-risk locations for aneurysms in adults, and may not include less common aneurysm locations, which are seen with greater frequency in children. Angiographically occult lesions including capillary telangiectasia, cavernous malformation, and developmental venous anomalies are seen on MRI but usually are not of consequence except in cases of the occasional large cavernous malformation.

A vein of Galen aneurysmal malformation (VGAM) is a misnomer because it is not the vein of Galen but a persistent embryonic vein that is dilated in association with a large fistula.[36] VGAMs presenting in the newborn period will manifest with cardiac symptoms resulting from the large shunt and high-flow congestive cardiac failure. Although the malformation can be seen with ultrasound, a CT scan is useful as a quick evaluation to visualize the malformation and determine the status of the cerebral cortex, which may be severely affected even at term. A noncontrast CT scan is sufficient because the density of blood (usually with an increased hematocrit) provides good contrast against the relatively less dense newborn brain (Figure 56-13). In the presence of a VGAM, MRI with MR angiography will give an overall vascular road map for planning endovascular intervention, because the limited amount of contrast that can be used in a neonate necessitates directed intervention.

Central Nervous System Infection

Imaging findings and the role of imaging in cerebral infection will depend on the organism and location of the infection (see also Chapter 65). The appearance will depend on the cell type infected and the host immune response. Infection can involve the subarachnoid spaces and meninges, the parameningeal spaces, or the brain parenchyma itself either primarily or secondarily. With bacterial meningitis the appearance on CT and MRI may range from normal to diffuse swelling with loss of gray-white differentiation and obliteration of ventricular and cisternal CSF spaces. Coxsackie virus, echovirus, and mumps infect the meninges more than the neurons, whereas poliovirus infects the neurons, particularly the motor neurons. Herpes simplex virus type I has a predilection for the limbic system, most commonly affects the temporal lobes, and is the most common sporadic viral encephalitis.[37] Herpes simplex virus type II encephalitis is most commonly acquired at birth and does not display a predilection for the temporal lobes. Although MRI is more sensitive than CT, a normal MRI still does not entirely exclude a viral encephalitis. In the clinical setting of suspected meningeal infection, CT may be indicated prior to lumbar puncture to exclude hydrocephalus or swelling that potentially would preclude lumbar puncture without neurosurgical consultation.

Imaging alone should not be used, however, to exclude meningeal infection. Particularly early in the setting of meningitis, contrast-enhanced CT is often normal. Although MRI

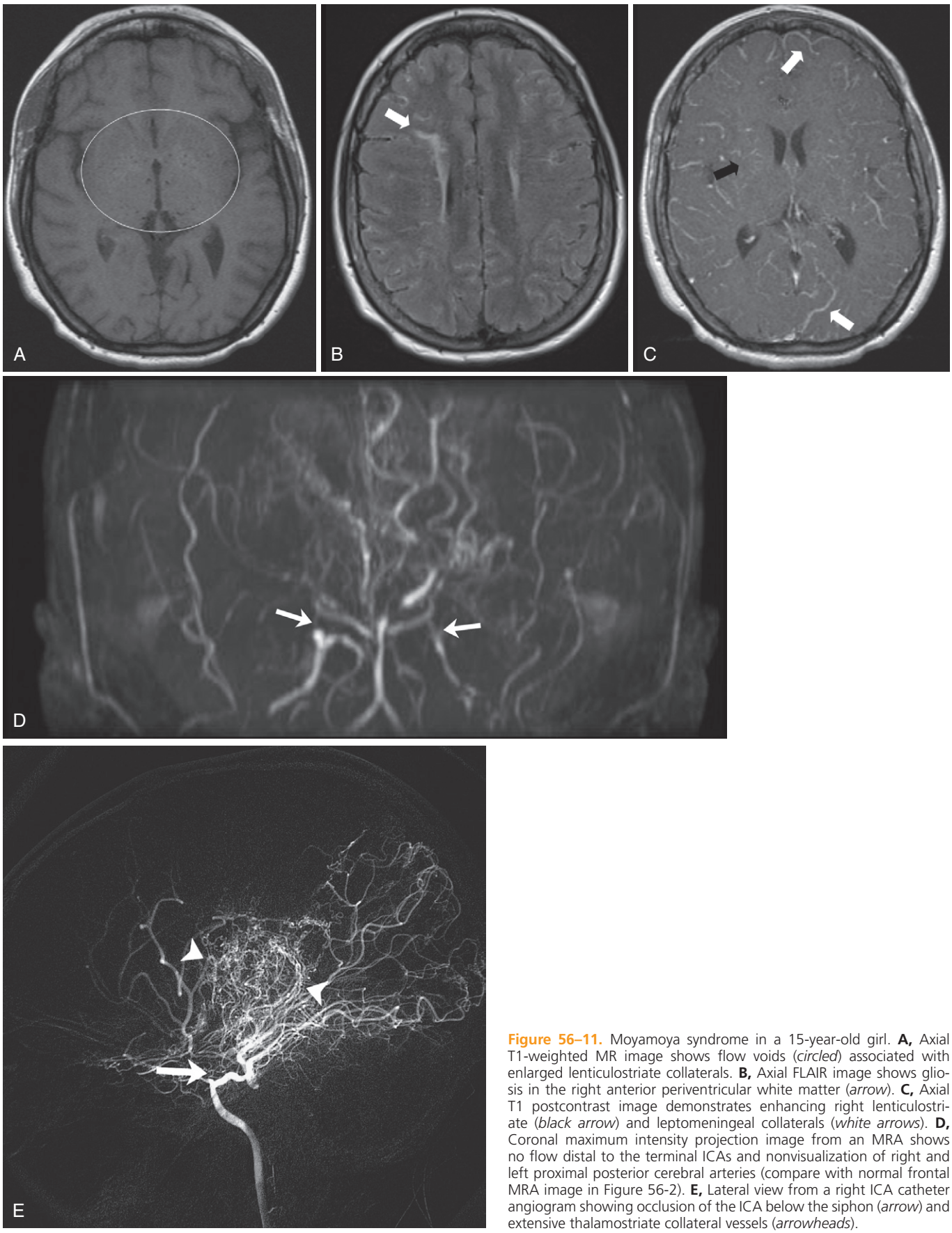

Figure 56–11. Moyamoya syndrome in a 15-year-old girl. **A,** Axial T1-weighted MR image shows flow voids (*circled*) associated with enlarged lenticulostriate collaterals. **B,** Axial FLAIR image shows gliosis in the right anterior periventricular white matter (*arrow*). **C,** Axial T1 postcontrast image demonstrates enhancing right lenticulostriate (*black arrow*) and leptomeningeal collaterals (*white arrows*). **D,** Coronal maximum intensity projection image from an MRA shows no flow distal to the terminal ICAs and nonvisualization of right and left proximal posterior cerebral arteries (compare with normal frontal MRA image in Figure 56-2). **E,** Lateral view from a right ICA catheter angiogram showing occlusion of the ICA below the siphon (*arrow*) and extensive thalamostriate collateral vessels (*arrowheads*).

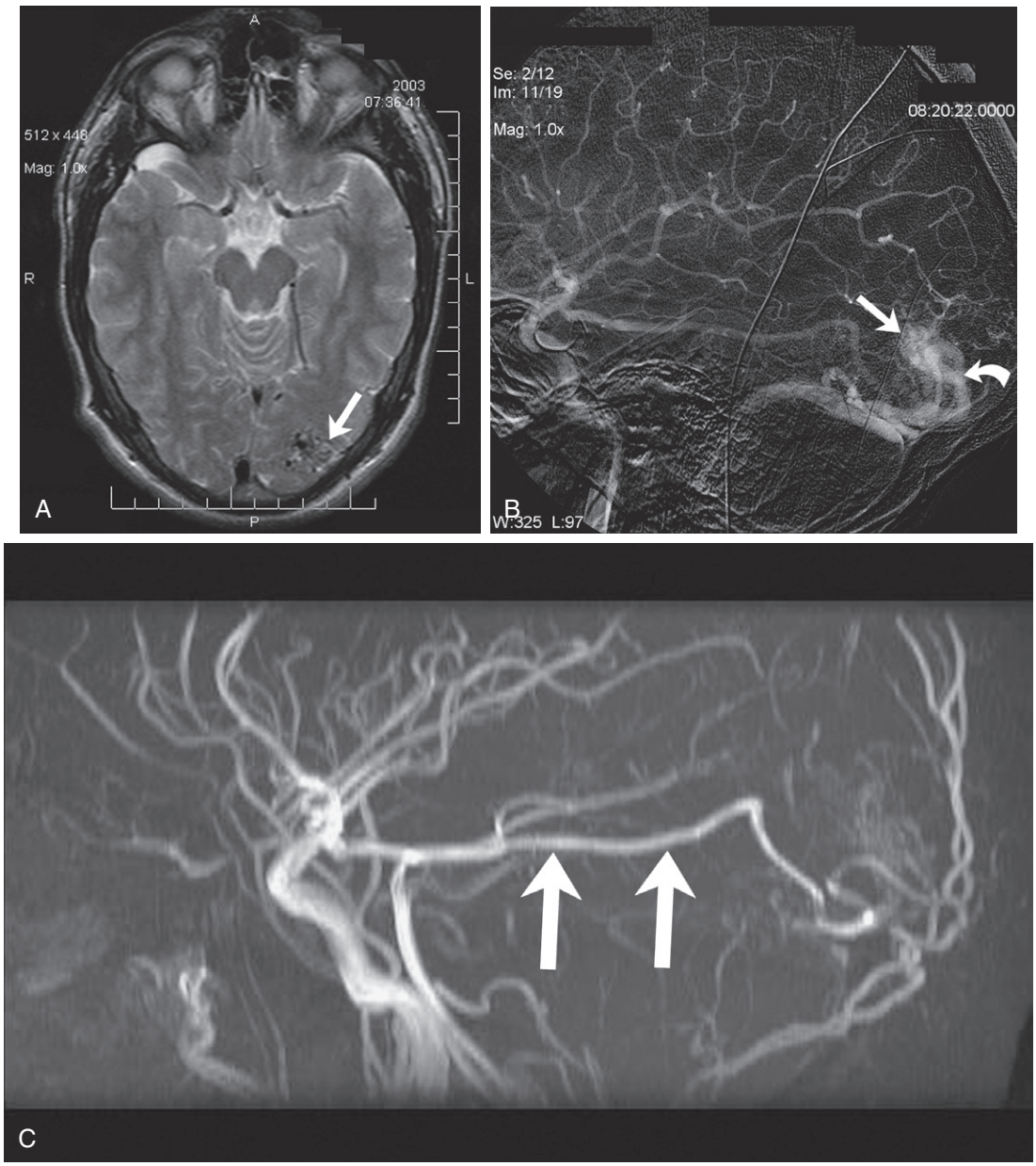

Figure 56–12. A 14-year-old child with a left occipital arteriovenous malformation (AVM). **A,** MRI shows multiple flow voids in the left occipital lobe (*arrow*). **B,** Lateral view from catheter angiogram confirms the presence of an AVM (*arrow*) and early draining veins (*curved arrow*). **C,** Lateral maximum intensity projection image from an MR angiogram shows an enlarged posterior cerebral artery branch (*arrows*), which feeds the tangle of abnormal vessels.

with gadolinium is more sensitive, only 55% to 70% of persons with proven meningitis have abnormal scans.[38] Some investigators believe that CSF hyperintensity on the FLAIR sequence is more sensitive than gadolinium-enhanced T1-weighted sequence for meningitis; however, CSF hyperintensity on FLAIR associated with supplemental oxygen and anesthesia as well as noninfectious meningeal irritation and leptomeningeal tumor render this finding less specific.[39,40]

Complications associated with meningeal infection include compromise of the BBB leading to vasogenic edema, arterial spasm that can cause ischemia with cytotoxic edema and eventual infarction, and hydrocephalus potentially with the development of transependymal CSF flow/interstitial edema. Hydrocephalus can be obstructive, typically at the level of the aqueduct (Figure 56-14) or outlet of the fourth ventricle, or more commonly communicating because of impaired CSF resorption from arachnoid granulation obstruction with exudates. This impairment of CSF resorption can become permanent because of leptomeningeal-ependymal fibrosis and require shunting. Ultrasound can be used in very young patients; otherwise, CT and more recently half Fourier acquisition single shot turbo spin echo (HASTE) or other rapid, heavily T2-weighted MRI sequences usually are used to follow ventricular dilation. The role of imaging in meningitis is primarily to evaluate for these complications. Two patterns of abnormal meningeal enhancement are seen on MRI with meningitis. A pachymeningeal pattern appears as diffuse linear thickening of the normal dural lining. This appearance,

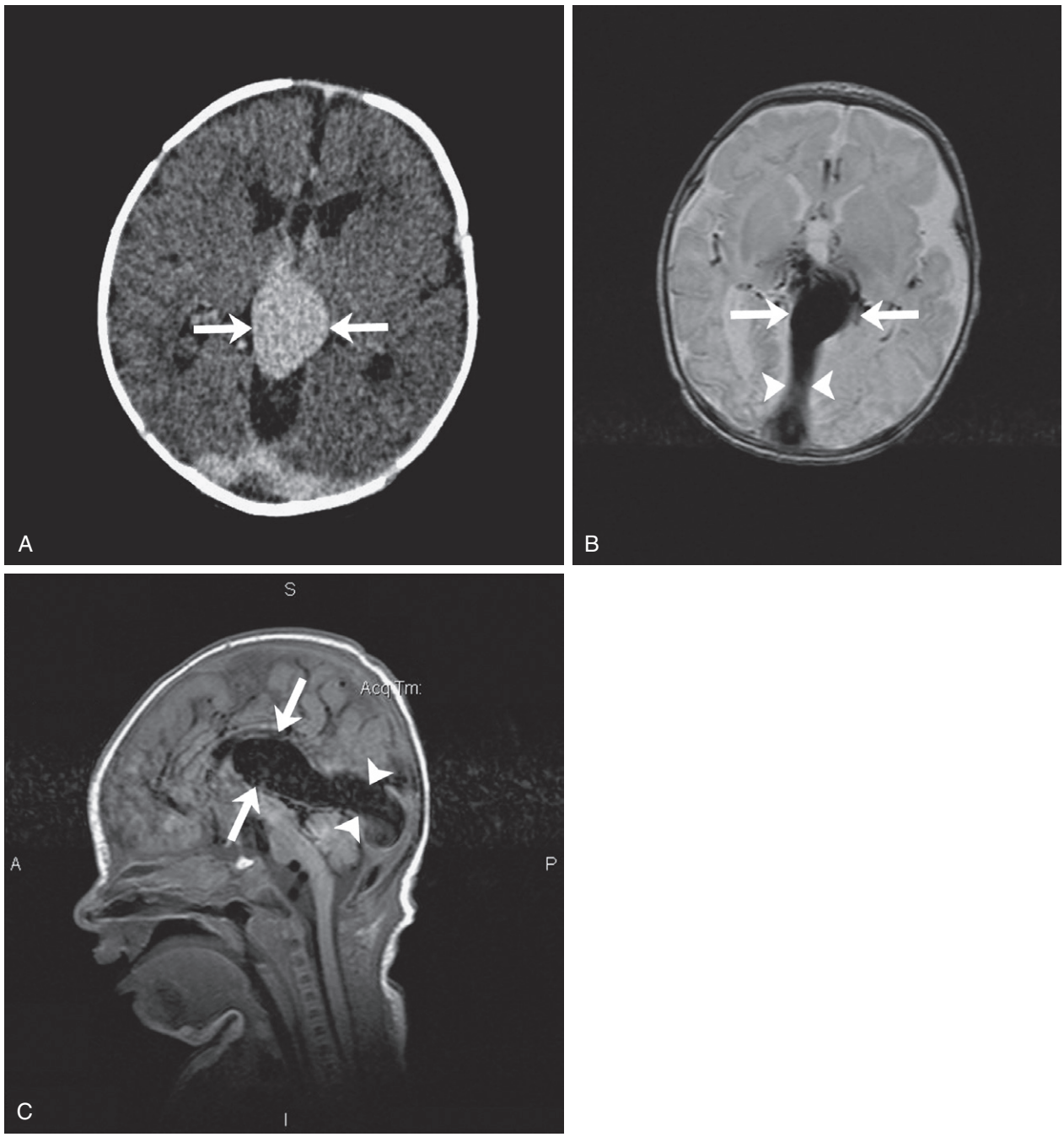

Figure 56–13. Vein of Galen aneurysmal malformation (VGAM). **A,** Axial noncontrast CT shows the dilated embryonic vein (*arrows*). Axial T2 (**B**) and sagittal T1 (**C**) MRI demonstrates the dilated embryonic vein (*arrows*) and the draining vein (*arrowheads*).

however, is not specific because the same pattern can be seen in other settings, including after surgery and occasionally following shunt revision, in some cases because of intracranial hypotension. The other pattern is a leptomeningeal enhancement, where enhancement is seen along the pia-arachnoid membranes, following the sulcal grooves. This pattern also is not specific, with a similar appearance being seen at times with leptomeningeal spread of tumor.

Extraaxial collections can develop in association with meningitis, including subdural effusions and, less commonly, subdural abscesses or empyema. Effusions are crescentic collections that typically are isodense to CSF on CT and isointense to CSF on most MRI sequences, although because the protein level may be increased, the collections may be hyperintense on T1 and FLAIR (Figure 56-15). Subdural abscesses can be crescentic or lentiform when larger and typically slightly denser than CSF on CT. A rim of enhancement of variable thickness is generally better detected on MRI (Figure 56-16). DWI can demonstrate restricted diffusion in subdural empyemas. Subdural (and brain) abscess also can occur as a direct extension of paranasal sinus or mastoid infection.

Infection of the brain parenchyma can take the form of a focal abscess(es) or a more diffuse encephalitis. Encephalitis in isolation or associated with meningitis generally will produce

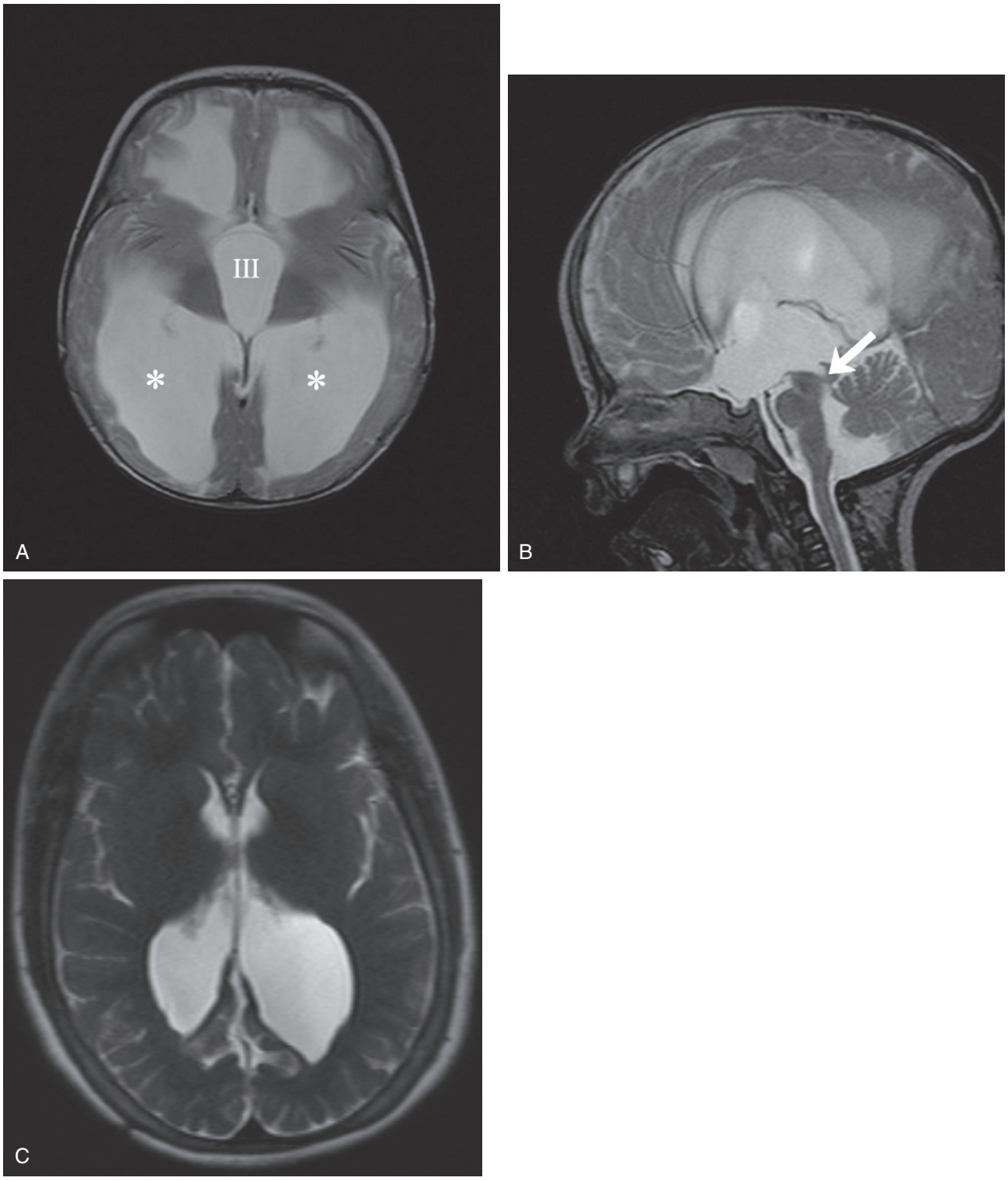

Figure 56–14. Obstructive hydrocephalus. Axial (**A**) and midline sagittal (**B**) T2 MRI shows dilated lateral (*asterisks*) and third (III) ventricles that result from aqueductal obstruction (*arrow*). **C**, Chiari II malformation with hydrocephalus. Image demonstrates utility of heavily T2-weighted, half-Fourier acquisition, single-shot, turbo spin-echo MRI in evaluation of ventricles. Sequence can be obtained rapidly without the need for sedation; this avoids the radiation associated with repeated CT scans.

nonspecific cerebral parenchymal changes or cerebritis that appear bright on T2 and FLAIR sequences. Differentiation of cerebritis from ischemic changes associated with meningoencephalitis by imaging is problematic, especially because cerebritis also can demonstrate restricted diffusion. Areas of cerebritis evolve into focal abscesses that will generally demonstrate a central focus of low density on CT and low T1, high T2, and FLAIR signal on MRI, with a ring of enhancement and variable surrounding edema (Figure 56-17). More commonly in adults with a ring-enhancing lesion, there can be

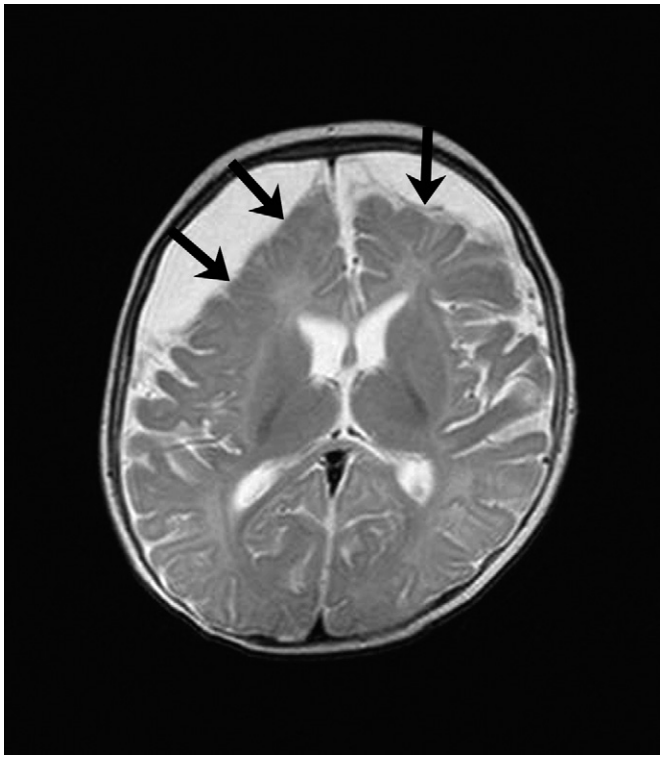

Figure 56–15. Chronic subdural effusions following meningitis. Axial T2-weighted MRI shows mass effect with sulcal compression associated with bifrontal subdural collections (*arrows*). Note that these subdural collections can be differentiated from enlarged subarachnoid spaces because the latter would have bridging vessels crossing the cerebrospinal fluid in the subarachnoid spaces.

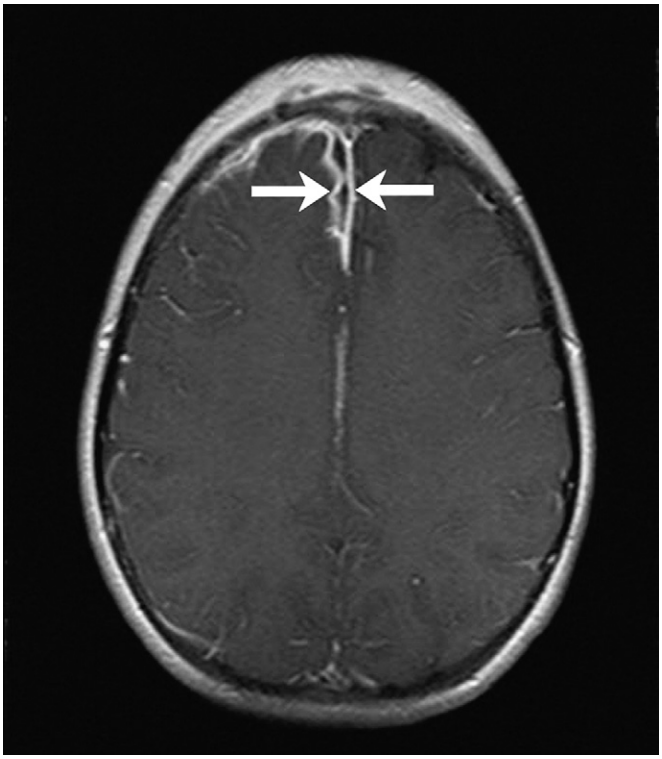

Figure 56–16. Subdural abscess or subdural empyema. Axial T1-weighted MRI with gadolinium demonstrates a small rim-enhancing right frontal paramedian subdural abscess (*arrows*). This area was restricted on DWI (not shown).

uncertainty between a brain abscess and necrotic tumor. The brain abscess generally will have a thinner rim of enhancement and on DWI a pyogenic abscess will demonstrate restricted diffusion. The necrotic tumor often shows a thick, irregular rim with increased diffusion or T2 shine-through. In differentiating pyogenic, tubercular, and fungal abscesses, some studies have described a greater likelihood of homogeneous diffusion restriction with pyogenic and tubercular abscesses but a variable pattern with fungal abscesses.[41,42] Exclusion of a meningeal or parameningeal abscess in the head can be accomplished largely with contrast-enhanced CT, looking for a fluid collection with a surrounding enhancing rim, although occasionally a small collection may be missed on CT but detected by MRI. Evaluation for meningeal or parameningeal abscess in the spine should be approached with MRI.

Demyelinating Disease

Multiple sclerosis (MS) is much less common in children than in adults, while ADEM primarily occurs in children. ADEM can at times manifest with very symmetric involvement (Figure 56-18), with an imaging picture that overlaps with some metabolic diseases. In other cases of ADEM, lesions can be scattered with a picture similar to vasculitis or embolic infarction. The appearance of MS and ADEM can be similar. The presence of lesions of multiple ages would be consistent with MS (Figure 56-19) rather than ADEM. Demyelinating lesions are seen most commonly in white matter but appear in gray matter as well. Acute demyelinating lesions demonstrate enhancement. Acute lesions also can demonstrate restricted diffusion, with an appearance on DWI that mimics an acute ischemic lesion. Often, however, the pattern of involvement is useful in distinguishing demyelinating disease from ischemic disease. The spinal cord can be involved with MS or ADEM (Figure 56-20), although relatively rarely in isolation, hence imaging the brain to look for additional involvement can be useful in some cases to distinguish between a cord demyelinating process and infarct, which can have a similar imaging appearance.

Trauma

CT remains the primary imaging modality in persons with acute cerebral trauma and has the advantage of relative ease of scanning compared with MRI, including speed of scanning and allowing non-MRI compatible monitoring and life support equipment to be used during imaging (discussed in Chapter 61). CT is usually sufficient for evaluation of most cerebral neurosurgical trauma, including assessment of swelling and acute hemorrhage within the intra-axial and extra-axial compartments. CT is generally more sensitive than MRI in detecting acute SAH and in the evaluation of bony injury (Figure 56-21). CT is generally sufficient to detect cerebral swelling associated with herniation syndromes and therefore identify the potential need for neurosurgical intervention (Figure 56-22). MRI is more sensitive for the detection of parenchymal injury and for more subtle extra-axial collections including more chronic epidural and subdural hematomas,

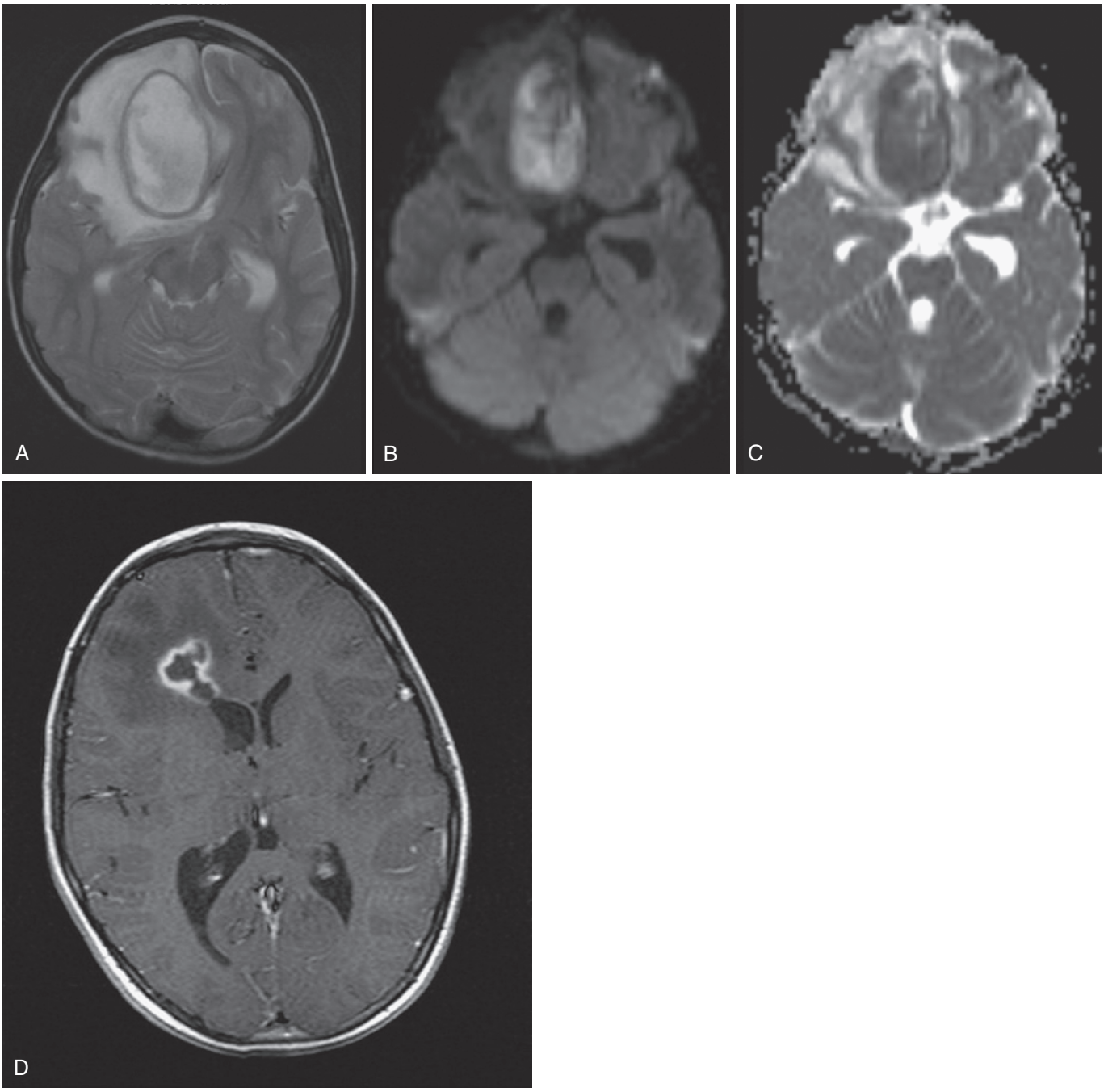

Figure 56–17. Frontal brain abscesses. Axial T2-weighted MRI (**A**) demonstrates a right frontal ring-enhancing lesion with a T2 hypointense capsule that has considerable surrounding vasogenic edema and leftward midline shift. The lesion is bright on diffusion (**B**) and dark on the apparent diffusion coefficient map (**C**), suggesting that it is diffusion restricted. **D,** In another patient, axial postcontrast T1-weighted MR image demonstrates a right frontal periventricular ring-enhancing lesion with T1 hypointense vasogenic edema surrounding it.

common in inflicted traumatic brain injury associated with child abuse. MRI is indicated when there is doubt as to the presence of a subdural collection in the setting of suspected trauma. Also, in the setting of inflicted traumatic brain injury, MRI can detect evidence of old parenchymal or extraaxial hemorrhage not seen with CT using the GRE sequence (see Figure 56-5, *D*) In particular, gradient sequences and susceptibility-weighted imaging can reveal evidence of old parenchymal hemorrhages. Bony injury of the spine also is better evaluated with CT, although cord compression and injury is better assessed with MRI.

Hydrocephalus

Hydrocephalus can be congenital, or caused by hemorrhage, tumor and meningitis. In the neonatal period, ultrasound is used as a screening tool in evaluating for ventricular enlargement, in particular associated with germinal matrix hemorrhage. Beyond this period, most monitoring of ventricular size and shunts is accomplished with CT. Recently, rapidly acquired heavily T2-weighted half Fourier acquisition single shot turbo spin echo MRI sequences have been used in the evaluation of hydrocephalus. These sequences can be

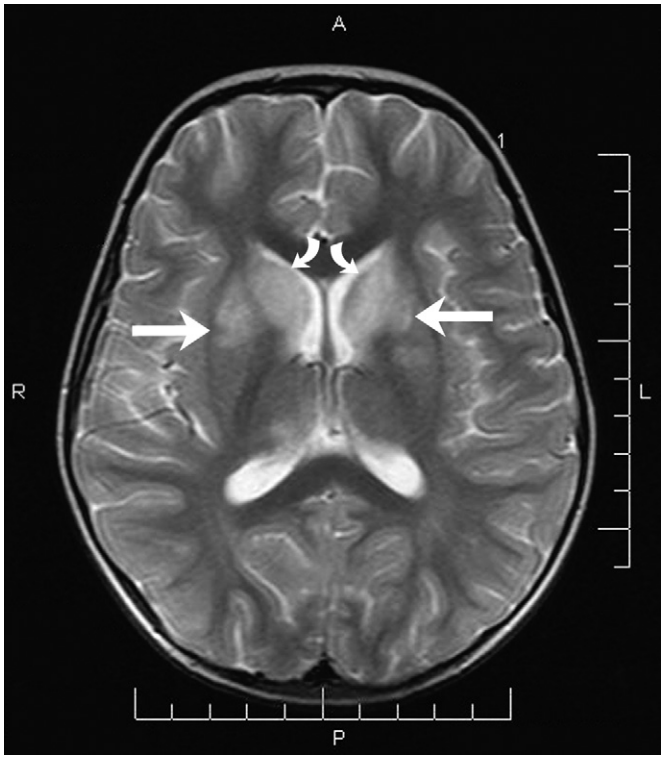

Figure 56–18. ADEM. Axial T2-weighted MR image shows symmetric increased signal in the head of the caudate nucleus (*curved arrows*) and anterior lentiform nuclei (*straight arrows*) associated with ADEM.

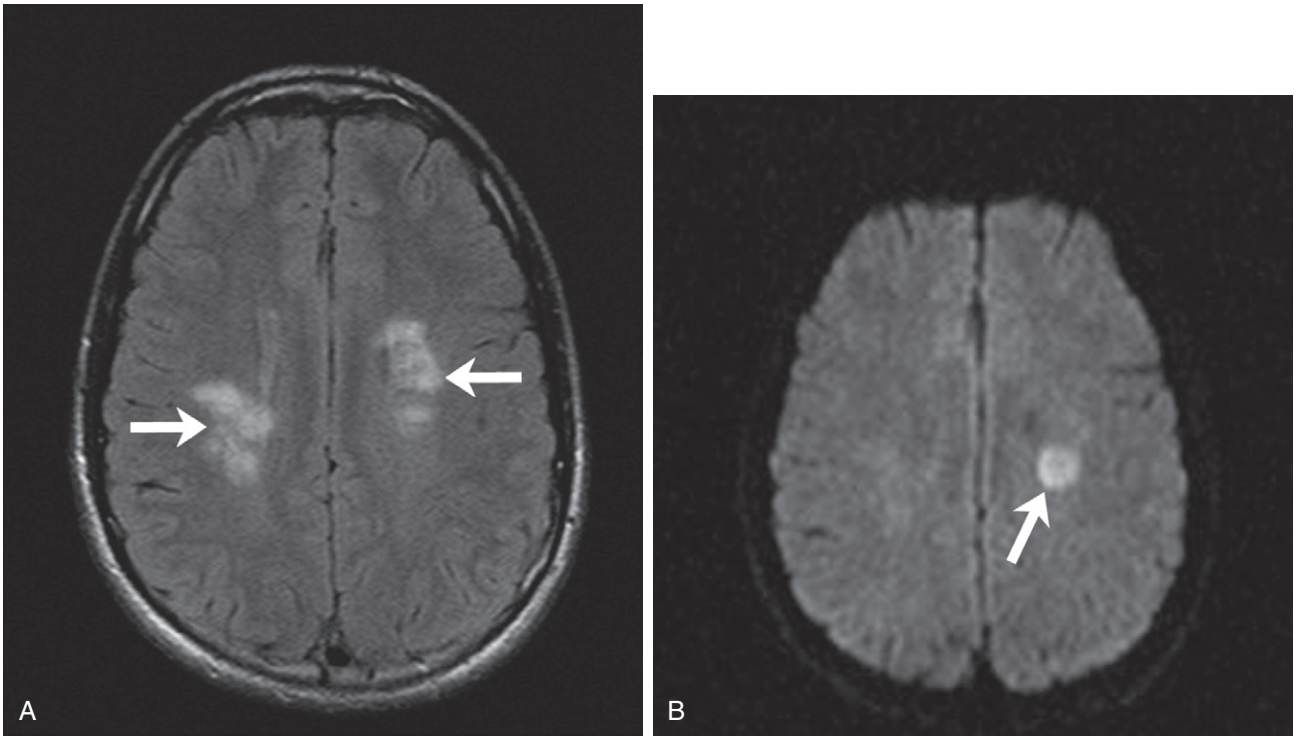

Figure 56–19. Multiple sclerosis in a 16-year-old child. **A,** FLAIR MRI shows bilateral white matter lesions. **B,** DWI demonstrates restriction of the left centrum semiovale lesion that was enhanced on postcontrast T1 MRI (not shown), suggesting an acute or active lesion (*arrow*).

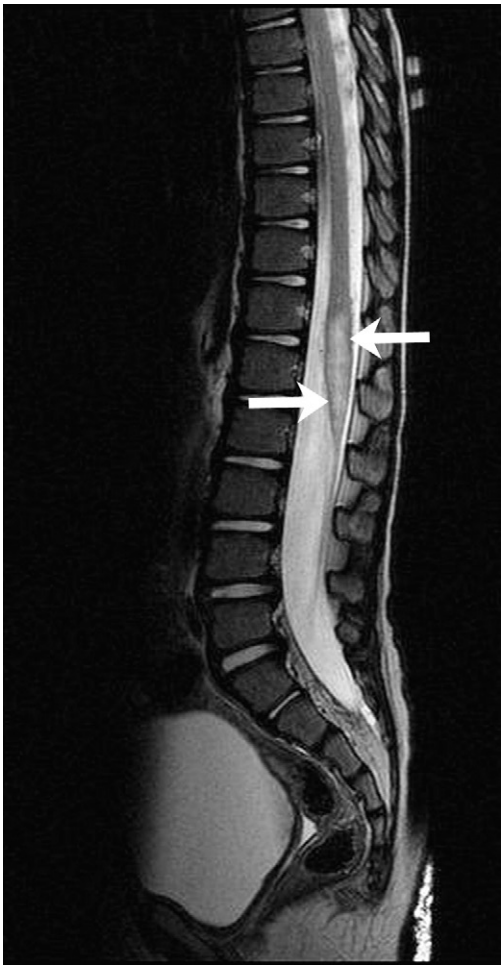

Figure 56–20. Patient with clinical picture of transverse myelitis. Sagittal T2-weighted MRI of the distal cord shows central T2 hyperintensity within the conus medullaris (*arrows*) in this case of ADEM. An acute spinal cord infarct also could have this imaging appearance.

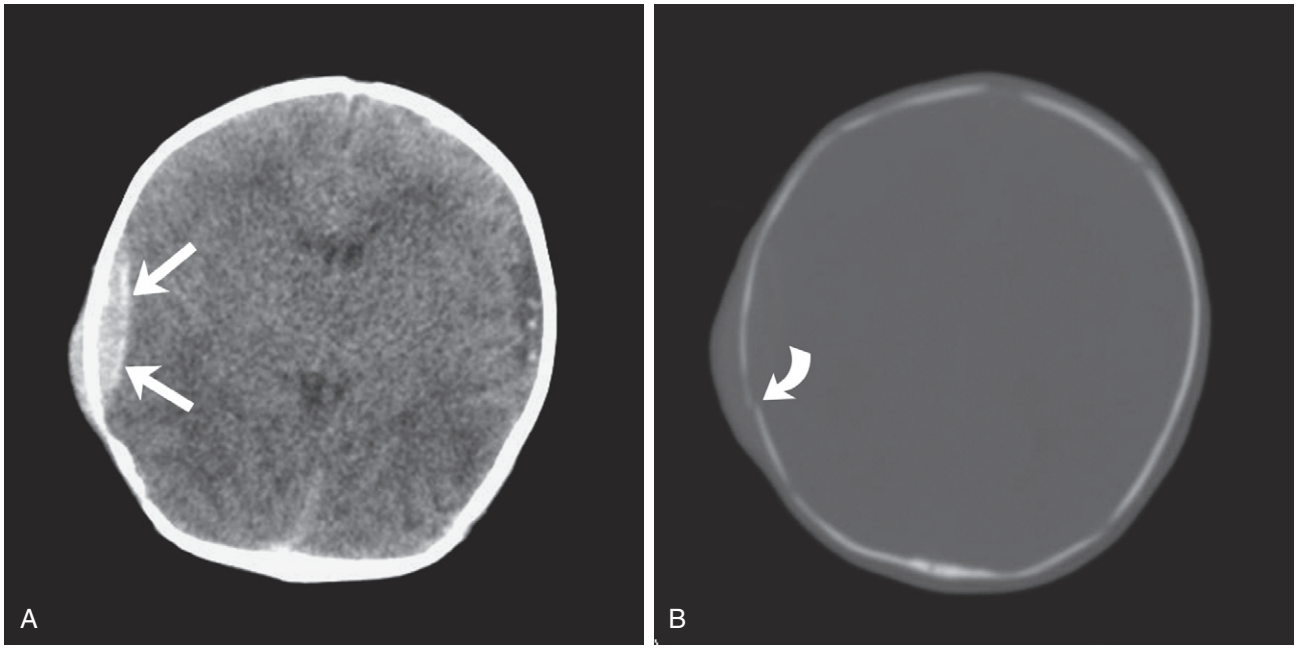

Figure 56–21. Epidural hematoma with skull fracture. A CT scan in brain (**A**) and bone (**B**) windows shows the typical lentiform configuration of right-sided epidural hematoma (*arrows*). The bone window reveals an associated fracture (*curved arrow*).

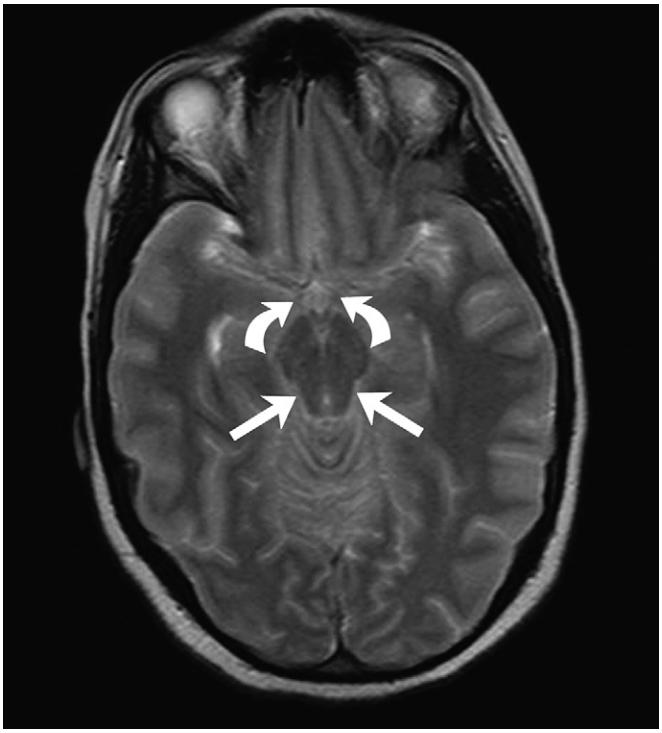

Figure 56–22. Diffuse brain edema with herniation. T2-weighted MRI shows diffuse cerebral swelling with effacement of cerebrospinal fluid spaces associated with the ambient (*straight arrows*) and suprasellar cisterns (*curved arrows*).

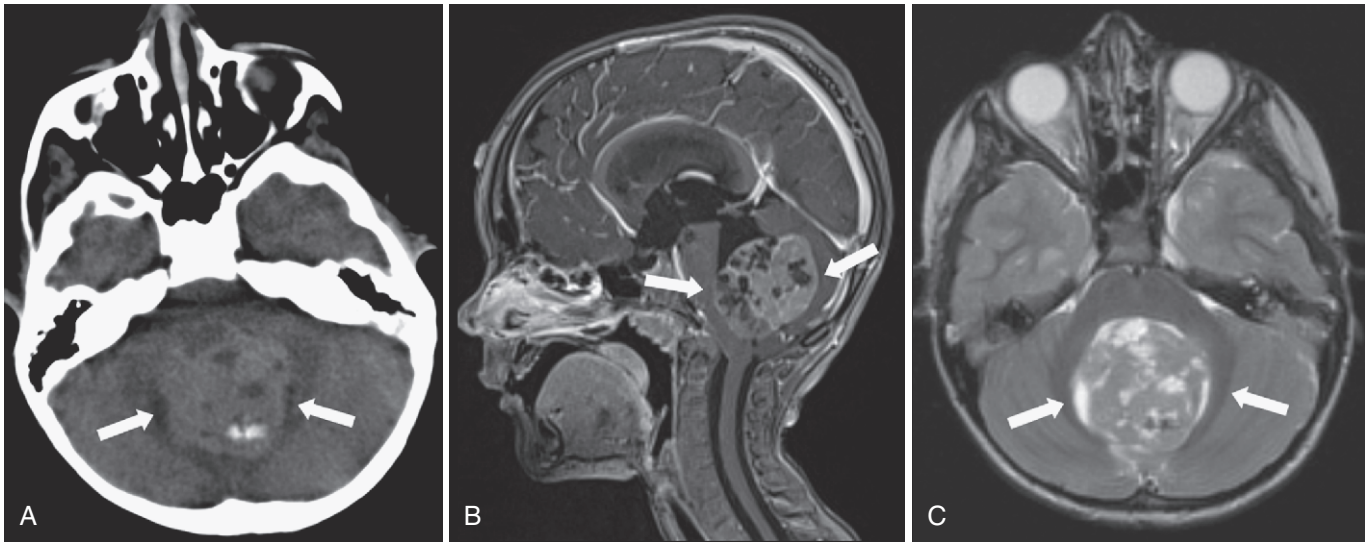

Figure 56–23. Posterior fossa medulloblastoma. Axial noncontrast CT (**A**) and sagittal T1-weighted MRI with gadolinium (**B**) show a midline posterior fossa mass that has heterogeneous enhancement on postcontrast T1 and heterogeneous signal on axial T2-weighted MRI (**C**).

obtained in as little as 12 seconds on a 3.0 Tesla scanner and 19 seconds on a 1.5 Tesla scanner and hence do not necessarily require patient sedation. Use of this technique offsets the radiation burden of repeated CT scans. In the initial evaluation of hydrocephalus, MRI can be helpful in determining the level and possible cause of CSF obstruction (see Figure 56-14). Acute hydrocephalus can be associated with evidence of transependymal CSF flow across the walls of the ventricular system, better appreciated on MRI. The absence of this appearance, however, does not reliably predict the absence of increased pressure. Physiologic/functional evaluation of shunt patency is achieved with nuclear medicine shunt studies, as described previously.

Tumor

Cerebral tumors are best imaged with MRI (Figure 56-23). Expedited evaluation of a cerebral mass can be accomplished in the acute setting with CT, which will demonstrate the degree of mass effect and any impending herniation or midline shift.

Posterior fossa tumors, which are more common in children and occur more often than supratentorial tumors in the 4- to 11-year age group,[43] and suspected acute spinal cord abnormalities, possibly associated with tumor, are best evaluated with MRI. CT is hampered by beam hardening artifact in the posterior fossa, at the skull base, and within the spinal canal.

Seizures

The CT imaging yield for a single self-limited seizure with no focal neurologic deficit is low, although most children currently will ultimately get scanned with CT or MRI. With focal neurologic deficit or prolonged seizure activity, the imaging yield increases. As discussed in Chapter 60, after seizures are controlled, MRI is indicated in the absence of a clinically apparent etiology for the seizures. Acute abnormalities on MRI, however, may be secondary to rather than reflecting the underlying cause of seizures. Prolonged seizures can be associated with transient enhancement due to BBB disruption and cytotoxic edema with hyperintensity on DWI that may be confused with stroke.

Conclusion

The ultimate selection of imaging modality will depend upon clinical question(s), age and condition of the patient, and the locally available imaging technology. Consultation with radiology colleagues is encouraged, and discussion of the clinical scenario and suspicions yields an appropriately tailored imaging protocol and a more relevant interpretation, which is becoming increasingly important with the ever-increasing complexity of imaging modalities.

References are available online at http://www.expertconsult.com.

Structure, Function, and Development of the Nervous System

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PEARLS

- In humans, general central nervous anatomy is established by birth. However, the brain undergoes substantial postnatal development including changes in synaptic density and dendritic arborization, maturation of neurotransmitter systems, and experience-dependent modification of neuronal circuits.
- Normal cerebral blood flow (CBF) changes significantly with age. For term human newborns, normal CBF is approximately 40 mL/100 g brain/min. CBF peaks around 4 to 8 years of age at approximately 100 mL/100 g brain/min, declining to adult values of 50 mL/100 g brain/min in late adolescents.
- Normal CBF regulation to changes in blood pressure, CO_2 and O_2 is operative from birth in term human newborns. While cerebrovascular reactivity to CO_2 and O_2 remains relatively unchanged with age, blood pressure-dependent autoregulation operates over a narrower blood pressure range in younger children than in older children and adults.

The nervous system, unlike any other organ system in the human body, stands at the intersection of biology and philosophy. While composed of cells and governed by chemical messages like all biological systems, it comprises the essence of each individual as a human being. The former can be quantified and studied; the latter enters the realm of religion, philosophy, and spirituality. Indeed, in a "brain-centric" approach to pediatric critical care, it can be argued that all interventions are ultimately targeted at preserving and protecting the child's nervous system function. Thus, knowledge of the structure and function of the nervous system, together with understanding of the developmental processes that are active in children who become patients in the intensive care unit (ICU), is essential to the practice of the pediatric intensivist. Furthermore, the impact of disease and injury in the context of the developing nervous system is only now beginning to be understood, with many new advances in diagnosis and treatment undoubtedly yet to come.

Major Cell Types

The nervous system contains two major cell types: neurons and glia. Neurons are responsible for the major operations traditionally ascribed to the nervous system: sensation, movement, thought, memory and emotion, as well as homeostasis of bodily functions. Interconnected networks of neuronal cells carry out all brain and spinal cord–based behaviors. Glia, although significantly more numerous than the neurons, function to support neuronally based information processing and long-distance information transfer. Both neurons and glia are broad classes of cells, each containing a multitude of specialized cells dedicated to carrying out specific functions in the nervous system.

All neurons, regardless of type and location within the nervous system, contain several standard cellular components that allow them to receive, process and relay information. The neuronal soma (cell body) contains the nucleus where genes are transcribed into mRNA, the endoplasmic reticulum where mRNA is translated into proteins and a multitude of mitochondria for cellular respiration and adenosine triphosphate synthesis. Originating from the soma are two types of processes: a number of dendrites and a single axon. Dendrites are short, local processes specialized for receiving information transmitted from other neurons via chemical or electrical synapses (see below). The axon is the output of the neuron, carrying information in the form of action potentials to be received by other neurons, muscles and many additional body organs, at distances up to meters away.

Glial cells are typically divided into microglia and macroglia. Microglia are phagocytic cells derived from peripheral macrophages, and normally exist in a resting, or quiescent state in the central nervous system (CNS). Microglia are activated by several physiologically relevant factors, including bacterial lipopolysaccharide in the setting of infection and thrombin in the setting of injury.[1] Whether microglial activation is neurotoxic or neuroprotective in these settings has yet to be fully characterized. In addition, activated microglia play an important role in the neuropathology of Alzheimer disease, HIV-associated dementia, and prion diseases. Therapeutic

strategies targeting microglial activation are just now beginning to emerge in animal disease models[2-3] and human clinical trials.[4]

Macroglia comprise several distinct cell subtypes within the nervous system: astrocytes and oligodendrocytes in the CNS, and Schwann cells in the peripheral nervous system (PNS). Astrocytes are by far the most numerous cell type in the brain, performing several vital functions. At the synapse, astrocytes regulate ion and neurotransmitter concentrations, contributing to the modern notion that the synapse is a tripartite structure consisting of the presynaptic and postsynaptic neurons and the astrocyte. At the blood-brain barrier (BBB), astrocytes direct their processes towards the endothelial cells and contribute to the proper development of tight junctions (see below). In contrast to the relatively diverse functions of astrocytes, oligodendrocytes' and Schwann cells' primary purpose is to provide myelination for axons in the CNS and the PNS, respectively. Myelination ensures faithful signal propagation along the entire axonal length. Each oligodendrocyte contributes myelin to between 10 and 15 axons in the CNS; each Schwann cell envelopes a single axon in the PNS. From a clinical perspective, disorders of myelination contribute significantly to a range of diseases observed in pediatric critical care, including perinatal asphyxia-induced periventricular leukomalacia, Canavan disease due to mutation in the oligodendrocyte-specific aspartoacylase gene, and Guillain-Barré syndrome, caused commonly by autoimmune-mediated injury to peripheral nerve myelin sheaths.

Intercellular Communication in the Nervous System

Early descriptions of neuronal cell structure by Camillo Golgi and Ramon Cajal in the late nineteenth century gave rise to two diverging theories of neuronal communication. Golgi proposed that neurons form an interconnected reticulum, much like cardiac muscle cells, and communicate directly with each other via openings in their membranes. Cajal, on the other hand, argued that neurons are individual cells with contiguous cell membranes, and that communication takes place chemically at the sites of contact between individual neurons. Despite the radically opposed views, both theories are now known to be correct and both mechanisms contribute to aspects of neuronal communication in the mammalian brain. Direct communication between neurons, known as the electrical synapse, is accomplished via gap junctions. Communication across cell membranes at sites where two neurons contact each other is accomplished using neurotransmitters, with the contact site known as the chemical synapse.

Electrical Synapses

At the electrical synapse, cell membranes of the adjoining neurons are tightly bound together into a gap-junction plaque.[5] Each plaque contains numerous channels made of connexin proteins. There are 21 known connexin genes in humans. Each channel consists of two hemichannels, with one on each cell membrane. Two hemichannels join together to form a functional gap junction between two neurons, allowing intercellular diffusion of ions and small molecules such as glucose, cyclic AMP, and ATP. Gap junctions thus allow neurons to share information about their metabolic and excitable states, providing a mechanism for large-scale regulation of energy demands and neuronal network dynamics. Additionally, gap junction channels close in response to lowered intracellular pH or elevated Ca^{2+} levels; since both events occur in damaged cells, paired hemichannels at the gap junction may function to isolate healthy neurons from those damaged during ischemia or trauma. Recent evidence suggests that unpaired hemichannels outside of the gap junction plaques may also contribute to ischemic neuronal cell death.[6]

Glia, like neurons, are also connected by gap junctions. For example, brain astrocytes form an interconnected cellular network, which allows long-distance propagation of calcium signals across many cells. Additionally, layers of myelin generated by oligodendrocytes in the CNS and by Schwann cells in the PNS are linked by gap junctions. Myelin gap junctions provide structural stability to the myelin sheath and allow for rapid diffusion of nutrients and other substances across the sheath towards the underlying axon. In humans, mutations in gap junction protein connexin 32 result in X-linked Charcot-Marie-Tooth disease, a demyelinating neuropathy.[7]

Chemical Synapses

Neuromuscular Junction

The neuromuscular junction (NMJ) is one of the most widely studied examples of chemical synaptic transmission in the nervous system. The overall concept is deceivingly simple: an action potential at the presynaptic neuron releases a neurotransmitter that in turn activates ion channels on the muscle cell membrane, resulting in postsynaptic action potential. Yet, every step in this process is exquisitely controlled and modulated in health and may be disrupted in disease. Our evolving understanding of the NMJ provides a critical window into synapse function and pathophysiology.

The NMJ consists of three distinct anatomic components: the presynaptic nerve terminal, the synaptic cleft containing the basement membrane, and the postsynaptic muscle fiber. The presynaptic nerve terminal originates from the myelinated axon of a motoneuron in the spinal cord. Lower motoneurons in the ventral gray matter of the spinal cord send their myelinated axons through the ventral root towards peripheral muscle targets. As the axon approaches the muscle fibers, it loses its myelin sheath and branches into a fine network of terminals, each approximately 2 μm in diameter. Each branch has several swellings along its course, termed presynaptic boutons, where the nerve makes synaptic contact with the muscle fiber. Presynaptic boutons are covered by terminal Schwann cells, which provide growth factors, recycle neurotransmitters, and may participate in recovery after nerve and muscle injury. Presynaptic boutons are positioned over specialized regions of the muscle cell membrane called the end-plate regions. Furthermore, underlying each bouton is a specialized invagination of the cell membrane that contains a very high concentration of nicotinic acetylcholine (ACh) receptors and voltage-gated Na^+ channels. The presynaptic bouton and the end-plate are separated by a 100 nm-wide synaptic cleft containing the basement membrane and the extracellular matrix. The basement membrane anchors a number of proteins, including acetylcholinesterase, the enzyme responsible for rapid hydrolysis of ACh in the synaptic cleft.

Several distinct functional steps occur during synaptic transmission at the NMJ. First, the action potential arriving from the motor axon depolarizes the membrane in the presynaptic boutons, causing Ca^{2+} entry via voltage-gated Ca^{2+} channels on the presynaptic membrane. Ca^{2+} entry results in fusion of synaptic vesicles containing ACh with the presynaptic cell membrane and release of ACh into the synaptic cleft. ACh rapidly diffuses towards the postsynaptic membrane and binds to the nicotinic ACh receptor (nACh); two ACh molecules are required to activate the nACh receptor. Upon activation, the nACh receptor opens and allows both Na^+ and K^+ to flow through the ion pore. The inward Na^+ current, however, dominates over the outward K^+ current, resulting in net depolarization of the muscle membrane at the end-plate. This so-called end-plate potential propagates a short distance before encountering voltage-gated Na^+ channels. These Na^+ channels open when membrane potential rises to a critical threshold value, allowing only Na^+ ions to flow into the cell and generating the all-or-none muscle action potential. Acetylcholinesterases in the synaptic cleft terminate the depolarizing action of ACh at the postsynaptic membrane by rapidly hydrolyzing ACh into acetate and choline.

A detailed understanding of diseases that affect synaptic transmission at the NMJ, as well as familiarity with clinical pharmacology as it applies to the NMJ, are essential in critical care. Specific diseases affecting the NMJ include toxin-mediated botulism and autoimmune disorders such as myasthenia gravis, Lambert-Eaton syndrome, and neuromyotonia. These are discussed in detail in Chapter 64 (see also Tseng-Ong and Mitchell[8] and Lang and Vincent[9]). Among the pharmacotherapies targeted at the NMJ are some of the most commonly used drugs in the pediatric ICU: neuromuscular blockers (NMB). NMB agents are reviewed in Chapter 122. Furthermore, a number of toxins either decrease (anticholinergic agents) or increase (acetylcholinestrase inhibitors) the amount of ACh available at cholinergic synapses, resulting in corresponding toxidromes (see Chapter 106).

Chemical Synapses in the Central Nervous System

Chemical synapses in the CNS operate on basic principles similar to those governing synaptic transmission at the NMJ, although the cadre of neurotransmitters and postsynaptic receptors is significantly more diverse in the CNS. Importantly, a given neuron in the CNS may synthesize and store more than a single neurotransmitter, but it releases the same set of neurotransmitters at all of its synapses (Dale's principle). CNS synapses are generally divided into asymmetric (Gray type I) synapses and symmetric (Gray type II) synapses on the basis of their appearance under electron microscopy. Physiologically, these correspond to excitatory and inhibitory synapses, respectively. Each neuron synthesizes its own complement of neurotransmitters, which are delivered to all synaptic contact sites in the axon and packaged into synaptic vesicles. When an action potential reaches the axon, Ca^{2+} currents cause the synaptic vesicles to fuse with the cell membrane, releasing neurotransmitters into the synaptic cleft. Neurotransmitters then act on their corresponding ionotropic and metabotropic receptors on the postsynaptic membrane. Ionotropic receptor activation leads to either a depolarizing, excitatory current or a hyperpolarizing, inhibitory current. These subthreshold currents are called excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs), respectively. Temporal and spatial summation of EPSPs in the dendritic tree of the postsynaptic neuron occasionally depolarizes the somatic membrane sufficiently to cross threshold and to generate an action potential. One of the distinguishing features of chemical synaptic transmission in the CNS, compared to the NMJ, is its lack of reliability on a single cell level; an action potential in the presynaptic neuron does not necessarily cause a postsynaptic neuron to fire its own action potential. Such lack of determinism likely allows for individual differences in responses to the same stimuli. After interaction with the receptor, the neurotransmitter is cleared from the synapse by diffusion, active reuptake into the terminal, or by enzymatic destruction, similar to ACh hydrolysis at the NMJ.

Neurotransmitter Systems

Several substances are employed for communicating information chemically between neurons in the nervous system or between a neuron and a muscle at the neuromuscular junction. These substances are called neurotransmitters, and generally fall into three categories: amines, amino acids, and peptides (Table 57-1). Each neurotransmitter requires its own synthetic machinery and exerts specific actions on the postsynaptic target. Furthermore, neurons tend to be characterized anatomically, immunohistochemically, and functionally by the main neurotransmitter they use, allowing insight into the role of each neurotransmitter system in CNS function.

Neurotransmitters

Acetylcholine

Acetycholine is an amine that functions as a neurotransmitter at the NMJ as well as in the CNS. At the NMJ, its actions are quick and precise, whereas in the CNS it functions as a slow, more global modulator of synaptic activity. Cholinergic CNS neurons include all the motoneurons in the spinal cord, as well as a number of cell nuclei in the brainstem reticular formation and the basal forebrain. Cholinergic neurons synthesize ACh using choline acetyltransferase (ChAT), which transfers an acetyl group from acetyl coenzyme A (CoA) to choline (Figure 57-1, *A*). Choline concentration in the extracellular fluid is the rate-limiting step in the reaction. Cholinergic neurons also synthesize acetylcholinesterase (AChE), the enzyme that breaks down ACh. AChE is released with ACh

Table 57–1 Neurotransmitter Classes

Amines	Amino Acids	Peptides
Acetylcholine	γ-Aminobutyric acid	Substance P
Dopamine	Glutamate	*Vasoactive intestinal peptide*
Norepinephrine	Glycine	Dynorphin
Epinephrine		Enkephalins
Serotonin		*Neuropeptide Y*
Histamine		*Cholecystokinin*

Neurotransmitters operative exclusively in the central nervous system are in normal font, those used both in the central and peripheral nervous systems are in *italics,* and those used exclusively in the peripheral nervous system are in **bold**.

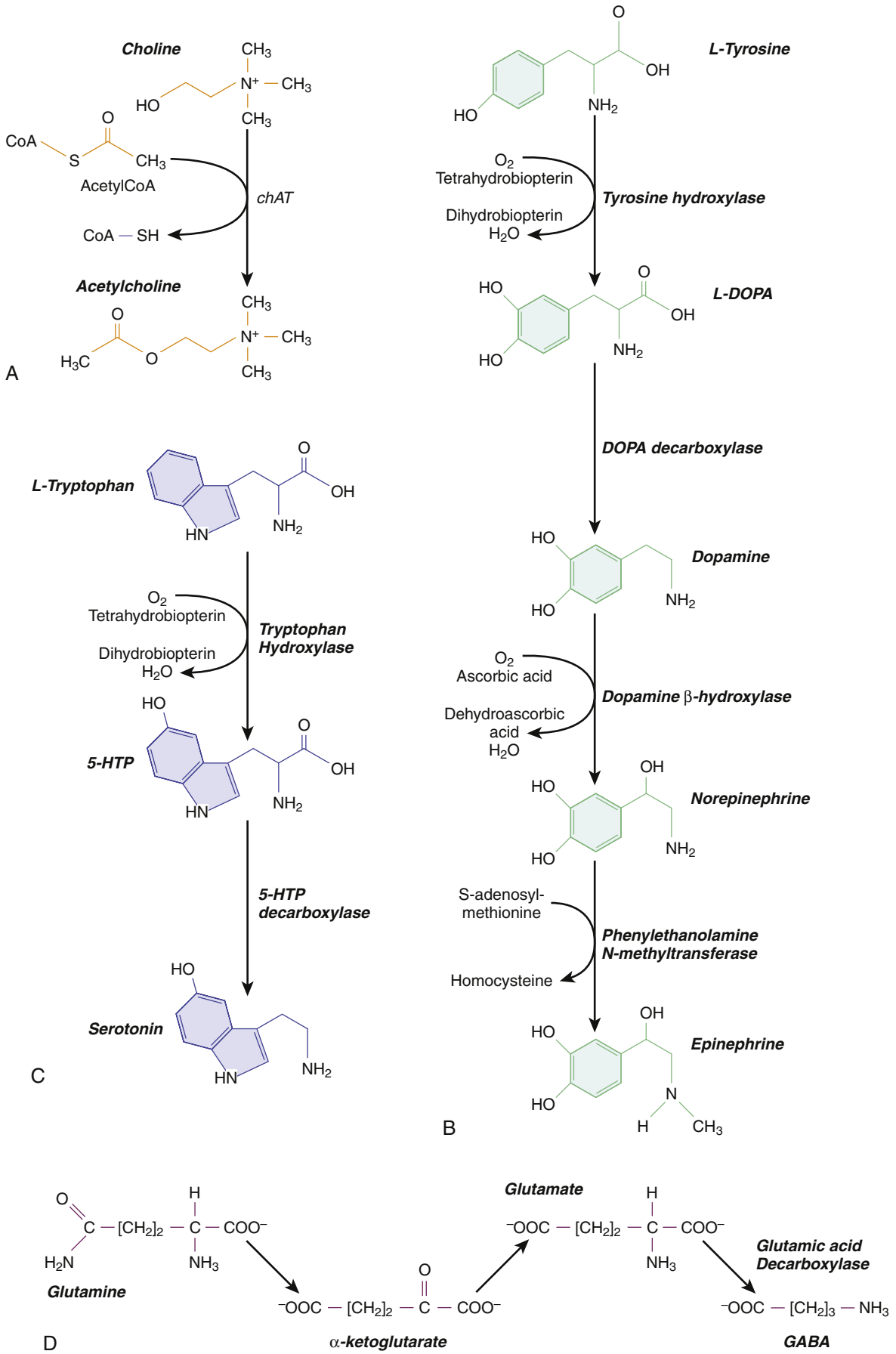

Figure 57–1. Neurotransmitter structure and synthesis. **A,** Acetycholine. **B,** Catecholamines. It should be noted that synthesis of norepinephrine and epinephrine requires dopamine as a precursor. **C,** Serotonin, an amine synthesized from tryptophan. **D,** Glutamate and GABA, amino acid derivatives.

into the synaptic cleft, where it rapidly hydrolyzes ACh into acetic acid and choline.

Low concentrations of choline in the CNS have been associated with neurologic impairment during fetal[10] and postnatal life.[11] Thus, choline supplementation represents an attractive therapeutic strategy in neurologic disorders characterized by decreased CNS choline. Interestingly, patients receiving long-term parenteral nutrition (TPN) occasionally develop choline deficiency, which has been associated with TPN-related liver failure[12] and possibly, cognitive dysfunction. Hence, choline supplementation in TPN-dependent patients may ameliorate some neurologic deficits.[13]

Catecholamines

Catecholamine neurotransmitters include dopamine, norepinephrine and epinephrine. For all three, the initial starting point in biochemical synthesis is the amino acid tyrosine (Figure 57-1, *B*). Tyrosine is converted into an intermediate compound, called dopa, by tyrosine hydroxylase (TH). In dopaminergic neurons, dopa is converted into dopamine by dopa decarboxylase. Noradrenergic neurons, which utilize norepinephrine as a neurotransmitter, further convert dopamine into norepinephrine using dopamine β-hydroxylase. Finally, norepinephrine is converted into epinephrine by an enzyme phentolamine *N*-methyltransferase, which is found only in adrenergic neurons. Thus all neurons that synthesize catecholamines contain TH and dopa decarboxylase, but only noradrenergic and adrenergic neurons contain the synthetic enzymes required to produce norepinephrine and epinephrine, respectively.

Catecholamine-utilizing neurons reside primarily in the brainstem. Dopaminergic neurons in humans are located in two mesencephalic nuclei: the substantia nigra and its medial neighbor, the ventral tegmental area. Dopaminergic neurons in the substantia nigra project primarily to the basal ganglia, where they are involved with initiation of voluntary movement. Ventral tegmental neurons send dopaminergic fibers to the amygdala and the cerebral cortex and participate in regulation of emotion, reward and addiction. Brainstem noradrenergic neurons are located in the locus ceruleus and in the reticular formation. They project widely to the thalamus and cortex as well as to the spinal cord, and play a significant role in arousal and vigilance. Adrenergic CNS neurons are located in the ventrolateral medulla, and participate in temperature regulation via their projections to the hypothalamus.

Unlike ACh, which is cleared from the synapse by hydrolysis, catecholamines are cleared from the synaptic cleft by reuptake into the axonal terminal. Once inside the cell, catecholamines are either repackaged into vesicles or destroyed by monoamine oxidase (MAO). Pharmacologic manipulation of synaptic catecholamine concentrations plays a therapeutic role in the management of several disorders, such as depression and attention deficit-hyperactivity disorder (ADHD). Furthermore, recreational drugs affecting catecholamine concentrations at the synapse continue to gain popularity and to grow in number. Therapeutic uses include treatment of severe depression with MAO inhibitors, which inhibit catecholamine breakdown, and treatment of ADHD with amphetamines, that interfere with dopamine transport and increase dopamine concentrations. Recreational drugs include amphetamine and its analogues, as well as cocaine, a selective norepinephrine transporter blocker. Excess catecholamine levels at the synapse result in sensations of euphoria, increased energy levels and improved focus, as well as anxiety, paranoia, and jitteriness. Notably, hypertensive crises leading to myocardial infarction and stroke may occur with use of cocaine, amphetamines, and MAO inhibitors.

Serotonin

Serotonin is an amine neurotransmitter synthesized from the amino acid tryptophan in a two-step process (Figure 57-1, *C*). First, tryptophan is hydroxylated by tryptophan hydroxylase to form 5-hydroxytryptophan (5-HTP). 5-HTP is then decarboxylated by 5-HTP decarboxylase to form serotonin, also known as 5-hydroxytryptamine (5-HT). After 5-HT is released at the synapse, it is cleared by a specific serotonin reuptake transporter. Serotonergic neurons are located in the rostral and caudal raphe nuclei in the brainstem. Rostral raphe neurons innervate the cerebral cortex, including the limbic system, where serotonin levels help regulate mood and attention. Caudal raphe neurons project to the brainstem and the spinal cord, where they are involved in regulation of general arousal and pain perception, respectively. Importantly, dysfunction of the serotonergic pathways originating in the raphe nuclei has been linked with sudden infant death syndrome (SIDS).[14] Additionally, serotonin levels play a key role in depression, giving rise to an entire class of drugs in clinical use called selective serotonin reuptake inhibitors (SSRIs). SSRI abuse or overdose is rare, but may result in patients presenting with the potentially life-threatening "serotonin syndrome," characterized by hypertension, tachycardia, mental status changes, myoclonus, and severe hyperthermia. The latter may lead to shock, rhabdomyolysis, renal failure, and death. The serotonin syndrome is particularly likely to occur when SSRIs and MAO inhibitors, inadvertently or intentionally, are taken together. Treatment includes serotonin antagonists, blood pressure control with either adrenergic antagonists or agonists as clinically indicated, and temperature control with benzodiazepines and neuromuscular blockade.

Amino Acids

Neurotransmitters derived from common amino acids include glutamate, gamma-aminobutyric acid (GABA), and glycine. These are among the most widely distributed neurotransmitters in the CNS. Glutamate and glycine exist as amino acids in all cells, where they are utilized as protein building blocks. Glutamatergic and glycinergic neurons have the additional capacity to package glutamate and glycine, respectively, into synaptic vesicles and release them at the synapse. GABA must be synthesized from glutamate via an additional reaction catalyzed by an enzyme glutamic acid decarboxylase (GAD) (Figure 57-1, *D*). Only GABA-ergic neurons contain GAD.

Glutamate is generally an excitatory neurotransmitter, whereas GABA and glycine are inhibitory. Excitatory glutamatergic neurons exert their influence both locally and over long distance, depending on the shape of their axons. Inhibitory neurons, on the other hand, tend to exert local inhibitory control over neuronal circuitry either in the brain (GABA) or in the spinal cord (glycine). A major exception are cerebellar Purkinje cells, which are GABA-ergic but project over long distances to the brainstem, thalamus, and cerebral cortex (see below).

Adenosine, Peptides, and Nitric Oxide

In addition to the "classic" neurotransmitters described above, a number of substances have been documented to mediate or modulate information transfer between neurons. These include adenosine triphosphate (ATP) and adenosine, which at the synapse is a metabolite of ATP released in the synaptic vesicle. ATP modulates neuronal excitability such that energy may be conserved during times of ATP depletion. Adenosine functions as a neurotransmitter in the autonomic nervous system (ANS), in the basal ganglia, and at some cortical synapses. It also modulates the respiratory rate, and adenosine antagonists, such as caffeine, are used to treat apnea and bradycardia of prematurity. In addition to ATP and adenosine, a number of peptides can be released in synaptic vesicles, including substance P, vasoactive intestinal peptide (VIP), endogenous opioids, and endogenous cannabinoids. These peptides are involved in pain sensation and perception (substance P and opioids), modulation of vascular tone (VIP), and as yet uncharacterized processes (cannabinoids).

Finally, several gaseous molecules function as neurotransmitters. These include nitric oxide (NO) and carbon monoxide (CO), and possibly hydrogen sulfide. NO, the most thoroughly studied of the gaseous neurotransmitters, is produced by brainstem neurons in the nucleus tractus solitarius, where it interacts with α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA)-type and *N*-methyl-D-aspartate (NMDA)-type glutamate receptors and regulates cardiovascular function.[15] Hydrogen sulfide is produced from the amino acid cysteine, and may influence cellular redox state and glutamatergic transmission.[16] Intriguingly, hydrogen sulfide induces a suspended animation-like state in animals.[17] and may be protective after resuscitation from cardiac arrest.[18]

Neurotransmitter Receptors

Nicotinic Acetylcholine Receptors

Nicotinic ACh receptors are ligand-gated ion channels, related structurally and functionally to $GABA_A$ channels, and a subset of serotonin receptors. Five transmembrane subunits comprise the nAChR and form a central pore that allows ionic currents to pass. There are two subunit classes, α and β, with multiple members in each class. nAChR is generally a heteromer, but homomer channels have been described. Each nAChR binds two acetycholine molecules, with affinity for ACh and for nicotine dependent on subunit composition. The receptor exists in three distinct states: closed, open, and desensitized. In the closed position, no ionic current passes through the central core. When an agonist, such as ACh or nicotine, binds the nAChR, the receptor opens, becoming permeable to monovalent and divalent cations. After a short period of time, the receptor spontaneously closes. Upon continued exposure to an agonist, however, the nAChR assumes a permanently closed, or desensitized, conformation.[19] As discussed above, nAChRs mediate neuromuscular coupling at the NMJ. In addition, nAChRs are widely distributed in the CNS, where they perform a variety of functions depending on subunit composition and location.

In the CNS, unlike at the NMJ, nAChRs are permeable to both Na^+ and Ca^{2+}. In neurons, however, nAChR-evoked Ca^{2+} current exceeds the Na^+ current twofold to tenfold. The greater Ca^{2+} permeability indicates that nAChRs mostly modulate synaptic transmission and release of other neurotransmitters. Indeed, although direct nAChR-dependent responses have been observed in the hippocampus and the developing visual cortex, the overwhelming evidence points to nicotinic receptors playing the role of modulator in the CNS. Their wide distribution in the CNS with locations presynaptically, postsynaptically, and extrasynaptically further supports that role. Activation of presynaptic nAChRs enhances release of ACh, dopamine, glutamate, and GABA. Coupling of enhanced glutamate release with nAChR-dependent increase in intracellular Ca^{2+} suggests that nAChRs participate in synaptic plasticity during learning. Postsynaptic and extrasynaptic nAChRs regulate excitability and signal propagation in neuronal circuits. In the hippocampus, for example, nAChR activation leads to increased release of GABA from inhibitory interneurons, which decreases the excitability of hippocampal pyramidal neurons. Nicotinic receptors also interact with the dopaminergic system in regulating neuronal circuitry in the basal ganglia and the limbic system. Thus, nicotinic receptors have been implicated not only in learning and memory, but also in regulation of addiction and reward. Furthermore, loss of cholinergic neurons represents one of the distinguishing neuropathologic features of Alzheimer disease, and cholinesterase inhibitors are widely used to improve cognition and memory in Alzheimer patients.[19] In pediatrics, a mutation in nAChR is responsible for a specific clinical epilepsy phenotype, called autosomal dominant nocturnal frontal lobe epilepsy.[20] Seizure onset usually occurs around 12 years of age in otherwise healthy children. Seizures originate in the frontal lobe, and occur predominantly during non-REM sleep.[21] The mutant nAChR is more sensitive to ACh than the wild-type receptor, suggesting that cholinergic medications should be avoided in these patients.

Muscarinic Acetylcholine Receptors

Muscarinic ACh receptors (mAChRs) comprise a group of metabotropic receptors that link ACh exposure at the surface with G protein activation inside the cell. There are five distinct subtypes of mAChRs, designated M_1 through M_5, and these subtypes are divided into two broad classes based on the identity of the G protein with which they interact. M_2 and M_4 mAChRs couple with G_i proteins, and inhibit adenylyl cyclase activity and reduce intracellular cAMP levels. M_1, M_3, and M_5 receptor subtypes couple with G_q proteins, and increase intracellular Ca^{2+} levels via activation of phospholipase C.[22] In the CNS, the M_1 mAChR is the most abundant subtype, located on neurons in the cortex, thalamus and striatum.[23] mAChRs are also present in the PNS in the sweat glands and organs of lacrimation and salivation, as well as in the heart, where they mediate the parasympathetic control of heart rate and contractility. Muscarinic AChRs thus mediate many of the systemic effects of organophosphate exposure and nerve gas poisoning.[24]

Glutamate Receptors

Glutamate is the major excitatory neurotransmitter in the central nervous system. In mammals, it depolarizes postsynaptic neurons by binding to three types of ionotropic glutamate receptors (iGluR), each of which is characterized by different affinities for synthetic analogues, by different selectivity to ions, and by different time-course of the current that is

permitted to pass through the cell membrane. The three types of iGluR are the AMPA receptor, the NMDA receptor, and the kainate receptor. All three channels types are widely present throughout the CNS, with AMPA and NMDA channels mediating the bulk of the excitatory transmission. At present, the function of the kainate channel remains to be clearly defined.

AMPA and NMDA receptors differ from each other with respect to ion permeability and time-course of ion flow through the channel. Upon binding of glutamate, AMPA receptors open their pores, which are permeable to Na^+ and K^+ ions. At the negative resting potential of the neuronal cell membrane, Na^+, driven by the electrochemical gradient, flows into the cell and causes a large, fast depolarization. AMPA receptors are generally impermeable to Ca^{2+}, although more recent findings indicate that Ca^{2+}-permeable AMPA receptors do exist and may significantly contribute to pathology observed in ALS and stroke.[25] In contrast, NMDA receptors are universally permeable to Ca^{2+}, as well as to Na^+ and K^+, generating a slow inward depolarizing current. NMDA receptors possess a unique property, however, that allows them to pass current only when the neuronal membrane is already depolarized. This property, termed *voltage-dependence*, stems from Mg^{2+} ions blocking the entry pore of the NMDA channel at negative membrane potentials even in the presence of glutamate. As the neuron depolarizes further, mostly due to current flow via the AMPA receptor, the Mg^{2+} block is relieved, and Ca^{2+}, as well as Na^+, flow into the cell. Once inside the cell, Ca^{2+} ions mediate a multitude of effects, from modifying protein phosphorylation and gene expression to overt *excitotoxicity* and cell death. NMDA receptors are thus thought to function as coincidence detectors, linking events at the cell membrane, e.g., AMPA receptor-mediated depolarization, with long-term changes in synaptic strength and gene expression in the neuron.

In addition to directly modulating current flow via the ionotropic channels, glutamate modulates effector molecules within the neuron by binding to a diversity of G protein-linked metabotropic glutamate receptors (mGluRs). Eight mammalian subtypes of mGluR are divided into three categories, based on sequence homology and coupling to secondary effector systems.[26] Group I mGluRs (mGlurR1 and mGluR5) are localized at the edge of the postsynaptic neuronal membrane and are positively coupled to phospholipase C (PLC) via the G_q protein. Group II and III mGluRs are located on the edge of the presynaptic neuronal membrane and are negatively coupled to adenylyl cyclase (AC) via the G_i protein. All three groups are activated only when excess glutamate spills out of the synaptic cleft and diffuses towards mGluRs located at the periphery of the synaptic membrane.

Differential secondary messenger coupling and synaptic localization of the three mGluR groups points to their divergent roles in regulating neuronal function. Binding of glutamate to group I mGluRs leads to activation of PLC, which releases two secondary messengers—diacylglycerol (DAG) and inositol triphosphate (IP_3)—from the membrane phospholipid phosphoinositol 1,4,5-bisphosphate (PIP_2). DAG activates protein kinase C in the neuronal membrane, whereas PIP_2 diffuses towards its receptor on the internal cell membrane and triggers a massive Ca^{2+} release into the cytoplasm. Downstream events lead to 1) modulation of K^+ currents, resulting in increased neuronal excitability and 2) potentiation of glutamate-dependent current at NMDA receptors specific to the synapses at which excess glutamate release has occurred. Group I mGluRs thus participate in activity-dependent strengthening of synaptic connections and play a significant role in learning and memory.

In contrast, group III, and probably group II, mGluRs on presynaptic neurons provide a negative feedback loop by inhibiting glutamate release. When glutamate binds to group III mGluRs, an inhibitory G protein (G_i) is activated, that then functions to decrease AC-mediated production of cAMP. A decrease in cAMP leads to lower Ca^{2+} concentrations at the presynaptic neuronal membrane and decreased synaptic vesicle fusion. The net effect is a decrease in the amount of glutamate released at the synapse and a reduction in synaptic transmission. Recently, mGluRs have emerged as a major therapeutic target due to the multitude of effects they exert on synaptic transmission. Their extrasynaptic location presumably will allow newly developed pharmaceutical agents to maximize therapeutic value and minimize unwanted side effects.[27]

$GABA_A$ and $GABA_B$ Receptors

GABA is the major inhibitory neurotransmitter in the brain. Like glutamate and ACh, it binds two distinct classes of GABA receptors; $GABA_A$ receptors are ionotropic, and $GABA_B$ receptors are metabotropic. Both receptor classes are involved in regulation of physiologic and pathologic states, and pharmacological manipulation of GABA receptors plays a major role in the management of pediatric critical illness.

$GABA_A$ receptors are chloride channels. At the normal resting membrane potential, opening of the $GABA_A$ receptor allows chloride ions to flow into the cell down their electrochemical gradient. Influx of negatively charged Cl^- ions results in hyperpolarization of the cell membrane. In neurons, membrane hyperpolarization decreases the probability that the neuron will reach threshold and fire an action potential. Thus, on an individual cell level, GABA decreases neuronal activity via the $GABA_A$ receptor.

$GABA_A$ receptors are heteropentamers, similar in structure to the nAChRs. At least eight subunit classes exist in mammals, including humans, and each class consists of several members, allowing for a staggering 150,000 possible subunit combinations to create one functional $GABA_A$ receptor. Only 500 combinations are known to exist, and most receptors contain a various complement of the α, β, and γ subunits.[28] Most $GABA_A$ receptors cluster at postsynaptic densities, and such clustering appears to depend on presence of the γ subunit. However, a subset of the $GABA_A$ receptors, in particular those containing the δ subunit, localize to extrasynaptic sites, mediate tonic levels of inhibition in the brain, and may underlie the pathophysiology of absence seizures.[29]

The pharmacology of the $GABA_A$ receptor is of particular relevance in critical care, since the two classes of first-line anticonvulsants and anxiolytics in clinical practice—the benzodiazepines and the barbiturates—allosterically modulate the $GABA_A$ receptor. GABA itself binds the receptor at the junction of the α and β subunits. Benzodiazepines bind the $GABA_A$ receptor at a different site, classically between the α and γ_2 subunits, and, in the presence of GABA, increase the frequency with which the chloride channel opens. Barbiturates, in contrast, bind at yet a different site and increase the duration of the open state in the presence of GABA. Thus both benzodiazepines and barbiturates increase the efficacy

of endogenous GABA in hyperpolarizing the cell membrane. A major difference between the two drug classes is that at increasing concentrations, barbiturates, but not benzodiazepines, become direct GABA agonists and can open $GABA_A$ channels independent of endogenous GABA release. Hence, barbiturates have a significantly narrower safety window compared to benzodiazepines.

Additional $GABA_A$ receptor ligands of clinical importance include (1) general inhalational anesthetics, which are thought to modulate tonic inhibition via the δ subunit-containing receptors; (2) alcohol, although its mechanistic action is poorly understood; and (3) flumazenil, a competitive benzodiazepine antagonist used clinically to reverse benzodiazepine overdose.

$GABA_A$ receptors mutations contribute to several known disease states in humans. Two different point mutations on chromosome 5, both affecting the γ_2 subunit, are associated with development of febrile seizures and generalized epilepsy as well as with a link between the two conditions.[30-31] In patients with temporal lobe epilepsy, $GABA_A$ receptor expression is altered in hippocampal neurons,[32] and GABA-evoked responses actually depolarize, rather than hyperpolarize, neurons in excised tissue (see also Developmental Processes section later in the chapter).[33] $GABA_A$ receptor dysfunction is also thought to contribute to anxiety, panic disorder, schizophrenia, and sleep disturbances.[34] Thus, pharmacologic modulation of $GABA_A$ receptor function represents an active area of research and novel drug development.

$GABA_B$ receptors are heterodimeric proteins that activate G protein-coupled second messenger systems upon interaction with GABA at the membrane.[35] The $GABA_{B1}$ subunit binds GABA at the cell membrane, while the $GABA_{B2}$ subunit interacts with the G protein on the cytosolic surface. $GABA_B$ receptors are widely distributed throughout the CNS but are particularly abundant in the thalamus, cerebellum, and hippocampus. They can be located both presynaptically and postsynaptically. Presynaptic $GABA_B$ receptors allow G protein–coupled Ca^{2+} influx into the cell, and leads to feedback inhibition of transmitter release. Postsynaptic $GABA_B$ receptors function as K^+ channels by allowing a slow, G protein–dependent K^+ current to leak out of the cell, and leads to cell hyperpolarization (since positive ions have left the inside of the cell membrane).[36]

Baclofen is the only pharmacologic $GABA_B$ receptor ligand in current clinical use. It directly activates the $GABA_B$ receptor and, through its action in the spinal cord, leads to reduction in muscle tone. Thus it is used primarily to relieve spasticity after CNS injury. When administered systemically, it has a significant side-effect profile, including hypotension and bradycardia.[35] Systemic side effects have been minimized with intrathecal administration via an indwelling catheter and pump.[37,38] Indeed, intrathecal baclofen infusion has emerged as an alternative to the more invasive dorsal rhizotomy in the treatment of spasticity refractory to medical therapy in pediatric patients.[39] Although intrathecal baclofen delivery systems are effective, they have a 10% to 20% failure rate over time. When an intrathecal baclofen pump fails, patients can develop baclofen withdrawal symptoms characterized by agitation, increasing spasticity and dystonia, hypertension, tachycardia, hyperthermia, and potentially death.[39] Thus baclofen withdrawal should be considered in the differential diagnosis of an agitated child with an indwelling baclofen pump.

Major Anatomic Organization of the Nervous System

The nervous system in mammals is organized along an evolutionarily conserved axis. It can be divided anatomically and functionally into the central and peripheral nervous systems. Broadly speaking, the CNS consists of the spinal cord and the brain inside the skull. All other components, such as nerves after they leave the spinal canal or exit the brain as well as autonomic ganglia in the body, comprise the PNS. The general subdivisions are shown in Figure 57-2. The following sections focus on well-defined functions of these subdivisions as well as on their clinical relevance in pediatric critical care medicine.

Central Nervous System

Spinal Cord

The spinal cord is organized into segments delineated by the exiting spinal nerves. In humans, there are 31 segments: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal.[40] The first seven cervical nerves exit the spinal canal above the corresponding vertebra, that is, the C1 nerve exits between the occiput and the C1 vertebra (the atlas). Since in humans there are only seven cervical vertebra and eight cervical nerves, the last cervical nerve, C8, exits the spinal canal between C7 and T1. From T1 on, each corresponding spinal nerve exits the spinal cord below its corresponding vertebra, that is, the T12 nerve exits between T12 and L1. Early in fetal life, the spinal cord extends throughout the entire length of the spinal canal. Beginning in gestation week 12, the growth rate of the vertebrae exceeds that of the spinal cord, such that by birth in humans, the spinal cord ends at L3. During postnatal development, further differential growth occurs, and in adults, the spinal cord ends more rostrally, between L1 and L2. The nerve roots continue to exit the spinal canal through their corresponding foraminae, such that the caudal spinal roots extend past the end of the spinal cord towards their exit points and form the cauda equina. The end of the spinal cord forms an important landmark during development, since the lumbar puncture must be performed below the spinal cord in order to avoid severe injury. Hence, in infants, the preferred location of the lumbar puncture is between L4 and L5 vertebrae, with an alternate site between L3 and L4. In adults, it is safe to perform the lumbar puncture between L3 and L4, with both the L2/L3 and the L4/L5 intervertebral spaces as alternative sites.

Spinal cord lesions result in two general subsets of neurologic deficits: those caused by interruption of ascending information flow towards the brain, and those caused by interruption of descending brain control of the spinal cord circuitry and the PNS. Thus complete spinal cord transection leads to loss of sensation and muscular paralysis below the level of the lesion due to injury to the ascending sensory pathways and descending motor pathways, respectively. Immediately after the transection, paralysis is flaccid with loss of deep tendon reflexes, characteristic of spinal shock (not to be confused with neurogenic shock, see below). After a period of time, paralysis becomes spastic, with increased muscle tone and hyperactive deep tendon reflexes, due to disrupted inhibitory control of spinal cord circuitry by the brain's motor centers.

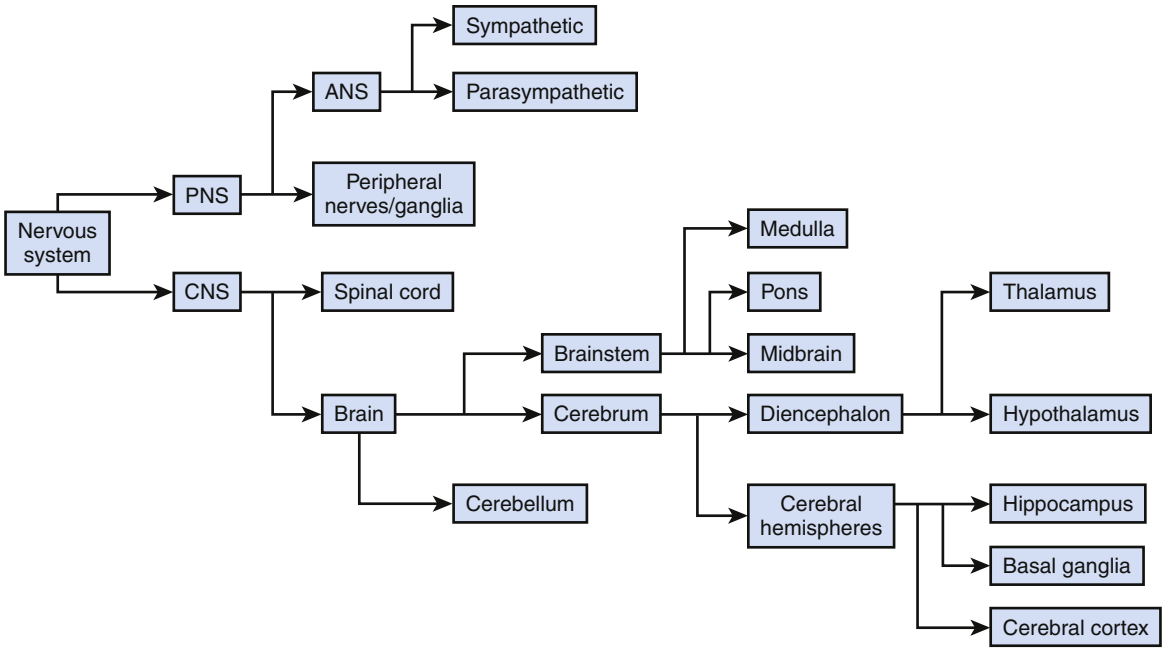

Figure 57–2. General subdivisions of the nervous system. *(Modified from Nolte J,* The human brain. An introduction to its functional anatomy, *ed 3, St Louis, 1993, Mosby–Year Book.)*

Medulla

The medulla extends rostrally from the spinal cord in the rough shape of an ice cream scoop.[40] The closed "handle" portion contains an enclosed central canal contiguous with that in the spinal cord. The open "scoop" portion is located rostrally where the central canal opens into the fourth ventricle. The medulla gives origin to four cranial nerves (CN): the glossopharyngeal (CN IX), vagus (CN X), accessory (CN XI), and hypoglossal (CN XII). It also contains decussations (crossings) of two major fiber tracts. The postsynaptic fibers from the nuclei gracilis and cuneatus, that carry tactile information from the lower and upper parts of the body, respectively, cross the midline in the caudal medulla, giving rise to the sensory decussation. The pyramidal tracts, that contain fibers descending from the motor cortex into the spinal cord, decussate slightly more rostrally, giving rise to the pyramidal, or motor decussation. These decussations are responsible for the fact that the left half of the brain controls and senses the right half of the body, and vice versa. Thus in general, damage to brain structures above the decussation gives rise to contralateral symptoms whereas damage below the decussation results in ipsilateral symptoms (except for the cerebellum as discussed below). Finally, the medulla contains the brain's respiratory control center, which is of paramount importance in determining brain death (see below). In the absence of neuromuscular blockade, complete apnea in response to rising $PaCO_2$ results only when the medulla has been extensively injured.

Although extensive damage to the medullary structures is often quickly fatal due to ensuing apnea, more localized injury produces a number of recognizable syndromes. Wallenberg, or lateral medullary, syndrome occurs when the territory supplied by posterior inferior cerebellar artery has been compromised, and consists of loss of temperature and pain sensation on the contralateral side of the body and on the ipsilateral side of the face. Additionally, Horner syndrome and varying degrees of vertigo, dysphagia, and dysarthria can be present. The medial medullary syndrome (Dejerine or inferior alternating syndrome) results from injury to the territory supplied by the anterior spinal artery or, occasionally, the vertebral artery. It is characterized by weakness or complete hemiplegia and loss of tactile and vibratory perception on the contralateral side of the body, together with preservation of temperature and pain sensation in the body and full sensation in the face. Medullary injury also occurs as a life-threatening, albeit rare, complication of tonsillectomy and adenoidectomy.[41]

Pons

The pons extends from the medulla to the midbrain, and is readily recognized by the massive, bulbous structure with horizontally-oriented fibers on its ventral surface that gives rise to its name (from the Latin, *bridge*). The pons begins at the pontine-medullary junction, characterized by a groove from which the abducens (CN VI), facial (CN VII) and vestibulocochlear (CN VIII) nerves emerge. It extends rostrally to the point of emergence of the trochlear nerve (CN IV) where it transitions into the midbrain. The trigeminal nerve (CN V) exits from the lateral aspect of the pons approximately midway between the medulla and the midbrain.

In addition to the cranial nerves, the pons contains several other important structures. Its eponymous bulb, called the basis pontis, is formed by bundles of corticopontine fibers that connect the cerebral cortex with ipsilateral pontine nuclei. Postsynaptic fibers originating in the pontine nuclei then cross the midline and form the middle cerebellar peduncle, which comprises one of the major input pathways into the cerebellum. Cerebellar output to the thalamus and other structures takes place via the superior cerebellar peduncle contained in the rostral pons. Additionally, the rostral pons contains the locus ceruleus (from the Latin, *blue spot*). Locus ceruleus

neurons utilize norepinephrine as a neurotransmitter, innervate wide-ranging areas of the brain, and likely regulate sleep and arousal.

Injury to pontine structures is of significant relevance in the PICU. First, increased intracranial pressure (ICP) from any cause may result in compression of the medially located small abducens nerve (CN VI), leading to paralysis of the lateral rectus eye muscle and associated turning in of the affected eye. Abducens nerve palsy due to increased ICP may precede the notorious fixed and dilated pupil phenomenon observed when CN III is compressed during impending uncal herniation (see below). Second, damage to the rostral pons (or lower midbrain) results in decerebrate posturing, characterized by extension of both upper and lower extremities upon painful stimulation. Importantly, decerebrate posturing corresponds to the motor score of 2 on the Glasgow Coma Scale (GCS). Finally, infarction of the basis pontis with sparing of the more dorsal pontine structures results in the "locked-in" syndrome. The locked-in state is characterized by complete paralysis of all voluntary muscles except the muscles of ocular movement and by complete cognitive awareness. Since the locked-in patient can communicate only via eye gaze, recognition of the locked-in state by the physician requires extreme diligence in patients with brainstem lesions, lest the patient be misdiagnosed as comatose, with potentially dire consequences.

Midbrain

The midbrain is the most rostral and the smallest of the brainstem structures. It is characterized by the presence of the bilateral inferior and superior colliculi on its dorsal surface. Additionally, the oculomotor nerve (CN III) emerges from its ventral surface, immediately below the temporal lobe of the cerebral hemisphere. The midbrain contains structures important for hearing, sound localization, and generation of saccadic eye movements. Furthermore, the substantia nigra in the midbrain contains neurons that utilize dopamine as their neurotransmitter. These dopaminergic neurons project to the basal ganglia where dopamine release participates in initiation of voluntary movements, to the limbic system in the cerebral cortex where dopamine plays a role in reward and emotion, and to the frontal and temporal cortices, indicating that dopamine affects thought and memory. Destruction of dopaminergic substantia nigra neurons underlies the pathology of idiopathic Parkinson disease in older individuals and of Parkinsonian symptoms in drug abusers exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, sometimes a contaminant in heroin preparations.

Two clinical phenomena of significant importance in pediatric critical care medicine arise from damage to midbrain structures. First, global injury to the midbrain results in decorticate posturing, characterized by flexion of upper extremities and extension of lower extremities in response to painful stimulation. Decorticate posturing corresponds to a motor score of 3 on the GCS. Second, the "blown" pupil universally recognized as a sign of increased ICP and impending transtentorial brain herniation results from compression of the oculomotor nerve (CN III) as it exits the midbrain. Pupillary dilatation results from compression and inactivation of the parasympathetic fibers that run on the outer surface of CN III and which are actually responsible for pupillary constriction. When these fibers are damaged, unopposed sympathetic stimulation arising from the cervical sympathetic ganglia results in a constitutively dilated pupil that cannot constrict in response to light stimulation, or in other words, is "fixed." Unilateral fixed and dilated pupil is an emergency that requires immediate medical and/or surgical intervention.

Reticular Formation

The brainstem reticular formation is not a separate anatomic structure but is instead distributed throughout the core of the brainstem from the medulla into the midbrain. It plays a fundamental role in arousal and consciousness, control of movement and sensation, and in regulation of visceral functions. A subset of the reticular formation neurons sends fibers to the intralaminar thalamic nuclei, which in turn project widely throughout the cerebral cortex. Damage to these ascending brainstem fibers, collectively called the ascending reticular activating system, results in loss of consciousness and coma, even in the absence of any damage to the cerebral hemispheres. Thus the cerebral cortex requires input from the brainstem to maintain awareness and arousal. In addition, the reticular formation contains neuronal circuits responsible for regulation of respiration, for cardiovascular responses to blood pressure and oxygen level modulations, as well as for coordination of swallowing and other oromotor functions. Finally, complex reflexes such as walking and maintenance of body orientation with respect to gravity are coordinated by the brainstem reticular formation and may occur in the absence of input from higher brain regions. Immaturity of the brainstem reticular formation, in particular of its serotonergic component, has been implicated in the etiology of SIDS.[14]

Cerebellum

The cerebellum overlies the majority of the brainstem and is separated from the cerebral cortex by a sheetlike reflection of the dura mater, called the tentorium cerebelli. Hence, the brainstem and the cerebellum are referred to as infratentorial structures while the cerebral cortex and the diencephalon are referred to as supratentorial structures. The cerebellum consists of a midline vermis and two large cerebellar hemispheres.[40] The outer surface of the cerebellum consists of a three-layered cortex, which includes the outer molecular layer, the Purkinje cell layer, and the granular layer. The molecular layer contains mostly axons and dendrites. The Purkinje cell layer contains the eponymous large GABA-ergic neurons that constitute the sole cerebellar output. Finally, the granular layer contains small granule cells that interact with other granule cells and with Purkinje neurons. In addition to the cerebellar cortex, each cerebellar hemisphere also contains a set of deep nuclei. From lateral to medial, these are the dentate, the interposed, and the fastigial nuclei.

Cerebellar function has traditionally been confined to regulation and coordination of movement of the eyes, head, and body in space. However, evidence from neuroanatomic and functional neuroimaging studies has suggested that the cerebellum, and in particular the dentate nucleus, plays a significant role in cognition, memory, and language.[42,43] Consequently, lesions to the cerebellum are characterized by ataxia, ipsilateral dysmetria, and intention tremor as well as by scanning speech, in which each syllable is produced slowly and separately, and by disorders of memory and executive function.[43] In the PICU, cerebellar lesions are seen most frequently in the setting of infratentorial tumors but also occasionally in cerebellar strokes.

Diencephalon

The diencephalon consists of four major structures: thalamus, hypothalamus, subthalamus, and epithalamus. Of these, only the thalamus and the hypothalamus will be discussed in detail as they serve crucial functions relevant to pediatric critical care medicine. The thalamus is the major relay station for all sensory information except olfaction as it travels from peripheral sensory organs to the cerebral cortex. For example, optic nerve neurons carrying visual information synapse onto neurons in the lateral geniculate nucleus in the thalamus, which process and transmit the signal to the primary visual cortex in the occipital lobe. Furthermore, the thalamus participates in coordination of motor activity via multiple neuronal loops that connect the cerebellum with the basal ganglia and the cerebral cortex.[43] Lastly, inhibitory thalamic nuclei such as the reticular nucleus (distinct from the brainstem reticular formation) are thought to participate in gating of attention and consciousness.[44]

Injury to the thalamus occurs frequently in both term and preterm neonates exposed to hypoxia-ischemia at birth.[45] Additionally, thalamic necrosis is observed in infectious encephalitis, particularly that associated with the influenza virus[46,47] and *Mycoplasma pneumoniae*.[48] Vascular diseases, such as occlusion of the basilar artery or systemic lupus erythematosus can result in thalamic injury that can occasionally be reversible.[49] Apparent life-threatening events have been rarely associated with thalamic lesions.[50] Thalamic damage is associated with a wide range of symptoms, including pure sensory loss due to destruction of sensory relay nuclei, acute abnormalities in mental status, labile emotions, and motor dysfunction.

The hypothalamus is located inferior to the thalamus and plays a major role in regulation of emotion, homeostasis, circadian rhythms, and ANS function. Most importantly, it controls hormone release in the pituitary gland via two separate pathways. Large hypothalamic neurons in the supraoptic and paraventricular nuclei project their axons via the pituitary stalk into the posterior pituitary lobe (neurohypophysis), where they release antidiuretic hormone (ADH) and oxytocin directly into the bloodstream. ADH promotes water reabsorption in the kidney, whereas oxytocin participates in parturition and milk secretion. Damage to the posterior pituitary produces diabetes insipidus. Hypothalamic projections into the anterior pituitary (adenohypophysis) also travel down the pituitary stalk and release a multitude of release-promoting or release-inhibiting factors into the pituitary portal vein.[40] These factors then control the release of all anterior pituitary hormones, including adrenocorticotropic hormone, thyroid stimulating hormone, growth hormone, prolactin, and luteinizing/follicle-stimulating hormone. Of these, only prolactin release is constitutively inhibited by the hypothalamus, while the release of all remaining pituitary hormones is under positive control. Thus, transection of the pituitary stalk, as can occur during skull base and pituitary surgery,[51] results in panhypopituitary syndrome characterized by diabetes insipidus, hypothyroidism, cortisol deficiency, and hyperprolactinemia.

Damage to hypothalamic nuclei, in addition to disrupting control of the pituitary gland, also results in emotional lability, aggression, and extreme overeating or anorexia leading to rapid weight gain or loss, respectively. Thus overwhelming aggression combined with acute weight changes should raise suspicion for a hypothalamic tumor in a child.

Basal Ganglia

The basal ganglia are a set of deep nuclei that reside below the surface of the cerebral cortex and surround the thalamus. They are comprised of the caudate, putamen, and globus pallidus, as well as by the substantia nigra and the subthalamic nucleus. The caudate receives most of its input from the prefrontal cortex and projects via the globus pallidus and thalamus back to the prefrontal cortex. It is thus involved with cognitive function, and tends to be one of the nuclei that degenerate slowly over time after a hypoxic-ischemic insult to the cortex. The putamen receives most of its input from the somatosensory and motor cortices, and, like the caudate, projects back to these cortices via the globus pallidus and thalamus. The putamen plays a major role in coordination of motor function. The globus pallidus serves as an inhibitory modulator in the cortex–basal ganglia–thalamus–cortex loop. Hence, deep brain stimulation in the globus pallidus in patients with Parkinson's disease results in resolution of motor symptoms attributable to hyperactivity in the loop, such as tremor and rigidity. The substantia nigra contains dopaminergic neurons that project to the other nuclei in the basal ganglia and participate in initiation and coordination of voluntary movement.

The basal ganglia are the site of injury in multiple processes in pediatrics. They are often injured by hypoxia and hypoglycemia due to interruption of energy supply. Similarly, carbon monoxide poisoning effectively prevents oxygen delivery to the basal ganglia, resulting in characteristic neuroradiologic findings.[52] A number of metabolic diseases, including methylmalonic acidemia, Leigh disease, maple syrup urine disease, and glutaric acidemia type II also result in degeneration in the basal ganglia. The basal ganglia accumulate iron and copper, and consequently can be injured by iron overload or in Wilson disease. Finally, a juvenile form of Huntington disease presents with characteristic degeneration in the caudate nucleus.[52] Clinical signs of injury to the basal ganglia are often nonspecific: lethargy, irritability, and decreased mental status. Movement disorders such as dystonia or chorea can be seen early in the course of injury but are relatively uncommon, being more likely to emerge with chronic deterioration in basal ganglia function.

Cerebral Hemispheres

The cerebral hemispheres are the most rostral part of the CNS, and in humans and some other mammals, are characterized by extensive folding of the cerebral cortex. The folding greatly expands the area of the cerebral cortex that can fit into the cranial vault. In humans, the cortical sheet has an area of 2.5 square feet when all the folds are flattened, yet the surface area of the adult skull is closer to 0.5 square feet. The folds consist of ridges termed gyri (singular, *gyrus*), and spaces separating the ridges termed sulci (singular, *sulcus*). Although the detailed organization of each gyrus and sulcus is quite individualized, the larger organizational features are common to all mammals.

Each cerebral hemisphere is divided into four lobes: frontal, parietal, temporal, and occipital (Figure 57-3). The frontal lobe extends caudally from the rostral pole of the brain to the central sulcus and inferolaterally to the lateral sulcus. The

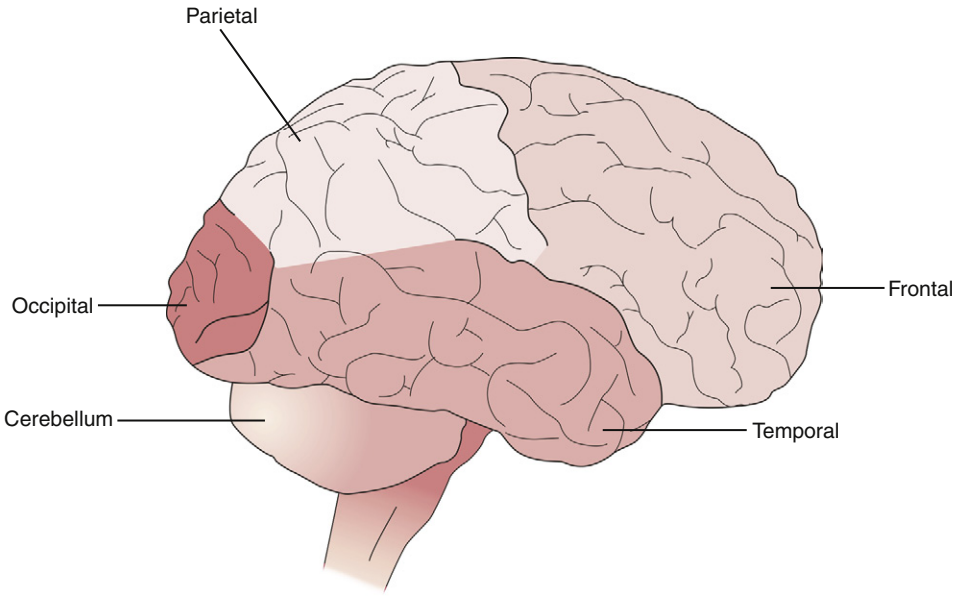

Figure 57–3. General subdivisions of the human cerebral cortex. Note that the cerebellum is not part of the cortex but is labeled for clarity.

parietal lobe begins at the central sulcus and extends caudally to the parietooccipital sulcus. Inferolaterally, the parietal lobe is bounded by the lateral sulcus and the imaginary line connecting the extension of the lateral sulcus with the parietooccipital sulcus. The temporal lobe is delineated primarily by the lateral sulcus. Finally, the occipital lobe resides posteriorly to the parietooccipital sulcus. Each of the four lobes performs dedicated functions, some of which are symmetric, occurring in both hemispheres, whereas others are lateralized, specific to either the right or the left cerebral hemisphere.

The frontal lobe is divided into four cortices, reflecting its functional organization. The primary motor cortex, located on the precentral gyrus, directly controls volitional movement on the contralateral side via upper motoneurons projecting to the lower motoneurons in the spinal cord. Moving rostrally, the premotor cortex is involved in planning, coordination and initiation of movement. The most rostral part of the frontal lobe, the prefrontal cortex, is generally associated with personality and foresight/planning. Additionally, one side of the frontal lobe, usually the left, contains the Broca area on its inferolateral surface. The Broca area participates in the production of spoken and written language.

The parietal lobe contains the primary somatosensory cortex, which is located on the postcentral gyrus and which receives all tactile and proprioceptive sensory information from the contralateral side of the body. The parietal cortex posterior to the primary somatosensory cortex possesses quite lateralized functional areas, with cortex on the left usually involved with language processing and comprehension, and that on the right responsible for perception of space and special orientation. The occipital lobe is generally devoted to vision in humans, containing the primary visual cortex and several secondary visual areas. The temporal lobe, on the other hand, serves more diverse functions. It contains the primary auditory cortex, which receives all auditory stimuli from the periphery. The temporal lobe also encompasses the hippocampus and the limbic system, thus participating in learning, memory, and emotion.

Peripheral Nervous System

The peripheral nervous system is generally divided into two components: the somatic PNS, which includes the peripheral nerves carrying information to and from muscle and skin, and the visceral (or autonomic) PNS, which regulates homeostatic bodily functions and mainly innervates visceral organs such as the heart, lungs, and intestines. Dysfunction of both the somatic and the autonomic systems contributes to the breadth of pathology encountered in pediatric critical care medicine, thus requiring the pediatric intensivist to be familiar with the basic organizational and functional principles of the PNS.

Somatic Peripheral Nervous System

The somatic PNS consists of efferent nerve fibers carrying information to muscle and skin, peripheral sensory receptors, and afferent nerve fibers carrying information from the periphery to the CNS. The efferent fibers emerge from neurons located in the spinal gray matter and exit the spinal cord via the ventral root. The afferent sensory fibers belong to neurons located in dorsal root ganglia, which send an axonal branch into the spinal cord via the dorsal root. The efferent and the afferent fibers travel together between the dorsal root ganglia and the target organ in the peripheral nerve. Diseases of the somatic PNS relevant to pediatric intensive care are generally disorders of myelination, such as Guillain-Barré syndrome, and are discussed in detail in Chapter 64).

Visceral or Autonomic Peripheral Nervous System

The autonomic nervous system regulates bodily functions that do not necessarily require conscious control or awareness, such as heart rate, blood pressure, sphincter function, and digestion. The ANS is divided into three distinct components: the enteric, parasympathetic, and sympathetic nervous systems. The enteric nervous system consists of the myenteric plexus of Auerbach and the submucosal plexus of Meissner,

both located in the wall of the alimentary canal. The enteric nervous system interacts with the CNS and the parasympathetic and sympathetic components of the ANS but can function entirely independently. It is responsible for sensation and coordination of peristalsis in the gut. Neurons in the enteric nervous system arise from the same progenitors as neurons in the CNS. Hence, many neurologic disorders concomitantly affect both the central and the enteric nervous systems, including irritable bowel syndrome, anxiety, and depression.[53]

Sympathetic Nervous System

The sympathetic nervous system consists of preganglionic and postganglionic components. Preganglionic fibers originate from neurons in the thoracolumbar region of the spinal cord, giving the sympathetic ANS its anatomic name: the thoracolumbar outflow. Preganglionic fibers exit the spinal cord via the ventral roots with the thoracic and lumbar nerves. After traveling together for a short distance, the preganglionic fibers diverge from the spinal nerves and enter the sympathetic ganglia via the white communicating rami (preganglionic fibers are thinly myelinated; hence, white). The preganglionic fibers carrying output to the head, thorax, and limbs synapse onto neurons in sympathetic ganglia located close to the spinal cord. These ganglia form the paravertebral sympathetic chain that extends from the cervix to the coccyx. The preganglionic fibers carrying output to the abdominal and pelvic viscera synapse onto cells located in sympathetic ganglia further away from the spinal cord, called the prevertebral ganglia. These include the celiac, the superior mesenteric, and the inferior mesenteric ganglia. Postganglionic neurons from either the paravertebral or prevertebral ganglia send their fibers to the target organs via the gray communicating rami (postganglionic fibers are unmyelinated, and, hence, gray). In the sympathetic ANS, preganglionic neurons use acetylcholine as a neurotransmitter, whereas postganglionic neurons utilize norepinephrine at the target organs. The exception is the sweat glands, which receive postganglionic sympathetic fibers utilizing acetylcholine.[40]

The sympathetic ANS generally functions to prepare the body for states of increased energy expenditure. Activation of the sympathetic ANS leads to increased heart rate, decreased peristalsis, redistribution of blood from the gut to the peripheral muscles, and pupillary dilatation (mydriasis). Furthermore, the sympathetic ANS directly innervates the adrenal medulla, and when activated, stimulates the medulla to release norepinephrine and epinephrine into the systemic circulation. Systemic catecholamine release produces relatively global and long-lasting effects. In critical care, a significant component of vasopressor support relies on mimicking the effect of sympathetic ANS activation with exogenously administered epinephrine and norepinephrine.

Although autonomous, the sympathetic nervous system is under significant central control. Interruption of the descending control pathways, such as occurs with spinal cord trauma above the level of T1, results in sudden loss of sympathetic tone, causing profound bradycardia and hypotension. This syndrome, termed neurogenic or spinal shock, emerges early after injury and requires aggressive pharmacologic intervention in order to minimize secondary insults resulting from hypoperfusion of the injured spinal cord.[54,55]

Parasympathetic Autonomic Nervous System

The preganglionic fibers of the parasympathetic ANS originate in the brainstem and sacral spinal cord. Hence, the parasympathetic ANS comprises the craniosacral outflow. The brainstem preganglionic fibers travel along cranial nerves III, VII, IX, and X, while the sacral preganglionic fibers travel with the pelvic splanchnic nerves. Parasympathetic ganglia are located close to their targets, unlike the ganglia in the sympathetic ANS. The parasympathetic ANS, also unlike its sympathetic counterpart, utilizes acetylcholine as a neurotransmitter both in presynaptic and postganglionic neurons. Target organs for the cranial portion of the parasympathetic ANS include the ciliary muscle and pupillary sphincter, innervated by CNIII via the ciliary ganglion; lacrimal and salivary glands; as well as the majority of thoracic and abdominal organs innervated by the vagus nerve (CNX). The sacral portion innervates the bladder and genitalia.

The parasympathetic system, in general, exerts effects opposite to those of the sympathetic ANS. Thus ACh release from parasympathetic fibers causes bradycardia, hypotension, increased gastrointestinal motility, and pupillary constriction. In critical care, atropine, a competitive antagonist of the muscarinic ACh receptor, is used to prevent or treat bradycardia associated with poor perfusion.[56]

Meninges

The CNS is protected by three membranous layers, which anchor the brain within the skull, contain CSF, and form the anatomic basis of the cerebral venous sinuses. From the outside in, these are the dura mater, arachnoid, and pia mater. Dura mater, often simply called dura, is physically the most substantial of the three membranes and is called the pachymeninx. The arachnoid and the pia together are referred to as leptomeninges. The dura attaches firmly to the inner surface of the skull and arachnoid. Under normal circumstances, no open space exists either between the dura and the skull (the epidural space) or between the dura and the arachnoid (the subdural space). Under pathologic conditions, however, blood can dissect the epidural and/or the subdural potential spaces to form potentially life-threatening hematomas. The dura's blood supply is provided by the middle meningeal artery, which traverses between the skull and the outer dural surface. Trauma to the skull and the middle meningeal artery can lead to an epidural hematoma. The dura also forms the cerebral venous sinuses into which cerebral veins drain. Rupture of the veins as they leave the brain and enter the venous sinuses can lead to a subdural hematoma.

The arachnoid membrane is significantly thinner than the dura, consisting of several cell layers and a spider web–like collagen network. Whereas it adheres to the dura on the outer surface, on the inner surface it is connected to the pia via thin strands of connective tissue called arachnoid trabeculae. The space between the arachnoid and the pia (subarachnoid space) forms the only true fluid-filled space around the brain, containing CSF, and forming the basis for CSF cisterns throughout the CNS. CSF from the subarachnoid space returns to the venous circulation via special adaptations in the arachnoid membrane called the arachnoid villi. Arachnoid villi protrude from the arachnoid into the dural venous sinuses and contain

special channels that allow the CSF to flow out of the subarachnoid space into the venous blood. Additionally, cerebral arteries and veins run in the subarachnoid space before diving below the brain surface. Hence, injury to these vessels results in subarachnoid hemorrhage.

The pia mater is the most delicate of the three membranes. Unlike the dura and the arachnoid, it follows the surface of the brain, diving into every sulcus and following blood vessels for some distance as they enter the brain. Around these blood vessels, it gives rise to potential perivascular spaces called the Virchow-Robin spaces that serve as a significant reservoir of malignant cells in pediatric leukemia and lymphoma, necessitating CNS irradiation and chemoprophylaxis.

Blood-Brain Barrier

Anatomy

Two experiments more than 100 years ago demonstrated conclusively the presence of a physical barrier between circulating blood and the brain. In 1885, Ehrlich injected a dye intravenously to show that the dye failed to stain the brain while staining almost all other internal organs.[57] In 1909, Goldman conducted the reverse experiment, injecting dye into the CSF to show that the dye stained the brain but did not penetrate into the general circulation.[58] Modern anatomical studies revealed that, actually, three physical barriers separate the blood and the brain: the BBB, established by the endothelial capillary cells in the brain; the blood-CSF barrier (BCSFB), established by cells in the choroid plexus; and finally, the CSF-brain barrier, comprised of ependymal cells lining the surface of the ventricles. All three systems shield the brain from changes in ionic and biochemical milieu that may jeopardize neuronal function, and all three are important for accomplishing drug transport into and out of the brain parenchyma.[59] However, from the standpoint of clinical relevance to pediatric critical care medicine, the subsequent discussion will focus primarily on the BBB and BCSFB.

The cellular component of the BBB in mammals comprises specialized endothelial cells in brain capillaries, pericytes, and foot processes of brain astrocytes as well as neurons (Figure 57-4). Endothelial cells in the brain are linked together by tight junctions, which prevent paracellular diffusion of substances from blood into the brain. The endothelial tight junctions in the brain possess extremely high electrical resistance, resulting in the exclusion of even small ions such as K^+ and Na^+.[60] In addition, the absence of fenestrations, high metabolic rate, and low vesicular transport in endothelial cells severely limit transcellular diffusion of water-soluble substances through the cell membrane. Pericytes surround the endothelial cells and display both contractile and phagocytic properties. Their presence likely contributes to the impermeability of the endothelial tight junctions, as well as to blood vessel reactivity[61] and vessel wall elastic properties in the brain.[62] Pericytes in turn are ensheathed by perivascular astrocytes,which extend cellular processes, known as "end feet," toward the brain vasculature.[60] The astrocytes are critical for the proper development of the brain-specific phenotype of endothelial cells comprising the BBB.[63] Finally, neurons have been shown to innervate the brain capillary endothelial cells directly, although their exact role in BBB function remains unknown.[64]

In addition to the cellular components, the BBB also contains two distinct and important acellular components: the basement membrane and the extracellular matrix. At present, the role of the extracellular matrix in maintaining or establishing the BBB is unknown. The role of the basement membrane, on the other hand, is better characterized. The basement membrane surrounding small draining venules consists of the endothelial layer, immediately adjacent to the brain capillary endothelium, and the parenchymal layer, which is adjacent to astrocyte end feet. Interposed between the two basement membranes is a layer of meningeal epithelium. Around the capillaries, however, the meningeal epithelium disappears, and the two layers of the basement membrane fuse to form a composite structure.[60] The basement membrane generally consists of four major types of glycoproteins: collagen type IV, laminin, nidogen, and heparan sulfate proteoglycan.

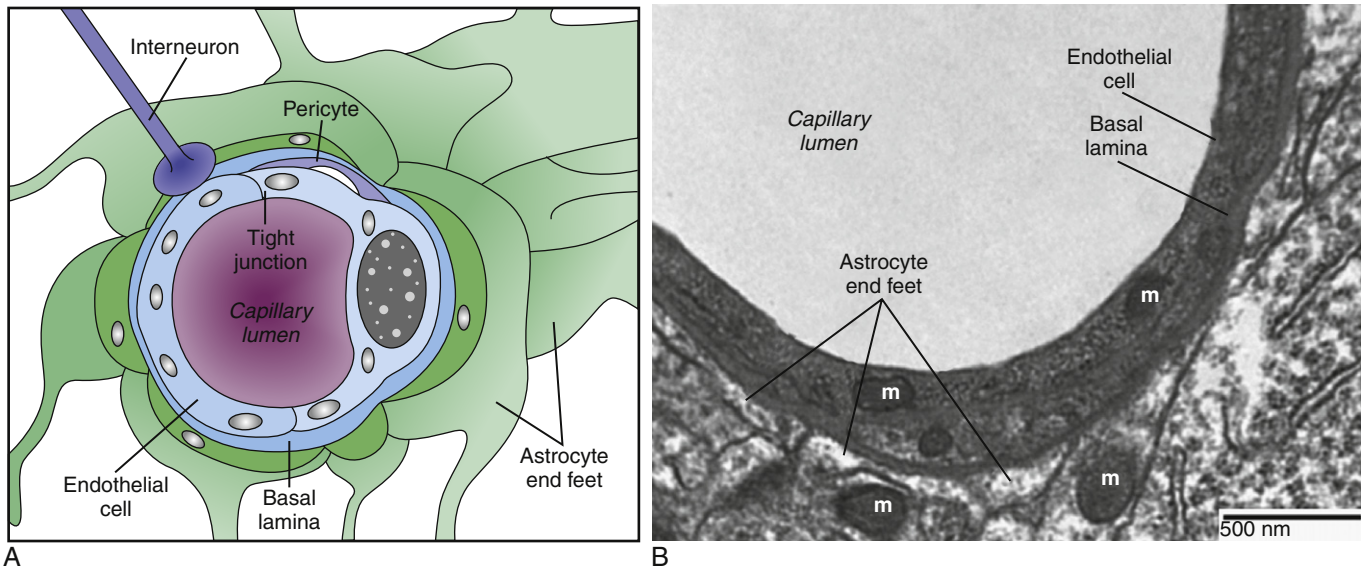

Figure 57–4. **A,** Schematic representation of the major anatomic features contributing to the BBB. It should be noted that endothelial cells surrounding the capillary are linked by tight junctions. **B,** An electron micrograph from mouse brain showing a brain capillary in cross-section. The BBB is an active structure, with high energy demands. Hence, BBB endothelial cells and astrocytes possess a large number of mitochondria (*m*).

The clinical relevance of these proteins, although not fully understood at this time, is underscored by mutations in collagen type IV that result in intracerebral hemorrhage and porencephaly in rodents and in humans.[65,66]

Selectivity

If the BBB limits the penetration of substances into the CSF, then how is transport of energy sources, signaling molecules, and drugs from blood into the CSF accomplished? Three general transport mechanisms allow chemicals to penetrate from the circulation into the CSF: (1) diffusion of lipid-soluble molecules; (2) receptor-facilitated transport, either energy-dependent or independent; and (3) ion channel-mediated transport. Additionally, several groups of transporters are dedicated to actively pumping substances out of CSF into the circulation.

As a general rule, lipid-soluble substances penetrate into CSF by diffusing across the endothelial plasma membrane, whereas water-soluble substances require active transport to cross the BBB. This property is illustrated by Figure 57-5, which demonstrates uptake of substances into the brain as a function of their oil-water partition coefficient. Compounds such as benzodiazepines, nicotine, and heroin are highly lipid-soluble and penetrate readily into the CSF. The synthetic opiate fentanyl induces the narcotic effect more rapidly than morphine because fentanyl is more lipophilic. The concentration of a lipophilic substance in the CSF is generally directly proportional to its concentration in the plasma. In contrast, mannitol and sodium ions are extremely water-soluble, do not penetrate into the CSF across the intact BBB, and are thus used clinically to increase serum osmolality relative to that of CSF and to draw water out of the brain in order to decrease ICP. Lipophilic substances with a significant protein-bound fraction (e.g., phenytoin) constitute an exception to the generalization that lipid-solubility and plasma concentration determine CSF concentration. Consequently, in the case of phenytoin and its commonly used prodrug fosphenytoin, therapeutic levels are determined by plasma, or free, concentration, rather than the total concentration, which includes the protein-bound fraction.

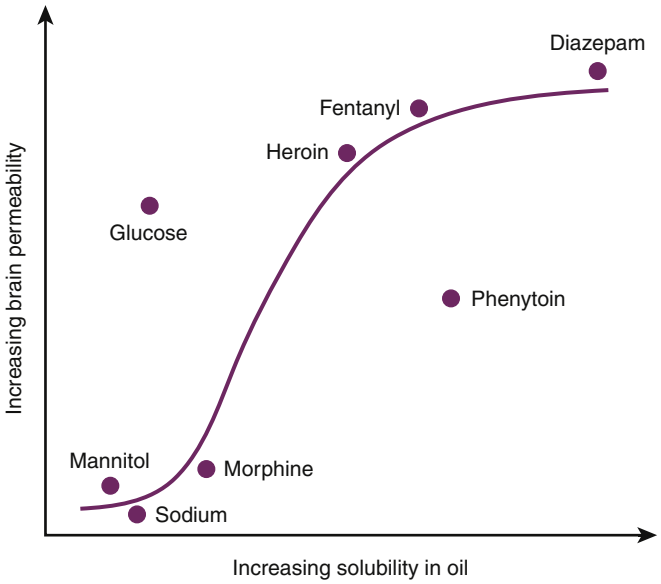

Figure 57–5. Lipid solubility predicts penetration across the blood-brain barrier (*BBB*). Substances to the left of the curve, such as glucose, cross the BBB at a higher rate than would be predicted on the basis of their oil solubility. These substances are transported by carriers across the BBB via either an energy-dependent or energy-independent process. In contrast, substances to the right of the curve, such as phenytoin, are highly lipid-soluble but are transported across the BBB out of the brain milieu. *(Adapted from Laterra J, Goldstein GW: Ventricular organization of cerebrospinal fluid: blood-brain barrier, brain edema, and hydrocephalus. In Kandel ER, Schwartz JH, Jessel TM, editors:* Principles of neural science, *New York, 2000, McGraw-Hill.)*

Receptor-facilitated transport across the BBB can be grouped into processes that require energy and those that do not. The best studied and perhaps most clinically relevant example of receptor-facilitated energy-independent transport is delivery of glucose from plasma into the CSF by the GLUT1 transporter. GLUT1 is a 492 amino-acid membrane protein that resides both on the luminal (facing the plasma) and the abluminal (facing the CSF) surfaces of the endothelial plasma membrane.[67] GLUT1 transports glucose down the concentration gradient, and can function in a bidirectional manner. The flow of glucose from plasma into the CSF, rather than in the opposite direction, is ensured by 1) higher plasma glucose concentration (approx 3:2 of CSF); 2) high glucose utilization rate by neurons and glia in the CNS such that glucose delivered into the CSF is exhausted rather quickly; and 3) higher density of GLUT1 transporters on the abluminal surface compared to the luminal surface.[68] In addition, metabolic factors such as hypoxia and ischemia exert transcriptional control over expression and distribution of the GLUT1 transporter, suggesting the existence of tightly-controlled mechanisms regulating glucose delivery into the CSF under stressful conditions. Recently, a disorder characterized by GLUT1 deficiency has been recognized in a subset of infants with developmental delay, intractable epilepsy, and delayed myelination.[69] Identification of the molecular underpinning of this disorder was driven by the clinical finding of low CSF glucose concentration (hypoglycorrhachia) on repeated lumbar punctures despite normal plasma glucose concentrations in two original patients from the study, highlighting the importance of biochemical BBB function.

While the energy-independent GLUT1 plays an important role in delivering its substrate down the concentration gradient into the CSF, energy-dependent transporters of the ATP-binding cassette (ABC) family function primarily to pump substances against the concentration gradient out of the CSF into plasma.[70] The ABC family of transporters is divided into seven known groups (A through G), of which groups B, C, and G are highly expressed on BBB endothelial cells. The best-described members of this family include the multidrug resistance (MDR) proteins, such as the P-glycoprotein (PgP), and the multidrug resistance-associated proteins (MRP). Human PgP transports a wide range of chemically and structurally diverse substances out of the CSF, including dexamethasone, phenytoin, ondansetron, and chemotherapeutic agents such as etoposide and vincristine.[70] MRPs also contribute to the ATP-dependent efflux of drugs such as 6-mercaptopurine, methotrexate, and, interestingly, pravastatin. The latter belongs to a class of drugs, hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, that confer protective effects in experimental models of ischemic and traumatic brain injury[71,72] and reduce stroke risk in humans by approximately 30%, to some extent independent of the reduction in cholesterol levels.[73] Thus, increasing the intracerebral levels of HMG-CoA reductase inhibitors via reduction in MRP-dependent efflux may represent a therapeutic strategy aimed at ameliorating

the effect of trauma and hypoxia on the brain parenchyma. Indeed, the general strategy of inhibiting MDR and MRP transporters to enhance drug delivery into the CNS is currently being tested in several clinical trials.

Blood-Brain Barrier–Deficient Areas

Several areas of the brain have special adaptations in the structure of the BBB that allow the CNS control centers to monitor and interact with the rest of the body. These include the posterior pituitary, the subfornical organ, and the area postrema; in all of these areas, capillaries contain fenestrations, and the BBB is quite leaky. The posterior pituitary contains projections of the hypothalamic vasopressin-containing secretory neurons. When salt concentration increases during volume depletion, these neurons are stimulated to release vasopressin (ADH) directly into the bloodstream, leading to increased water retention in the renal tubules and restoration of intravascular volume. The subfornical organ, located at the foramen of Monro on the ventral surface of the fornix, is also involved in maintaining salt-water homeostasis. Angiotensin II production during states of decreased renal perfusion is detected by neurons in the subfornical organ, which then stimulate vasopressin-containing neurons to release vasopressin and also stimulate neurons in the lateral hypothalamus to create an overwhelming sensation of thirst. Finally, neurons in the area postrema are exposed to toxins circulating in the plasma, and stimulate the vomiting reflex. Drugs such as ondansetron are thought to prevent nausea and vomiting by blocking serotonin receptors in the area postrema. All brain regions with a leaky BBB are surrounded by specialized cells, called tanycytes. Tanycytes are connected by tight junctions that prevent uncontrolled diffusion of substances out of these homeostatic brain regions into the rest of the CSF.

Ventricles and Cerebrospinal Fluid

Ventricular system

The ventricular system arises from the hollow space within the developing neural tube and gives rise to cisterns within the CNS, from the brain to the spinal cord. In the brain, the ventricular system consists of paired lateral ventricles that connect to the midline third ventricle via bilateral foramina of Monro. The third ventricle in turn connects to the fourth ventricle located in the pons and the medulla via the aqueduct of Sylvius. The fourth ventricle terminates caudally in the central spinal canal, and continues as a miniscule midline structure through the spinal cord. The ventricles contain the choroid plexus, which produces CSF, and serve as conduits for CSF flow in the CNS. Ventricular walls are lined with ependymal cells, which are connected by tight junctions and constitute a CSF-brain barrier.

Cerebrospinal Fluid Production and Flow

CSF is produced both by the choroid epithelial cells and by the brain parenchyma, with each system contributing approximately 50 percent to new CSF production. CSF produced by the choroid plexus flows directly into the ventricles, whereas CSF produced by the brain parenchyma must cross the ependymal lining to reach the ventricular system. CSF in humans is produced at a rate of 350 μL/min, resulting in total daily CSF production of approximately 500 mL. Daily CSF production rates, when taken in context of the ventricular volume (30 mL in adults) and of the total CSF volume present in the CNS at any given time (130 mL in adults), indicate that CSF circulates out of the ventricular system where it is produced and that CSF is continuously reabsorbed.

CSF flows via foramina of Monro out of the lateral ventricles into the third ventricle, and then via the aqueduct of Sylvius into the fourth ventricle. The former two are closed systems, whereas the latter, the fourth ventricle, has three openings that connect the ventricular space with the subarachnoid space. The midline median aperture (foramen of Magendie) and the paired lateral apertures (foramina of Luschka) connect the fourth ventricle with the cisterna magna and the pontine cistern, respectively. Thus, out of the fourth ventricle, CSF flows into the subarachnoid space surrounding the brain and the spinal cord. CSF is then reabsorbed by the arachnoid villi into the superior sagittal venous sinus (Figure 57-6). Knowledge of CSF flow and reabsorption patterns allows for prediction of pathologic findings when either process is interrupted. Obstruction to CSF outflow at any point in the pathway, such as often occurs with tumors, or abnormal CSF reabsorption, such as seen in meningitis or hemorrhage due to cellular debris blocking the arachnoid villi, results in intraventricular CSF accumulation and hydrocephalus. Hydrocephalus may then lead to increased ICP and cerebral herniation, either spontaneous or iatrogenic, for example when a lumbar puncture is performed on a patient with obstruction above the level of the foramen magnum.

Cerebrospinal Fluid Composition and Function

Cells in the choroid plexus actively secrete CSF from the plasma that filters through leaky choroid plexus capillaries. The process is controlled by multiple mechanisms, resulting in CSF ionic, chemical, and cellular composition that is distinct from blood and plasma. In general, CSF contains higher magnesium and chloride concentrations and lower potassium and calcium concentrations compared with plasma. Glucose concentrations in CSF are approximately two thirds of plasma levels. CSF has very few cells and a constant protein level. As is well known, these constituents are disrupted in disease. In bacterial meningitis, glucose concentrations are lower than expected and protein concentration is increased. In contrast, in viral meningitis, CSF glucose is usually normal while protein concentration is increased. More recently, levels of various cytokines and proteins leaked from neurons and myelin sheaths have been explored as potential biomarkers of the severity and type of brain injury.[74]

The primary purpose of the CSF is to provide a supportive buoyant environment for the brain. The human brain has the consistency of an incompletely hardened bowl of gelatin. Without the CSF, the human brain flattens significantly under the force of gravity, whereas, suspended in CSF, it retains its native shape. Furthermore, CSF provides a fluid cushion against acceleration-deceleration insults that may be delivered to the brain by the surrounding skull. CSF also functions both as a source of nutrients and a relatively large-volume sink for waste and toxic substances produced in the course of normal neuronal activity. For instance, excess glutamate released at

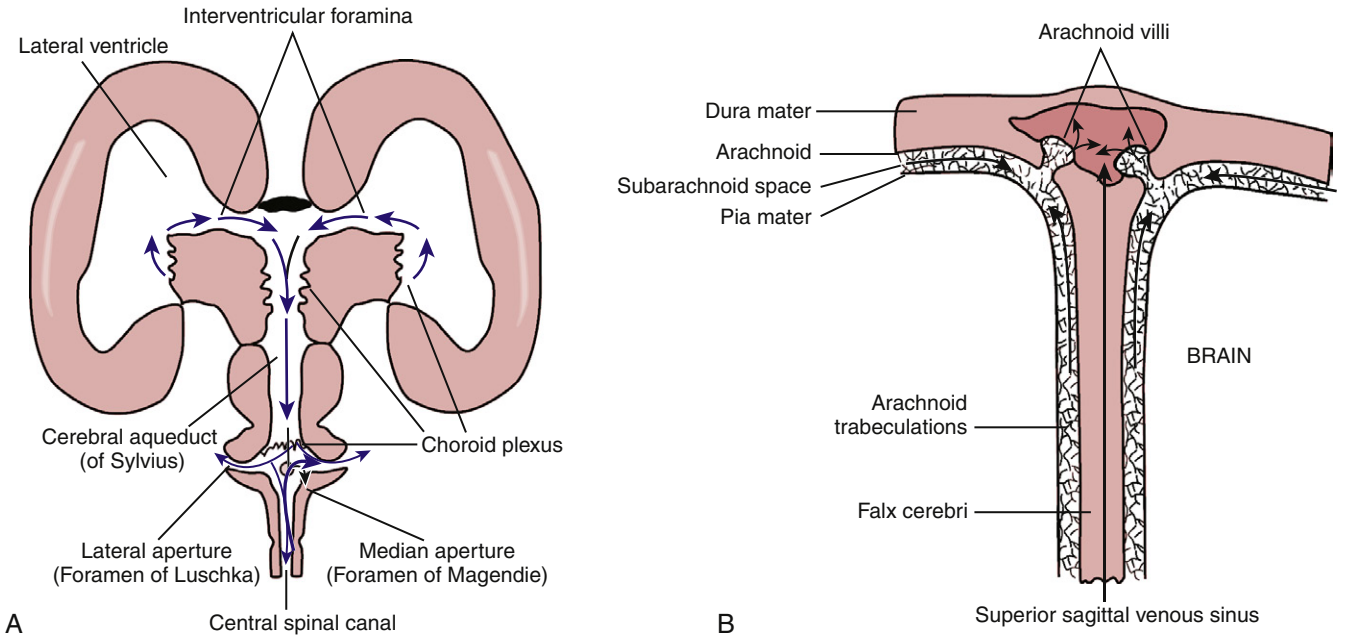

Figure 57–6. The ventricles and CSF flow. **A**, Flow of CSF from choroid plexus through the ventricular system into the subarachnoid space. Note that a portion of the CSF circulating into the distal spinal cord returns to the fourth ventricle. **B**, Schematic representation of CSF absorption from the subarachnoid space into the cerebral venous sinus system.

the synapse rapidly diffuses into the CSF, minimizing potential excitotoxicity to both presynaptic and postsynaptic neurons. Excess magnesium ions in the CSF may also participate in the Mg^{2+} block at the NMDA receptors (see section on glutamate receptors), allowing for coincidence detection and learning.

Vasculature in the Central Nervous System

Brain Vasculature

The arterial blood supply to the brain is traditionally divided into an anterior portion supplied by the paired internal carotid arteries and the posterior portion supplied by the paired vertebral arteries. The anterior and posterior arterial circulations are interconnected at the base of the brain via circle of Willis.

The internal carotid artery originates from the common carotid artery at approximately the level of angle of the jaw in humans. It enters the skull through the carotid canal anterior to the jugular foramen, takes a relatively standard but tortuous course through the temporal bone and the cavernous sinus, and then enters the dura mater above the sinus, running horizontally inferolateral to the optic nerve. At this point, it gives off the ophthalmic artery, and a short distance later, the anterior choroidal artery and the posterior communicating artery. The former supplies several clinically relevant structures, including parts of the thalamus, hippocampus, optic tract and the internal capsule. The latter, the posterior communicating artery, forms part of the circle of Willis and connects the anterior internal carotid circulation with the posterior vertebral circulation. After generating the posterior communicating artery, the internal carotid bifurcates into major vessels supplying the brain: the anterior and middle cerebral arteries (ACA and MCA, respectively).

The bilateral ACAs connect via the anterior communicating artery at the circle of Willis. Both ACAs then run along the medial surface of the brain and supply the corpus callosum and the medial portions of the cerebral cortex on their respective sides, extending up to and including the postcentral gyrus. Thus ACA occlusion results in damage (among other areas) to the medial portions of the primary sensory and motor cortices, which correspond to the more caudal parts of the human body, such as legs, trunk, and shoulders.

While the ACA supplies blood to the medial cerebral cortex, the MCA provides blood flow to almost the entire lateral portion of the cortex. After diverging from the internal carotid artery, the MCA dives deep into the Sylvian fissure, where it supplies the insula. In addition, within the Sylvian fissure, the MCA gives off small lenticulostriate arteries that supply the thalamus and the basal ganglia. The MCA then emerges from the Sylvian fissure and divides into multiple branches responsible for nourishing the lateral components of the frontal, temporal, and parietal lobes. MCA occlusion secondary to ischemic stroke generally results in devastating neurologic deficits. Additionally, in cases of globally decreased perfusion such as seen during cardiac arrest or prolonged hypotension, the border (watershed) zone between the cortical areas supplied by the ACA and the MCA tend to be vulnerable to early injury.

The posterior circulation arises from the paired vertebral arteries, each of which gives rise to a posterior inferior cerebellar artery (PICA) before coalescing into a single basilar artery at the level of the junction between the medulla and the pons. The PICAs supply the inferior portion of the cerebellum as well as the choroid plexus in the fourth ventricle and the lateral medulla. The basilar artery proceeds rostrally and gives rise to the paired anterior inferior cerebellar and superior cerebellar arteries (AICA and SCA, respectively). At the level of the midbrain, the basilar artery bifurcates into the posterior cerebral arteries (PCA), which supply the occipital lobes and portions of the temporal lobes. In addition, the PCAs nourish

a number of thalamic sensory nuclei. Each PCA is connected to the ipsilateral internal carotid artery by the posterior communicating artery. Since the PCA supplies the areas of the thalamus concerned with sensation and cortical areas dedicated to vision, PCA occlusion often results in sensory and/or visual loss on the side contralateral to injury.

Spinal Cord Vasculature

The spinal cord is supplied by two interconnected arterial systems: the longitudinal vasculature that arises from the vertebral arteries and the segmental vasculature that arises from multiple levels along the vertebral arteries and the aorta. The longitudinal arteries consist of a single anterior spinal artery and paired posterior spinal arteries. The anterior spinal artery runs along the anterior median fissure and supplies the ventral two thirds of the spinal cord. Occlusion of the anterior spinal artery, which can occur with traumatic dissection or autoimmune arteritis, results in the anterior spinal syndrome, or Beck syndrome. Beck syndrome is characterized by symmetric weakness and loss of temperature and pain sensation with relative sparing of vibration and position sensation below the level of injury. The paired posterior spinal arteries run along the dorsal columns and supply blood to the posterior one third of the spinal cord, which includes the dorsal columns and most of the dorsal horns. Posterior spinal arteries are extensively interconnected and receive blood supply from multiple segmental arteries along their course. Thus, isolated lesions due to posterior spinal artery occlusion are rare.

The segmental arterial blood supply to the cervical spinal cord arises from the vertebral arteries via the radicular arteries, whereas that to the thoracic and lumbar spinal cord arises from the aorta via the thoracic intercostal arteries and the lumbar arteries. Both thoracic and lumbar segmental arteries give rise to smaller radicular arteries that penetrate the intervertebral foramina and supply the spinal cord. In addition, the lower thoracic aorta often gives rise to a single great radicular artery (artery of Adamkiewicz) that supplies the entire lower two thirds of the spinal column. The artery of Adamkiewicz is often the sole source of blood flow to the lower thoracic spinal cord during surgical repair of coarctation of the aorta. Thus, care is taken to ensure adequate distal perfusion pressure during cross-clamp to minimize the risk of paraplegia. In general, spinal cord watershed areas exist at the upper thoracic (T1-T4) and upper lumbar (L1) levels, where interconnections among the segmental arteries are less developed. At any given level, the interior portion of the spinal cord is most susceptible to hypoxic-ischemic injury. For example, in cases of severe cervical hyperextension, hypoxic and/or vascular injury to the central portion of the cervical spinal cord results in central cord syndrome, characterized by muscle weakness in upper extremities to a greater extent than in lower extremities, by urinary retention, and by variable degree of sensory loss.

Regulation of Cerebral Blood Flow

In healthy mammals, the perfusion of cerebral tissues is exquisitely controlled. Blood flow to the brain, as to many other vital organs, is autoregulated by homeostatic mechanisms designed to maintain adequate perfusion. Cerebral autoregulation occurs on the basis of three primary mechanisms: perfusion pressure-based autoregulation, pH-based (PCO_2-based) autoregulation, and metabolic coupling. All three play a major role in determining cerebral blood flow (CBF) in health and in disease, such as trauma and hypoxia-ischemia.

Perfusion Pressure–Related Autoregulation

Experiments in the mid-twentieth century demonstrated that normal CBF in young adults is 50 to 55 mL/100 g brain/minute, resulting in approximately 750 mL/min total CBF.[75] Thus under resting conditions, the brain receives approximately 15% of total cardiac output. In children, CBF is generally higher than in adults, on the order of 100 mL/100 g brain/min for an 8-year-old child.[76] CBF is kept relatively constant over a range of mean arterial blood pressures (MAP) by continuous adjustment of vascular tone in brain arterioles (Figure 57-7, *A*). In adults, CBF remains essentially invariant while MAP is between 50 and 150 mm Hg. Also in adults, CBF decreases and increases passively as a function of MAP when MAP is below 50 or above 150 mm Hg, respectively. The pressure-dependent autoregulatory range is different in newborns, with important clinical implications. The lower limit of autoregulation in neonates appears similar to that in adults at approximately 40 mm Hg; the upper limit, however, is much lower for infants than adults, with CBF increasing linearly as a function of MAP greater than 90 mm Hg.[77] Since infants have an MAP that is much closer to the lower limit of CBF autoregulation, even moderate hypotension in young children may severely impede oxygen delivery to the brain. Similarly, at the upper limit, moderate hypertension may result in unacceptable increases in CBF and damage to the BBB. One of the many clinical applications of this principle is the need for meticulous control of MAP in infants on cardiopulmonary bypass in order to minimize the risk of intracranial hemorrhage.

Oxygen-Related Autoregulation

CBF generally remains constant while PaO_2 remains over 60 mm Hg. When PaO_2 decreases below this threshold value, CBF increases almost exponentially as a function of PaO_2 (Figure 57-7, *B*). Several distinct pathways contribute mechanistically to oxygen-related regulation of CBF, including hydrogen and potassium ions, nitric oxide, arachidonic acid, adenosine, and ATP-sensitive potassium channels.[78,79] The shape of the PaO_2-CBF curve is explained by the hemoglobin-oxygen dissociation curve and the fact that, in humans, CBF depends on blood oxygen content and not on PaO_2.[80] When PaO_2 is less than 60 mm Hg, the percentage of oxyhemoglobin decreases sharply, significantly decreasing the blood oxygen content. CBF rises as a consequence of decreased oxygen delivery. Conversely, increasing PaO_2 above 60 mm Hg does not significantly increase blood oxygen content since hemoglobin is more than 90% saturated with oxygen at these partial pressures. Hence, in healthy people, CBF remains constant once PaO_2 crosses the threshold of 60 mm Hg.[81] Furthermore, when inspired oxygen fraction is increased further from 21% to 100%, CBF actually decreases by approximately 15% to 20%.[80] Both hypoxia-related vasodilatation and hyperoxia-related vasoconstriction may be impaired under pathologic conditions such as traumatic brain injury and may portend a poorer outcome. Nevertheless, a PaO_2 less than 60 mm Hg should be rigorously avoided in patients with increased ICP lest hypoxia-related vasodilatation further contribute to decreased compliance within the cranial vault.

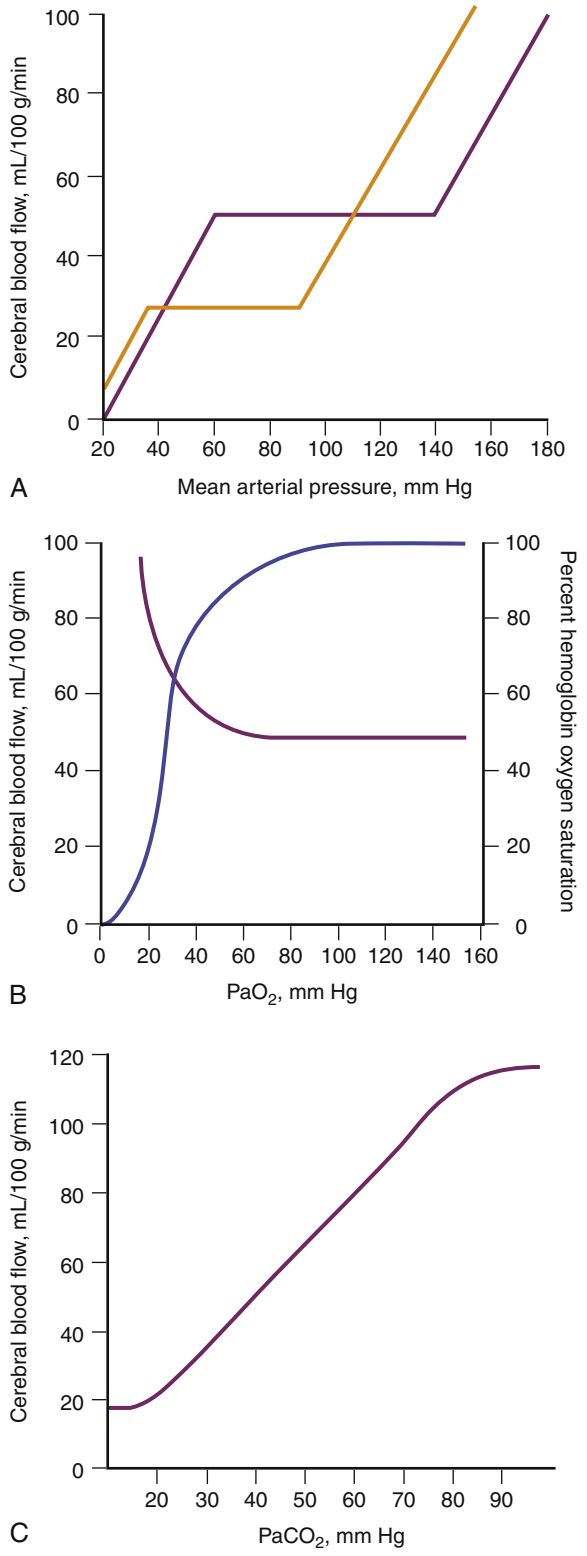

Figure 57–7. Regulation of cerebral blood flow (*CBF*). **A,** Blood pressure–dependent autoregulation, adult (*red curve*) and infant (*orange curve*). **B,** Oxygen-dependent regulation. *Red curve,* CBF (left ordinate); *blue curve,* hemoglobin-oxygen saturation curve (right ordinate). Note that CBF begins to increase at the PaO_2, at which hemoglobin oxygen saturation begins to decrease. Since oxygen delivery is determined by hemoglobin oxygen saturation to a much larger extent than by PaO_2 and dissolved oxygen in the blood, CBF in humans increases in response to decreasing oxygen delivery, which in turn is correlated with decreasing PaO_2. **C,** $PaCO_2$-dependent regulation CBF should increase linearly with $PaCO_2$ except at the extremes of the physiologic range.

Hydrogen Ion–Related Autoregulation

CBF is directly proportional to perivascular pH and, therefore, inversely proportional to the perivascular hydrogen ion concentration. In clinical practice, this relation translates into dependence of CBF on $PaCO_2$, since $PaCO_2$ is related to pH via the bicarbonate buffer system. Within a $PaCO_2$ range from 20 to 100 mm Hg, CBF increases by 2.5% to 4% for every 1 mm Hg increase in $PaCO_2$.[82] No further changes in CBF are observed when $PaCO_2$ is either below 20 mm Hg or above 100 mm Hg (Figure 57-7, *C*). The observed change in CBF in response to change in $PaCO_2$ is relatively transient, lasting hours. Restoration of intracerebral bicarbonate concentration is thought to be responsible for the temporary nature of the CBF response. Therefore, once the brain and the CBF have been "reset" to a new $PaCO_2$, acutely restoring $PaCO_2$ into a physiologically normal range actually results in disruption of the acid-base balance in the brain and may exacerbate injury. As such, chronic hyperventilation is not recommended as a therapy for increased ICP. Nevertheless, hyperventilation with concomitant rapid reduction in $PaCO_2$ remains one of the acute treatments for life-threatening increases in ICP and impending brain herniation.

Metabolic Coupling

Local CBF is coupled to the metabolic tissue demands in a relatively small, circumscribed area, reflecting both neuron- and astrocyte-specific energy needs. At rest, areas with greater energy needs, such as the gray matter, receive a greater proportion of CBF than areas with lesser energy needs, such as the white matter. The metabolic rate can be expressed as either cerebral metabolic rate of glucose (CMRGlu) or cerebral metabolic rate of oxygen ($CMRO_2$). Both CMRGlu and $CMRO_2$ have been correlated with CBF. Under conditions of sensory stimulation, however, the increase in CBF to the cortical sensory areas exceeds the increase in $CMRO_2$, suggesting that neuronal activity itself can influence CBF independent of the metabolic demand.[83] Neuronal activity–dependent increases in CBF forms the presumed basis of functional magnetic resonance imaging, allowing for detailed studies of brain processes in humans.[84] In children, $CMRO_2$ increases until about 14 years of age and then decreases to adult values.[85] Similarly, CMRGlu increases from infancy until around 9 years of age and then decreases until adulthood.[86] The relationship between disturbances in metabolic coupling of CBF and injury is unclear at this time, although emerging evidence indicates occurrence of metabolic crises in the brain after traumatic injury and cardiac arrest.[76] Whether these crises reflect abnormal CBF regulation and predict outcome remains under investigation.

Developmental Processes Relevant to Pediatric Critical Care Medicine

Cell Origin and Differentiation

Neurogenesis and gliogenesis in the human begin well before birth, in the eighth gestational week.[87] Neurons are born in the specialized proliferative zones located next to the lateral ventricles and migrate outwards towards the cortical surface during development. The neurons migrate along a subset of glial cells called the radial glia, that span the distance between

the ventricular zone and the brain surface early in development. The cortex is generated in an inside-out fashion, such that the deeper cortical layers are formed first. Glutamatergic neurons appear to originate in the dorsal aspect of the ventricular zone, whereas GABA-ergic inhibitory interneurons likely come primarily from the ventral aspect. Thus, GABA-ergic neurons have a longer migration path into the cortex than their glutamatergic counterparts, and occasionally must migrate tangentially rather than perpendicular to reach their final destination.[87] The process of establishing cortical layers appears complete in humans by the thirtieth gestational week.[88] Disruption of the radial migration process, due to either genetic or environmental factors, results in lissencephaly and seizures of varying severity.[89]

Synaptogenesis and Synaptic Pruning

By the time of birth in humans, both neurogenesis and neuronal migration have essentially been completed. Thus infants generally have the same neuronal density (number of soma per mm^3) as adults. Yet the human brain undergoes substantial postnatal development, reflected clinically as the maturation of behavioral milestones. The underlying process is evolution of axonal and dendritic processes by neurons in the CNS, together with an explosive increase in the number of synaptic contacts in the brain (Figure 57-8). Neuronal dendritic arbors increase in complexity, developing more branches and sampling a wider physical space during the first 2 years of life.[40] The number of synapses increases from birth until approximately 2 years of age, when it actually surpasses the number of synapses found in the adult brain. From 2 years until early adolescence, neurons the CNS undergo synaptic pruning, or elimination. Both synaptic development and pruning are under exquisite control by genetic and experience-dependent factors. For example, a major CNS abnormality found in individuals with fragile X syndrome, the most common cause of mental retardation, is overproduction and impaired pruning of synapses in cortical neurons.[90] Furthermore, a number of drugs used extensively in the PICU, including benzodiazepines, barbiturates, steroids, and opiates exert a profound effect on synaptogenesis and synaptic function. Steroid use in premature neonates has been associated with worse neurologic outcome,[91] and benzodiazepine use during experience-dependent critical periods in the visual system is associated with premature decline in synaptic plasticity.[92] Thus, the true extent of the interaction between the PICU environment and synaptic organization in the developing brain remains to be fully characterized.

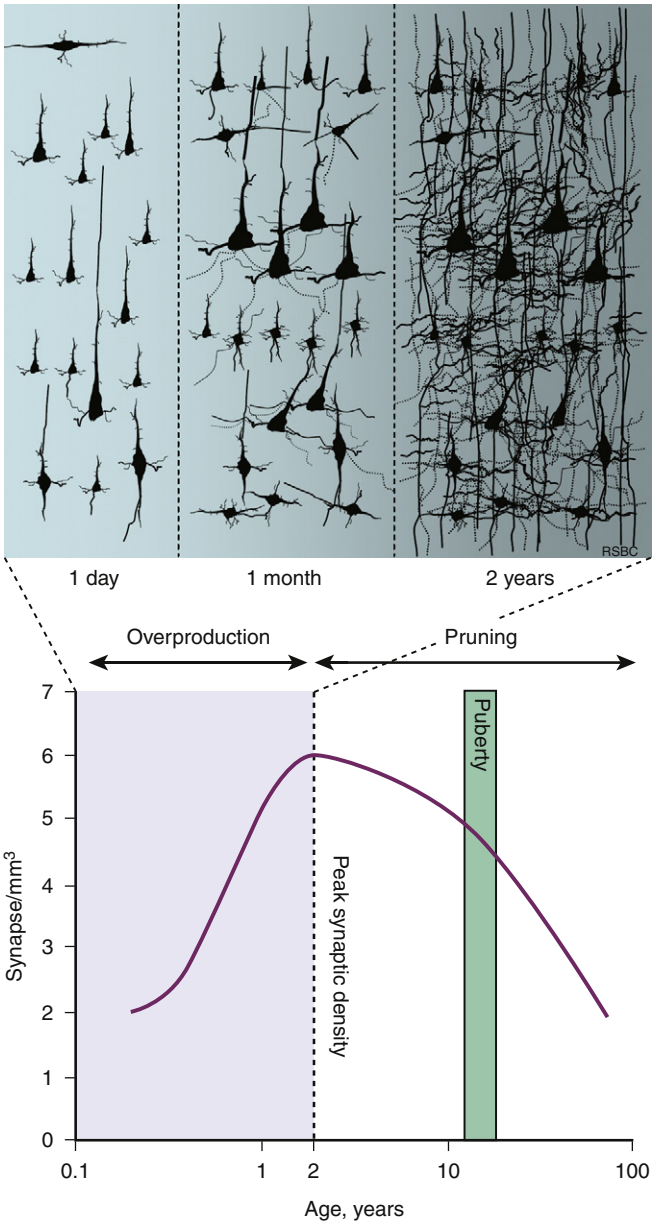

Figure 57–8. Cortical synaptic density and development of axons and dendrites with age. The synapse density is derived from the visual cortex. Note the logarithmic age scale as abscissa. *Top panel* is a schematic representation of synaptogenesis and dendritic arborization and maturation from birth to 2 years of age. *(Modified from Levitt P: Structural and functional maturation of the developing primate brain,* J Pediatr *143:S35-S45, 2003; and Nolte J:* The human brain. An introduction to its functional anatomy, *ed 3, St Louis, 1993, Mosby–Year Book.)*

Neurotransmitter System Maturation

Maturation of the neurotransmitter systems in the human CNS is a complicated and protracted process. It is complicated because each neurotransmitter system matures along its own developmental time course, and because the time course itself may be specific to each brain region. For some neurotransmitters, the process lasts into early adulthood. The complexity of the process is compounded further by the relative lack of human data, requiring extrapolation from animal studies. Nevertheless, some general principles that apply to critically ill children can be derived from the current knowledge.

The earliest neurotransmitter system to become apparent in the cortex is ACh. Thalamic afferent fibers contain AChE, and ACh staining in the cortex coincides with arrival of thalamic input during midgestation.[87,88] Cholinergic innervation in the cortex continues to mature through the third year of life. Development of the GABA-ergic system also begins in midgestation and continues until several months postnatally. GABA receptor α subunits expressed in cortex before birth differ from those expressed after birth.[93] Indeed, in young animals and probably in humans prior to late gestation, GABA is an excitatory neurotransmitter, evoking large depolarizing currents in postsynaptic neurons.[94] The precise significance of GABA as an excitatory neurotransmitter in guiding

organization of neuronal circuits remains to be determined. Development of the glutamatergic system occurs slightly later, with AMPA-type receptors becoming apparent in the basal ganglia in the thirty-second postnatal week. In the cortex, NMDA-type receptors precede the AMPA-type receptors in the course of their appearance at the synapse. Since NMDA receptors do not evoke fast depolarizations leading to an action potential, NMDA-only synapses are functionally silent. Yet, these silent synapses contribute to experience-dependent plasticity and possibly injury.[95]

Myelination

Myelination in the human CNS begins 1 to 2 months prior to birth in the visual system and extends to the other sensory systems over the first year of life.[96] Further myelination of subcortical and cortical tracts continues in the posterior to anterior direction well into the third decade of life, consistent with the time course of maturation of cognitive functions in children and adolescents.[87] Myelination is initiated by the preoligodendrocytes, which are exquisitely sensitive to injury by hypoxia and inflammation. Oligodendrocyte injury, with resulting disruption in axonal myelination, contributes significantly to the development of periventricular leukomalacia in preterm infants.[97]

Development of the Cerebrovasculature and Blood-Brain Barrier

Vascularization of the brain begins very early during development, with the first vascular plexus surrounding the primitive neural tube prior to the first heartbeat. Blood vessels then invade the developing brain, growing radially from the pia toward the deeper structures. The process is driven, at least in part, by oxygen sensing. Deeper cortical layers/structures are thought to be relatively oxygen-deficient.[98] Relative hypoxia leads to transcription of the hypoxia-inducible factor 1 (HIF1), that in turn leads to release of the vascular endothelial growth factor (VEGF). VEGF drives angiogenesis in the brain both prenatally and postnatally. Interestingly, chronic hypoxia such as is seen in patients with cyanotic heart disease increases the capillary density in the brain via an HIF1-dependent mechanism.[99] The increase is reversed over several weeks by restoring normal oxygenation in animal models, suggesting that brain vasculature has the potential to undergo continuous remodeling.

Development of the BBB coincides with early vascularization of the brain. Immunologic markers of tight junctions redistribute from the cytoplasm to their appropriate locations in the cell membrane by approximately 14 weeks of gestation.[100] Although anatomically intact, the BBB remains more permeable to amino acids, some drugs, and possibly toxins until approximately 6 months of age in humans.[100] However, the exact nature of BBB dynamics during development remains incompletely characterized.

Developmental Aspects of Cerebral Blood Flow, Autoregulation, and Cerebral Metabolism

In humans, gray matter CBF increases several-fold early in development and then decreases gradually after puberty (Figure 57-9). In normotensive preterm infants, CBF has been measured at 13 to 14 mL/100 g/min.[101] Estimated CBF increases with gestational age from 14 mL/100 g/min at 30 to 32 weeks to 20 mL/100 g/min at 38 to 40 weeks postconception.[102] Furthermore, CBF increases significantly in the first 2 days of life, regardless of gestational age.[103] In children aged 4 to 12 years, gray matter CBF reaches values of 90 to 100 mL/100 g/min, and then declines throughout adolescence to reach adult values of 50 to 60 mL/100 g/min by approximately 20 years of age.[104] Interestingly, white matter CBF is only 20% higher in children compared with adults, reflecting perhaps the greater degree of developmental changes in gray versus white matter.[104]

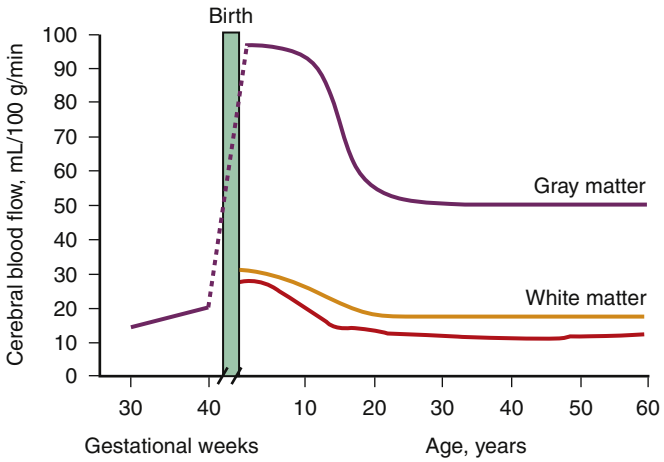

Figure 57–9. Cerebral blood flow (*CBF*) as a function of age. Gray matter CBF increases significantly after birth to reach a peak at approximately 4 years of age (note the change from age in gestational weeks to age in years). The *broken line* between the neonatal period and childhood indicates that data are extrapolated from existing experimental data. Gray matter CBF then decreases gradually to adult values. White matter CBF also decreases between 4 years of age and adulthood, but not as significantly as that in gray matter. At present, no data exist on the white matter CBF in premature or term newborns.

Perfusion pressure-related, $PaCO_2$-related and PaO_2-related autoregulation of CBF also undergo postnatal maturation. Studies in preterm infants suggest that perfusion pressure-related autoregulation of CBF is present shortly after birth, such that CBF changes by less than 1.5% per 1 mm Hg change in MAP.[105] As mentioned above, the upper and lower MAP limits in pressure-related autoregulation in neonates are shifted to the right, compared to adults,[77] leading to different thresholds for intervention in infants. Pressure-related autoregulation may be lost in critically ill infants, resulting in pressure-passive CBF[106] and poor outcome.[106] Similarly, $PaCO_2$-related autoregulation appears present in humans shortly after birth, with CBF changing approximately 1% for every 1 mm Hg change in $PaCO_2$.[101,103,107] In preterm infants, CBF also depends on the interaction between $PaCO_2$-related and MAP-related autoregulation, such that the percent change in CBF as a function of change in $PaCO_2$ increases as MAP increases.[107] Finally, oxygen tension-related CBF autoregulation also appears functional early in life, although much of the current data are derived from animals studies.[108,109] Thus in healthy humans, CBF autoregulation mechanisms are functional at birth and should be taken into account during management of systemic and intracerebral pathologic states, such as sepsis, hypotension, hypoxemia, and hypercarbia.

Cerebral metabolism undergoes substantial maturation during postnatal development in humans with respect to metabolic rate, distribution of metabolic activity, and energy source utilization. Shortly after birth, the CMRGlu is highest in sensory and motor cortices, thalamus, and brainstem.[110] Over the next 4 years, CMRGlu increases substantially in the thalamus and in the cortex but remains essentially stable in the brainstem. Cortical areas experiencing the most significant increase in CMRGlu during the first 4 years of life include the frontal, temporal, and occipital regions.[110] Between 4 and 9 years of age, CMRGlu in the cortex remains at consistently high values relative to adults, declining to adult levels by approximately 20 years of age.[86]

In addition to relying on glucose as a substrate, the developing brain also extensively utilizes ketone bodies as an energy substrate. Ketone utilization peaks during the period of maternal milk ingestion, accompanied by an increase in expression of monocarboxylate transporters in the BBB, that facilitate ketone entrance into the CNS.[111,112] Although reliance on ketones as an energy sources declines in the CNS with age, recent evidence indicates that ketone production and utilization may play a significant role during times of injury and stress even in an adult brain.[111]

Conclusion

The nervous system is undergoing active development and is often the primarily affected organ when children are hospitalized with a life-threatening illness. Appreciation of normal anatomy and development as well as knowledge of neurotransmitter systems and homeostatic mechanisms is required for prompt diagnosis and effective clinical care. Most importantly, ongoing research into the interaction between developmental processes and injury is likely to yield a wealth of new information, implying the need for continuous reevaluation of current knowledge and clinical practice in the light of new discoveries.

References are available online at http://www.expertconsult.com.

Coma and Depressed Sensorium

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PEARLS

- A Glasgow Coma Scale score less than 15 in children should be taken seriously.
- The ABCs (airway, breathing, and circulation) should be the priority during management of a child with coma.
- A spinal tap should be deferred until the possibility of raised intracranial pressure has been ruled out.
- The patient's blood glucose level should be checked with urgency during the initial presentation of coma.
- When in doubt, it is better to protect the airway and prevent hypoxemia and hypercarbia electively.
- Unequal size of the pupils can be a sign of uncal herniation.
- The goal of therapy should be the prevention of secondary brain injury.

Coma, a state of unresponsiveness and unconsciousness, presents in many disorders ranging from structural central nervous system (CNS) injuries to diffuse systemic abnormalities. As a medical emergency, coma presents a challenge to providers because optimal care requires timely intervention; however, information is frequently limited during the initial evaluation. Knowledge of CNS anatomy and structures responsible for consciousness provide helpful clues as one attempts to interpret physical findings and optimize patient care. A careful general physical examination with a focused neurologic examination can suggest the diagnosis, aid in the location of lesions, guide therapeutic intervention, and determine prognosis. Further adjunctive radiologic and laboratory evaluation will then confirm physical findings. This chapter therefore considers CNS anatomy, the pathophysiology of coma, historical and physical findings that aid in localization of lesions, the emergent management and evaluation of patients presenting with an altered level of consciousness, and the prognosis of patients who present with coma.

Pathophysiology

The brain tolerates only limited physical or metabolic injury. Coma implies advanced brain failure, and the longer the brain failure lasts, the greater the possibility that the injury will result in permanent neurologic impairment. Coma may be described simplistically as a lack of consciousness. Posner and colleagues[1] describe coma as a "state of unresponsiveness in which the patient lies with eyes closed and cannot be aroused to respond appropriately to stimuli even with vigorous stimulation." Comatose patients may grimace in response to pain and the extremities may move in stereotypical withdrawal patterns, but the patient cannot localize responses or make defensive movements. As a coma deepens, responsiveness even to painful stimuli may be lost. Because motor reflexes are preserved, the depth of a coma cannot be assessed based only on motor responses. In many comatose patients, reflex movements will develop in response to stimuli. The depth of coma is best assessed by the patient's level of consciousness.

Consciousness is a set of neural processes that allows an individual to perceive, comprehend, and act on and in the internal and external environment.[1,2] Two neurophysiologic functions, *arousal* and *awareness,* which have discreet neuroanatomic locations, are integrated in the conscious person.[3] *Arousal* or *wakefulness* describes the degree to which an individual appears to be able to interact within the environment. *Awareness* reflects the depth and content of the arousal state. When one is aware, one is alert (or aroused) and cognizant of self and surroundings. The relationship between wakefulness and awareness is hierarchical: Awareness cannot occur without wakefulness, but wakefulness may be observed in the absence of awareness (e.g., sleep/wake cycles in a vegetative patient).

Sleeping and waking are common examples of different states of arousal. Although coma and sleep both abolish conscious interaction with the environment, they differ physiologically because sleep is an active physiologic process with several distinct stages, and mechanisms for arousal remain intact. Sleep is dominated by a cortically generated slow wave (electroencephalogram [EEG]) activity within networks of neurons and glia, modulated by extracellular ion currents. Wakefulness is produced through the activation of brainstem and basal forebrain structures that disrupt sleep oscillations and elicit a global change in extracellular ion flow that results in modifications of glial and cerebral blood flow. Coma, however, occurs as a result of an impairment of physiologic components responsible for arousal and an inability to consciously interact.[4-6]

Anatomy of Arousal and Ascending Reticular Activating System

Arousal occurs by physiologic mechanisms that can be selectively impaired by toxins, anesthetics, or physical destruction of the brain stem. Neuroanatomically, the ascending reticular

activating system (ARAS) and related structures responsible for arousal are primarily located in the brainstem in the paramedian tegmental grey matter immediately ventral to the pons. Three ARAS principle pathways have been identified (Figure 58-1). Communications have been identified between the ARAS and the cortex and the limbic system via the thalamic reticular nucleus, the cortex hypothalamus, the basal forebrain, and the brainstem median raphe (locus caeruleus).[4] Because the ARAS receives collaterals from and is stimulated by every major somatic and sensory pathway directly or indirectly, it is best regarded as a physiological rather than an anatomic entity. This partly explains why patients with very large discreet lesions (brain tumors) may be entirely alert, whereas patients with anatomically undetectable but biochemically widespread lesions (e.g., hepatic encephalopathy) may be deeply comatose.

Primarily, two types of lesions depress the level of arousal: direct brainstem-diencephalic injury involving the reticular formation and nuclei, or bilateral cerebral dysfunction. Consequently, conscious behavior depends on the interplay between the cerebral cortex and ARAS because these neural components are required for arousal and to maintain awareness.[1,4] Because the brain maintains a rich network of connections between the cortex, the ARAS, and the brainstem, patients with large discreet lesions might be alert on presentation, although localized neurological deficits are noted on physical examination. On the other hand, patients with only minimal exposure to CNS depressants present with a depressed sensorium. Changes in a patient's level of consciousness imply significant dysfunction and can occur with variable degrees of wakefulness.

States of Impaired Sensorium

Precise definitions and descriptions of the various levels of consciousness are helpful in establishing a baseline, communicating with other health care providers, and interpreting changes in a patient's condition. Box 58-1 describes definitions for varying levels of consciousness; however, many terms used to describe alterations in sensorium lack precision and are better avoided. Colloquial use of the terms lethargy, obtundation, somnolence, and stupor have rendered them imprecise, and health care workers are best served to avoid them when describing patients with altered consciousness. Numerous scoring systems have been developed to assess acute neurologic conditions. By far the most common is the Glasgow Coma Scale (GCS). Developed to classify the depth of coma in adults who have sustained a head injury, the use of the GCS has been expanded to evaluate patients who have sustained a variety of neurologic injuries. A GCS score of eight or less has been used as an alternative definition of coma. Although other scales are used to assess the severity of illness in coma (e.g., Liege coma scale, Apache II scale, and Reye syndrome), the GCS has gained wider acceptance because of its ease and familiarity.[7] A modified GCS has been devised that is more applicable to infants.

Several states of depressed consciousness are described and deserve mention. Consciousness disorders should be distinguished from *brain death*, an irreversible loss of all brain and brainstem function.[8-10] *Coma* is a state characterized by the absence of arousal and awareness. To differentiate coma from more transient causes of depressed sensorium (e.g., syncope and concussion), coma must last more than 1 hour. Comatose patients do not speak, open their eyes spontaneously, follow commands, move spontaneously, or respond meaningfully to painful stimuli. Spinally mediated stereotypical movements may be made in response to pain, but patients do not actively withdraw. Sleep-wake cycles are not preserved in patients who are in a coma. Patients in a coma are in a transitional state and can either deteriorate to a more permanent state of depressed sensorium, deteriorate to fulfill brain death criteria, or recover.

In a *vegetative state*, arousal mechanisms are preserved but patients completely lack an awareness of self or the environment.[8, 9] Patients in a vegetative state demonstrate spontaneous eye opening without the ability to visually track or fixate. Although they may display "sleep-wake cycles," they cannot follow commands or move in a purposeful manner. Patients in a *minimally conscious state* do not meet the criteria for coma or the vegetative state. They demonstrate wakefulness and sleep-wake cycles and intermittently demonstrate self or environmental awareness. These patients may intermittently follow commands, communicate, and display purposeful behavior. Although data are limited, the minimally conscious state may be associated with a greater possibility of recovery than the vegetative state. Lesions associated with this state involve the

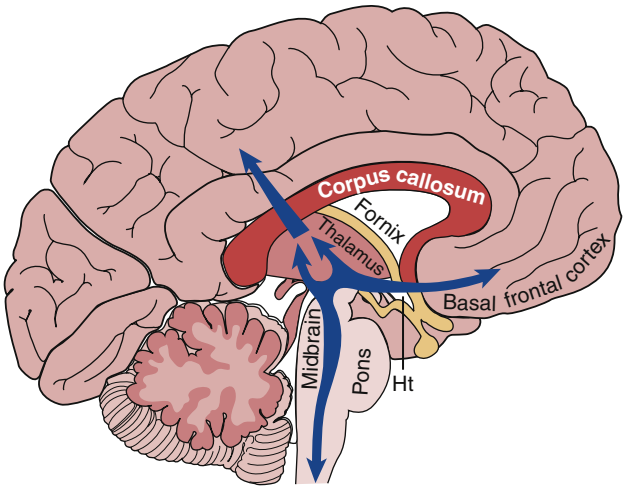


Figure 58–1. Reticular activating system. *(Modified from Hudson AJ: Consciousness: physiological dependence on rapid memory access,* Frontiers Biosci *14:2779-2800, 2009.)*

Box 58–1 Traditional Definitions of Levels of Conciousness

1. Clouding of consciousness—impaired capacity to think clearly and to remember current stimuli
2. Delirium—disturbed consciousness with motor restlessness, disorientation, and hallucination
3. Obtundation—reduced alertness; appears to sleep but responds to verbal and/or tactile stimuli
4. Stupor—markedly reduced alertness; only responds to noxious stimuli
5. Coma—no response to even noxious stimuli and will not utter understandable words

cerebral hemispheres, with possibly greater sparing of corticocortical and corticothalamic connective fibers.

Akinetic mutism is a state of wakefulness with limited evidence of awareness. Patients with akinetic mutism frequently have more diencephalic injury than injury to the motor tracts. Akinetic mutism[8-10] has been associated with bilateral medial frontal lobe injury. The medial frontal lobe injury leads to a profound deficiency in motivation and an inability to plan and initiate activity. Akinetic patients generally are unable to move or speak and have sleep-wake cycles indicated by eye opening. Unlike patients in a minimally conscious state, akinetic patients have no motor responsiveness to verbal, tactile, or noxious stimuli. Further, spasticity or abnormal reflexes do not develop in these patients as a result of relative sparing of the corticospinal tract.

Table 58–1 Common Considerations of Altered Mental Status at Various Ages

Infant	Child	Adolescent
Infection	Ingestion	Ingestion
Inborn error of metabolism	Infection	Intentional
Metabolic	Intussusception	Trauma
Abuse	Seizure	Drug/alcohol overdose
Trauma	Abuse	
	Trauma	

The *locked-in syndrome* is not a disorder of consciousness as much as it is an entity frequently confused with states of depressed sensorium due to the limited ability of these patients to communicate.[8,9] Locked-in patients are quadriplegic and anarthric, but awareness and arousal are preserved. The locked-in syndrome is associated with injury to the ventral pons below the level of the third nerve nuclei and sparing of the ascending reticular activating system. Vertical eye movements and blinking usually are spared. More rostral injury may result in a total locked-in syndrome with loss of eye and eyelid movement that eliminates the ability of the patient to interact or communicate.

Identification of Cause

Coma may present as part of the progression of a known neurologic illness or the unpredictable consequence or complication of a known systemic disease, or it may result from a totally unexpected event or illness.[10] An accurate history of the events and circumstances before the onset of the symptoms and information concerning the patient's medical history and use of medications may be invaluable in determining the cause of coma and quickly lead to the most appropriate diagnostic testing and treatment. As in most pediatric disease, the differential diagnosis of coma is age related as described in Table 58.1. Common etiologies of coma seen in the pediatric population are described in Box 58-2.

Box 58–2 Etiologies of Impaired Consciousness and Coma

Metabolic-Toxic

A. Hypoxia-ischemia
   1. Shock
   2. Cardiac or pulmonary failure
   3. Near drowning
   4. Carbon monoxide poisoning
   5. Strangulation
B. Metabolic disorders
   1. Hypoglycemia
   2. Acidosis
   3. Diabetic ketoacidosis
   4. Organic and aminoacidemias
   5. Hyperammonemias
   6. Hepatic encephalopathy
   7. Reye syndrome
   8. Urea cycle disorders
   9. Disorders of fatty acid metabolism
   10. Valproic acid encephalopathy
   11. Uremia
C. Fluid and electrolyte imbalance, dehydration, hyponatremia, calcium and magnesium imbalance
D. Endocrine disorders: thyroid dysfunction, adrenal insufficiency, hypoparathyroidism
E. Hypertensive encephalopathy
F. Vitamin deficiency (e.g., thiamin, pyridoxine, niacin)
G. Mitochondrial disorders
H. Exogenous toxins and poisons
   1. Narcotics, neuroleptics, antidepressants, antiepileptic drugs, stimulants
   2. Over-the-counter drugs, acetaminophen, mushroom
   3. Industrial toxins (e.g., heavy metals, organic phosphate, cyanide, volatile hydrocarbons)
   4. Substance abuse (e.g., alcohol, cocaine, heroin, amphetamine)
I. Poisoning in cases of Munchausen by proxy
J. Infection
   1. Bacterial
   2. Viral
   3. Rickettsial
K. Paroxysmal disorders
   1. Epilepsy
   2. Migraine

Structural-Intrinsic

A. Trauma
   1. Concussion
   2. Cerebral contusion
   3. Epidural hematoma
   4. Subdural hematoma/effusion
   5. Intracerebral hematoma
   6. Diffuse axonal injury
B. Neoplasms
C. Vascular disease
   1. Cerebral infraction
   2. Thrombosis, embolism
   3. Cerebral hemorrhage
   4. Arteriovenous malformation
   5. Aneurysm
   6. Vasculitis
   7. Trauma to carotid or vertebral artery in the neck
D. Focal infection
   1. Cerebritis
   2. Abscess
E. Hydrocephalus

Initial Assessment and Immediate Resuscitation

The initial assessment of the comatose patient should start with an evaluation of airway patency, the adequacy of ventilation, and the status of the patient's perfusion. Appropriate life support intervention should occur whenever life-threatening illness evolves throughout the assessment. Measurement of core temperature is an important adjunct. Many practitioners assign an initial GCS score at this time.

It is important to observe the respiratory pattern. The rate and regularity of respiration depends on a complex interplay of chemical and neural control systems that operate automatically to reset the rate and depth of breathing as changes occur in gas tensions and pH. In the comatose patient, abnormality may occur in rate and in the pattern. A low respiratory rate is associated with CNS depressants, for example, alcohol, barbiturates, benzodiazepines, and narcotics, and leads to hypoventilation. It also can be associated with elevated intracranial pressure (ICP). Tachypnea is far more commonly due to a physiologic response to hypoxia, metabolic acidosis, or fever, but central hyperventilation can be a sign of brainstem herniation.

The hemodynamic disturbance and hypotension leading to shock that occurs coincident with coma is mainly seen in systemic diseases (e.g., sepsis, drug ingestions, myocardial injury, and adrenal insufficiency), but it is not uncommon to see neurogenic shock related to severe traumatic brain injury (TBI) and spinal trauma as well. Hypertension is suggestive of an intracranial structural lesion and raised ICP but may be due to primary hypertensive encephalopathy.

Once the patient's airway, breathing, and hemodynamics are stabilized, a complete general examination and specific neurologic examination should be noted, along with any signs of trauma. Cervical immobilization should be maintained until trauma has been excluded or cervical spine has been cleared by radiographic and physical examinations. The patient should be completely exposed to allow a visual appraisal of swelling, lacerations, bruises, and other obvious signs of trauma. Blood or clear fluid noted in the nose or ears suggests a basilar skull fracture. Injuries with characteristic patterns (e.g., cigarette burns and glove and stocking burns), characteristic shapes, and characteristic locations (e.g., finger marks on the buttocks and bruises over ear lobes) suggest child abuse (see also Chapter 113).

Focused Neurologic Examination

A focused neurologic examination is key to documenting a baseline neurologic status and helps to locate lesions and determine prognosis in patients with diminished level of conscious (LOC).[11] Because a diminished LOC requires either reticular system or bilateral hemispheric dysfunction, testing the structures immediately adjacent to the reticular system provides clues to the etiology of coma and directs subsequent investigations.[2] A thorough physical examination must be systematic and is as valuable as radiographic and laboratory studies. The neurologic examination of a comatose patient differs from that of an awake, communicative subject and involves pupillary response, respiratory pattern, stimuli required to illicit a motor response, and the general character of the responses. History and presenting symptoms should be evaluated in the context of neurologic findings. Taken together, the history and presenting symptoms help determine the cause of diminished LOC. The level of neurologic dysfunction often is best defined by the respiratory pattern (Table 58-2), associated eye findings, and motor examination (Table 58-3).

Table 58–2 Respiratory Patterns in Patients with Altered Mental Consciousness

Pattern	Description	Localization
Posthyperventilation apnea	Apnea for >10 seconds after 5 deep breaths	Bilateral hemispheric dysfunction
Cheyne-Stokes respiration	Rhythmic waxing and waning of respiratory amplitude	Bilateral hemispheric dysfunction
Central reflex hyperpnea	Continuous deep breathing	Bilateral hemispheric (e.g., trauma), lower midbrain, upper pons
Apneustic respiration	Prolonged aspiratory time ("inspiratory cramp")	Pons
Ataxic respiration	Infrequent irregular breaths	Lower pons or upper medulla
Ondine's curse	Failure of involuntary respiration with retained voluntary respiration	Medulla
Apnea	No respiration	Medulla down to C4: peripheral nerves, neuromuscular junction

Table 58–3 Differentiating Characteristics of Structural and Metabolic Coma

Supratentorial Lesions	Infratentorial Lesions	Toxic, Metabolic, or Infectious Processes
Initial focal signs Retrocaudal progression Asymmetric examination often present early	Brainstem abnormalities often initial signs Sudden onset of coma Cranial nerve abnormality often seen Respiratory pattern often altered, such as central reflex hyperpnea	Confusion/stupor often precede signs Symmetric examination Pupillary reactions preserved Respiratory rate often altered, such as Cheyne-Stokes breathing

Respiratory Pattern

Breathing abnormalities in rate, depth, or regularity are associated with altered LOC. These abnormalities could be signs of overdose, increased ICP, or herniation. Observance of the respiratory pattern also can assist in localizing a lesion. Anatomic correlations between areas of injury and the resultant respiratory patterns are found in Table 58.2 and Figure 58-2.

Eye Examination

Specific eye findings can help localize the level of lesions and establish prognosis. Pupillary changes are informative during the examination of coma because the brainstem areas that control consciousness are adjacent to those that control pupillary response. It is important to distinguish between pupillary dilatation caused by disease or injury and that caused by medication. Pupillary changes due to structural lesions depend on the site of the primary lesion and secondarily on the effects of increased ICP as described in Table 58.3 and presented in Figure 58-3. Because pupillary pathways are relatively resistant to metabolic insults, the presence or absence of a light reflex is the single most important physical finding that distinguishes structural from metabolic disease. Any reactivity is indicative of intact pathways and would rule out brain death.

Pupillary size is the result of a balance in tone between two opposing muscle groups of the iris: the dilator pupillae and the sphincter pupillae muscles. The dilator pupillae is responsible for dilation of the pupils under the control of sympathetic nerve fibers. The sphincter pupillae muscle is responsible for constriction of the pupils under control of parasympathetic nerve fibers. Pupillary size is regulated by reflex mechanisms that occur as a result of ambient light. Size is further affected by age, emotional state, state of arousal, and intraocular pressure.

Anatomically, the pupillary light reflex requires a four-neuron pathway. Light information from retinal ganglion cells travels through the optic nerves, the optic chiasm (where the nasal fibers decussate), the optic tracts, and synapse in the pretectal nuclei of the dorsal midbrain. Pretectal nuclei receive input from both eyes and send axons to both Edinger-Westphal nuclei. The contra-lateral innervation of the Edinger-Westphal nuclei is the anatomic basis for the consensual light response.

Pupillary constriction occurs as a result of parasympathetic activity (Figure 58-4). Parasympathetic nerve fibers travel along the third cranial nerve to the ipsilateral ciliary ganglion within the orbit. The pupillary sphincter muscle (and ciliary muscle for lens accommodation) is innervated by the post-ganglionic parasympathetic fibers. Pupillary constriction to near stimuli occurs as a result of parasympathetic fibers that descend from higher cortical centers directly to the Edinger-Westphal nuclei, bypassing the pretectal nuclei in the dorsal midbrain. This redundancy explains the preservation of the near response when the dorsal midbrain and pretectal nuclei are injured.

Pupillary dilation is mediated through the three-neuron sympathetic (adrenergic) pathways (Figure 58-5). Sympathetic fibers originate in the hypothalamus and descend caudally to synapse in the cervical spinal cord between levels C8 and T2 at the area of the ciliospinal center of Budge. Neurons then travel from the cervical spinal synapse through the brachial plexus, over the lung apex, and ascend to the superior

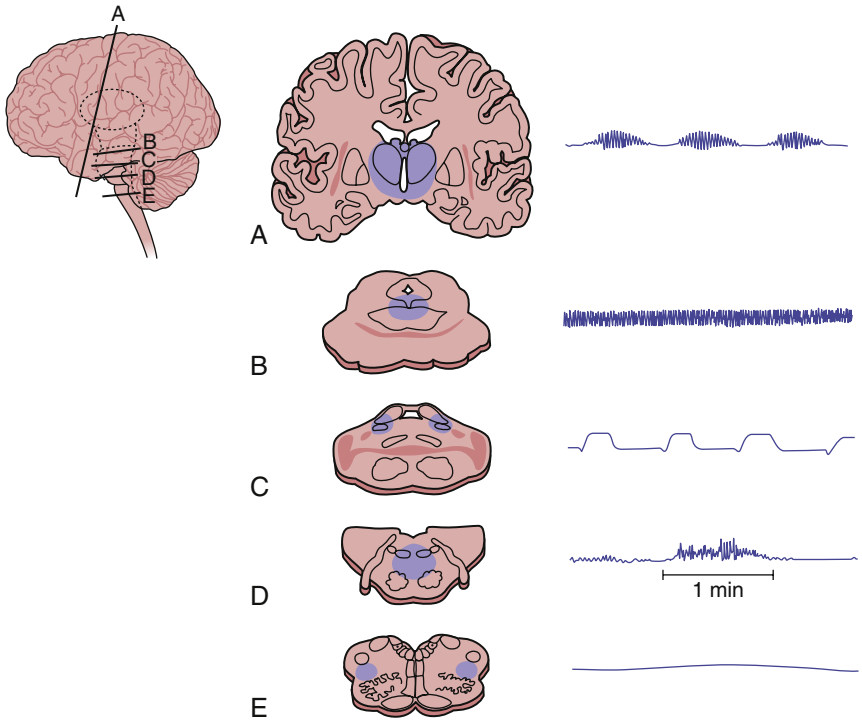


Figure 58–2. Respiratory patterns and associated levels of injury. **A,** Cheyne-Stokes respiration is seen with metabolic injury and lesions in the forebrain and diencephalon. **B,** Central neurogenic hyperventilation is most commonly seen with metabolic encephalopathies. **C,** Apneustic breathing (inspiratory pauses) is seen in patients with bilateral pontine lesions. **D,** Cluster breathing and ataxic breathing are seen in lesions at the pontine medullary junction. **E,** Apnea occurs when the medullary ventral respiratory nuclei are injured. *(Modified from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma, *ed 4, New York, 2007, Oxford University Press.)*

cervical ganglion near the angle of the mandible at the bifurcation of the common carotid artery. Postganglionic fibers then ascend within the adventitia of the internal carotid artery through the cavernous sinus in close relation to the sixth cranial nerve. Finally, the oculosympathetic pathway joins the ophthalmic division of the fifth cranial nerve (trigeminal nerve) and innervates the dilator pupillae and Müller's muscle (a small smooth muscle in the eyelids responsible for a minor portion of the upper lid elevation and lower lid retraction).

Anisocoria is indicative of a lesion in the efferent fibers supplying the pupillary sphincter muscles (dilator pupillae and the sphincter pupillae). Pupillary size is determined by the average amount of illumination detected by each eye. Because the efferent limb of the pupillary reflex is bilateral, both pupils receive the same command and are always the same size. Lesions in the afferent limb of the pupillary reflex do not produce anisocoria if the consensual pupillary response to light is intact. Afferent pupillary defects are noted when the direct and consensual responses to light are different. The examiner will note that pupil's reaction to direct light is more sluggish, initially slower, or absent. If the afferent defect is severe, the pupil in the affected eye will dilate with direct light. An afferent papillary defect is a sensitive marker for abnormalities of the afferent limb of the visual pathways.

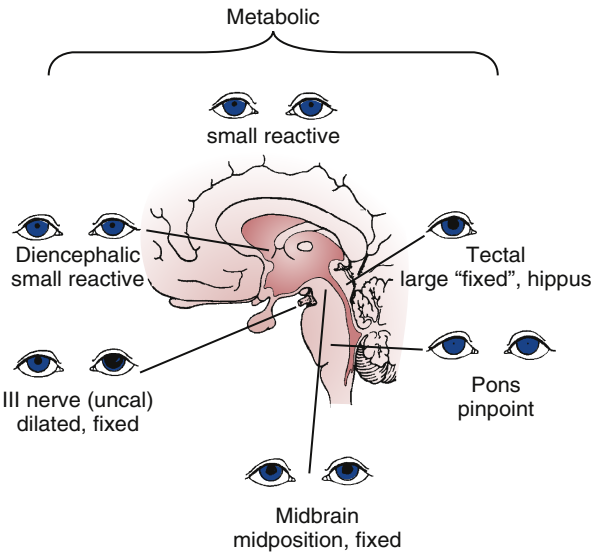


Figure 58–3. Pupils in comatose patients. *(Modified from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma*, ed 4, New York, 2007, Oxford University Press.)*

When anisocoria develops, it is important to determine the abnormal pupil (Figure 58-6). If the small pupil is abnormal, anisocoria is greater in darkness than in light and one will note poor pupillary dilation on the abnormal side. This problem is seen with abnormalities of the sympathetic system. If the larger pupil is abnormal, anisocoria is greater in light than in darkness and one notes poor pupillary constriction on the abnormal side. Poor pupillary constriction is consistent with an abnormality of the parasympathetic system.

Third nerve palsy is the result of lesions anywhere between the oculomotor nucleus and the extraocular muscles. The third cranial nerve originates in the region of the superior colliculus in the midbrain. Fibers travel ventrally in the midbrain and pass the red nucleus and the corticospinal tracts. The nerve exits the midbrain and passes along the brainstem and courses along the lateral wall of the cavernous sinus. The third nerve enters the orbit at the superior orbital fissure. In the orbit, parasympathetic fibers join the periphery of the nerve and travel to the ciliary ganglion. The third nerve innervates the levator muscle of the eyelid, four of the six ipsilateral extraocular muscles (the medial rectus, the superior rectus,

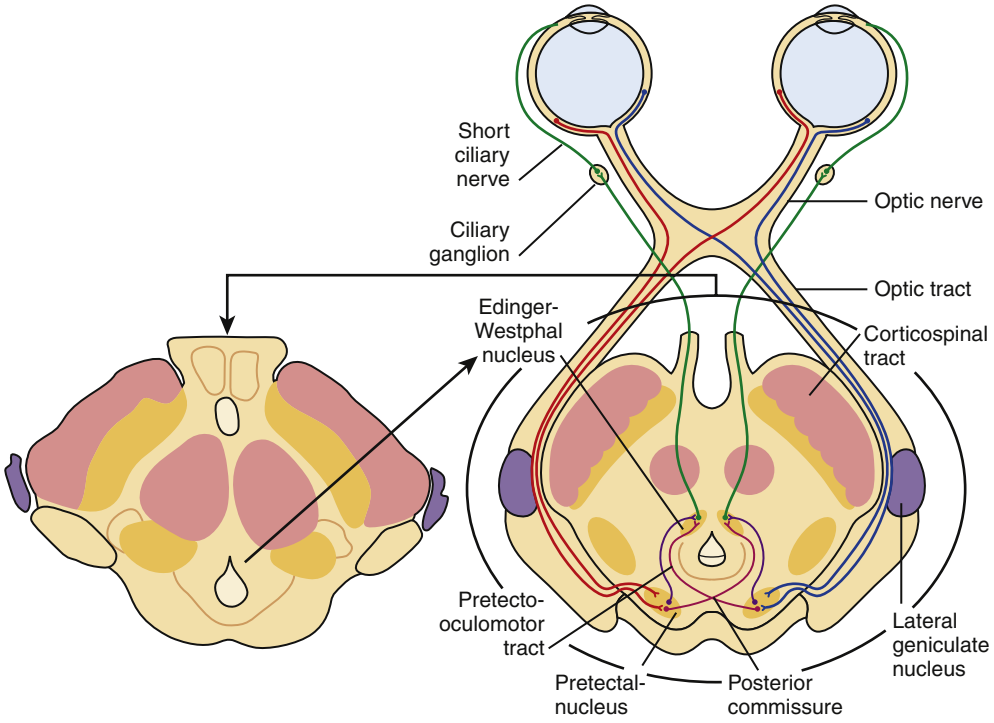


Figure 58–4. Parasympathetic pathway for pupillary innervations. *(Modified from Martin TJ, Corbett JJ: The pupil. In Krachmer JH, editor:* Neuro-ophthalmology: the requisites in ophthalmology*, St Louis, 2000, Mosby. Copyright 2000 Elsevier.)*

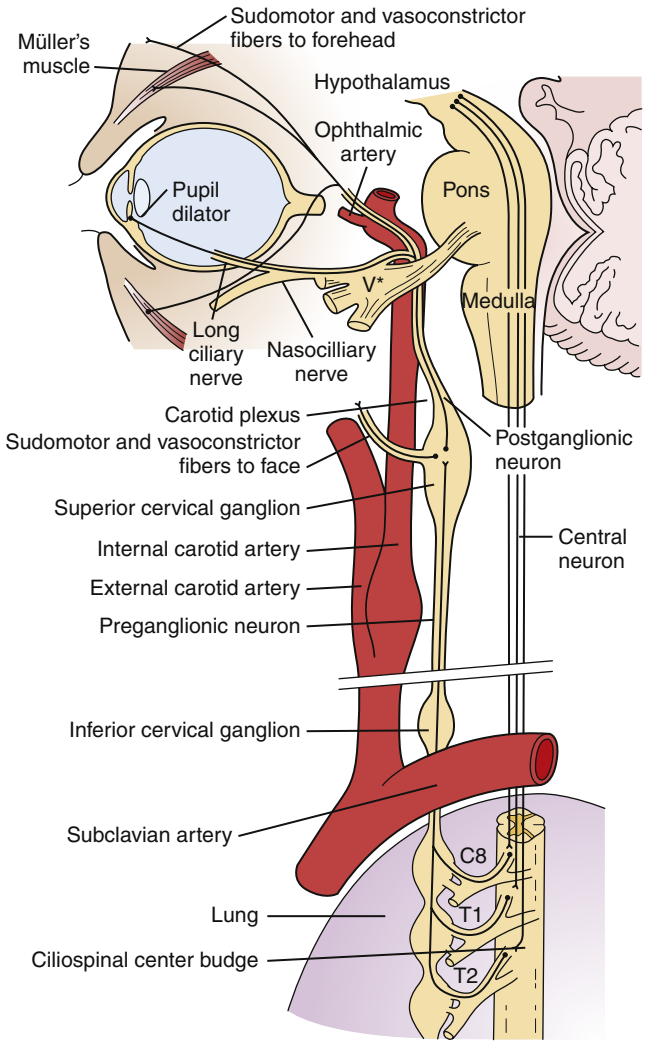


Figure 58–5. Sympathetic pathway for pupillary innervations. *(Modified from Martin TJ, Corbett JJ: The pupil. In Krachmer JH, editor:* Neuro-ophthalmology: the requisites in ophthalmology, *St Louis, 2000, Mosby. Copyright 2000 Elsevier.)*

the inferior rectus, and the inferior oblique), and the sphincter pupillae (parasympathetic fibers). Remaining extraocular muscles, the superior oblique muscle and the lateral rectus muscle, are innervated by fourth and sixth cranial nerves, respectively.

Third nerve palsies present with ptosis, gaze abnormalities, and varying degrees of pupillary dysfunction.[11a] Pupillary response will vary with the degree of injury, and pupils may be normal size with normal responses to light, dilated and poorly reactive to light, or dilated and unresponsive to light and near stimulus. Gaze abnormalities also vary with the site and severity of injury. Adduction abnormality occurs as a result of medial rectus weakness; the eye is turned out. Injury to the nerve supply of superior rectus or inferior oblique results in elevator muscle weakness, and the eye is turned down. Weak downward gaze results from injury to the nerve supply of the inferior rectus muscle, and the eye is turned up. Classically, third nerve palsy is complete and all muscles are affected, resulting in an eye that is turned down and out.

Fundi should be examined to assess the presence of papilledema and retinal hemorrhages. Papilledema is a late sign of increased ICP and its absence does not rule out raised ICP. Signs of papilledema include blurring of the margins of the optic disc and a decrease in venous pulsations. Retinal hemorrhages are most commonly associated with child abuse, although they may be seen following cardiopulmonary resuscitation. Hemorrhages in the retina appear as perivascular collections of blood that may coalesce to include large areas of the retina. Retinal hemorrhages appear to be associated primarily with significant head injury that disrupts retinal blood vessels between the internal limiting membrane and the ganglion cell layer and vessels in the nerve fiber layer of the retina.

The oculocephalic or "doll's eye" reflex and oculovestibular or caloric reflex are the two specific eye maneuvers used in evaluating the comatose child. A positive or normal response to these reflexes indicates that much of the brainstem is intact. Conjugate deviation is noted toward the side of cerebral lesions and away from the side of brainstem lesions. The corneal reflex is a good test for mid and low pontine function.

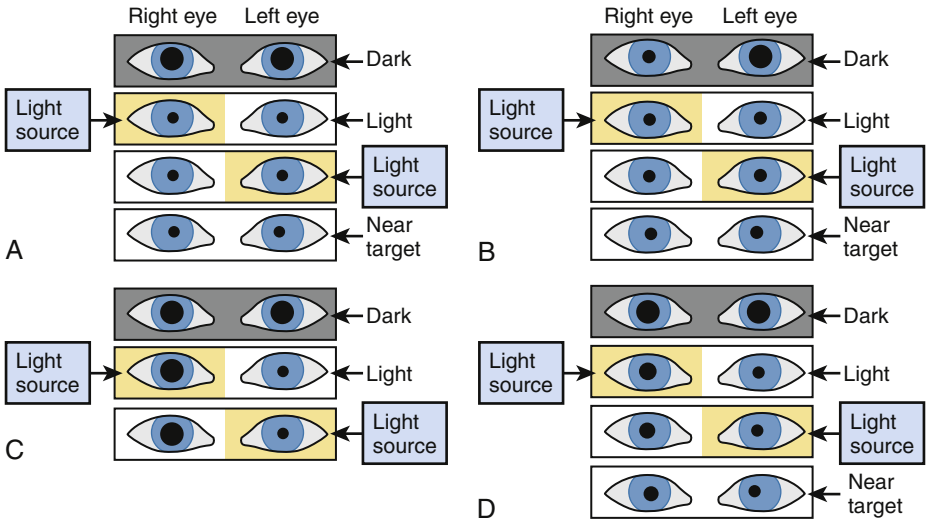


Figure 58–6. The pupillary examination. Identification of the abnormal pupil when anisocoria is present. **A,** Normal pupillary reactions. Both pupils are symmetric in the light and dark. **B,** The small pupil is abnormal. The right pupil does not dilate well in the dark. **C,** The large pupil is abnormal. The right pupil does not react well to light. **D,** Physiologic anisocoria. The amount of anisocoria is the same in light and dark. *(Modified from Kedar S, Biousse V, Newman NJ: Approach to the patient with anisocoria. In Brazis PW, Wilterdink JL, editors:* Up to date. Available at *www.uptodate.com.)*

Motor Examination

Motor examination may reveal focal or generalized neurologic deficits. The presence or absence of focal lateralizing neurologic signs sharply shortens the differential diagnosis. If a single anatomic lesion can explain all the signs, then the differential diagnosis shortens to structural CNS causes of coma. If there is neuroanatomic inconsistency, toxic and metabolic causes of coma are most common (Table 58.4). It is important to remember that focal dysfunction may be misinterpreted as altered LOC (i.e., a patient with receptive aphasia who is misdiagnosed as confused or psychotic).[12]

Figure 58-7 describes the path of the corticospinal tracts through the midbrain, pons, and medulla and their relationship to cranial nerve nuclei. The anatomic relationships between the cranial nerves and motor tracts can provide clues to the location of lesions when a careful physical examination is performed. Physical examination findings and their expected anatomic correlates are presented in Table 58.3.

Focal Neurologic Lesions Could Be Supratentorial or Subtentorial

The *supratentorial* compartment mainly contains the cortex, thalamus, and other structures above the midbrain (Figures 58-8 and 58-9). Patients presenting with asymmetrical examinations are indicative of those with cortical lesions. Given a "focal" or asymmetrical examination, hemiparesis suggests a lesion in a contralateral upper motor neuron pathway. Hypotonia, diminished LOC, and equal reactive pupils are likely to be localized to a cortical lesion on the contralateral side. It has been noted, however, that unilateral cortical lesions often dampen alertness but do not lead to stupor or coma, because ARAS is widely spread in the cerebral cortex region. Expansion of cortical lesions resulting in raised ICP may reduce cortical blood flow in the other areas of the brain, causing diminished LOC.

Contralateral thalamic lesions and cortical lesions with a retrocaudal progression present with contralateral hemiparesis, decorticate (flexor) posturing, eyes deviated inferiorly and medially, and pupils remaining equal, small, and reactive. Decorticate posturing (i.e., tonic flexion of upper extremities and tonic extension, adduction, and internal rotation of lower extremities) reflects a lesion above the midbrain as described in Figure 58-10.

The history and physical findings are relevant and may help determine the cause of the injury. A sudden change in LOC in an otherwise normal child may be due to a cerebrovascular accident from an arteriovenous malformation, a bleeding CNS tumor, or a ruptured aneurysm. Acute sinusitis may result in intracerebral or subdural empyema resulting either from direct extension or hematogenous spread. These infections may produce diminished LOC either as a result of the systemic inflammatory response to the infection or consequences of the expanding mass lesion. A history of fever associated with a diminished LOC may suggest encephalitis associated with herpes simplex or arboviruses infections (see also Chapter 65).

Table 58–4 Clinical Findings with Different Levels of Central Nervous System Dysfunction

Dysfunction	Response to Noxious Stimuli	Pupils	Eye Position and Movements	Breathing	Motor Findings for Structural Lesions
Both cortices	Withdrawal	Small, reactive	Extraocular movements can be elicited; ipsilateral deviation in frontal lobe lesion	Post hyperventilation apnea or Cheyne-Stokes respiration	Contra lateral hemiparesis
Thalamus	Decorticate posturing	Equal and small, unless the optic tract are also damaged	Eyes deviated down and in toward the side of lesion	Same as above	Contra lateral hemiparesis
Midbrain	Decorticate or decerebrate posturing	Midposition, fixed to light, spontaneous fluctuation	Nystagmus may be present; absent vertical but retained horizontal movements; loss of ability to adduct Both eyes may be deviated laterally and down in third cranial nerve damage	Usually same as above; potential for central reflex hyperpnea	Hemiplegia with contra lateral third cranial nerve palsy
Pons	Decerebrate posturing	Bilateral pinpoint pupils, reactive to light (especially with midline pontine hemorrhage); Horner's syndrome with lateral lesions	Ocular bobbing; absent conjugate horizontal movements with retained vertical movements and accommodation; often eyes are deviated medially; seventh cranial nerve damage	May exhibit central reflex hyperpnea, cluster (Biot's) breathing, or apneustic breathing	Hemiplegia with contralateral sixth and/or seventh cranial nerve palsy
Medulla	Weak leg flexion (or none)	Nonreactive, normal size; small, Horner syndrome with lateral lesions	Usually no effect on spontaneous eye movements; may interfere with reflex responses, nystagmus	Rarely ataxic respiration, apnea if respiratory centers involved	Flaccid weakness with difficulty swallowing, phonating, and incoordination
Spinal cord	None	Normal reaction, abnormal response if brainstem affected	Normal response	Normal	Flaccid weakness, loss of bowel and bladder control

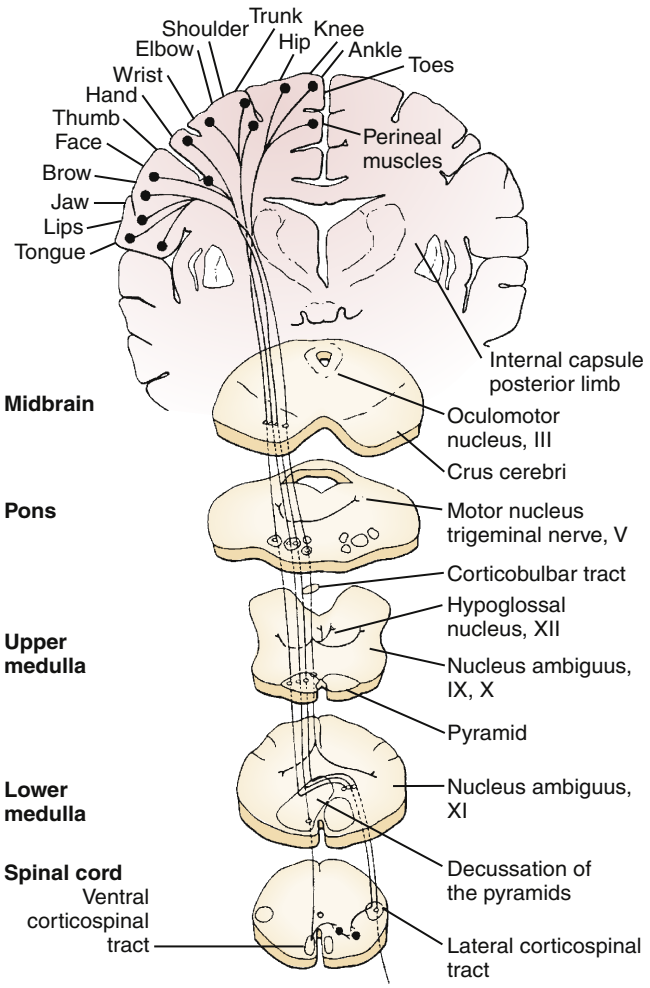


Figure 58–7. The corticospinal tracts in relation to the cranial nerve nuclei. *(Modified from Gilman S, Newman SW:* Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology, *ed 9, Philadelphia, 2003, FA Davis.)*

A murmur, gallop, and/or dysrhythmias detected during a cardiovascular examination may suggest congenital heart disease or endocarditis, which may be associated with stroke or intracranial abscess formation.

When a traumatic injury occurs, coma may exist from the moment of impact or may be preceded by a lucid interval, suggesting an expanding epidural hematoma. A complete description of TBI is provided in Chapter 61.

Generalized petechia and purpura may be seen with thrombocytopenic purpura, which is a risk factor for spontaneous intracranial bleeding.

Patients presenting with an altered level of consciousness and underlying illnesses such as systemic lupus erythematosus, sickle cell anemia, nephrotic syndrome, homocystinuria, leukemia, or coagulation disorders such as protein C and S deficiency are at risk for cerebral infarction resulting from a vascular obstruction. Patients with diabetic ketoacidosis may have a sudden onset of coma that could be a result of cerebral edema or central venous thrombus (see also Chapter 78). Hypoxic insults and penetrating injuries to vertebral or carotid arteries (as a consequence of vascular disruption) result in cerebral infarction. Patients with strokes may have a period of lucidity following the acute vascular incident. Stupor and coma develop as swelling increases ICP and the blood supply to the midbrain and brainstem are compromised.

Vomiting and diarrhea leading to severe dehydration and hypercoagulable states may lead to sinus venous thrombosis, particularly in young infants. Orbital cellulitis can result in cavernous venous thrombosis. Children with congenital heart disease, especially with right-to-left shunts, are susceptible to cerebral embolism resulting from blood or air thrombus, or particles when patients are treated with intravenous therapy.

Diminished LOC also may occur because of bleeding, convulsions, or rapidly rising ICP as a result of a brain tumor. A history of headache may suggest elevated ICP resulting from hydrocephalus or neoplasm but also may be seen in migraine

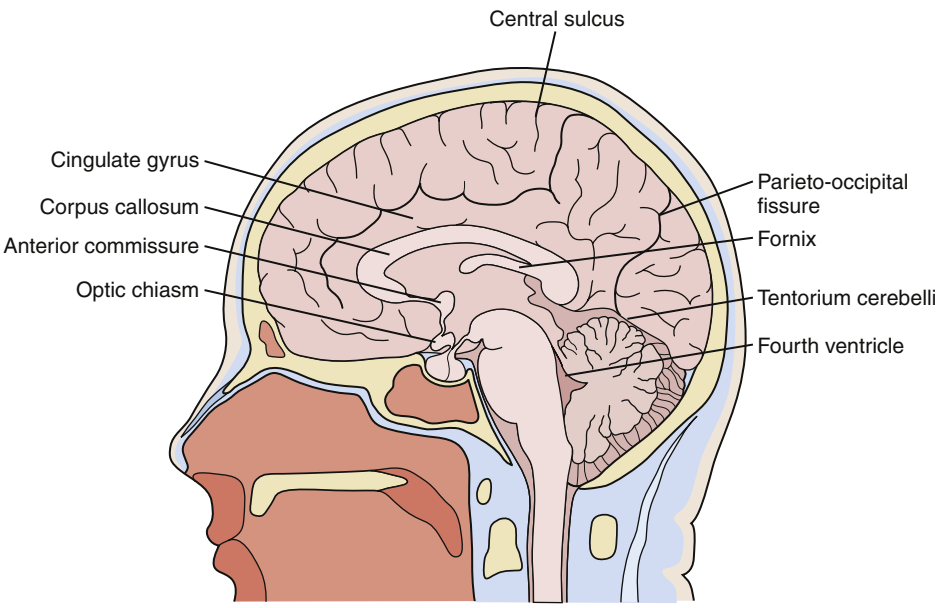


Figure 58–8. Supratentorial and subtentorial compartments. *(Modified from Gilman S, Newman SW:* Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology, *ed 9, Philadelphia, 2003, FA Davis.)*

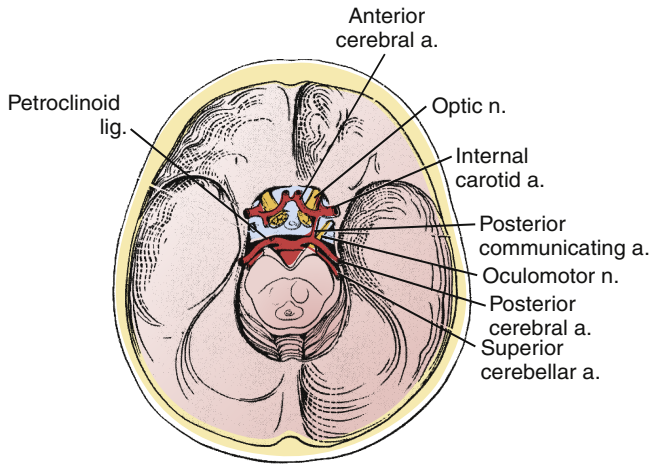


Figure 58–9. The floor of the anterior and middle fossa, illustrating the tentorial notch and relationship of the third nerve with other intracranial structures. *(Modified from Plum F, Posner JB:* The diagnosis of stupor and coma, *ed 3, Philadelphia, 1982, FA Davis.)*

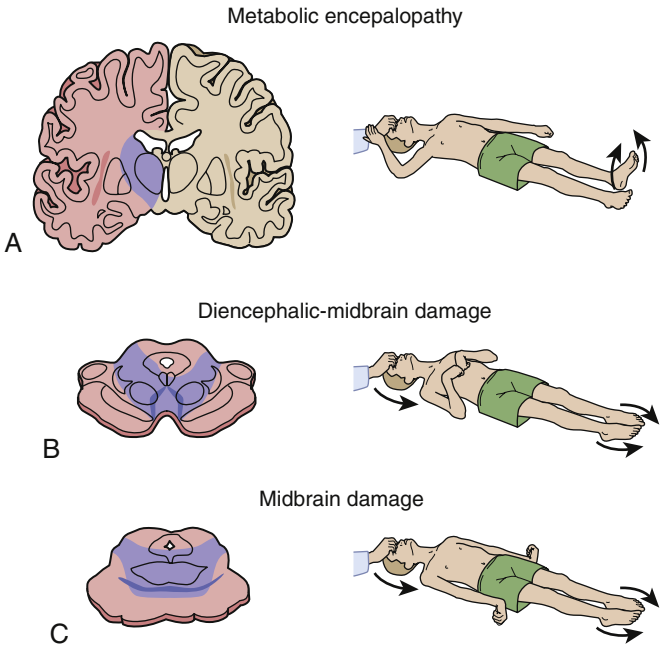


Figure 58–10. Motor responses to noxious stimulation in patients with cerebral dysfunction. *(Modified from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma, *ed 4, New York, 2007, Oxford University Press.)*

syndrome with impaired consciousness. The presence of neurocutaneous lesions, such as depigmented areas of tuberous sclerosis, can suggest that seizures or intracranial masses are the cause of diminished LOC.

The *subtentorial* compartment is the area beneath the tentorium and contains most of the brainstem, the cerebellum, the exit sites for most of the cranial nerves, and passages for CSF movement (see Figures 58-8 and 58-9). Injury and insult can alter function of these components by either destruction or compression. Brainstem lesions are capable of creating immediate LOC because of the close proximity of ARAS. The relationship of cranial nerves to the brainstem is described in Figure 58-11.

Lesions in the brainstem may be due to demyelinating diseases, cerebrovascular diseases, neoplasm, or head trauma. Uncal herniation can occur following head trauma, which may be due to rapidly expanding subdural or epidural hematoma or diffuse axonal injury. A history of fever, vomiting, and LOC are noted in brainstem and cerebellar infarction. Cerebrovascular lesions disrupt blood supply and result in brainstem dysfunction. A history of headache, vomiting, and gait unsteadiness may suggest a neoplasm.

Midbrain lesions frequently present with ipsilateral weakness and midposition, nonreactive contralateral pupils due to third cranial nerve palsy. Third cranial nerve palsy generally causes both eyes to deviate laterally or inferiorly and laterally. When gaze is deviated down and out, the patient is said to have the "sun setting sign." Decerebrate (extensor) posturing is elicited in response to noxious stimuli in patients with midbrain lesions. Decerebrate posturing is tonic extension of upper extremities as well tonic extension, adduction, and internal rotation of lower extremities (see Figure 58-10).

Hemiparesis with medial deviation of the contralateral eye are hallmarks of pontine lesions (see Figure 58-3). Pupils remain small and reactive to light. However, bilateral pinpoint pupils are also seen when midline pontine hemorrhages occur. Horner's syndrome with a mildly constricted pupil ipsilateral to the lesion can be seen in lesions affecting pathways between the hypothalamus and brainstem.

Although hypertonia is a feature of preexisting corticospinal tract injury, it can be seen in acute injury to the midbrain or pons, when the more rostral corticospinal tract is disrupted, but the vestibulospinal motor system continues to exert a tonic influence on the spinal cord. These patients exhibit decerebrate posturing to noxious stimuli. It should be noted that acute lesions often cause extensor posturing regardless of anatomic location and both decorticate and decerebrate posturing may occur in combination. These facts render posturing less reliable for localization of CNS lesions. Although not always reliable for localization, posturing suggests that cortical control centers are not functioning.

Patients presenting with flaccid quadriplegia, swallowing difficulties, problems with phonation, nonreactive normal-sized pupils, and normal extraocular eye movements are likely to have an injury in the medulla. The eighth to twelfth cranial nerves exit the brainstem in the area of the medulla. Medullary lesions are associated with problems in bulbar muscles such as speech and swallowing. If respiratory centers are affected, patients may present with apnea. Cerebellar lesions usually produce coma by brainstem compression. Cerebellar signs in confused patients should raise the possibility of intoxication or nutritional deficiency (e.g., vitamin B_{12}).

Presentation of Nonfocal Neurologic Lesions

Once causes of focal neurologic lesions have been excluded, further evaluation should proceed to seek causes of coma as described in Box 58-2. Patients with nonfocal lesions and coma commonly lay motionless in an unnatural posture. In most metabolic conditions, pupils are small and reactive to light and extraocular movements are absent. Patients may hyperventilate or present with apnea or Cheyne-Stokes respiration.

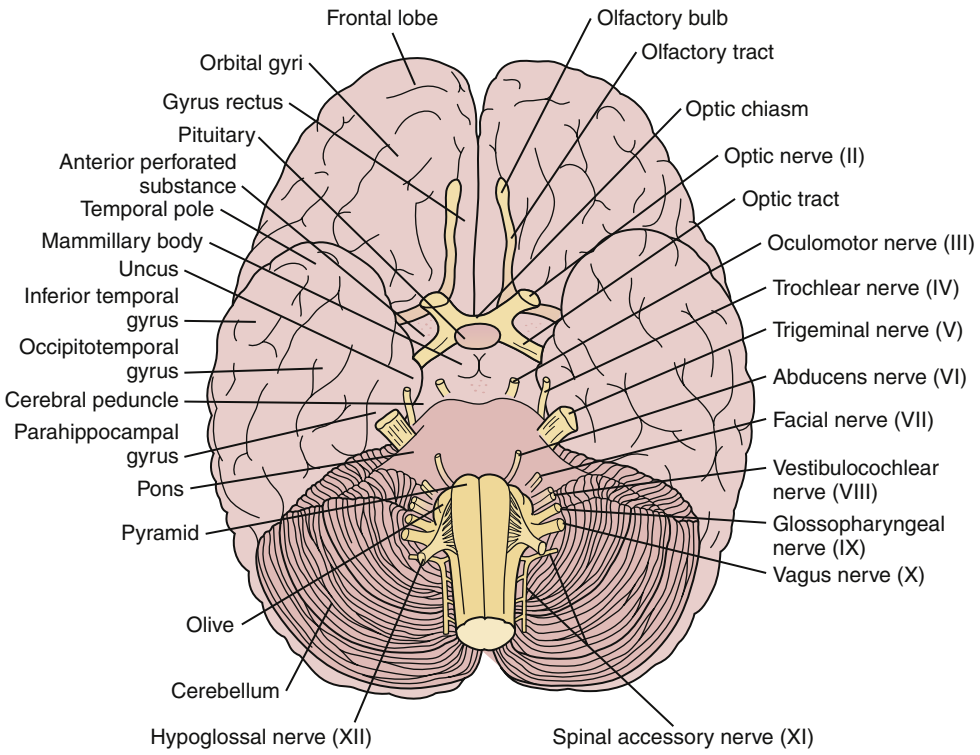


Figure 58–11. Ventral surface of the brain demonstrating the position of cranial nerves. *(Modified from Gilman S, Newman SW:* Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology, *ed 9, Philadelphia, 2003, FA Davis.)*

Hypoxia and ischemia/reperfusion injury are important causes of coma in pediatric patients. These entities are thoroughly discussed in Chapter 62. Most of the causes of nonfocal neurologic lesions may be very obvious. In cases of unusual presentation, a detailed history and physical examination may give a clue to the diagnosis.

Coma preceded by sleepiness or unsteadiness suggests ingestion of a drug or toxin in a previously healthy child. Seizures may lead to a prolonged and deep loss of consciousness if there is an underlying reason for the seizure (e.g., cerebral palsy, hypoglycemia, and electrolyte abnormalities) or if metabolic demand during the seizure is not met by a concomitant increase in substrate delivery. A recent history of fever or upper respiratory tract illness may suggest complications of infectious diseases such as acute disseminated encephalomyelitis, Reye's syndrome, or mitochondrial disorders.

Intermittent episodes of coma may be due to recurrent drug overdose, inborn error of metabolism, or Munchausen syndrome by proxy. A toddler presenting with intermittent irritability followed by a decreased level of consciousness could be experiencing intussusceptions, perhaps because of a release of endorphins.

Inspection of skin can provide clues to an underlying illness (e.g., jaundice in patients with liver failure, or a cherry-red color in persons with carbon monoxide poisoning). Generalized increased pigmentation may be seen in Addison's disease or adrenoleukodystrophy.

Herniation Syndromes

Expanding mass lesions develop at the expense of one of the CNS compartments (brain, blood, or cerebrospinal fluid) (see also Chapter 59). Herniation occurs when the brain is subjected to pressure gradients that cause portions of it to flow from one intracranial compartment to another. Although the brain has substantial elasticity, the arteries and veins responsible for its blood supply are relatively fixed in space, creating a risk that brain shifts will cause moving portions to lose their blood supply. The supratentorial compartment is connected to the subtentorial compartment via the tentorium cerebelli, which passes through the tentorial notch (see Figure 58-9). Located in the tentorial notch are the midbrain, the third cranial nerve, and several arteries including choroidal arteries, the posterior cerebral arteries, and the superior cerebellar arteries. The cerebellum occupies the posterior part of notch. Close proximity of these important structures explains the constellation of symptoms that occur when supratentorial lesions lead to transtentorial shifts.[13]

Two herniation syndromes are principally important: central herniation and uncal herniation (Figure 58-12). *Central herniation* occurs when diffuse brain swelling or a centrally located mass causes the diencephalon to move caudally through the tentorial notch. Figures 58-13 and 58-14 describe the remote and catastrophic effects of supratentorial lesions leading to a shift of intracranial structures through the tentorial notch. Dysfunction of the ARAS and cerebral hypoperfusion cause the alteration of consciousness. Patients initially become less alert and later progress to stupor and coma. Diencephalic dysfunction initially produces small reactive pupils because sympathetic output from the hypothalamus is lost. At this stage, decorticate (flexor) posturing may be spontaneous or elicited by noxious stimuli, and Cheyne-Stokes respiration is noted (see Figures 58-10 and 58-14). It is important to recognize this constellation of symptoms because herniation at this stage is reversible. As rostral-caudal progression of central herniation continues into the midbrain and pons, the likelihood of reversibility markedly decreases. As the midbrain begins to fail,

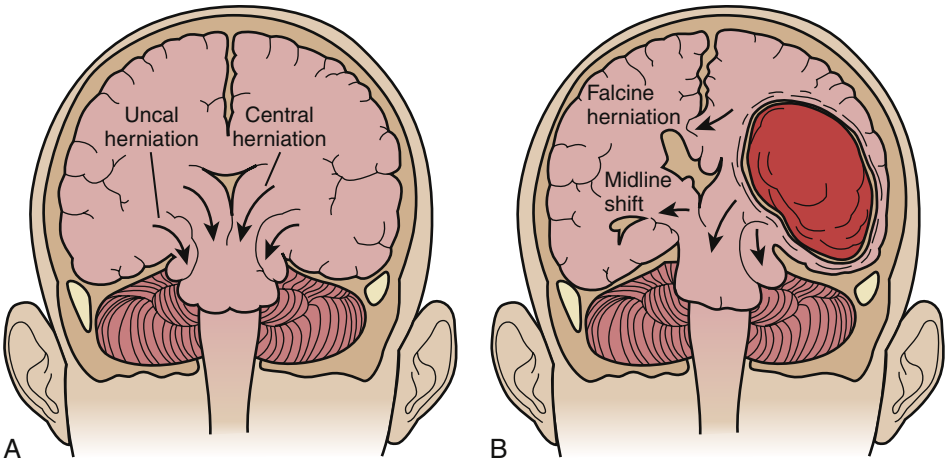


Figure 58–12. Central (**A**) and uncal (**B**) herniation. *(Adapted from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma, *ed 4, New York, 2007, Oxford University Press.)*

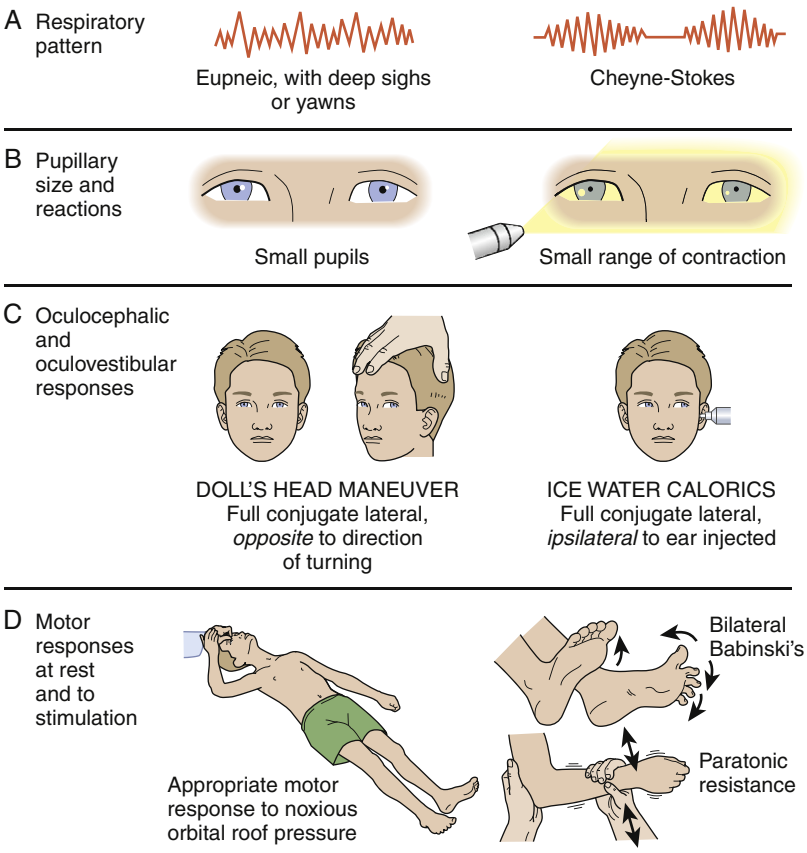


Figure 58–13. Central transtentorial herniation—early diencephalic stage. *(Modified from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma, *ed 4, New York, 2007, Oxford University Press.)*

pupils enlarge to midposition, and decerebrate (extensor) posturing is noted. Attempts to elicit horizontal eye movements with either cerebroocular reflex or cerebrovestibular reflex fail and the respiratory rhythm becomes irregular. The patient becomes overtly comatose. Further progression affects the medullary respiratory centers. Virtually all brainstem reflexes are absent and death becomes imminent. The initial cardiovascular response to diminished brainstem perfusion is hypertension, which leads to reflex bradycardia. Classic Cushingoid reflex responses are seen mostly after the development of herniation syndromes. Radiographically, downward herniation is characterized by obliteration of the suprasellar cistern from temporal lobe herniation into the tentorial hiatus with associated compression on the cerebral peduncles.

Uncal herniation occurs when a lateral expanding cerebral mass pushes the uncus and hippocampal gyrus over the lateral edges of the tentorium, putting pressure on the brainstem, especially the midbrain. As the diencephalons begin to shift away from the mass, consciousness begins to diminish, and ipsilateral third cranial nerve palsy develops. When the third cranial nerve

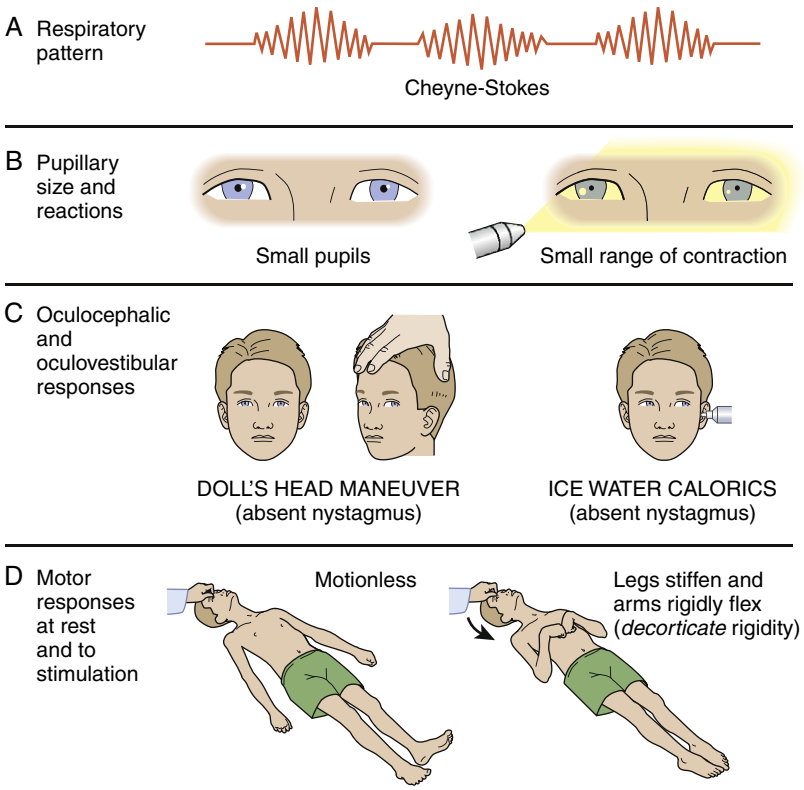


Figure 58–14. Central transtentorial herniation—late diencephalic stage. *(Modified from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma, *ed 4, New York, 2007, Oxford University Press.)*

is compressed against the tentorial notch, the pupillary fibers controlling the parasympathetic control are primarily damaged, resulting in a large pupil of the affected side, which fails to constrict to the light. A unilateral dilated pupil that is first to appear, often without severe impairment of consciousness, and contralateral hemiparesis are the hallmark findings of uncal herniation (Figures 58-15 and 58-16). Other findings, such as impaired ocular motility pushing an eye "down and out," may take some time to develop. Cranial arteries may be compressed during herniation. Once present, changes in brainstem function, ipsilateral hemiplegia, and altered oculocephalic reflexes may proceed very rapidly. In some patients bilateral pupillary dilatation develops, presumably because of distortion of third cranial nerve anatomy and midbrain ischemia. At this point, uncal herniation begins to affect the midbrain and upper pons, producing fixed pupils and extensor posturing, lethargy, bradycardia, and respiratory abnormalities. Further progression is indistinguishable from central herniation.

Cerebellar tonsillar herniation is seen in patients with posterior fossa masses that cause compression of the brainstem, cranial nerve dysfunction, and obstructive hydrocephalus. As the pressure gradient across the foramen magnum increases, cerebellar tonsils may be pushed through the foramen and also can compress the upper cervical spinal cord. Increased pressure on the brainstem can result in dysfunction of brain centers responsible for controlling respiratory (and cardiac) functions, which may result in apnea. Patients with cerebellar tonsillar herniation may complain of neck pain before losing consciousness. *Upward transtentorial herniation* occurs when contents of the posterior fossa herniate into the diencephalic region. This syndrome is seen in patients who have ventricular drains placed for relief of hydrocephalus. If the ventricular drain is set to drain at a very low pressure, a pressure differential is created between the supratentorial and subtentorial regions, with the supratentorial pressure being lower.

Diagnostic Evaluation

Initial investigation falls into two broad categories, investigation facilitating supportive therapy during the child's illness and investigation to confirm a specific diagnosis (Box 58-3). These investigations, however, should be tailored to the individual child's history and physical examination. Blood chemistry profile should include glucose, sodium, potassium, blood urea nitrogen, calcium, magnesium, carbon dioxide (CO_2), and ammonia. Hypoglycemia may be a presenting feature of some endocrine disorders or inborn errors of metabolism (see also Chapters 76 and 77). Therefore all patients with significant impairment of consciousness should have a blood glucose determination performed immediately after presentation. Abnormalities of calcium and magnesium may precipitate unexpected seizures, especially in infants and young children. Hyperammonemia and metabolic acidemia may occur as a result of an inborn error of metabolism. If metabolic acidosis is noted, then lactate and pyruvate levels also should be determined. A complete blood cell count will assist in determining the presence of infection, anemia, and exposure to toxins such as lead. Blood and urine cultures should be obtained if infection is suspected. A urine sample also should be sent for toxicology screening.

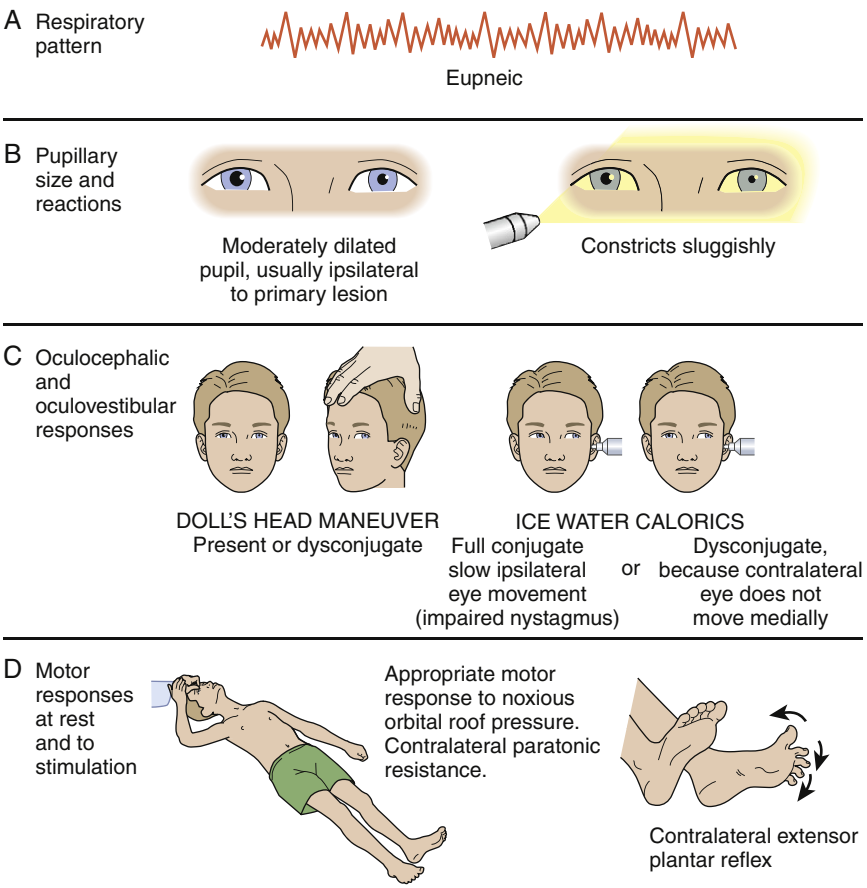


Figure 58–15. Uncal herniation—early third nerve stage. *(Modified from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma, *ed 4, New York, 2007, Oxford University Press.)*

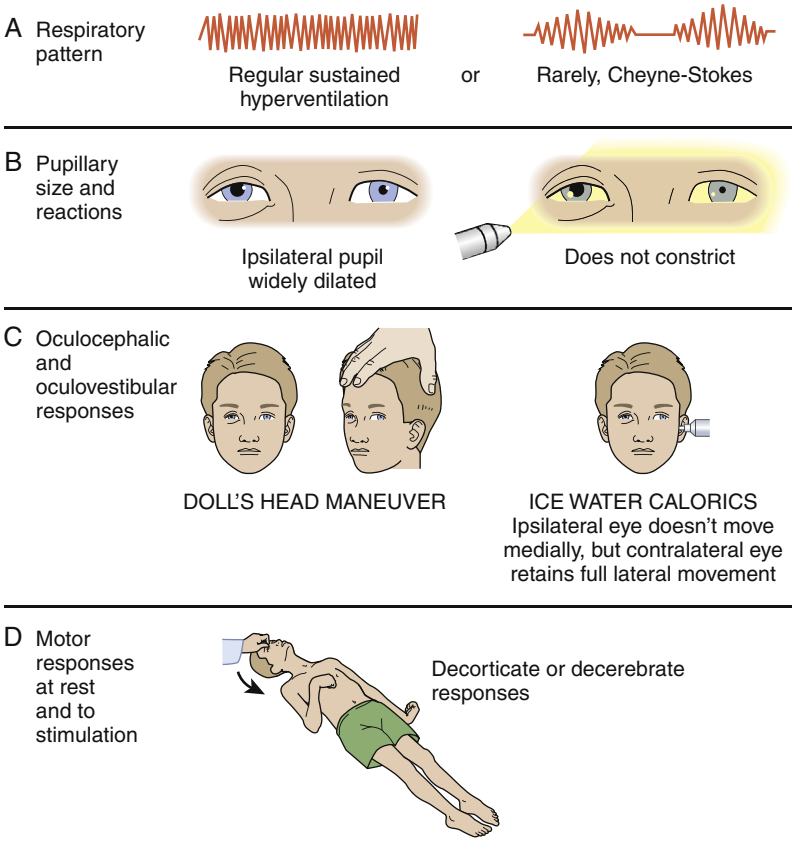


Figure 58–16. Uncal herniation—late third nerve stage. *(Modified from Posner JB, Saper CB, Schiff ND, et al, editors:* The diagnosis of stupor and coma, *ed 4, New York, 2007, Oxford University Press.)*

Box 58–3 Diagnostic Evaluation in a Patient with Coma

Investigations that Facilitate Supportive Therapy

Arterial blood gas level
Urea, electrolytes and creatinine, calcium, and magnesium levels
Blood sugar level
Osmolality of plasma and urine
Urine for ketones, sugar, and pH measurements
Complete blood cell count
Coagulation screening
Blood culture, urine culture, tracheal culture
Blood levels of anticonvulsants
Virology
Chest radiograph
Electrocardiogram
Electroencephalogram
Cerebral imaging: CT, MRI
Brainstem auditory-, visual-, and somatosensory-evoked potentials

Tests that May Provide a Specific Diagnosis

CSF examination
Toxicology screen
Blood ammonia level
Blood pyruvate and lactate levels
Amino acid profile
Organic acid analysis
Porphyrin levels
Liver function tests
Carnitine level
Serum lead level
Cortisol level
Skeletal survey
Cerebral imaging

Once they are medically stable, most patients with impaired consciousness of undetermined etiology should have a head computerized tomography (CT) scan or brain magnetic resonance imaging (MRI) performed to evaluate for structural causes of pathology (e.g., trauma, tumor, bleeding, infarction, abscess, or calcifications). MRI also is valuable in identifying sinus thrombosis, herpes simplex encephalitis, or acute demyelinating process (see also Chapter 56). Lumbar puncture should be deferred until the patient is neurologically and hemodynamically stable and the possibility of raised ICP is eliminated.[14] A normal CT scan is not a definitive indication of normal ICP; however, it can provide evidence in support of the physical examination. CSF should be collected to rule out bacterial infection as soon as it is deemed safe. Freezing a portion of the sample may assist in identifying viral or metabolic causes later. Additional blood or urine samples also may be obtained for further studies at later stages depending on the patient's clinical course and the initial laboratory evaluation. The EEG is essential to diagnose clinically apparent or subclinical seizures; it also is helpful in determining the prognosis in patients with hypoxic-ischemic encephalopathy (HIE) and in the diagnosis of brain death.[15,16]

Therapeutic Intervention

Pathophysiology following brain injury occurs in two phases: primary and secondary. Primary brain injury refers to the initial insult, whether it is ischemic, anoxic/hypoxic, or shear injury, each potentially resulting in irreversible neuronal cell injury or death. The only available treatment is prevention. Secondary brain injury occurs in otherwise salvageable brain tissue as a result of cerebral hypoxia, increased ICP, or decreased cerebral blood flow and may result in further neuronal damage. The goal of therapy is to prevent secondary brain injury.

In neurologic emergencies, evaluation of the patient's airway patency, ventilation, and circulatory status are paramount. Compared with other organs, metabolic activity in the brain is relatively high. The brain has little capacity to store glucose and accordingly depends on constant delivery of substrate and oxygen to maintain normal metabolic functions. Comatose patients often are hypercapnic and have hypoxemia. Thus supplemental oxygen should be provided to the patient with hypoxemia during the initial evaluation.

Upper airway obstruction as a result of decreased muscle tone of the pharyngeal soft tissue is a common problem in unresponsive patients. Once the cervical spine is protected, the clinician should always be prepared to support the airway with maneuvers that improve patency or with endotracheal intubation in unstable patients and in patients likely to become unstable. Once the patient's airway is maintained, adequacy of ventilation must be evaluated by examining the respiratory rate and respiratory effort. It also is common practice to endotracheally intubate patients with a GCS score less than 8, hemodynamic instability, and/or neurologic instability. In most circumstances, it is safer to endotracheally intubate electively rather than emergently to protect an already compromised brain from further injury as a result of respiratory failure. During endotracheal intubation, special precautions should be taken to protect cerebral circulation and prevent further increases in ICP. Pretreatment with lidocaine and thiopental may help to diminish raised ICP associated with airway manipulation. It is also important to maintain $Paco_2$ between 35 and 40 mm Hg.

Following stabilization of the airway and breathing, provision of adequate perfusion supersedes the need to treat any CNS lesion. Systemic shock must be corrected to reestablish adequate cerebral blood flow and hence oxygen and substrate delivery.[17] Once shock is corrected, some evidence indicates that blood pressure should be maintained higher than the 50th percentile for age to maintain adequate cerebral perfusion pressure pending placement of ICP monitoring equipment. Current guidelines suggest that isotonic solutions without dextrose are the preferred fluid for traumatic or ischemic CNS resuscitation in the absence of hypoglycemia.[18] However, any level of hypoglycemia must be avoided (see the next section).

Immediately Treatable Forms of Coma

After initial stabilization, clinicians should rapidly consider the causes of unresponsiveness that could easily and quickly be reversed. Experience gained from unresponsive adults suggests that all unresponsive infants and children should be immediately checked for hypoglycemia. Infants are susceptible to hypoglycemia because of relatively reduced glycogen storage and a higher metabolic rate. The blood glucose level can be checked quickly with use of a glucose reagent strip and abnormalities can be treated immediately with a bolus of D10W or D25W.

An overdose of narcotics should be considered in older children and adolescents. Particularly if the history and physical findings suggest narcotic ingestion, a trial of naloxone is warranted.

Seizures should always be considered, especially when the cause of coma is undetermined. Seizures should be treated immediately because prolonged status epilepticus has a high mortality rate and has been shown to cause neuronal necrosis. An extensive discussion of seizures and their treatment is provided in Chapter 60.

Rapidly Progressive Reversible Lesions

Space-occupying lesions frequently result in increased ICP, and this situation must be addressed immediately to avoid further damage and death. Therapy must be directed toward limiting the extent of secondary damage and preventing herniation by reversing the rapid rise in ICP and/or surgically addressing the lesion or hydrocephalus if present. When signs of central or uncal herniation are noted, the physician must respond rapidly and attempt to decrease ICP by altering the volume of one of the three intracranial constituents: brain, blood, or CSF. Interventions include elevating the head 30 degrees, keeping the head in midline position, hyperventilation, and administration of mannitol and/or hypertonic saline solution to rapidly decrease intracranial volume and ICP.[18,19] A complete discussion of treatment of ICP is presented in Chapters 59 and 61.

States Amenable to Prolonged Therapy

Certain brain insults are not readily reversible and require prolonged treatment to obtain the best possible outcome. Although the primary insult may not be reversible or may require extended care, secondary injury such as hypoxia and raised ICP can occur and cause further deterioration, despite the fact that the initial injury may not progress. Examples of primary insults that can have major secondary changes include encephalitis, meningitis, hypoxic-ischemic insults, and certain metabolic abnormalities such as hepatic failure and renal failure. Thus broad-spectrum antibiotics and antiviral therapy should be empirically started when meningitis or encephalitis is suspected, even if the lumbar puncture is deferred. Electrolyte imbalance, especially related to serum sodium either as an underlying cause or as a result of CNS insult due to inappropriate antidiuretic hormone secretion or diabetes insipidus, also should be appropriately corrected. It may be preferable to keep the serum sodium level around 150 mEq/L for first 72 hours. Hypoglycemia and/or hyperglycemia and variation in glucose level are associated with increased morbidity and mortality. These potential developments should be monitored and prevented, and hypoglycemia should be immediately treated.[20] Adequate blood pressure to maintain cerebral perfusion pressure is immensely important and can be ensured with appropriate fluid resuscitation and/or inotropic support. Untreated hypotension in patients with TBI is associated with increased morbidity and mortality.[17] It is important to maintain a mean arterial pressure of at least 50 mm Hg or higher for older pediatric patients. Although therapeutic hypothermia for the initial 24 to 48 hours following an anoxic-ischemic reperfusion event is helpful among adults following cardiac arrest or depressed newborns,[21,22] normal body temperature may be necessary for resolution of acidosis. Agitated patients may require sedation to prevent elevations in ICP. Patients should be adequately sedated for comfort and prevention of complications related to ventilation. Analgesia/anxiolysis titration using a standard scoring system can be helpful. Patients at risk of or demonstrating overt or subclinical seizures should be treated appropriately.

Outcome

The major causes of pediatric coma involve HIE and trauma. These conditions are serious and are common reasons for admission to the pediatric intensive care unit. Coma is associated with high morbidity and mortality. It also is hard to predict outcome early in the course. In children, improvement can continue over a very protracted time, even several years, long beyond the time when most adult patients will have reached their plateau of recovery.[23] Thus it is important to provide accurate and timely prognostic information if possible so that appropriate levels of care can be provided. The combination of physical signs, EEG, evoked potentials, and MRI provide useful prognostic information after 24 hours of HIE and can help in predicting outcome. These tests may need to be delayed to rule out compounding factors, and/or multiple tests may be required to provide the best prognostic information to families.[15,16]

TBI is a leading cause of death and disability in the pediatric age group. Neuropsychological and behavioral outcomes depend not only on the severity and type of injury and age at injury but also on premorbid conditions and the families' socioeconomic status.[24-26] Hypotension alone and hypoxemia associated with hypotension are significant predictors of disability and death in patients admitted with moderate to severe TBI. Early fluid resuscitation for hypotension, oxygen supplementation for hypoxemia, and ventilation for apnea in patients with TBI can have a significant impact on outcome.[17] Also, the presence of vascular injury, refractory ICP, elevated ICP, and cisternal effacement at presentation had the highest correlation with subsequent mortality and morbidity. Controlling elevated ICP is an important factor associated with survival following severe pediatric TBI.[27]

The outcome of coma following cardiopulmonary arrest is associated with greater than 80% mortality. Patients with out-of-hospital arrests have a worse outcome than those with inhospital arrests. Factors associated with 100% mortality were duration of asystole more than 15 minutes and administration of more than 1 dose of epinephrine.[22] Patients who were alert before resuscitation had better survival beyond 24 hours versus those who were comatose.

The precise prognosis of children with severe submersion injuries is difficult to determine within the first few hours of injury. In general, prolonged cardiopulmonary resuscitation, fixed and dilated pupils, and a GCS score of 3 portend a poor outcome.[28,29] Orlowski[16] developed a scoring system for evaluating prognosis in submersion injury based on five unfavorable prognostic factors: age less than 3 years, estimated submersion longer than 5 minutes, no attempts at resuscitation for 10 minutes, coma on admission to the emergency department, and severe acidosis with arterial blood pH 7.10 or less. A total score of 2 or less was associated with 90% chance of recovery, but a score of 3 or greater was associated with only

a 5% chance of recovery.[30] Coma following cerebral edema in patients with diabetic ketoacidosis is unpredictable, and outcomes are variable and may not be related to any specific management strategy.[31]

Ethical Considerations

The main purpose of coma prognostication is not merely to satisfy a parent's anxiety to know what the future holds but primarily to assist with difficult management decisions.[32] If within the acute period there is a high probability of death without regaining consciousness, decisions to withdraw life-sustaining technologies often are made. By contrast, a decision to withdraw support based on a high probability of survival with severe motor or mental disability is ultimately a judgment about quality of life, with the implication that "life with severe disability is worse than no life at all." Currently it is not possible to precisely predict outcome in patients in persistent vegetative states,[33] as distinct from death on the one hand or severe disability on the other. Life and death judgments based on quality of life appear more complex in pediatric versus adult patients. There are age-specific differences in coping and adapting to injuries that cause physical or mental disability. Younger children adapt better to physical and mental disability, and those adaptations may be better incorporated in family life.

Terms such as "mild," "moderate," or "severe" disability can subjectively describe levels of neurologic dysfunction. Categories such as "favorable" or "unfavorable" convey value judgments. Thus it is important to use appropriate terminology for coma prognosis. Parents of disabled children tend to strongly disagree with subjective and judgmental terminology, such as life with a "poor" or "unfavorable" outcome even if at a time after brain insult that they might feel utterly incapable of ever learning to cope with such an outcome. Thus with respect to ethical implications as well as the neurobiology of coma prognosis, the adage holds true: "children are not miniature adults."

References are available online at http://www.expertconsult.com.

IV Chapter 59

Intracranial Hypertension and Brain Monitoring

Robert C. Tasker and Marek Czosnyka

PEARLS

- As intracranial hypertension progresses, changes may occur in the vital signs, with an elevation of blood pressure, a decrease or an increase in pulse, and irregularity in the respiratory rhythm. These signs, sometimes associated with episodes of decerebrate rigidity, indicate the occurrence of transtentorial herniation or "coning" and imply the possibility of impending death if the process cannot be reversed.
- The continuous measurement of intracranial pressure is an essential modality in most brain monitoring systems. After a decade of enthusiastic attempts to introduce newer modalities for brain monitoring (e.g., tissue oxygenation, microdialysis, cortical blood flow, transcranial Doppler ultrasonography, and jugular bulb oxygen saturation), the measurement of intracranial pressure has become increasingly noticeable as a robust and only moderately invasive modality, and it can be realistically conducted in most critical care units.

In most organs in the human body, the environmental pressure for blood perfusion is either low or coupled to atmospheric pressure. The environmental pressure for the brain differs in this respect because the brain is surrounded and protected by a stiff skull. Thus a rise in environmental pressure—intracranial pressure (ICP)—may impede blood flow and cause ischemia. In pediatric critical care, ICP may be of acute significance in a number of instances (e.g., traumatic brain injury, bacterial meningitis, and the Fontan circulation). In this chapter we discuss how information from ICP monitoring helps our understanding and treatment of brain disorders.

Clinical Background

In critical illness, the early recognition and treatment of intracranial hypertension is important because it is a major cause of mortality and morbidity. Therefore an attempt should be made to collate the clinical evidence for and against its presence. The early symptoms and signs of this complication, however, which are invariably subtle and nonspecific (Table 59-1), make this form of assessment somewhat limited. As will be discussed later, as intracranial hypertension progresses, changes may occur in the vital signs, with an elevation of blood pressure, a decrease or an increase in pulse, and irregularity in the respiratory rhythm. These signs, sometimes associated with episodes of decerebrate rigidity, indicate the occurrence of transtentorial herniation or "coning" and imply the possibility of impending death if the process cannot be reversed. Unfortunately recognition at this stage is often too late to prevent death.

Brain tissue shifts may produce various "syndromes." First, transtentorial or cerebellar herniation may result in midbrain or medullary compression. Many of the clinical signs observed in association with herniation result from direct compression of structures by the impacted tissue or are due to angulation of nerves or arteries against normal structures in the area. These herniations can cause increasing coma, with distortion of the brainstem leading to midbrain and pontine hemorrhages. Cerebellar herniation is likely to occur when the increase in ICP is maximal in the posterior fossa. Such herniation occurs more commonly downward, squeezing one or more of the cerebellar tonsils through the foramen magnum; compressing the medulla; and leading to neck stiffness, head tilt, lower cranial nerve palsies, respiratory irregularities, or sudden cardiorespiratory arrest. Cerebellar herniation may occur upward through the tentorial notch, causing midbrain compression and leading to paralysis of upward gaze, dilated

Table 59–1 Early, Subtle Symptoms and Signs of Raised Intracranial Pressure

	Infant	Child
General state	Poor feeding	Anorexia and nausea
	Vomiting	Vomiting
	Irritability to coma	Lethargy to coma
	Seizures	Seizures
Head/eyes	Full fontanelle	False localizing signs
	Scalp vein distention	
	False localizing signs	
Other	Altered vital signs	Altered vital signs
	Hypertension	Hypertension
	Pulmonary edema	Pulmonary edema

Table 59–2 Clinical Features of Central Syndrome or Rostrocaudal Deterioration

Stage	Level of Consciousness	Respiration	Pupil Size and Reactivity	Oculocephalic and Oculovestibular Responses	Posture and Tone
Diencephalic (early to late) ↓	Agitation Drowsiness Stupor	Deep sighs or yawns Occasional pauses Cheyne-stokes or periodic breathing	Small (1–3 mm) with brisk reaction to light	Conjugate at rest and respond quickly	Normval or slightly increased Generalized muscular hypertonus
Midbrain to upper pontine ↓	Coma	Central hyperventilation	Midpositon (3–5 mm) with sluggish reaction to light	Dysconjugate	Decorticate posturing and increased tone
Lower pontine to upper medullary ↓	Deep coma		Midposition and fixed	Absent	Flaccid: (1) retained bilateral extensor plantars, (2) occasional flexor responses in the lower limbs
Medullary (terminal)	Deep coma	Irregular breathing interrupted by deep sighs, gasps, and then terminal apnea	May be unequal	Absent	Flaccid

Modified from Plum F, Posner JB: *Diagnosis of stupor and coma,* Philadelphia, 1966, FA Davis.

and fixed pupils, and respiratory abnormalities, although this type of cerebellar herniation is uncommon.

When intracranial hypertension is more marked in the supratentorial compartment, for instance, with acute intracerebral hematoma, the temporal lobe on the affected side may be displaced into the tentorial notch and result in unilateral transtentorial herniation. The herniation may be more marked anteriorly (uncal) or posteriorly (hippocampal) and is usually accompanied by displacement of the ipsilateral cingulate gyrus under the falx (cingulate herniation). Clinical manifestations of this condition may include ipsilateral third nerve palsy, contralateral hemiparesis, respiratory irregularities, deepening coma with decerebrate posturing, and ultimately cardiorespiratory arrest.

Finally, when bilateral or a general increase in ICP in the supratentorial compartment occurs, as in diffuse cerebral edema, central transtentorial herniation may occur. This condition leads to impairment of upward gaze, pupillary constriction, hypertonus, and decerebrate posturing. Temperature irregularities and diabetes insipidus may develop, and cardiorespiratory arrest may occur eventually. A summary of the clinical features of "central syndrome" is given in Table 59-2.

Physiology of the Intracranial Vault

A physiologic process underlies the clinical picture of intracranial hypertension, and in this section of the chapter our intention is to familiarize the pediatric intensivist with new approaches to understanding the hydrodynamic function of the intracranial vault. In other words, what happens before brain tissue shifts occur? Most of the developments in this field have occurred in the setting of adult neurosurgery and critical care. In common with any aspect of physiology, the tasks have been straightforward: Can it be measured? Can it be modeled? How do the models help in the understanding of the underlying homeostasis and the mechanism of derangement and perturbation? We highlight these topics and hope you will see the obvious application to pediatric critical care; that is, use of this form of cerebral monitoring and potential approaches to ICP assessment. In many specific conditions, however, knowledge is still lacking with regard to which parts of the adult-generated theory may be fully applicable to children.

Intracranial Pressure

The brain is an expansile structure that expands and contracts with each beat of the heart. Because there are no valves within the venous drainage from the brain, any changes in intrathoracic pressure are transmitted to ICP. Such phenomena can be seen and palpated simply through the examination of a baby's fontanelle and quantified with cerebrospinal fluid (CSF) pressure recording. Once the cranial sutures have fused, any change in cerebral blood volume (CBV) on the arterial-to-arteriolar side of the cerebral circulation must be compensated by either reduction in cerebral venous volume or by phasic movement of CSF out of the intracranial vault through the foramen magnum. Such expansion of the cerebral mantle with compression of the lateral ventricles during systole and movement of CSF through the aqueduct of Sylvius and to and fro through the foramen magnum was first visualized with pneumoencephalography. These changes now can be seen more easily with dynamic magnetic resonance imaging (MRI). Inevitably a lag phase exists between the systolic increase in CBV and the effect of the compensatory mechanisms so that CSF pressure increases to reflect, in part, the systolic waveform. The CSF pressure waveform is not an exact replica of the arterial waveform because it has been "filtered" by the combined effects of arterial wall compliance of the cerebral arteries, cerebrovascular resistance, and intracranial compliance (Figure 59-1).[1]

Hydrodynamic Model of Intracranial Pressure

ICP is a function of the circulation of cerebral blood and CSF in which ICP is related to a vascular component ($ICP_{vascular}$) and a CSF component (ICP_{CSF}). There is considerable interest

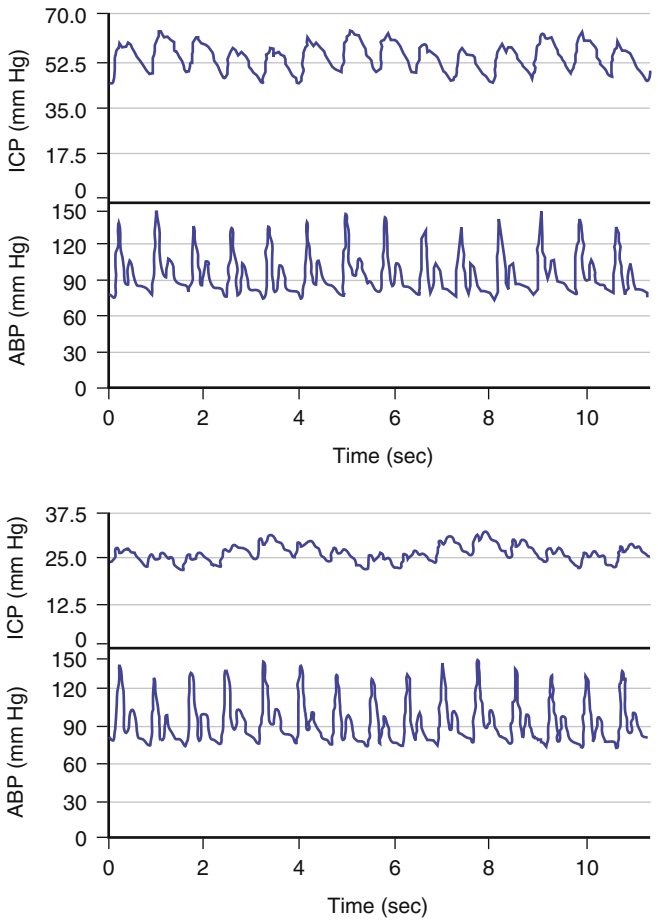


Figure 59–1. Examples of waveforms of intracranial pressure *(ICP)* and arterial blood pressure *(ABP)* recorded at a high level of ICP (*upper plots*) and a lower level of ICP (*lower plots*). Note that the pattern of ABP waveform is relatively invariant, but ICP changes its shape considerably.[1]

in modeling these relationships as an aid to understanding some of the complex phenomena seen in critically ill patients. The vascular component is difficult to express quantitatively.[2] It is probably derived from the pulsation of CBV that is detected and averaged by nonlinear mechanisms of regulation of CBV. More generally, multiple variables such as the arterial blood pressure (ABP), autoregulation, and cerebral venous outflow all contribute to the vascular component. In regard to the other component, circulation of CSF, 80% of CSF is the product of active secretion by the choroid plexus, and movement of interstitial fluid into the ventricles and subarachnoid space contributes the remainder. Drainage is largely passive via arachnoid villi and granulations into the superior sagittal sinus and spinal root sleeve venous drainage. Some drainage, which is currently unquantifiable, occurs through the olfactory bulb and mucosa into the deep cervical lymphatics. The equation by Davson and colleagues[3] shows the immediate relationships controlling CSF pressure, in which ICP_{CSF} = (Resistance to CSF outflow) × (CSF formation) + (Pressure in sagittal sinus). With these two components—vascular and CSF—taken together, Figure 59-2 shows the hydrodynamic model of cerebral blood flow (CBF) and CSF circulation and the equivalent electrical circuit.[4] This model can be used to interrogate CSF dynamics clinically (described later in this chapter).

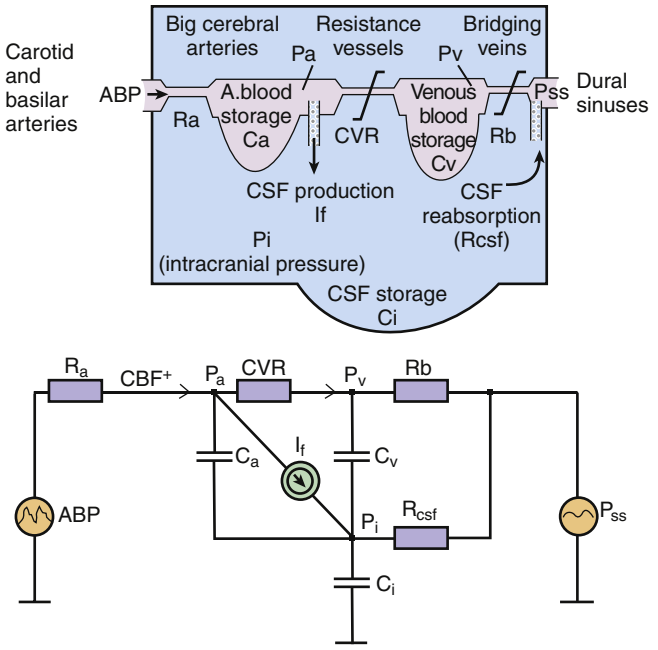


Figure 59–2. Hydrodynamic model of cerebral blood and cerebrospinal fluid (CSF) circulation (*upper plot*) and its electrical equivalent (*lower plot*).[4] *ABP,* Arterial blood pressure; *CBF,* cerebral blood flow.

Cerebral Vasodilation and Cerebrospinal Fluid Pressure

Three major factors regulate CBF: cerebral perfusion pressure (CPP), partial pressure of arterial carbon dioxide ($Paco_2$), and partial pressure of arterial oxygen (Pao_2). Hypercapnia causes cerebral vasodilatation, increases CBF, and increases ICP. Hypoxia also causes cerebral vasodilatation and a rise in ICP. CPP is taken as the difference between mean ABP and ICP and represents the pressure gradient acting across the cerebrovascular bed; therefore it is an important factor in regulation of CBF.[5] Under normal circumstances, over a wide range of CPP, CBF is autoregulated (i.e., it remains constant when CPP varies). Thus in regard to the effect of this phenomenon on ICP, active cerebral arteriolar constriction occurs and ICP consequently falls to maintain CBF when ABP is increased (i.e., hypertension). At the other extreme, systemic hypotension (within the autoregulatory range) provokes cerebral vasodilatation and an increase in ICP. When autoregulation is defective, ICP increases and decreases with ABP (Figures 59-3 and 59-4).[4]

In practice, measurement of ICP can be used to estimate the CPP when it is the most significant "downstream" pressure acting on vascular perfusion. However, in some instances, venous pressure may be of more significance, such as critical Fontan circulation.

Cerebral Perfusion Pressure and Autoregulation

In adults, the lower limit for CPP is taken as a threshold of 60 to 70 mm Hg. In children, however, it is evident from measurement of normal ABP that the lower limit for CPP must be lower than this adult level for much of childhood (Figure 59-5).[6] A new concept that has arisen in the adult critical care

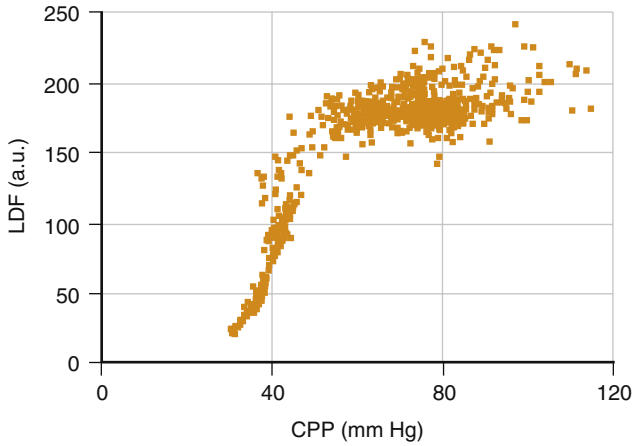


Figure 59–3. Pressure autoregulation where cerebral blood flow *(CBF)* stays constant. CBF is measured with laser Doppler flowmetry *(LDF)* (*y axis*). During changes in cerebral perfusion pressure *(CPP) (x axis),* CBF remains constant until a critical threshold is reached, below which CBF falls passively with decreasing CPP.

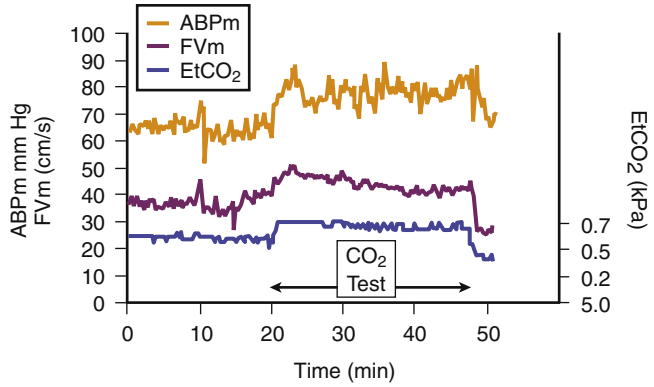
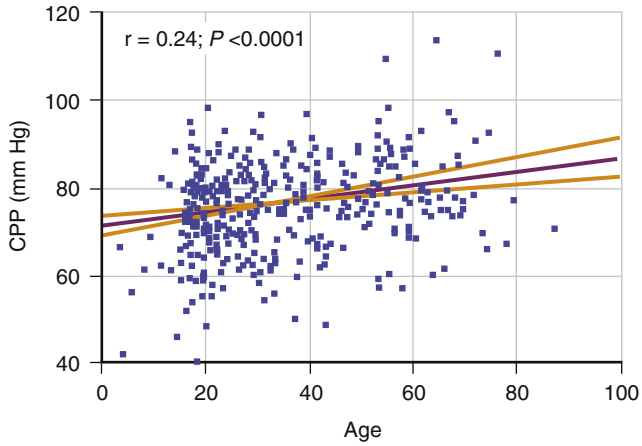


Figure 59–4. Cerebral vessels dilate when arterial content of carbon dioxide (here measured with end-tidal carbon dioxide [E_tCo_2]) increases. A rise in cerebral blood flow (here assessed with transcranial Doppler velocity [FVm]) also increases.[5] *ABPm,* Mean blood pressure.



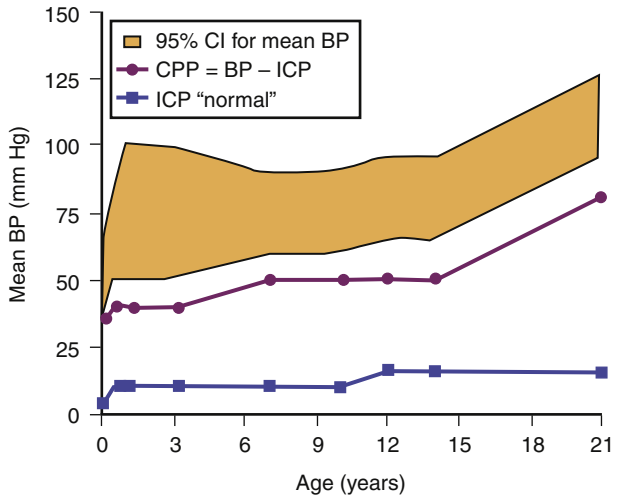


Figure 59–5. *Top panel,* The empiric relation between cerebral perfusion pressure *(CPP)* and age in nearly 400 adults after head injury. *Bottom panel,* Estimated lower limit of CPP by age in the pediatric range on the basis of normal blood pressure *(BP)* and intracranial pressure *(ICP)* data.[6]

literature is worth considering in this context. The idea is that a autoregulatory reserve exists that is considered to be the difference between current mean CPP and the lower limit of autoregulation.[7] This reserve may become exhausted. Alternatively, it may change over time, and it has been argued that the border between adequate and nonadequate CPP should be assessed individually and frequently.

How is this assessment performed? Autoregulation of CBF may be assessed by artificial manipulation of ABP with medication, but only at infrequent intervals and with the risk that the drugs used may have a direct cerebrovascular effect. Alternatively, transient hyperemia after transient carotid compression has been used as an all-or-none index of whether autoregulation is intact. A more sophisticated approach is to examine the effect of natural variation in ABP; however, this technique requires precise signal processing. For example, to date, the most robust clinical method is to monitor the slow fluctuations in ABP that last from 30 seconds to a few minutes and are almost always present in patients who undergo ventilation[8-9]; the rate of change observed is usually sufficient to provoke a noticeable vasomotor response. Figure 59-6 shows that continuous monitoring of cerebrovascular reactivity is possible with this method even during large spontaneous ICP waves (B and plateau waves; discussed later in this chapter).[10]

Measurement of Intracranial Pressure

Monitoring Devices

ICP monitoring devices can be categorized according to the anatomic site of placement and the manner in which the pressure record is transduced. For example, in babies, surface tonometry, applied to the anterior fontanelle, was an early method used for noninvasive transduction of the ICP waveform. This method, however, is limited because the force of applanation influences the pressure record. More standard approaches for the measurement of ICP rely on manometry of catheters placed in the ventricular system or in other CSF space. Alternatively, pressure sensors may be placed within the brain.

The complications of ICP monitoring include infection, hemorrhage, CSF overdrainage, and monitor malfunction. The overall incidence of infection for the various forms of ICP monitors is not significantly different regardless of their location, but the severity of infection may differ slightly depending on the anatomic site of the device. Hemorrhage is a rare

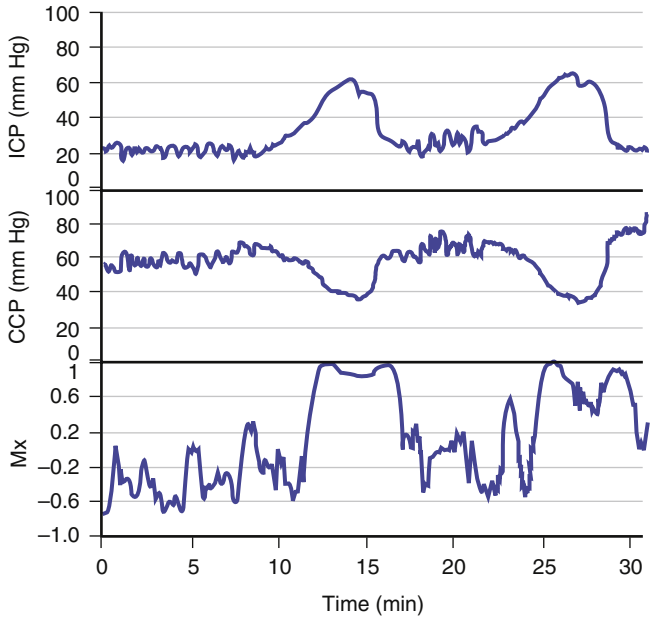


Figure 59–6. Continuous monitoring of cerebral autoregulation during plateau waves of raised intracranial pressure *(ICP)*. Positive values of the autoregulation index *(Mx)* indicate faulty autoregulation.[9] Autoregulation fails during the waves, when cerebral vasodilation occurs.[10] *CPP,* Cerebral perfusion pressure.

complication of ICP monitoring and is a direct result of surgical placement of the device. Overdrainage of ventricular catheters can result in rapid emptying of the ventricular system and accumulation of subdural hematomas. Close attention must be made to prevent drainage systems from being placed too low or falling to the floor. This complication is most serious when intraventricular pressure is monitored in children with hydrocephalus. Overdrainage also may result in pneumocephalus.

Overall, an intraventricular drain connected to an external pressure transducer is still considered the gold standard for measuring ICP.[11,12] ICP can be controlled by CSF drainage, and the transducer can be adjusted to zero externally. After 5 days of monitoring, however, the risk of infection starts to increase, with an overall risk estimated to be about 5%.[13] Insertion of the ventricular catheter may be difficult or impossible in cases of advanced brain swelling. As an alternative, modern catheter-tipped ventricular, subdural, or intraparenchymal microtransducers have been used (the most popular types are the Camino ICP Bolt, Camino Laboratories, San Diego, Calif., and Codman MicroSensor, Johnson and Johnson Professional Inc, Raynham, Mass.). These microtransducers are said to reduce the infection rate and risk of hemorrhage[13] and have excellent metrologic properties.[14] One disadvantage of microtransducer systems is that they cannot, in general, be readjusted to zero after insertion, and considerable zero drift sometimes can occur in long-term monitoring.[15]

Regarding other forms of monitoring, contemporary epidural sensors are much more reliable now than they were 10 years ago. Nevertheless, the question as to whether epidural pressure can express ICP with confidence and under all circumstances is still unanswered. Lumbar CSF pressure is seldom measured in patients receiving neurointensive care. This form of assessment of craniospinal dynamics is more often used in the assessment of hydrocephalus and benign intracranial hypertension. It is unreliable if the instantaneous value of the fluid column pressure is recorded; at least 30 minutes averaging in resting conditions (with a period of overnight monitoring as the gold standard) is the desired requirement. Finally, attempts to monitor ICP noninvasively are still in a phase of technical evaluation,[16] with the most promising methods based on transcranial ultrasonography.[17,18]

Noninvasive Inference of Intracranial Pressure

It would be helpful to measure ICP or CPP without invasive transducers. To this end, transcranial Doppler (TCD) examination,[19] tympanic membrane displacement,[20] and ultrasound "time of flight"[18] techniques have been suggested. The description of TCD sonography by Aaslid, Markwalder, and Nornes[21] permitted bedside monitoring of one index of CBF noninvasively, repeatedly, and even continuously. The problem has been that it is a "big tube technique" that measures flow velocity in branches of the circle of Willis, most commonly the middle cerebral artery (MCA). Compliant branches of the MCA can be compared with two physiologic pressure transducers. The pattern of blood flow within these tubes is certainly modulated by transmural pressure, that is, CPP and the distal vascular resistance (also modulated by CPP). What is the calibration factor, and how should we compensate for unknown nonlinear distortion?

Reasonable correlation exists between the pulsatility index of MCA velocity and CPP after head injury, but absolute measurements of CPP cannot be extrapolated.[22] Other investigators have suggested that "critical closing pressure" derived from flow velocity and arterial pressure waveform approximated the value of ICP.[23] The accuracy of this method, however, has never been satisfactory.[24] Aaslid et al.[25] suggested that an index of CPP could be derived from the ratio of the amplitudes of the first harmonics of the ABP and the MCA velocity (detected with TCD sonography) multiplied by mean flow velocity. Recently, a method for the noninvasive assessment of CPP has been reported, derived from mean ABP multiplied by the ratio of diastolic to mean flow velocity.[26] This estimator can predict real CPP—in the adult range (60 to 100 mm Hg)—with an error of less than 10 mm Hg for more than 80% of measurements. This method is of potential benefit for the continuous monitoring of changes in real CPP over time in situations where direct measurement of CPP is not readily available. Finally, a more complex method aimed at the noninvasive assessment of ICP has been introduced and tested by Schmidt et al.[27] The method is based on the presumed linear transformation between ABP and ICP waveforms. All of these techniques still require validation in pediatric series.

Last, there is one other potential method for predicting increased ICP that has emerged from the adult literature and is now being tested in children. Optic nerve sonography can be used to assess enlargement of the optic nerve sheath, and it is sheath diameter that appears to be directly related to the level of ICP.[28] A recent study by Le et al[29] included 64 children, 24 (37%) of whom had a confirmed diagnosis of increased ICP. An optic nerve sheath diameter greater than 4.0 mm in subjects younger than 1 year and greater than 4.5 mm in older children was considered abnormal. The sensitivity of optic nerve sheath diameter as a screening test for increased ICP was 83% (95% confidence interval [CI], 0.60 to 0.94); specificity

was 38% (95% CI, 0.23 to 0.54); positive likelihood ratio was 1.32 (95% CI, 0.97 to 1.79); and negative likelihood ratio was 0.46 (95% confidence interval, 0.18 to 1.23). Taken together, it is clear that this technique may be useful, but currently it is inadequate as an aid to decision making about whether raised ICP is present in a particular child.

Pressure Compartments

In a fluid-filled container, pressure is the same wherever one chooses to measure it within that space. Generally, uniformly distributed ICP can be seen only when CSF is circulating freely among all of its natural pools, equilibrating pressure everywhere. When little or no CSF volume is left (because of brain swelling), the assumption of one uniform value of ICP is questionable. (It is for this reason that brain tissue shift and herniation occur: they move down tissue pressure gradients.) It is worth remembering that with the commonly used catheter-tipped, intraparenchymal probes, the measurement of pressure is at a particular point, an area of cortex within a hemisphere, and the ICP may merely reflect pressure in that compartment rather than be representative of pressure within the ventricular system (i.e., real CSF pressure).[30]

Analysis of Intracranial Pressure

Normal Values in Intracranial Pressure Monitoring

Establishing a universal "normal value" for ICP is difficult because it depends on age, body posture, and clinical condition. In the horizontal position, a normal ICP value in healthy adults was reported to be within the range of 7 to 15 mm Hg.[31] In the upright position ICP is a negative value, with a mean of around ~10 mm Hg but not exceeding ~15 mm Hg.[32] In infants and children, normal values for ICP, usually taken at the time of a "negative" diagnostic lumbar puncture, are lower than the adult values and are probably between 5 and 10 mm Hg.

The definition of a raised ICP value depends on the specific disease. In hydrocephalus, a pressure above 15 mm Hg can be regarded as elevated. After head injury, any pressure above 20 mm Hg is considered abnormal, and aggressive treatment is usually started with values above 25 mm Hg.[33] Also, in most cases, ICP varies with time. Decent averaging for at least 30 minutes is needed to calculate "mean ICP." The patient should be in a horizontal position during the measurement, and movement should be avoided.

Normal Trends in Intracranial Pressure and Waveform Analysis

Overnight monitoring, during natural sleep, provides a "grand average" with a good description of the dynamics of ICP. When monitored continuously in acute states (e.g., in the presence of head injury, poor-grade subarachnoid hemorrhage, and intracerebral hematoma), changes in the time-averaged mean ICP may be classified into relatively few patterns (Figure 59-7).[34] The first pattern, low and stable ICP (below 20 mm Hg) is seen after uncomplicated head injury (Figure 59-7, *A*). Such a pattern also is seen commonly in the initial period after brain trauma before brain swelling evolves. The second pattern, high and stable ICP (above 20 mm Hg), is the most common pattern to follow head injury (Figure 59-7, *B*). The third pattern is vasogenic waves, that is, B waves (Figure 59-7, *C*) and plateau waves (Figure 59-7, *D*). The fourth pattern is ICP waves related to changes in ABP and hyperemic events (Figure 59-7, *E* to *G*). The final pattern, refractory intracranial hypertension (Figure 59-7, *H*), usually leads to death unless surgical decompression is undertaken.

In addition to these patterns, more information can be gained from analyzing the ICP waveform. The ICP waveform consists of three components, which overlap in the time domain but can be separated in the frequency domain (Figure 59-8).[34,35] The pulse waveform has several harmonic components; of these, the fundamental component has a frequency equal to the heart rate. The amplitude of this component (AMP) is useful for the evaluation of various indices. The respiratory waveform is related to the frequency of the respiratory cycle (8 to 20 cycles/min). "Slow waves" are usually not as precisely defined as in Lundberg's original work[36]; that is, all components that have a spectral representation within the frequency limits of 0.05 to 0.0055 Hz (20-second to 3-minute period) are considered slow waves. The magnitude of these waves can be calculated as the square root of the power of the signal, of the passband, or of the equivalent frequency range at the output of the digital filter.

Assessment of Pressure-Volume Compensatory Reserve and Cerebrovascular Pressure Reactivity

Theoretically, the compensatory reserve in intracranial hydrodynamics can be studied through the relation between ICP and changes in volume of the intracerebral space, known as the pressure-volume curve.[37,38] For example, the RAP index, an index of reserve based on the correlation coefficient (R) between AMP amplitude (A) and mean pressure (P), can be derived. This calculation can be done in real time with bedside computing to calculate the linear correlation between consecutive, time-averaged data points of AMP and ICP (usually 40 such samples) acquired over a reasonably long period to average over respiratory and pulse waves (usually 6- to 10-second epochs). The RAP index indicates the degree of correlation between AMP and mean ICP over short periods (~4 minutes). An RAP index close to zero indicates lack of synchronization between changes in AMP and mean ICP. This index denotes good pressure-volume compensatory reserve at low ICP (i.e., a change in volume produces little or no change in pressure) (Figure 59-9).[39] When the RAP index rises to +1, AMP varies directly with ICP and indicates that the "working point" of the intracranial space shifts to the right toward the steep part of the pressure-volume curve. Here compensatory reserve is low; therefore any further rise in volume may produce a rapid increase in ICP. After head injury and subsequent brain swelling, the RAP index is usually close to +1. With any further increase in ICP, AMP decreases and RAP values fall below zero. This phenomenon occurs when cerebral autoregulatory capacity is exhausted; the pressure-volume curve bends to the right, the capacity of cerebral arterioles to dilate in response to a fall in CPP is exhausted, and the arterioles tend to collapse passively. This phenomenon indicates terminal

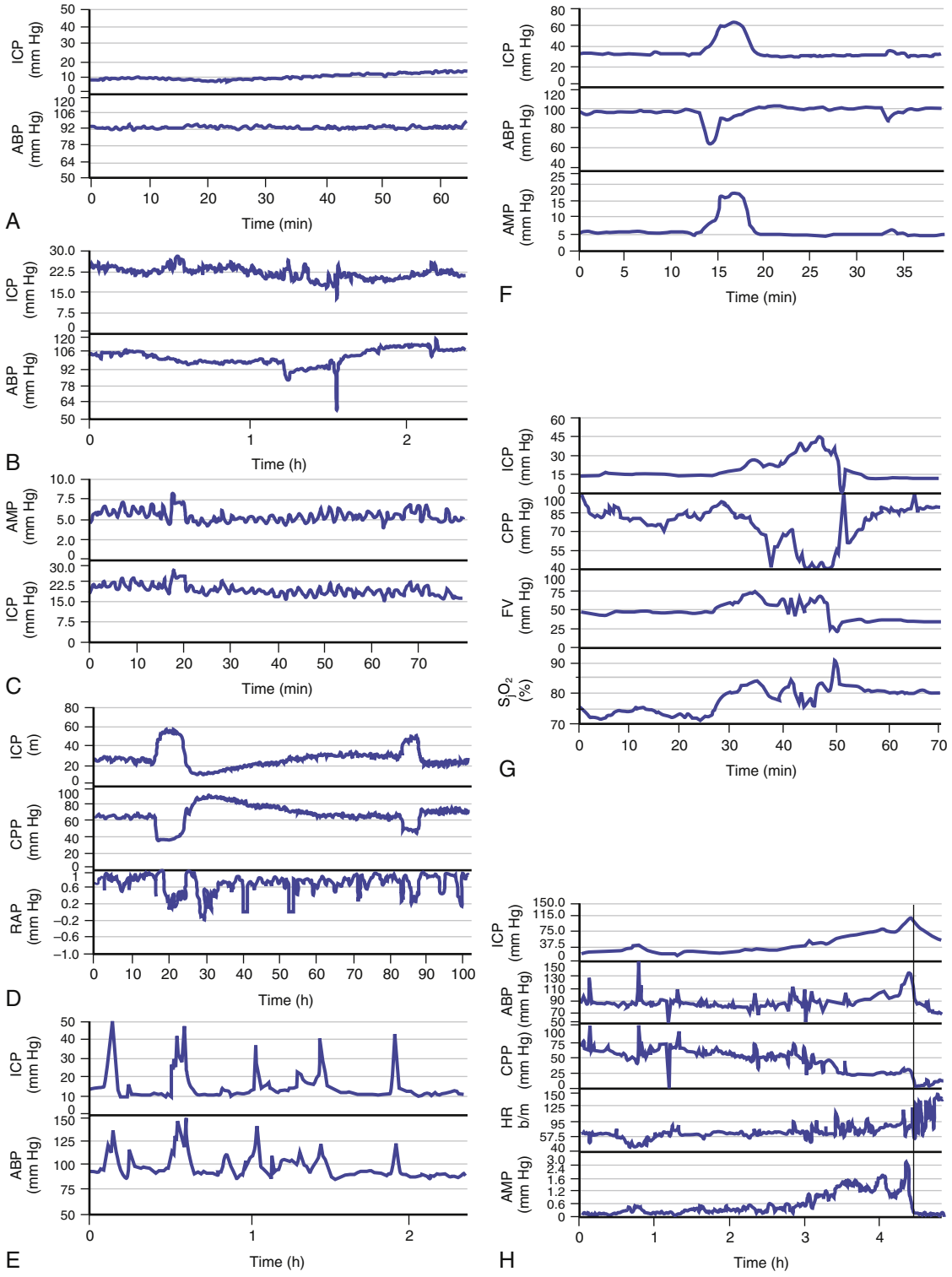


Figure 59–7. Examples of intracranial pressure *(ICP)* recording in various clinical scenarios after head trauma[34]; note the different scales. **A,** Low and stable ICP: mean arterial blood pressure *(ABP)* is plotted in the *bottom panel*. **B,** Stable and elevated ICP: such a picture can be seen most of the time in patients with head injuries. **C,** B waves of ICP: these are seen both in mean ICP and spectrally resolved pulse amplitude of ICP *(AMP)*. They also are usually seen in a plot of time-averaged ABP, but not always. **D,** Plateau waves of ICP: cerebrospinal compensatory reserve is usually low when waves are recorded (the correlation coefficient between AMP and mean ABP, RAP, is close to +1). At the top of the waves, during maximal vasodilatation, integration between pulse amplitude and mean ICP fails, as indicated by afall in RAP. After the plateau wave, ICP usually falls below the baseline level and cerebrospinal compensatory reserve becomes better. *CPP,* Cerebral perfusion pressure. **E,** High, spiky waves of ICP caused by sudden increases in ABP. **F,** Increase in ICP caused by temporary decrease in ABP. **G,** Increase in ICP of hyperemic nature: both blood flow velocity *(FV)* and jugular bulb oxygen saturation *(Sjo_2)* increase in parallel with ICP. **H,** Refractory intracranial hypertension: ICP increases within a few hours to 100 mm Hg. The *vertical line* denotes the likely moment when the vasomotor centers in the brainstem became ischemic. At this point the heart rate *(HR)* increased and CPP decreased abruptly. Note that pulse amplitude of ICP *(AMP)* disappeared around 10 minutes before this terminal event.

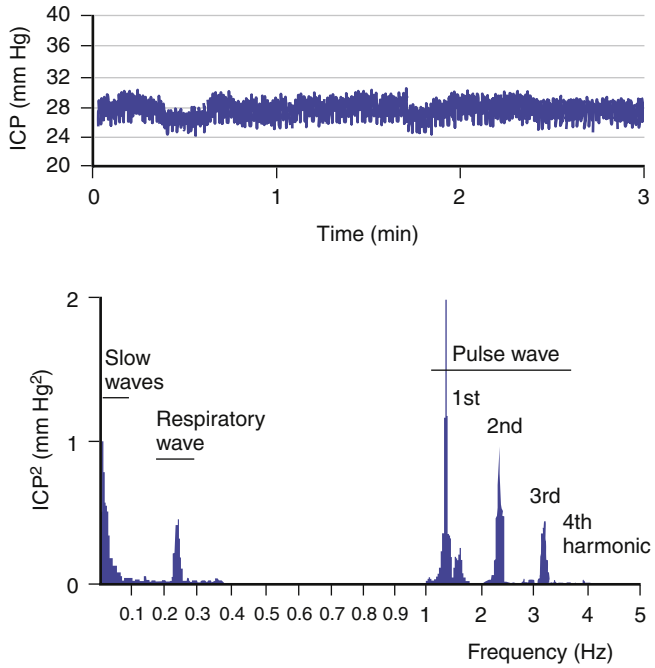


Figure 59–8. Example of intracranial pressure *(ICP)* recording showing pulse, respiratory waves, and "slow waves" overlapped in the time domain (*top panel*) and separated in the frequency domain (*bottom panel*).[35]

cerebrovascular derangement with a decrease in pulse pressure transmission from the arterial bed to the intracranial compartment.

Another ICP-derived index is the pressure-reactivity index (PRx), which incorporates the idea of assessing cerebrovascular reaction by observing the response of ICP to slow spontaneous changes in ABP (discussed previously).[40] For example, when the cerebrovascular bed is normally reactive, any change in ABP produces an inverse change in CBV and thus ICP. When cerebrovascular reactivity is disturbed, changes in ABP are transmitted passively to ICP. Again, with the use of computational methods similar to those used for the calculation of the RAP index, PRx is determined with the calculation of the correlation coefficient between 40 consecutive, time-averaged data points of ICP and ABP. A positive PRx signifies a positive gradient of the regression line between the slow components of ABP and ICP, which is suggested as being associated with passive behavior of a nonreactive vascular bed (Figure 59-10, *A*).[8] A negative value of PRx reflects a normally reactive vascular bed, because ABP waves provoke inversely correlated waves in ICP (Figure 59-10, *B*). In practice, this index correlates well with TCD ultrasonography indices of autoregulation.[8] Also, abnormal values of both PRx and RAP, which are indicative, respectively, of poor autoregulation or deranged cerebrospinal compensatory reserve, have been shown to be predictive of a poor outcome in adults after head injury.[7]

To date, there are few data on the use of these hydrodynamic indices in children. One report in 32 hydrocephalic children, however, examined maximum ICP, RAP index, magnitude of slow waves, and AMP in individuals presenting with possible ventriculoperitoneal shunt dysfunction.[41] The authors concluded that, because of the association between abnormalities in the parameters studied and improvement in symptoms in patients undergoing shunt revision, such computerized ICP assessments are beneficial. In another study of 21 children with head injuries, Brady et al.[42] used continuous monitoring of the PRx and found this parameter to be associated with outcome. In addition, they found that impaired cerebrovascular pressure reactivity was evident at low levels of CPP. The implication is that PRx may be useful for defining age-specific and possibly patient-specific optimal targets for CPP (see the following section).

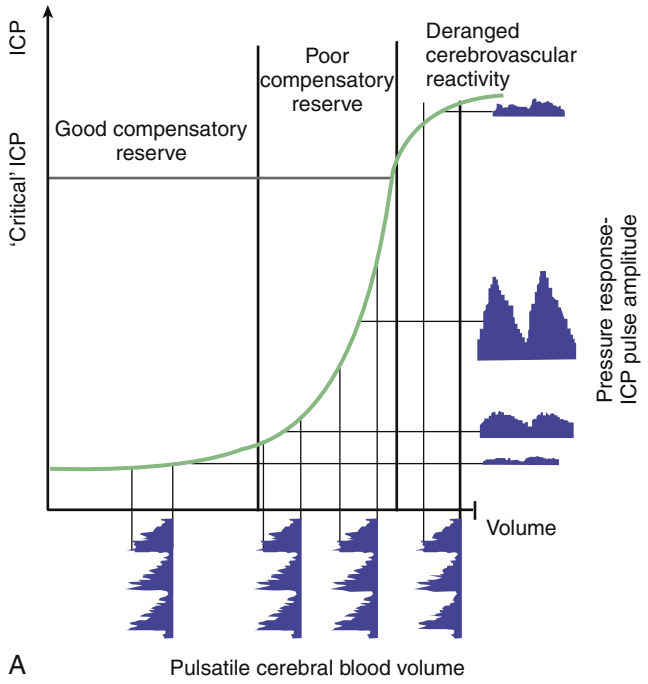
Monitoring Optimal Cerebral Perfusion Pressure Derived from Intracranial Pressure Parameters

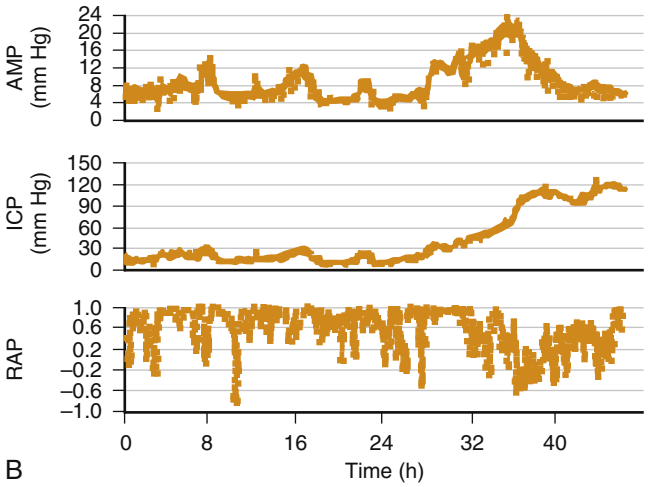
Both the PRx and the RAP index can be used to evaluate secondary variables that combine the value of absolute ICP and CPP with information about the state of autoregulatory and compensatory reserves. In adults with head trauma, PRx plotted against CPP gives a U-shape curve that indicates, for most patients, a value of CPP for which pressure-reactivity is optimal.[7] This optimal pressure can be estimated with the plotting and analyzing of the PRx-CPP curve in sequential 6-hour periods; the greater the distance between the current and the "optimal" CPP, the more likely outcome will be poor. This potentially useful method attempts to refine the current approach to CPP-oriented therapy: levels of CPP that are either too low (ischemia) or too high (hyperemia and a resulting increase in ICP) are detrimental. It has been suggested that CPP in adults should be optimized to maintain CPP in the most favorable global state.[7]

Quantifying the Cumulative Intracranial Pressure/Cerebral Perfusion Pressure Insult to the Brain

In adults with severe head injury, the cumulative insult to the brain can be quantified in a number of ways. For example, an average ICP above 25 mm Hg during the entire period of monitoring doubles the risk of death.[7] Averaged values of the RAP index and the PRx also are strong predictors of fatal outcome. Both these indices suggest that good vascular reactivity is an important element of brain homeostasis, which enables the brain to protect itself against an uncontrollable rise in intracerebral volume. Also, a low value of slow waves of ICP also is indicative of a fatal outcome after head injury. Because each of these parameters—ICP, PRx, and the power of ICP slow waves—is an independent predictor of outcome, these three variables, although mutually correlated, should be considered jointly in any analysis.

With regard to mean CPP, it is now one of the variables that is actively targeted with treatment; therefore, it may have lost its predictive power for outcome. This fact does not mean that short-term decreases in CPP ("CPP insults") have become any more benign. Reductions in CPP below specific threshold values are associated with poor outcome. In cases of severe pediatric head injury, studies have defined the CPP associated with poor outcome as between 40 and 65 mm Hg. For example, Downard et al[43] studied 118 children (mean age, 7 years) with an overall mortality rate of 28% and found that the CPP associated with survival was greater than 40 mm Hg. No further improvement in outcome was seen with mean CPP in deciles from 40 to 70 mm





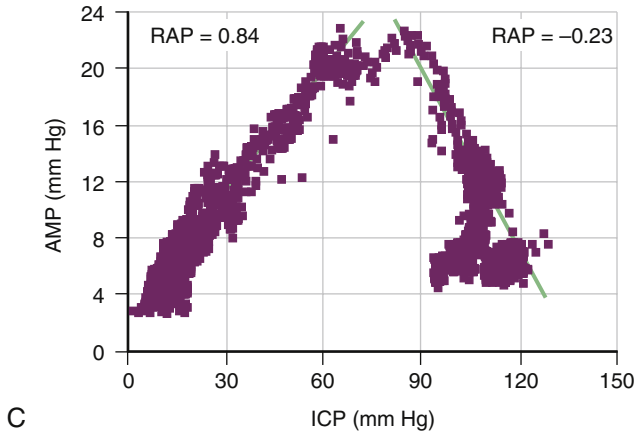


Figure 59–9. **A,** In a simple model, pulse amplitude of intracranial pressure *(ICP)* (AMP, expressed along the *y* axis on the right side of the panel) results from pulsatile changes in cerebral blood volume (expressed along the *x* axis) transformed by the pressure-volume curve. This curve has three zones: a flat zone, expressing good compensatory reserve; an exponential zone, depicting poor compensatory reserve; and a flat zone again, seen at very high ICP (above the "critical" ICP), depicting derangement of normal cerebrovascular responses. The pulse amplitude of ICP is low and does not depend on mean ICP in the first zone. The pulse amplitude increases linearly with mean ICP in the zone of poor compensatory reserve. In the third zone, the pulse amplitude starts to decrease with rising ICP. **B,** Example of the relation between AMP and mean ICP recorded during a 46-hour period, during which terminal intracranial hypertension developed. Pulse amplitude increased first proportionally to the change in ICP but started to decrease when ICP increased above 80 mm Hg. **C,** The regression plot between AMP and ICP indicates a biphasic relation of positive and negative slopes. The correlation coefficient between AMP and ICP *(RAP)* was positive before 32 hours but negative after that; this indicated terminal cerebrovascular deterioration.[39]

Hg. The pediatric guideline for severe head injury is that "CPP greater than 40 mm Hg should be maintained."[33] A modification of this recommendation is to titrate the CPP threshold according to age: a threshold of 40 to 50 mm Hg in infants and toddlers, 50 to 60 mm Hg in children, and greater than 60 mm Hg in adolescents.

Clinical Utility of Intracranial Pressure Monitoring with Other Monitoring Modalities

The continuous measurement of ICP is an essential modality in most brain monitoring systems. After a decade of enthusiastic attempts to introduce newer modalities for brain monitoring (e.g., tissue oxygenation, microdialysis, cortical blood flow, TCD ultrasonography, and jugular bulb oxygen saturation), it is becoming increasingly obvious that ICP is robust, only moderately invasive, and can be realistically conducted in most critical care units. In previous sections of this chapter we noted that ICP measurement is a complex modality that contains information about compensatory mechanisms intrinsic to the brain and regulation of CBF. Thus continuous monitoring is required to control raised ICP. For example, most authors agree that ICP should be measured in patients with acute states such as head injury, poor-grade subarachnoid hemorrhage, and intracerebral hematoma and that monitoring should be linked with therapy. CPP-oriented protocols,[44] osmotherapy, and the Lund protocol[45] cannot be conducted correctly without guidance from real-time ICP recording. Similarly, a decision about performing a surgical intervention such as decompressive craniectomy should be supported by the close inspection of the trend of ICP and, preferably, by information derived from its waveform (see previous discussion).[46]

Newer modalities, however, may provide supplementary information about the state of the injured brain in a comatose patient. We now discuss the role of these modalities, but first, by way of context, some consideration should be given to the mechanisms underlying brain injury.

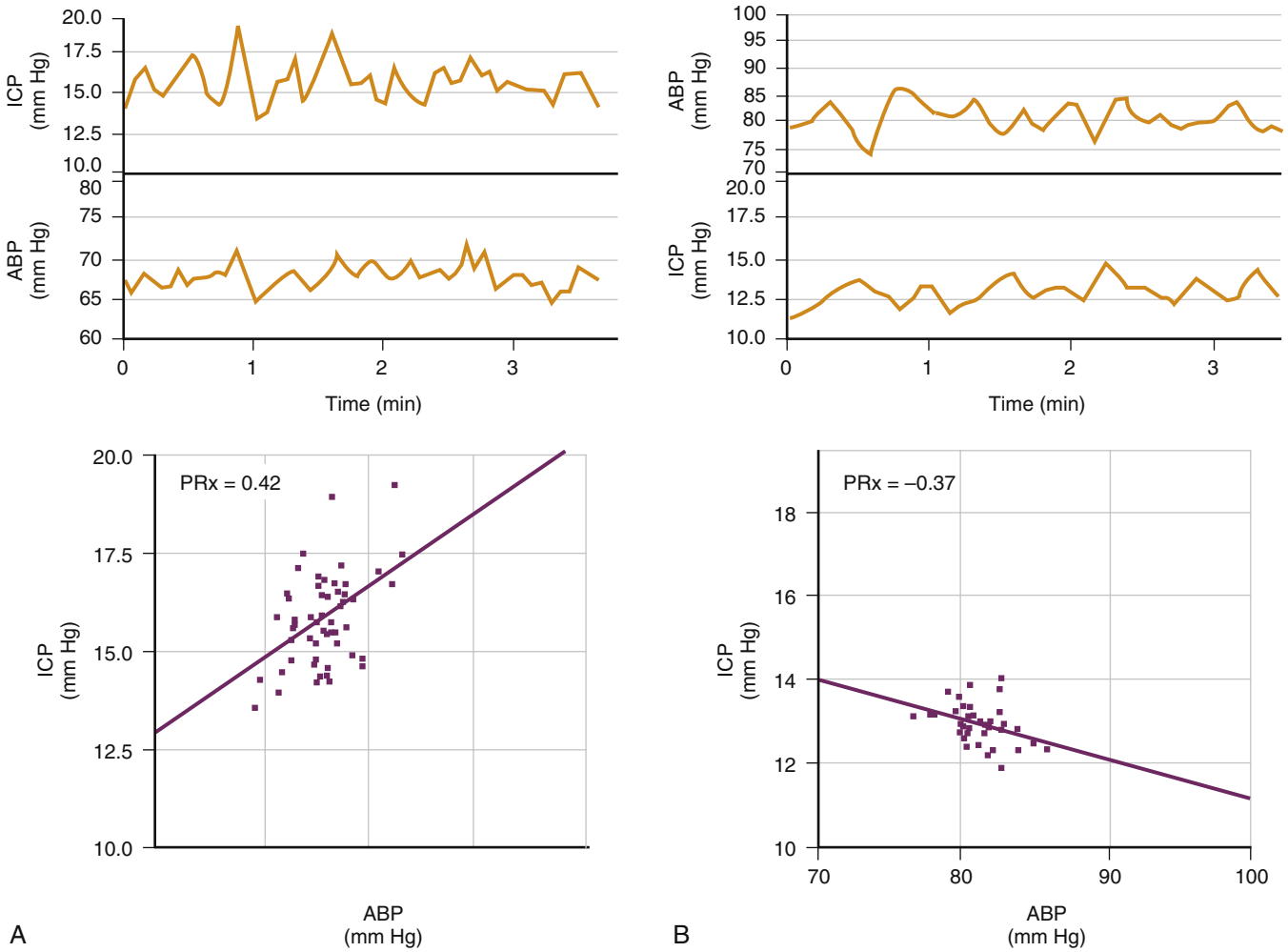


Figure 59–10. Relation between slow waves of arterial pressure *(ABP)* and intracranial pressure *(ICP)*. **A,** Slow waves in ICP and ABP produce a positive correlation (*lower left panel*), giving a positive value of the pressure-reactivity index *(PRx),* which indicates loss of cerebrovascular reserve. **B,** Coherent waves both in ABP and ICP produced a negative correlation coefficient when plotted on the regression graph (*lower right*), giving values of PRx that were clearly negative.

Mechanism of Brain Injury Where Intracranial Hypertension Occurs

In patients with a head injury, MRI commonly reveals focal lesions within the frontal and temporal lobes, the temporal poles, and the limbic system, including its connections with the orbitofrontal surface of the frontal cortex.[47,48] Pathologic change may occur by means of several injurious mechanisms in these regions. In the temporal lobes or its connections, manifestations of the following conditions may be found:

1. Direct high-speed impact injury with or without acceleration-deceleration forces. In this instance, the medial temporal lobe is vulnerable to mechanical deformation and contusion.[49]
2. Metabolic perturbation resulting from vascular or systemic factors such as hypoxia, ischemia, hypoglycemia, and seizures. In these head injury–related insults, there is a predilection for vulnerability within a structure in the temporal limbic system, the hippocampus.[50]
3. Diffuse axonal injury as a consequence of rotational forces at the time of injury affecting axonal integrity; thereafter, secondary or postacute deafferentation or deafferentation of structures such as the hippocampus occurs.[51,52]
4. Raised ICP with brain swelling resulting in pressure necrosis of the main cortical input to the hippocampus, to the parahippocampal gyrus, and against the free edge of the tentorium cerebelli.[53]

Each of these four mechanisms may result in injuries that, in the long term, induce deficits in neuropsychologic function.[54] However, only the fourth mechanism (pressure necrosis of the parahippocampal gyrus) depends on the development and presence of brain swelling.[53] A fifth injurious mechanism, which is important in regard to morbidity, is best shown by the disease to the frontal lobes. Recent research in children suggests that emerging or developing executive functions may be particularly vulnerable when the frontal lobes are injured in childhood.[55] In the context of head injury, such an insult is not excluded by the absence of focal brain lesions detected with MRI. For example, Slawik et al.[54] used MRI-volumetric analysis to study pediatric survivors of severe head injury. On follow-up 4 years after the accident, a decrease in the frontal gray and white matter volume was found in those with raised ICP, even when there had been no focal areas of abnormal signal in the frontal lobes during the acute episode. The substrate for this change

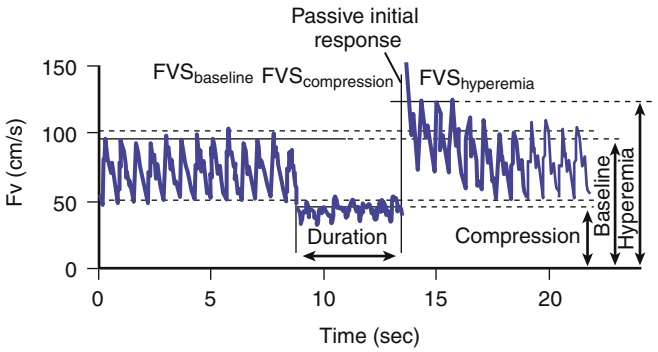


Figure 59–11. Transient hyperemic response used test to assess autoregulation: middle cerebral artery blood flow velocity *(Fv)* is measured with transcranial Doppler ultrasonography before, during, and after a 6-second compression of the carotid artery. Hyperemia after release of compression signifies properly functioning vascular reactivity. *FVS*, Flow velocities.

in the frontal lobes is most likely compromised perfusion to the frontal or anterior cranial compartment[56,57] that may well represent a "frontal compartment syndrome."[54] Another potentially remediable physiology is posttraumatic vasospasm.[58,59] Thus in this final pathophysiologic mechanism, a manifestation of the following condition may occur:

5. Frontal hemodynamic perfusion failure as a consequence of inadequate local CBF, failed local cerebral autoregulation, raised ICP, or anterior compartment syndrome (Figure 59-11).

When consideration is given to monitoring other modalities besides ICP, two problems are encountered. The first problem is understanding the extent to which these mechanisms contribute to the physiologic derangements that can be followed in the intensive care unit. The second problem is making a difference in patient assessment and outcomes, provided these mechanisms can be influenced.

Monitoring and the Postinsult Natural History

In a patient with a severe head injury, the value and utility of monitoring may serve a spectrum of functions. Given the five potential mechanisms outlined in the previous section (i.e., direct mechanical effect, metabolic perturbation, axonal injury, brain swelling, and hemodynamic perfusion failure), specific foci, whether for assessment or treatment, can be identified for monitoring. The potential for treatment rather than for assessment, however, will be limited by the time course over which the pathophysiologic monitoring is enacted. For example, the following need to be considered: What processes occur at the time of injury, what are the subsequent epiphenomena of these events, and what are the secondary factors that are amenable to treatment and altered outcome? Mechanisms 1 and 3 occur at the time of injury, and mechanism 2 starts during the interval between the accident and arrival in the intensive care unit, although this mechanism may, in part, be avoidable with attention to emergency care and life support. Mechanisms 4 and 5 are processes in which treatment that is directed by intensive care monitoring presumably has the potential for altered outcome (i.e., focal brain tissue shifts and hemodynamic perfusion failure). One important issue, therefore, is the natural history of brain swelling and local compartment syndrome after severe head injury.

In persons with a traumatic head injury, intracranial hypertension occurs when there is brain swelling or a hematoma that occupies significant space. In persons with severe traumatic injury and abnormalities shown with computed tomography (CT) scans on admission, a greater than 50% chance of raised ICP exists.[60] In adults, this complication may occur in persons whose CT scans appear normal, particularly if two of the following three features are present: age older than 40 years, unilateral or bilateral motor posturing, or systolic ABP below 90 mm Hg. In children, the occurrence of this complication has been analyzed in a United Kingdom national data set of all 501 children receiving critical care after sustaining a severe head injury. Forsyth et al[61] found that by modeling demographic, acute physiologic, and cranial imaging variables they could derive an empiric decision rule that predicted the development of raised ICP at any point during intensive care unit admission with a sensitivity of 73% and a specificity of 74% (positive predictive value, 82%; negative predictive value, 63%). Overall raised ICP was present in 25% of those undergoing invasive monitoring. Importantly, the decision rule predicted raised ICP in 20% of children not undergoing ICP monitoring. Natale et al.[62] have shown that the natural history of raised ICP in children not requiring surgery after head injury can be as short as 3 days, but not infrequently it lasts for 7 to 10 days. Thus in regard to brain tissue shifts and frontal compartment perfusion failure, the potential of a postinsult "therapeutic window" exists, which also implies a goal for therapy directed by monitoring.

Newer Modalities: Supplementary Monitoring of Intracranial Pressure

Many of the supplementary, often research-based modalities that are used in monitoring have only been tested in patients with a head injury, because this is the most common reason for instituting ICP monitoring.

Neurochemical Protein Markers of Injury

Interest has been growing in markers that are concerned with broadly assessing tissue integrity and cell-specific injury. The clinical measurement of two proteins may serve this purpose.[63] Neuron-specific enolase (NSE), an enzyme involved in glycolysis that is localized in neurons and axonal processes, potentially escapes into the blood and CSF at the time of neural injury. (This enzyme is also found in erythrocytes.) S-100B protein, a calcium-binding protein localized to astroglia, also may be released from cells at the time of cerebral damage.

A number of clinical monitoring studies of these proteins have been undertaken in patients with head injury. For example, in patients with mild traumatic brain injury, de Kruijk et al[64] found that in blood samples taken shortly after trauma, the median and range of NSE levels were similar in patients (n = 104) and control subjects (n = 92). They found, however, that S-100B levels were significantly higher, particularly in patients with trauma who were also vomiting. Ingebrigtsen et al.[65] selected a similar group of 50 patients (i.e., those with a Glasgow Coma Scale (GCS) score of 13 to 15 and a CT scan showing no abnormalities). They found that serum S-100B protein levels were highest immediately after the trauma and then declined each hour thereafter so that the level was undetectable 6 hours after injury. Four of the five patients

with an MRI-detectable brain contusion had detectable levels of S-100B. In patients with more severe injuries (GCS score = 8), Raabe et al.[66] found that the level of S-100B in venous blood was higher in nonsurvivors, and on logistic regression, the S-100B level was an independent predictor of outcome along with age, GCS score, ICP, and CT scan findings. These authors also reported that persistent elevation of S-100B for 3 to 5 days occurred even in patients with favorable outcome and no signs of secondary insults.[35,67] Finally, in this class of patient, venous NSE appears to perform poorly as a diagnostic marker of severity.[67] Its level rises acutely in patients with both favorable and unfavorable outcome. With a cut-off level of more than 100 μg/L, the likelihood ratio for positively identifying an unfavorable outcome is approximately 2 (i.e., specificity 0.96 and sensitivity 0.09), which is of indeterminate diagnostic impact.

As with the studies in adults, the pediatric studies are somewhat inconclusive, and it may be that age and mechanism of injury—hypoxic-ischemic versus trauma—are important factors. For example, Berger et al.[68] followed the levels of S-100B and NSE in CSF samples from patients with inflicted and noninflicted trauma. Of note, these authors found that in both mechanisms of trauma a single peak in S-100B occurred at approximately 27 hours after injury, but a difference existed in the profile for NSE. After an initial or transient peak in NSE (~11 hours after injury) in both forms of insult, inflicted trauma had the additional feature of a sustained and delayed peak at around 63 hours after injury. In a more recent study of serum biomarkers, Berger et al.[69] assessed whether serum biomarkers concentrations obtained at the time of injury are associated with outcome in 152 children with acute head injury. For all biomarkers and time points, higher biomarker concentrations were associated with worse outcome. Initial and peak NSE concentrations and initial myelin basic protein concentrations were more strongly correlated with outcome in children younger than, or equal to, 4 years compared with those older than 4 years. The authors concluded that obtaining serum biomarkers at the time of injury "may be useful in predicting outcome." In less severe forms of head injury in children, other investigators have found that serum S-100B and NSE do not discriminate between those who do and do not have symptoms.[70]

Taking both the adult and pediatric studies together, a dilemma still exists. Does the very nature of sustaining a head injury initiate a normal yet insignificant transient release (albeit marked in CSF) of NSE and S-100B into the circulation, or are patterns of injury with varying mechanisms such as cerebral contusion in the case of S-100B and unappreciated hypoxia-ischemia or diffuse neuroaxonal injury in the case of NSE unable to be identified?

Brain Oxygenation

Jugular bulb oxygen saturation is commonly used to assess cerebral oxygenation. However, this form of monitoring has several shortcomings, not the least of which is that it is a global measure that is insensitive to small, though important, regional changes. The relatively recent development of implantable tissue oxygen and pH microsensors has meant that more direct regional assessments are now being made. The questions, though, are: What is normal tissue oxygen tension, and what does it mean? Recent reports in adults indicate that the threshold for abnormality is around 10 mm Hg,[71-73] although the validity and appropriateness of using such an exact measure has been questioned by Gupta et al.[74] These investigators used positron emission tomography scanning in 19 adults with head injuries to validate the reading of brain tissue oxygen pressure (P_tO_2) from a NeuroTrend sensor inserted into the frontal region. End-capillary oxygen tension (P_vO_2) was calculated from oxygen extraction fraction in a 20-mm region of interest around the sensor and compared with P_tO_2. No correlation was found between the absolute values of P_tO_2 and P_vO_2. In contrast, a significant correlation was obtained between the change in P_tO_2 and the change in P_vO_2 produced by a decrease in arterial carbon dioxide by approximately 1 kPa (7.5 mm Hg). Therefore these authors could only conclude that such monitoring should be used to assess, in real time, the changes attributable to a particular intervention.

Ushewokunze and Sgouros[75] have reported on five children with head trauma for whom this monitoring has been used. In common with findings in adults, the low P_tO_2 levels that occur during the first 24 hours following head injury do not correlate necessarily with poor outcome, and an increase in ICP may be accompanied by a decrease in P_tO_2.

Microdialysis and Brain Tissue Biochemistry

Tissue biochemical metabolic markers—rather than serum or cerebrospinal biomarkers (see previous discussion)—can be assessed continuously using cerebral microdialysis; essentially, one is potentially sampling cerebral extracellular fluid and using changes to make inferences about cell homeostasis and perturbation. Currently, this approach is used predominantly for research purposes. The technology enables bedside measurement (usually hourly in the case of head injury) of levels of cerebral dialysate glucose, lactate, pyruvate, glutamate, and glycerol. Typically, glucose level and lactate-pyruvate ratio (LPR) are used as indices of inadequate substrate delivery, altered metabolism, and ischemia. The use of a ratio (i.e., LPR), rather than absolute concentrations, means that an alteration in dialysate recovery rate does not result in spurious changes in LPR. A ratio less than 20 suggests uncomplicated cerebral metabolism,[76] and an increase in ratio is a sensitive indicator of a decrease in P_tO_2.[77] Dialysate increases in glutamate and glycerol are used as indices of cumulative tissue responses to secondary ischemic events such as intracranial hypertension, systemic hypotension, seizures, and contusions.

In adults with head injury, an increased ratio results from a tenfold to 100-fold reduction in pyruvate concentration in association with a twofold to fivefold increase in lactate concentration.[78] Two recent studies in adults with head injuries, however, suggest that the LPR (and levels of the components that make up the ratio) might be telling us more about other forms of cerebral metabolic perturbation besides ischemic crisis. Hlatky et al[79] found that in the first few hours after injury—at a time when P_tO_2 was normal (i.e., nonischemic)—the LPR was increased because of low pyruvate concentration and not raised levels of lactate. Later when the P_tO_2 was at its lowest level, signifying "hypoxia/ischemia," increased LPR was due to a combination of increased lactate and decreased pyruvate levels. Vespa et al.[80] found that even though a raised lactate level or LPR was present in 25% of cerebral microdialysis samples, the occurrence of cerebral ischemia—defined as a

raised lactate level, LPR, and a low glucose level—was much less frequent (~3%). Furthermore, upon combining these studies with positron emission tomography for assessing the metabolism of oxygen, the incidence of a high oxygen extraction fraction (i.e., ischemia) was rare, at approximately 1%. Hillered et al.[81] has commented on these clinical reports in adults and suggested that the findings represent two metabolic states:

- Type 1, classical cerebral ischemia, is characterized by reduced microdialysis pyruvate and an increased level of lactate, leading to increased LPR (in association with depressed P_tO_2). This state is a result of an overt lack of oxygen and glucose at the mitochondria.
- Type 2, cerebral metabolic perturbation, occurs when P_tO_2 is normal (i.e., nonischemic) and a reduction in pyruvate is the sole change in dialysis metabolites. The rise in LPR in this state is "perhaps reflecting a limited glucose supply or an impairment of the glycolytic pathway."

However, the mechanism of these early type 1 and type 2 changes are not fully understood, and there is an important difference between the study by Hlatky et al.[79] and that reported by Vespa et al.[80]: in the first study the microdialysis probes were placed perilesional or pericontusional; in the second study the microdialysis probes were cited as being placed in the nondominant, normal-appearing frontal lobe tissue. This difference is likely to be significant because, as Engstrom et al.[82] reported, microdialysis monitoring of normal-appearing tissue is not representative of perilesional tissue. Raised LPR persisted for at least 72 hours in perilesional tissue. In the first 36 hours this rise was associated with raised lactate levels and raised pyruvate concentrations. After that time, raised LPR was a reflection of raised lactate levels with normal pyruvate concentrations. All microdialysis parameters were in the normal range in normal-appearing tissue. These observations suggest that perilesional tissue has features of type 1 cerebral metabolic crisis, but the absence of depressed P_tO_2 suggests that increased lactate occurs as a consequence of increased glycolytic activity, which may be due to perilesional depolarizations.[83] Such hyperglycolysis is marked by increased metabolism relative to utilization and, after trauma, it represents an uncoupling between predominantly glycolytic and oxidative metabolism.[84]

In the broader context of managing intracranial hypertension, one needs to consider whether microdialysis and monitoring brain tissue biochemistry will have a role beyond the physiologic insights previously described. For example, if measurements are made hourly—dialysate flow rate of 0.3 μL/min is the most common—then what does a change represent: a concurrent acute event, a prolonged ongoing event, or an acute event that has now resolved but with abnormal tissue biochemistry? Belli et al.[85] have addressed this issue by examining whether metabolic impairments preceded rises in ICP. The authors found that an abnormal LPR could predict an ICP rise in 89% of cases. An LPR above 25 was associated with an odds ratio of 9.8 (95% CI, 5.8 to 16.1) of imminent intracranial hypertension. With regard to the utility of this form of monitoring in children, we know that in the United Kingdom national data set of critical care for severe traumatic brain injury less than 1% of children undergo such monitoring.[86] To date, a case series of only nine children has been reported.[87,88]

Transcranial Doppler Ultrasonography and Assessment of Autoregulation

TCD ultrasonography has a number of uses in the assessment of cerebrovascular health. In the field of adult neurocritical care, much progress has been made in applying this technology to head injury practice. The following discussion highlights the key issues.

TCD ultrasonography provides noninvasive measurement of blood flow velocity in basal cerebral arteries.[21] Most data have been derived from the MCA. This vessel is readily accessible to the ultrasonographer; it is the most convenient for probe fixation and long-term monitoring, and it delivers the largest percentage of supratentorial blood. Although the blood flow velocity cannot express a baseline volume of flow, dynamic changes of CBF are usually reflected in the TCD readings.[21,89] The response of blood flow velocity to a critical decrease in CPP is sensitive and usually immediate (see Figure 59-11). It is this high-dynamic resolution and close correlation with other hemodynamic modalities that has encouraged the development of the technique in clinical practice.

Increased baseline flow velocity (>100 cm/sec) may indicate cerebral vasospasm or hyperemia.[90,91] Uncoupling between CBF and flow velocity in vasospasm has been documented both experimentally and clinically.[92] For example, if the ratio of flow velocity in the insonated artery to the velocity in the ipsilateral internal carotid artery is greater than 3, vasospasm is likely. A ratio lower than 2 indicates hyperemia as the cause for accelerated blood flow.[89] After a severe head injury is sustained, cerebral autoregulation is frequently disturbed, although the extent of this disturbance may fluctuate with time.[7,8] The range of assessments that can be conducted at the bedside are:

1. **Static test of autoregulation:** Methods for the static assessment of autoregulation rely on measurement of MCA blood flow velocity during changes in mean ABP induced by a vasopressor infusion. The static rate of autoregulation (SoR) can be calculated as the percentage increase in vascular resistance divided by the percentage rise in ABP. An SoR of 100% indicates fully intact autoregulation, whereas an SoR of 0% indicates fully depleted autoregulation.
2. **TCD reactivity to changes in carbon dioxide concentration:** Testing for carbon dioxide cerebrovascular reactivity has been shown to have an important application in the assessment of severe head injuries and other cerebrovascular conditions. Many authors have shown that cerebral vessels are reactive to changes in carbon dioxide when cerebral autoregulation had been impaired.[93] Carbon dioxide reactivity correlates significantly with outcome after a head injury.[94] In patients with an exhausted cerebral compensatory reserve, however, hypercapnia may provoke substantial changes in ICP. Therefore this method cannot be used without consideration of patient safety, particularly if baseline ICP is already elevated.
3. **Dynamic test of autoregulation:** Aaslid et al.[95] have described a method in which a step decrease in ABP is achieved by the deflation of compressed leg cuffs while TCD flow velocity in the MCA is simultaneously monitored. An index called the dynamic rate of autoregulation describes how quickly cerebral vessels react to the sudden fall in blood pressure. The dynamic rate of autoregulation

is thought to express the autoregulatory reserve and, in adult volunteers, has been shown to correlate with blood carbon dioxide concentration in volunteers.[96]

4. **Transient hyperemic response test:** Short-term compression of the common carotid artery produces a marked decrease in MCA blood flow velocity in the ipsilateral hemisphere. During compression, the distal cerebrovascular bed dilates if autoregulation is intact. On release of the compression, transient hyperemia, which lasts for a few seconds, occurs until the distal cerebrovascular bed constricts to its former diameter. This sequence of events, which underlies the transient hyperemic response test, indicates a positive autoregulatory response (see Figure 59-11). In persons with a head injury, preliminary results show a positive correlation between the presence of a hyperemic response and outcome.[97]
5. **Continuous analysis of TCD ultrasonography with respiratory waves:** An interesting method of deriving the autoregulatory status from natural fluctuations in MCA blood flow velocity involves the assessment of phase shift between the superimposed respiratory and ABP waves during deep breathing.[98] A 0-degree phase shift indicates absent autoregulation, whereas a phase shift of 90 degrees indicates intact autoregulation. Such an approach may allow for the continuous assessment of autoregulation without performing potentially hazardous test maneuvers on arterial pressure.
6. **Continuous analysis of TCD flow velocity waveform:** In patients with severe head injuries, CPP monitoring can be correlated with mean blood flow velocity continuously. For example, consecutive CPP samples (averaged over 5-second periods) can be assessed with average flow velocity (collected over 5-minute epochs). The correlation coefficient (named mean index) may be positive or negative, and the regression line describing the relationship between the systolic-, mean-, and diastolic-flow velocity and the CPP may be used for assessment. A positive correlation coefficient signifies positive association of flow velocity with CPP; a negative correlation coefficient signifies a negative association. In persons with a head injury, group analysis has shown that clinical outcome depends on the averaged autoregulation indices.[9] Furthermore, time analysis has shown that failure of autoregulation is a strong independent predictor of fatal outcome after a head injury.[99]

Some data on TCD assessments of cerebral autoregulation in children with traumatic brain injury are now available. For example, in a series of 36 children, the incidence of impaired cerebral autoregulation was greatest following moderate to severe traumatic brain injury.[100] Impaired autoregulation was associated with poor outcome, and hyperemia was associated with both impaired autoregulation and poor outcome. In severe cases, cerebral autoregulation often changes over the course of a critical illness, with worsening autoregulation mirroring progression of worsening injury.[101] Importantly, in children, bilateral assessment of cerebral autoregulation is required because hemisphere differences are common in those with an isolated focal injury.[102] Finally, inflicted traumatic brain injury probably should be considered a special case: in a small case series, Vavilala et al.[103] found that none of their critically ill cases had intact autoregulation.

Clinical Neurophysiology

In comparison with the other categories already discussed, clinical neurophysiology data are unique in that they can provide some assessment of what the brain produces— activity. This assessment may take the form of its global integrity (e.g., general brain activity) or of some specific electrophysiologic function (e.g., dysrhythmic or seizure activity and sensory pathway performance).

In comatose states, the electroencephalogram (EEG) can provide useful information about the severity and distribution of altered function of the cerebral cortex. Multiple factors, however, may affect the level of such activity, and in the context of pediatric head injury, the signals reflect the summed effects of brain temperature, cerebral perfusion, metabolic state, anesthesia, and drug action on the normal background activity expected for age or stage of brain development. Thus while the technique itself is sensitive, the changes observed generally are not that specific, particularly when one considers the range of variables that will lead to altered EEG activity. Serial EEGs, however, can provide important, albeit intermittent, assessment of changes in cerebral function.[104] Alternatively, automated, signal-processed, continuous EEG can be used for uninterrupted surveillance of brain function. Various methods of displaying modified EEG data in an understandable and interpretable form have been developed and reported upon,[105-107] although the value of these methods in identifying persons who likely have a poor prognosis has been questioned. For example, in adults with severe head injury (n = 103, GCS score = 8), Moulton et al.[108] reported that signal-processed EEG data could not be relied upon as a basis for critical management decisions. In contrast, Thielen et al.[109] found that in a group of 32 adults with head injuries (GCS score <8), a cut-off of EEG-silence ratio (which was derived from a mathematically processed EEG) at 20% was of high diagnostic impact in the identification of the Glasgow Outcome Scale (GOS) category at 6 months (GOS 4-5 compared with GOS 1-3). (The sensitivity was 0.91, the specificity was 0.91, and the likelihood ratio was <0.1.) Finally, Murdoch-Eaton et al.[107] have reported a similar experience with continuous monitoring in 108 children with a variety of brain insults, although the presence of seizure activity featured highly in the prognostication.

In addition to the identification of background EEG activity (which, as discussed, has limited specificity) in the patient with a head injury, identifying seizure activity may be more pertinent because its presence will result in a change in therapy. In this regard, Vespa et al.[110] undertook continuous EEG monitoring in 94 adults with moderate to severe brain injuries. Convulsive and nonconvulsive seizures occurred in 22% of the patients, with six persons displaying electrical status epilepticus. In more than half of the patients, the seizures were diagnosed solely on the EEG monitoring. Of particular concern was the finding that these seizures occurred despite the unit's use of prophylactic anticonvulsant therapy. In another EEG study of comatose patients (n = 236), including children, Towne et al.[111] also found that nonconvulsive status epilepticus was underrecognized, occurring in 8% of their comatose patients without signs of seizure activity. Finally, in children with a head injury, Chiaretti et al.[112] reviewed their clinical experience in 125 patients, 12% of whom had seizures within 24 hours of trauma. Taken together with the adult EEG studies, there certainly appears to be some merit in characterizing the

role of seizure monitoring in children with head injuries, particularly because anticonvulsant prophylaxis seems to be failing to confer protection, and we can easily provide a remedy.

Somatosensory evoked potentials (SEPs) are widely used to assess neurophysiologic function in patients with severe head injury.[108] The strong predictive value of these potentials in comatose patients has been demonstrated in a number of pediatric series. The bilateral absence of the cortical components of the SEP is usually regarded as an ominous sign, invariably indicating a poor outcome. For example, Carter et al.[113] reported a series of 105 children with severe brain injury for whom they had long-term (5 years) functional and health status outcomes. For children with bilaterally absent SEP responses, the positive likelihood ratio of identifying unfavorable functional outcome was approximately 15 (specificity, 0.96; sensitivity, 0.57; and high diagnostic impact). The results for health status were of equally high diagnostic impact. The question that arises, however, is this: Are these data sufficient for influencing practice, or should such assessment merely be used for stratifying patient prognosis at an early stage?

In 1997, Pohlmann-Eden et al.[114] reviewed 18 studies in which the predictive value of SEPs in 758 comatose patients was analyzed. These investigators identified 300 reports of patients with bilateral loss of cortical SEP responses, and of these patients, 286 died or remained in a vegetative state. Two of the remaining 16 surviving patients had a good outcome with functional independence; both were children.[115,116] In 1999, Schwarz et al.[117] reported on four adults who survived despite bilateral loss of the cortical SEP; three of these patients had an excellent outcome. Wohlrab et al.[118] reviewed 53 children with bilateral absent cortical SEP, 13 of whom had sustained a severe head injury. Thirty (57%) of 53 children died within the first 4 weeks, and another eight children died within 4 years of the event (i.e., a total of 72%). Of the 15 surviving children (six of whom had a severe head injury), two children remained in a persistent vegetative state, nine children had severe deficits (two of these children had head injuries), and four children had mild or moderate deficits (all of these children had head injuries). Interestingly, 30 of the 53 children underwent repeated examinations, and in eight of these children, unilateral or bilateral cortical responses reappeared. Taken together, the poor prognostic implications of bilateral loss of SEPs are indisputable. Nevertheless, the occurrence of recovery from, in the main, transiently absent cortical responses indicates that this finding alone does not imply irreversible dysfunction of the somatosensory pathway in the child with a severe head injury. Absent SEPs should be interpreted carefully, particularly in conjunction with hypothermia, deep sedation, intoxication, or decompressive craniectomy.[119]

References are available online at http://www.expertconsult.com.

Status Epilepticus

Cecil D. Hahn, Sam D. Shemie, and Elizabeth J. Donner

PEARLS

- Prolonged convulsive and nonconvulsive seizures cause neuronal injury by excitotoxic and hypoxic-ischemic mechanisms related to the intense metabolic demands of seizures and associated cardiorespiratory compromise.
- The longer seizures continue, the more difficult they are to abort with medications. Early diagnosis and aggressive intervention for both convulsive or nonconvulsive seizures is essential for their successful treatment.
- Outcomes following status epilepticus are primarily related to the underlying cause of the seizures and are generally more favorable in children than in adults.
- Clinically subtle or nonconvulsive seizures are common among patients in the intensive care unit, particularly following prolonged convulsive seizures. Postictal stupor or coma due to the sedative effects of medications are often difficult to distinguish from continued nonconvulsive seizures without the aid of continuous electroencephalographic (EEG) monitoring. Treatment of refractory status epilepticus requires continuous EEG monitoring because pharmacologic therapy is titrated to EEG seizure suppression or burst-suppression.
- The dose limitations of traditional high-dose suppressive therapies (barbiturates or benzodiazepines) generally are related to cardiovascular toxicity rather than to any predefined upper limit of dosing.

Definition

Status epilepticus (SE) is a life-threatening medical emergency. In children, SE often necessitates urgent treatment and monitoring in the pediatric intensive care unit (PICU) and requires that the pediatric intensivist be comfortable with the diagnosis and management of this common condition.

The International League Against Epilepsy defines SE as a seizure that persists for a sufficient length of time or is repeated enough to produce a fixed and enduring epileptic condition.[1] From the practical perspective of the treating physician, this definition is difficult to apply. A more commonly used clinical definition includes duration of seizure activity, specifying SE as seizures lasting 30 minutes or longer, which is based on the theory that neuronal damage may begin after 30 minutes of continuous seizures. No clinical data support the 30-minute rule, however, and more recent definitions of SE include a shorter duration of seizure activity. An operational definition has been proposed, in which generalized convulsive SE in adults and children older than 5 years is "greater than or equal to 5 minutes of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness."[2] This definition has been supported by clinical studies showing that most secondarily generalized convulsive seizures in adults last less than 5 minutes[3]; these results suggest that seizures lasting more than 5 minutes should be regarded as more significant. Similar data in children have shown that new-onset seizures cluster by duration; most seizures (76%) last less than 5 minutes and 24% last longer, with a mean duration of 31 minutes.[4] The shorter duration definition of SE remains controversial, however, because although it is less common for seizures to persist beyond 5 minutes, it also has been shown that seizures lasting 10 to 29 minutes that stop spontaneously are associated with a significantly lower mortality rate than seizures lasting beyond 30 minutes.[5] Thus before the definition of SE includes a seizure duration of less than 30 minutes, further study and discussion are required.

Regardless of the definition of SE, there is a consensus in the medical community that continuous or prolonged seizures require urgent intervention. Children with prolonged seizures should receive prompt and aggressive treatment with the aim of stopping seizures as soon as possible.

Classification of Status Epilepticus

SE should be classified with the same terminology used for seizure classification. The International League Against Epilepsy Task Force on Classification and Terminology identifies two major categories that may be applied to both self-limited and continuous seizures.[6] *Generalized seizures* refer to seizures involving both cerebral hemispheres, which are believed to originate within, and rapidly engage, bilaterally distributed neuronal networks. Consciousness is usually impaired. Generalized seizures include seizures with motor movements as well as absence seizures during which no convulsive signs may be present. Electroencephalography (EEG) indicates seizure activity involving both cerebral hemispheres. *Focal seizures*, previously referred to as partial seizures, are those in which the first clinical and EEG changes indicate seizures that originate within one cerebral hemisphere. Generalized seizures that begin as focal seizures are termed secondarily generalized seizures. Complex focal seizures are associated with an impairment of consciousness. Simple focal seizures have no impairment of consciousness. When simple focal seizures are prolonged and have a

focal motor component, the term *epilepsia partialis continua* is used.[7] These same terms are also used to describe continuous seizures and SE. SE also may be defined more specifically by seizure type, including myoclonic status, tonic status, and absence status.[6] Although these distinctions are helpful to predict the cause and outcomes of SE, the differentiation may require EEG and has limited utility in the acute clinical situation.

A more clinically useful classification scheme involves categorizing SE by the presence of motor movements (Box 60-1). *Convulsive SE* (CSE) consists of continuous clonic or tonic motor activity with bilateral epileptiform discharges on the EEG. As CSE progresses, the motor movements are reduced and may be characterized only by subtle twitching of the limbs, face, or trunk. This condition is termed *subtle CSE.*

Nonconvulsive SE consists of continuous electrographic seizures with no motor movements. This type of seizure may occur after prolonged generalized CSE. Nonconvulsive SE also refers to SE consisting of absence seizures or focal onset seizures that do not produce motor movements.

In children, an additional category, febrile SE, may be considered. SE occurring in association with fever represents one form of complex febrile convulsions.

Finally, SE also may be classified with respect to cause. Symptomatic implies a known cause for SE and can be further divided into *acute symptomatic* and *remote symptomatic* on the basis of cause. Examples of acute symptomatic causes include toxins and acute infections. Remote symptomatic SE is most often associated with a long-standing history of epilepsy or remote central nervous system (CNS) insult. The term *idiopathic SE* is used when there is no known or suspected cause for the seizures.

Nonepileptic seizures, also known as *nonepileptic events,* also may present as SE. Patients with and without a prior history of epileptic seizures may have nonepileptic SE. In this situation, EEG may be necessary for diagnosis to confirm the absence of abnormal electrical discharges in the brain.

Epidemiology of Status Epilepticus

Incidence

Two population-based studies have examined the incidence of SE in the United States. The incidence of SE in Richmond, Va.,[8] was determined to be 41 per 100,000 population, and in Rochester, Minn.,[9] the incidence was 18 per 100,000 population. The difference may reflect a different racial composition in the communities studied; in the Richmond study, the incidence of SE was higher in the nonwhite population.

Box 60–1 Classification of Status Epilepticus

Generalized Convulsive
Overt
Subtle

Nonconvulsive
Associated with coma or paralysis
Following prolonged convulsive seizures
Absence status epilepticus

Focal
Simple: without altered consciousness
Complex: with altered consciousness

A population-based United Kingdom study determined the incidence of CSE in children to be 17 to 23 per 100,000 per year. The incidence of CSE was highest in children younger than 1 year (51 per 100,000 per year) falling to only 2 per 100,00 per year in 10- to 15-year-olds. The incidence of CSE was similar in girls and boys.[10] Lower socioeconomic status, independent of ethnicity, was associated with prolonged febrile seizures and acute symptomatic CSE.[11] SE was found to be the admission diagnosis of 1.6% of children admitted to a pediatric intensive care unit.[12]

Cause

One of the largest series of SE in children was published in 1970. This review of 239 cases of SE in children identified 47% of cases to be symptomatic (26% acute symptomatic and 21% remote symptomatic) and the remaining 53% of cases to be idiopathic, including febrile SE.[13] The cause of SE is age dependent; infection plays a larger role in the cause of SE in children than in adults. In a 1996 study in Richmond, Va., the three major causes of SE in children were infection with fever, remote symptomatic cause, and low anticonvulsant drug levels (Table 60-1).[8] The three major causes in adults were low antiepileptic drug (AED) levels, remote symptomatic cause, and stroke.[8] The cause also differs among younger and older children. Febrile and acute symptomatic SE are more common in children younger than 2 years, whereas idiopathic and remote symptomatic causes are most common in children older than 4 years.[12,14]

A recent prospective population-based study found that more than half of children with a first event of CSE were previously neurologically healthy. One third were identified as having prolonged febrile seizures, 17% as having acute symptomatic seizures, and 16% as having remote symptomatic seizures, and the remaining 12% had cryptogenic or idiopathic epilepsy.[10] A retrospective case series of SE in children report similar results.[15] Prolonged febrile seizures represent a significant burden in the PICU. A report of 119 prolonged febrile seizures, defined as lasting longer than 30 minutes, found that the seizures lasted a median of 68 minutes, and 24% lasted more than 2 hours. Analysis suggested that the longer a seizure lasts, the less likely it is to spontaneously remit.[16]

Table 60–1 Causes of SE in Children from the Richmond, Va., SE Database

Cause	% of SE
Non-CNS infection	52
Remote symptomatic	38
Low AED level	21
Cerebrovascular disease	10
Metabolic	7
Hypoxia	5
Idiopathic	5
CNS infection	2
Drug overdose	2

AED, Antiepileptic drug; *CNS,* central nervous system; *SE,* status epilepticus.
From DeLorenzo RJ, Hauser WA, Towne AR, et al: A prospective, population based epidemiologic study of status epilepticus in Richmond, Virginia, *Neurology* 46:1029, 1996.

In children with a first seizure, 12% present in SE.[17] In a report of 613 children with newly diagnosed epilepsy, 9.1% had provoked or unprovoked SE before the diagnosis of epilepsy and a nearly equal number, 9.5%, had an episode of SE following the diagnosis of epilepsy (8-year median follow-up).[18,19] Children who had SE before a diagnosis of epilepsy were most likely to have remote symptomatic epilepsy. Younger age of epilepsy onset and symptomatic epilepsy increased the risk of SE.[19]

Outcome

Mortality

Status epilepticus is a clinical expression of potentially severe brain disease and may threaten life through impairment of airway control and respiratory function. Once intubation and mechanical ventilation are established, the outcome is primarily related to the underlying brain disease and the ability to control seizures. Age and etiology are strong predictors of outcome in SE, reflecting the fact that morbidity and mortality are more related to the underlying disorder than to the seizures. Mortality rates as high as 23% have been reported in SE in adults[20,21]; however, such high rates have not been reported in children. Case fatality was 3% in a prospective population-based study of first episodes of CSE in children. Death was associated with bacterial meningitis, underlying metabolic disease, and progressive neurodegenerative disorders.[10] In a study of 193 children with SE, 3.6% died within 3 months of the SE; the etiology of SE was the strongest predictor of death. All deaths that occurred were associated with an acute CNS insult or progressive encephalopathy, and no children with unprovoked or febrile SE died.[22] Similar findings were documented in a study of 40 cases of pediatric SE, in which mortality rate was 10% and the cause of SE in all children who died was acutely life-threatening.[23] Refractory SE carries higher risks of significant morbidity and mortality (see the section on Refractory SE later in this chapter).

Subsequent Development of Epilepsy

Epilepsy, which is defined as recurrent unprovoked seizures, is a potential long-term complication of SE. In children, the risk that epilepsy will develop after SE ranges from 26% to 36%.[23,24] This risk is not significantly different from rates of epilepsy following a brief first unprovoked seizure.[25] As with mortality, the development of epilepsy after SE is strongly related to the etiology of SE. In children with acute symptomatic SE, the risk for development of subsequent epilepsy was found to be 41%, three times higher than that for children with self-limited acute symptomatic seizures. This risk was highest in children with anoxic encephalopathy, followed by structural and then metabolic causes.[26]

In contrast, children with a first unprovoked seizure presenting as SE were not more likely than children with self-limited first unprovoked seizures to have recurrent seizures.[17] Furthermore, the increased risk of the development of epilepsy after febrile SE is generally reported to be small to none.[22-24,27]

Pathophysiology

The exact mechanism that permits a seizure to become sustained is not known. Theoretically, either a failure of physiologic neuronal inhibition or an excess of excitation is required. Much of the research in this area has focused on the failure of neuronal inhibition by the major inhibitory neurotransmitter in the CNS, γ-aminobutyric acid (GABA). Prolonged seizures have been associated with deficits in GABA-mediated neuronal inhibition because of the rapid internalization of synaptic $GABA_A$ receptors. Clinically this phenomenon may be demonstrated by the poor response of prolonged seizures to the GABA agonists benzodiazepines and barbiturates,[28] a phenomenon known as time-dependent pharmacoresistance.[29-31]

SE causes neuronal injury by both hypoxic-ischemic and excitotoxic mechanisms. The pathophysiology of SE-induced hypoxic-ischemic injury is illustrated in Figure 60-1.[32] Early in SE, an increase in neuronal metabolic demand occurs with a compensatory increase in cerebral blood flow (CBF) and brain oxygenation. Later in SE, these homeostatic mechanisms are unable to keep up with the sustained increase in cerebral metabolic demand. Autoregulation of CBF fails, and consequently a higher mean arterial pressure is required to maintain adequate brain perfusion. As systemic blood pressure falls, a subsequent reduction in brain parenchymal oxygenation occurs. In the face of increased neuronal metabolic demand, uncontrolled muscular contractions, hyperthermia, and impaired airway control, both impaired oxygenation and ventilation contribute to the mismatch between metabolic supply and demand. However, neuropathologic injury occurs even when these systemic factors are controlled and before CBF is reduced, presumably because of unmet neuronal metabolic demands alone.

Excitotoxicity is the second major mechanism for neuronal injury in SE. Glutamate is the major excitatory neurotransmitter in the CNS, and glutamate agonists are used to induce seizures in experimental animal models of SE. Studies have implicated both the *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutamate receptors in the pathophysiology of SE.[33] The NMDA receptor may have a dual function in the pathophysiology of SE. Magnesium blocks the NMDA channel when it is in its normal state. With depolarization, magnesium no longer blocks the channel, and calcium, which is allowed to flow into the cell, produces further depolarization. Thus the NMDA receptor is activated when the cell is depolarized and responds by further depolarizing the cell, sustaining the excitation. This process also has been implicated in SE-induced neuronal injury, as the accumulation of intracellular calcium activates pathologic processes resulting in both necrotic and apoptotic cell death.[34,35]

Diagnosis

The clinical presentation of SE is variable, depending on seizure type and the baseline developmental and medical status of the child. Diagnosis depends on the identification of continuous or repetitive seizures, which is usually straightforward in the presence of convulsive seizures. However, after prolonged convulsive seizures the motor manifestations often diminish, and the seizures may become subtle or even nonconvulsive. Differentiating between such nonconvulsive seizures and a postictal state can be challenging. Patients with nonconvulsive SE, including absence SE, may be difficult to identify by history and physical examination alone. These patients can have intermittent altered awareness and continuous lethargy or unresponsiveness with or without subtle myoclonic jerks

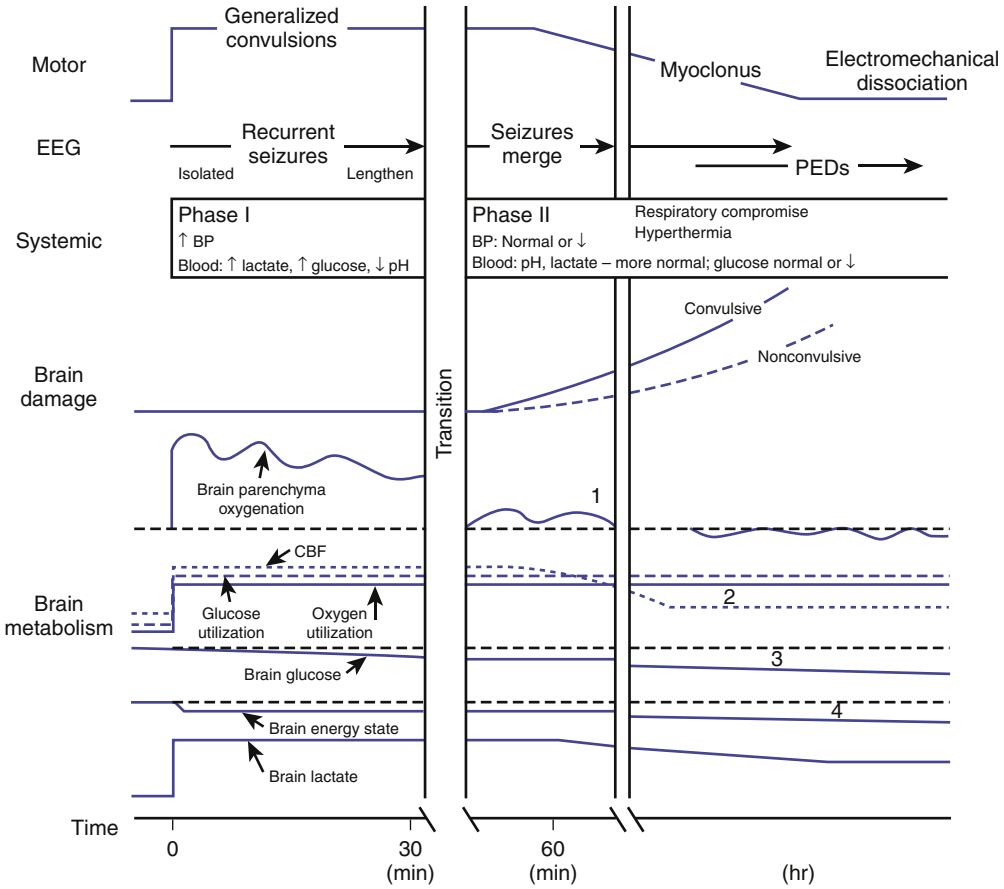


Figure 60–1. Pathophysiology of hypoxic-ischemic brain injury in status epilepticus. *(Modified from Lothman E: The biochemical basis and pathophysiology of status epilepticus,* Neurology *40(5 suppl 2):13-23, 1990.)*

of the face or limbs. In such cases, continuous EEG monitoring is critical for diagnosis. EEG monitoring also can be used to identify nonepileptic (psychogenic) SE. Although uncommon, prolonged delays in the EEG-based diagnosis of nonepileptic SE can lead to unnecessary medical intervention.[36]

EEG measures extracellular electrical activity generated by cortical neurons. Data are collected with a standard array of scalp electrodes and presented for visual display onto a paper or digital record.

Because EEG provides real-time information regarding brain activity, it is invaluable in the evaluation of patients with SE, permitting direct correlation between patient behavior and neuronal activity. EEG interpretation should be performed with the assistance of a trained neurologist or neurophysiologist to reduce the potential for both over- and under-identification of seizures.

Recent advances in computing and networking technology have facilitated the remote interpretation of continuous EEG recordings. Regular communication between ICU staff and the neurology team remains essential to optimizing the care of SE patients. Quantitative EEG trending tools such as amplitude-integrated EEG and color density spectral array are increasingly being incorporated into portable EEG systems and bedside monitors (Figure 60-2). These tools may be applied to visualize single or multiple channels of EEG, providing a time-compressed overview of cerebral function that is simpler to interpret than conventional EEG. However, because these displays are generally less sensitive and specific for the identification of seizures, they should be used judiciously, with corroboration by careful analysis of the underlying raw EEG tracing.

Abnormal waveforms on EEG can be divided into two categories: epileptiform abnormalities and nonepileptiform abnormalities. Epileptiform abnormalities are abnormal discharges associated with an increased risk of seizures, including sharp waves, spikes, polyspikes, and spike and slow wave discharges (Figure 60-3). When present between seizures, these waveforms are termed "interictal" abnormalities. Seizures are defined electrographically by the presence of "ictal" EEG abnormalities, whose hallmark is their rhythmicity and their evolution in frequency or distribution over the course of a seizure. Generalized seizures are characterized by widespread bilateral rhythmic epileptiform discharges (Figure 60-4, *A*). Focal seizures are characterized by rhythmic epileptiform discharges that are confined to one brain region (Figure 60-4, *B*). Focal seizures may spread to involve both cerebral hemispheres, a process termed secondary generalization.

Nonepileptiform abnormalities are not necessarily associated with a risk of seizure but suggest CNS dysfunction. Slow waves are a nonspecific finding, suggesting a structural or functional abnormality, and often are seen after a seizure or SE. The location of slow waves after a seizure may aid in the differentiation between generalized and focal seizures. Generalized slow waves are associated with a diffuse encephalopathy such as due to metabolic disturbance, hypoxia-ischemia, or a postictal state.

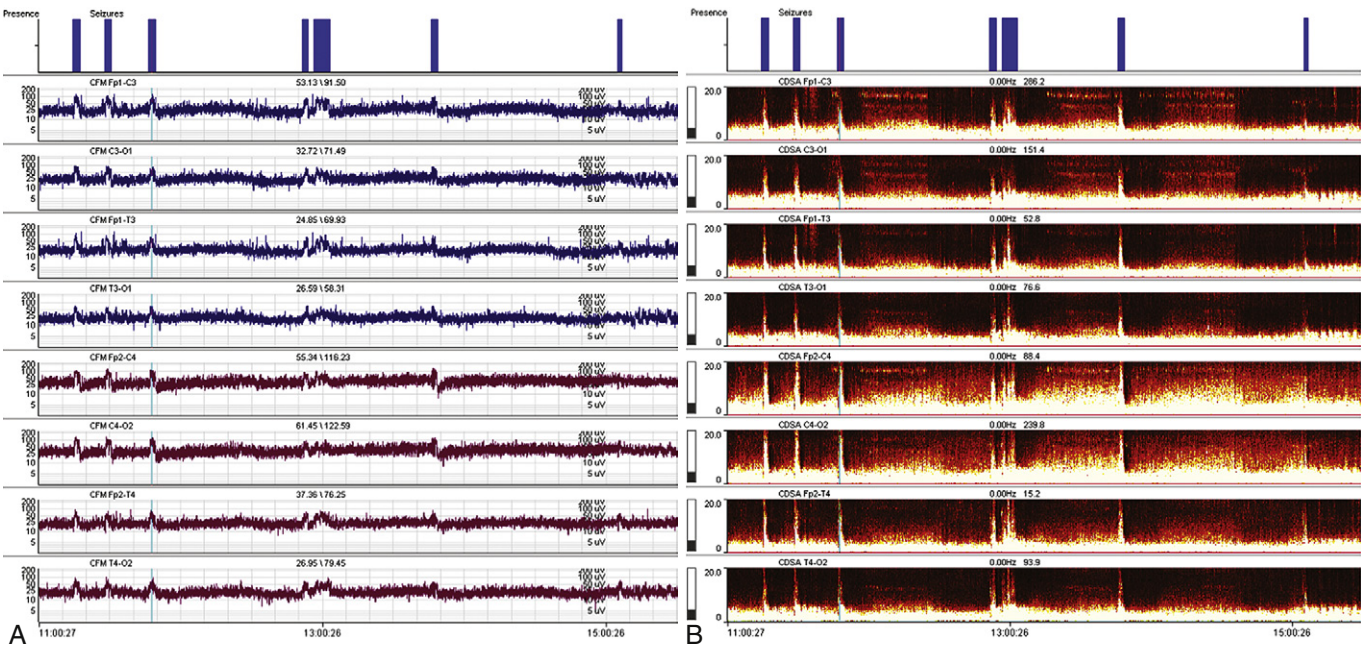


Figure 60–2. Examplesof 8-channel quantitative electroencephalographic (EEG) displays depicting 4 hours of raw EEG containing several generalized seizures. The timing of seizures is indicated at the top of each display. **A,** On an amplitude-integrated EEG display, seizures are characterized by elevations in the upper and lower margins of the tracing. **B,** On a color density spectral array display, seizures are characterized by bright bands of color.

Two further EEG patterns are of particular relevance to the treatment of prolonged seizures. Burst-suppression is characterized by brief bursts containing a mixture of spikes, sharp waves, and slow waves alternating with periods of very low voltage (Figure 60-4, *C*). An isoelectric EEG pattern refers to a continuous low voltage record without any discernable cortical activity. Both burst-suppression and isoelectric EEG patterns can be seen in persons in a coma and may carry a poor prognosis in certain clinical situations. However, in the context of refractory SE, these patterns are often the desired endpoint for treatment with high-dose barbiturates or benzodiazepines (see section on Treatment of Refractory Status Epilepticus).

Refractory Status Epilepticus

Refractory status epilepticus (RSE) is characterized by seizures that persist beyond 60 minutes and fail to respond to first- and second-line therapy. In adults, SE may be refractory in 9% to 31% of patients and carries increased rates of morbidity and mortality.[37] In children, the incidence of RSE has not been well documented; however, in a large series of children with SE, 26% of the children had seizures lasting more than 60 minutes.[22] Pediatric mortality rates from RSE have been reported to be 16% to 32%.[38,39] As with all cases of SE, outcome appears to be related to cause, with deaths occurring predominantly in acute symptomatic cases.[38,39]

A group of patients who are particularly severely affected have seizures that persist for more than 24 hours; this condition has been termed *sustained* RSE. Prolonged therapy for days or weeks may be required for patients with sustained RSE. Although it is virtually always possible to control the seizures with high-dose seizure-suppressive medications, continued seizure remission is not always possible when these high-dose medications are withdrawn.

The outcome of acute symptomatic RSE in seven children who received long-term high-dose seizure suppressive medication was reported to be uniformly poor, with all children having medically intractable epilepsy and developmental deterioration.[40] We have reviewed seven cases of acute symptomatic sustained RSE. In these cases, sustained RSE is most often associated with viral encephalitis or a postinfectious process. This experience shows that SE persisting longer than 24 hours identifies a prolonged course, with our patients requiring high-dose seizure suppressive medication for up to 108 days. Outcome was consistently poor, with a 57% mortality rate and severe disability in the surviving children.

Treatment of Status Epilepticus

The principal goal of therapy in SE is to abort the seizure before irreversible neuronal injury occurs. In experimental models of SE, irreversible neuronal injury begins after 20 minutes to 1 hour of continuous seizure activity, despite the maintenance of adequate brain oxygenation and perfusion. Furthermore, evidence indicates that SE becomes more difficult to control as its duration increases.[29,41-43] Therefore prompt and aggressive pharmacologic management is paramount, for which the formulation of institutional guidelines is invaluable. Figure 60-5 illustrates guidelines for the treatment of prolonged seizures and **SE** in use at The Hospital for Sick Children in Toronto, Canada.[44]

General Supportive Measures

The initial approach to therapy should always focus on securing the airway and maintaining adequate ventilation and circulation. Patients should be positioned on their side with the head below the torso to minimize the risk of aspiration. An oral or nasopharyngeal airway should be inserted. If oxygenation is inadequate, early intubation may be required, in

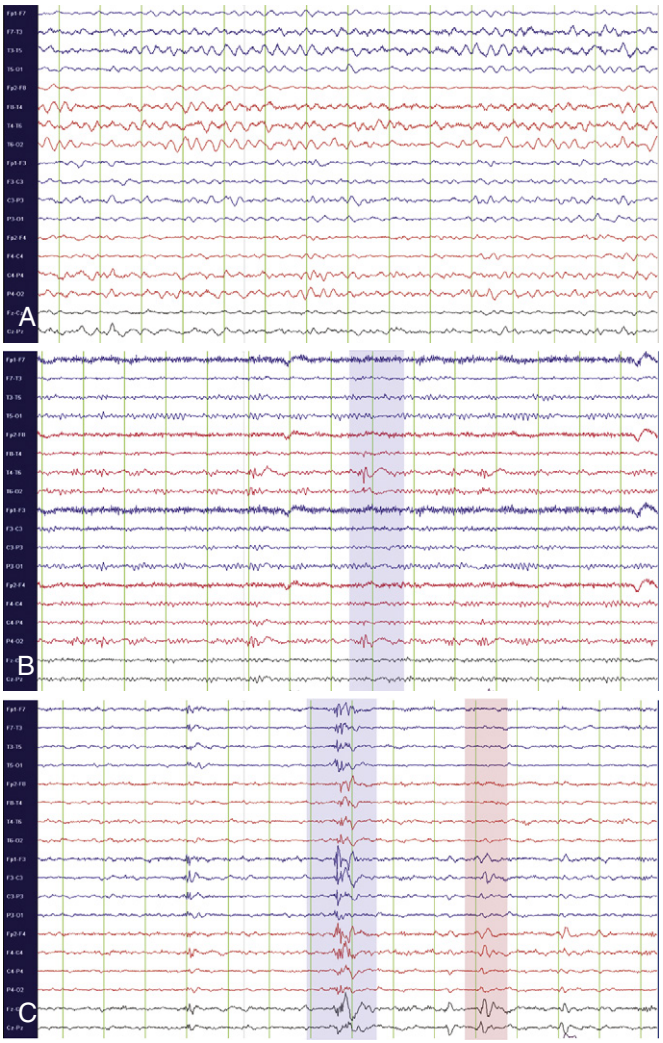


Figure 60–3. Examples of normal electroencephalographic (EEG) background and interictal epileptiform discharges. **A,** Normal 3- to 4-Hz awake background rhythm in a 7-month-old boy. **B,** Normal 9-Hz awake background rhythm in a 4-year-old girl, with a right temporo-occipital spike-wave discharge highlighted in blue. **C,** Normal sleep background in an 8-year-old girl, with a vertex sleep wave highlighted in red and a generalized polyspike discharge highlighted in blue.

which case only short-acting neuromuscular blocking agents and sedatives should be used to avoid compromising the neurologic assessment. Vital signs should be checked at frequent intervals, including the patient's heart rate, blood pressure, and temperature. A cardiac monitor and transcutaneous oxygen saturation monitor should be applied. A rapid test of blood glucose should be performed, and hypoglycemia should be treated with intravenous dextrose. In parallel with the efforts to abort the seizure, investigations into the cause should be undertaken as soon as the patient's medical condition permits (see the section on Investigations later in this chapter).

Initial Management

Most AEDs used to treat SE have the potential to compromise airway control and respiratory drive and therefore should be used with necessary precautions. Table 60-2 provides details of drugs that may be used in the treatment of SE.

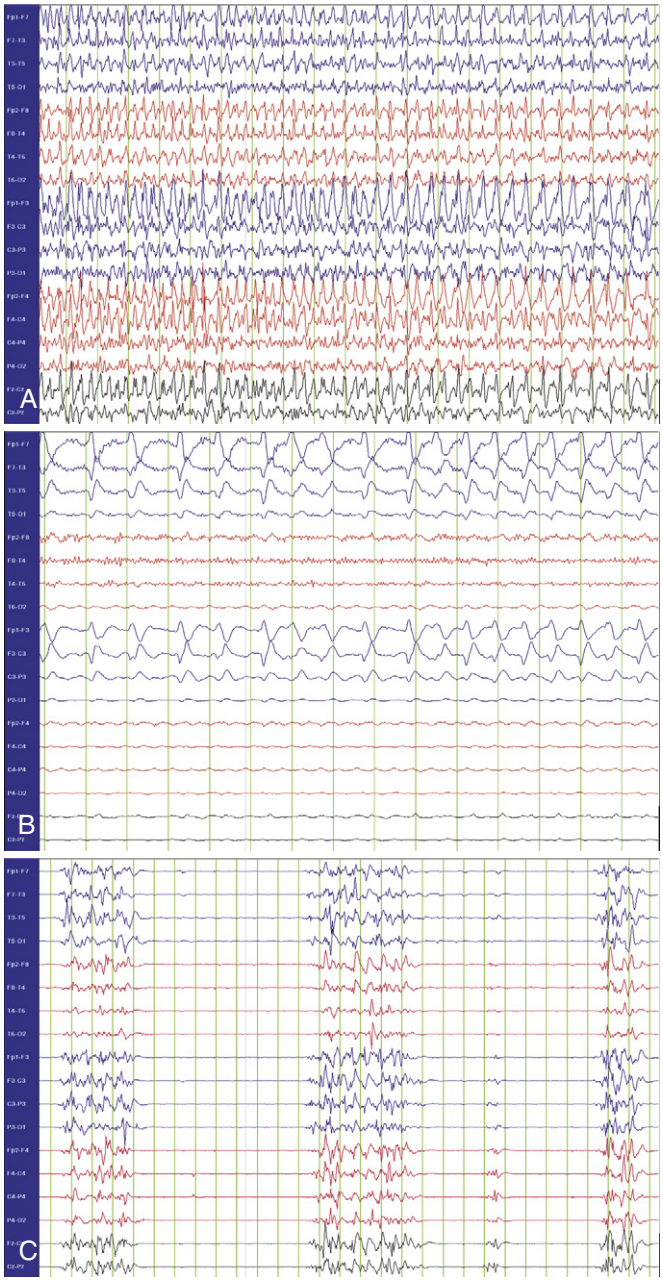


Figure 60–4. Electroencephalography in status epilepticus (SE). **A,** Generalized seizure. **B,** Left focal seizure. **C,** Burst-suppression pattern in a patient treated with a midazolam infusion for refractory SE.

Benzodiazepines

Benzodiazepines are considered the first-line agents for the initial therapy of prolonged seizures and SE. Benzodiazepines enhance inhibitory neurotransmission by binding to a specific benzodiazepine site on the $GABA_A$ receptor. Lorazepam and diazepam have been shown to be equally effective at aborting seizures.[45] However, seizure recurrence is higher with diazepam because of rapid protein binding,[46] leading to an abrupt fall in the unbound (and pharmacologically active) serum diazepam concentration. For these reasons, lorazepam has become the drug of choice in many centers for the initial management of SE.[29] Intravenous administration of benzodiazepines is the preferred route because of its rapid onset of action, but alternatives include

buccal administration of the sublingual preparation and rectal administration of the liquid form. Diazepam may be rectally administered in a commercially available gel preparation. Buccal midazolam may be an equally effective and more socially acceptable alternative to rectally administered diazepam.[47]

Barbiturates

Phenobarbital and other barbiturates enhance inhibitory neurotransmission by binding to a specific barbiturate site on the $GABA_A$ receptor. Phenobarbital is generally considered a second-line agent for the treatment of SE and is usually administered when benzodiazepines do not promptly abort the seizure. Advantages of phenobarbital include a relatively rapid infusion time and efficacy against a wide spectrum of seizure types, including generalized tonic-clonic, absence, myoclonic, and focal seizures. The main drawbacks of phenobarbital are sedation, respiratory depression, and hypotension. Phenobarbital is the primary AED used for neonatal seizures, although phenytoin appears to be equally effective.[48]

Phenytoin

Phenytoin blocks the fast repetitive firing of neurons through the use-dependent inhibition of voltage-gated sodium channels. Advantages of phenytoin include minimal sedation and respiratory depression at therapeutic levels. The main disadvantage of phenytoin is that it must be infused relatively slowly to minimize the risk of cardiac arrhythmia, infusion site pain, and thrombophlebitis. The maximum recommended infusion rate is 1 mg/kg/min (maximum, 50 mg/min); therefore an infusion of 20 mg/kg requires 20 minutes. Extravasation of phenytoin at the infusion site has been associated with a "purple glove syndrome," which consists of localized extremity edema and discoloration that occasionally requires fasciotomy or amputation. Purple glove syndrome, as well as the more common adverse effects of hypotension and cardiac arrhythmia, is attributed to the fact that phenytoin is dissolved in a solution of propylene glycol and ethanol with a pH of 12.

Fosphenytoin

Fosphenytoin, a water-soluble phenytoin pro-drug, has several advantages over phenytoin and has been widely adopted in the United States. Fosphenytoin may be administered intramuscularly or intravenously. The maximal recommended infusion rate is 150 mg phenytoin equivalents per minute, and the pro-drug has a 7-minute half-life of conversion to phenytoin.[49] Although it remains to be proved that the greater speed of administration of fosphenytoin results in improved seizure control compared with phenytoin, fosphenytoin often is preferred because it is better tolerated at the infusion site, carries a lower risk for cardiac arrhythmia and hypotension, and has not been associated with the purple glove syndrome.[50] The higher cost of fosphenytoin and the lack of definitive evidence for superior efficacy, however, may limit its widespread use, despite the suggestion by phamacoeconomic analysis that fosphenytoin is cost effective.[51]

Paraldehyde

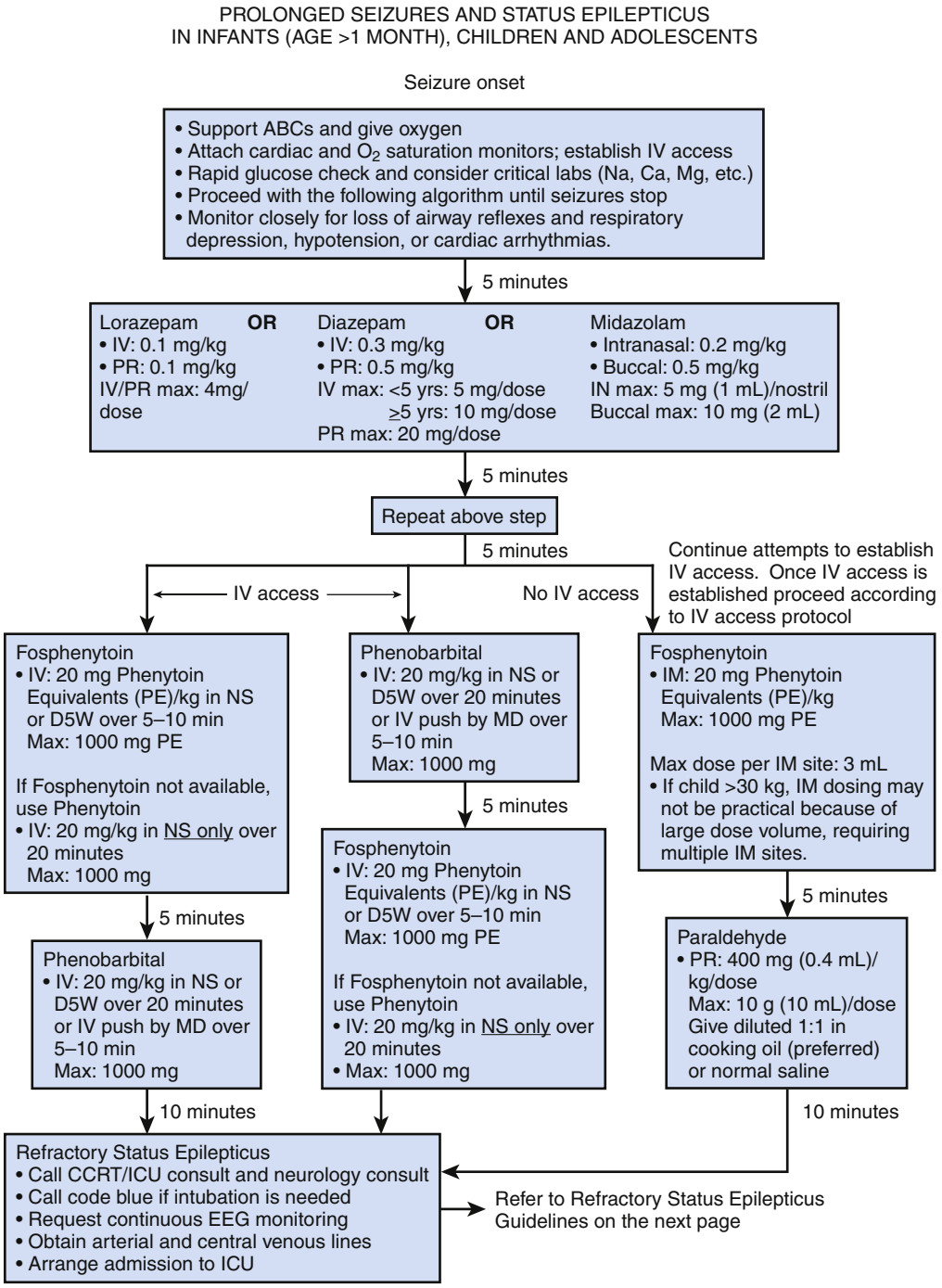
Paraldehyde is an alternative to phenytoin and phenobarbital for the treatment of early SE and also may be used for RSE. The primary advantages of paraldehyde are its wide spectrum of efficacy for different seizure types and relatively modest respiratory depressant effect. Disadvantages of paraldehyde include limited availability, its irritant effect on the rectal mucosa, and its unpleasant pungent odor. Paraldehyde is usually administered rectally, diluted in an equal volume of mineral or cooking oil at a dose of 200 to 400 mg/kg. Intravenous administration is possible but difficult because paraldehyde may dissolve plastic intravenous tubing and decompose into acetaldehyde and acetic acid when exposed to air and light. Plastic syringes may be used safely for rectal administration if the injection is performed promptly. Pulmonary toxicity, which is likely due to the partial excretion of paraldehyde through the lungs, has been reported; therefore the drug should be used with caution in patients with significant pulmonary disease.[49]

Treatment of Refractory Status Epilepticus

SE that persists beyond 1 hour despite AED therapy is considered refractory. Conventional AEDs have low efficacy in RSE, and although conventional AEDs (e.g., topiramate, levetiracetam, and carbamazepine) should be continued during this treatment phase, higher dose or higher potency agents are required to abort RSE. Therapeutic options include high-dose benzodiazepines, barbiturates, propofol, valproic acid, ketamine, lidocaine, and inhalational anesthetic agents. Currently, insufficient evidence exists to conclude which of these high-dose suppressive medications, either alone or in combination, has superior efficacy in the treatment of RSE.[38] High-dose midazolam is the preferred initial approach at The Hospital for Sick Children, Toronto because of an accumulated historic experience of profound cardiovascular depression with high-dose barbiturates.

Goals of Therapy

In the treatment of RSE, as in SE, the goal is termination of all clinical and electrographic seizure activity, and thus continuous EEG monitoring is required. ICU practitioners should resist the temptation to assess seizure control on the basis of clinical signs alone because the clinical expression of seizures can be very subtle and the examination is often confounded by the use of sedative medications. Therefore treatment of RSE should be guided by EEG monitoring. However, the exact target of EEG-guided therapy remains controversial. In addition to achieving seizure suppression, it is generally recommended to escalate therapy to achieve a burst-suppression pattern on EEG. The rationale for achieving burst-suppression is that profound suppression of brain activity may have a protective effect and "break the cycle" of seizures, thus reducing the chance of seizure recurrence upon tapering of medications.[52] Debate continues regarding the recommended length of the periods of EEG suppression (the interburst interval) and how long the burst suppression pattern should be maintained. Furthermore, because of a concern that seizures may persist even when the EEG is interspersed with a burst-suppression pattern, some experts recommend achieving complete EEG suppression, in other words an isoelectric EEG pattern.[41] As a general approach, once seizure control or a burst-suppression pattern has been achieved, a suggested practice is to maintain the burst-suppression pattern for at least 12 hours before a medication taper is attempted. If seizures recur when medication is tapered, then therapy is reinstated to achieve a burst-suppression pattern for at least another 48 hours.



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In parallel with high-dose suppressive therapies described in detail in the following sections, conventional AEDs (i.e., topiramate, levetiracetam, and carbamazepine) should be titrated to high-therapeutic doses, both to assist in aborting RSE and to provide continued anticonvulsant coverage following tapering of high-dose suppressive therapies.

High-Dose Barbiturates

Barbiturates including pentobarbital, thiopental, and phenobarbital are widely used medications for RSE that also may have neuroprotective effects.[53] Pentobarbital is the best-studied drug, and the most data are available on its use. Pentobarbital is administered as an intravenous loading dose of 5 to 12 mg/kg, followed by a continuous infusion of 1 mg/kg/h, increasing as needed to a maximum rate of 10 mg/kg/h. Breakthrough seizures may be treated with additional boluses of 3 to 5 mg/kg.[49] High-dose phenobarbital is an alternative to pentobarbital. Phenobarbital may be given in incremental boluses of 10 mg/kg, without reference to a predetermined maximum level or dose, until seizures are suppressed. There appears to be no maximum dose beyond which further doses are ineffective, and serum levels of up to 344 mg/mL (1490 mmol/L) have been reported.[54] The main drawback of all of the barbiturates in high doses is

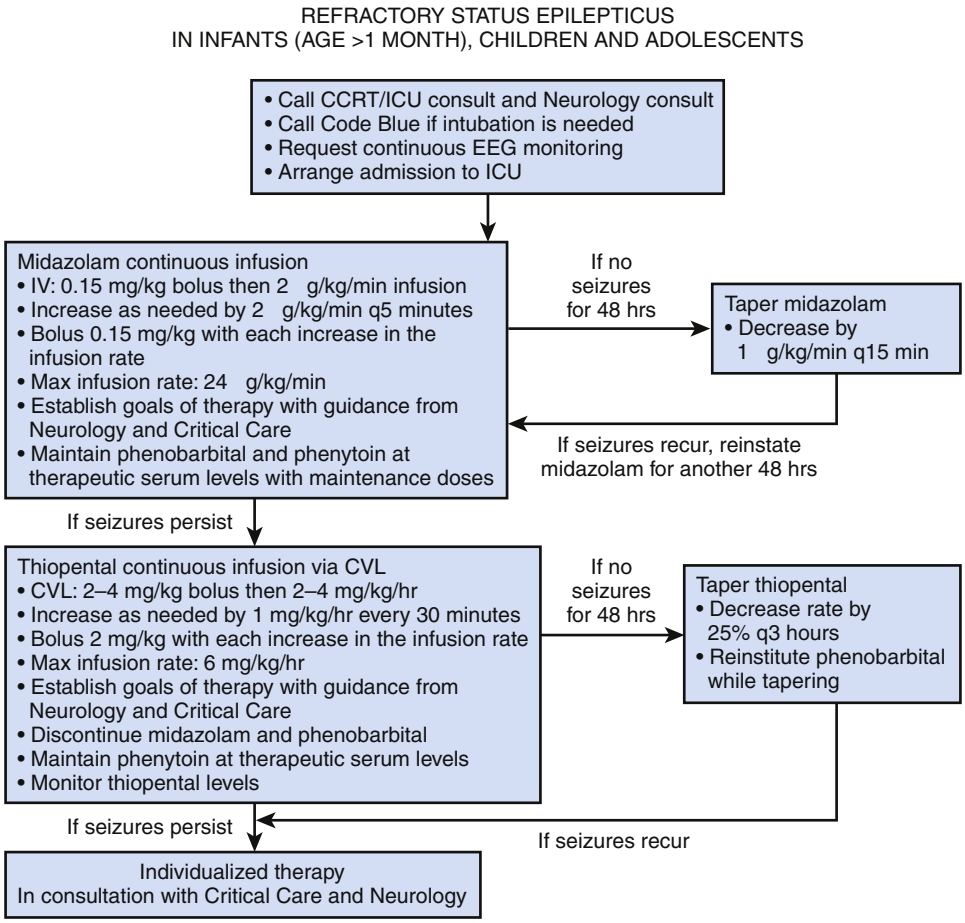

Figure 60–5. Guidelines for the treatment of prolonged seizures and status epilepticus in infants (age >1 month), children, and adolescents *(From The Hospital for Sick Children Toronto, Canada.)*

the high risk of cardiovascular depression and hypotension. This situation frequently requires inotropic and vasopressor therapy and, in rare instances, cardiopulmonary resuscitation. In addition, the need for mechanical ventilation and the time to regain consciousness are also greater with barbiturates than with benzodiazepines.[38] Among the barbiturates, phenobarbital probably carries the lowest risk of hypotension and respiratory depression.[54] Finally, evidence indicates that high-dose, prolonged barbiturate therapy is immunosuppressive, and thus particular vigilance for nosocomial infections is indicated.[55,56]

High-Dose Benzodiazepines

Midazolam is a short-acting benzodiazepine with an efficacy equal to pentobarbital in controlling RSE.[57] It is administered as a loading dose of 0.15 mg/kg, followed by a continuous infusion beginning at 1 μg/kg/min. The infusion rate may be increased as tolerated to a maximum of 24 μg/kg/min, although even higher infusion rates have been reported. The advantages of midazolam include a rapid onset of action, a short half-life, and a lower incidence of cardiovascular depression and need for vasopressors than with pentobarbital.[38,58] The major disadvantage of midazolam is the need for escalating doses because of tachyphylaxis. High-dose infusions of diazepam and lorazepam represent other alternatives.[59,60]

Propofol

The $GABA_A$ agonist propofol is an anesthetic agent with potent anticonvulsant properties that has been widely used for the treatment of RSE, particularly in adults. The advantage of propofol is its rapid onset of action and short half-life; however, rapidly tapering propofol can precipitate seizures.[61] The main adverse effects of propofol are respiratory depression and hypotension due to myocardial depression. Early concerns about a possible proconvulsant effect of propofol have been largely allayed.[62,63] The use of propofol, particularly at high doses and with prolonged infusions, has been associated with a "propofol infusion syndrome" characterized by metabolic acidosis, lipemia, rhabdomyolysis, bradyarrhythmias, and death.[64,65] A recent retrospective series of 31 adults treated with propofol for RSE found a 6% mortality rate and 10% rate of cardiorespiratory arrest directly attributable to the propofol infusion syndrome. In addition, 39% of patients developed one or more features of the syndrome.[66] Therefore propofol infusions should be used with caution and should be limited to short duration with careful monitoring for adverse effects. Few data have been published on pediatric dosing of propofol for RSE. One recent case series reported safety and efficacy using a bolus dose of 1 to 2 mg/kg, followed by a continuous infusion of 1 to 2 mg/kg/h.[67]

Table 60–2 Drugs Used in the Treatment of Status Epilepticus

Drug	Initial Dose	Maximum Single Dose	IV Administration	Onset of Action	Half Life	Principal Adverse Effects in Short-Term Use
Lorazepam	0.05–0.1 mg/kg IV	4 mg	0.5 mg/min bolus	1–3 min	Neonates: 40 h Children: 10 h	Sedation, hypotension, bradycardia, respiratory depression, paradoxical hyperactivity
Diazepam	0.05–0.3 mg/kg IV	<5 y: 5 mg ≥5 y: 10 mg	0.1 mg/kg/min bolus	1–3 min	Neonates: 50–95 h Infants: 40–50 h Children: 15–20 h	Sedation, hypotension, bradycardia, respiratory depression, paradoxical hyperactivity, thrombophlebitis
Phenobarbital	15–20 mg/kg IV	1 g	1 mg/kg/min bolus to max. 60 mg/min	5 min	Neonates: 45–200 h Infants: 20–133 h Children: 37–73 h	Hypotension, sedation, respiratory depression, paradoxical hyperactivity, immunosuppression
Pentobarbital	5–12 mg/kg	100 mg	1 mg/kg/h infusion, then titrate	1 min	25 h	Sedation, bradycardia, hypotension, cardiac arrhythmia, respiratory depression, laryngospasm, extravasation causes skin necrosis
Phenytoin	15–20 mg/kg IV	1 g	1 mg/kg/min bolus, to max. 50 mg/min		7–42 h (first-order kinetics do not apply)	Dysarthria, ataxia, sedation, hypotension, cardiac arrhythmia, thrombophlebitis, extravasation causes "purple glove syndrome"
Fosphenytoin	15–20 mg PE/kg IV	1 g PE	3 mg PE/kg/min bolus to max. 150 mg PE/min		12–29 h (first-order kinetics do not apply)	Dysarthria, ataxia, sedation, hypotension, bradycardia, tachycardia
Valproic acid	10–30 mg/kg IV	30 mg/kg	5 mg/kg/min bolus		Children >2 mo: 7–13 h Children 2–14 y: 3.5–20 h	Hypotension, cardiac arrhythmia, hepatitis, pancreatitis
Paraldehyde	200–400 mg/kg PR	10 g	NA		4–10 h	Rectal irritation, lung toxicity
Midazolam	0.15 mg/kg IV	0.15 mg/kg	1 μg/kg/min infusion, titrate to max. 24 μg/kg/min	1-5 min	Neonates: 4–12 h Children: 3–4 h	Sedation, hypotension, bradycardia, respiratory depression, apnea, laryngospasm, paradoxical hyperactivity
Propofol	1–2 mg/kg IV		1–2 mg/kg/h infusion		1.5–12 h	Sedation, hypotension, bradycardia, respiratory depression, bronchospasm, hallucinations, pain when injected, propofol infusion syndrome: metabolic acidosis, rhabdomyolysis, lipemia, cardiac bradyarrhythmias, death
Ketamine	0.5–2 mg/kg IV		2–7 mg/kg/h*	30 sec	2.5 h	Hypertension, increased intracranial pressure, hallucinations, vomiting, emergence reactions, laryngospasm
Thiopental	2–4 mg/kg IV		2–4 mg/kg/h infusion	30–60 sec	14–34 h	Sedation, hypotension, respiratory depression, accumulation due to lipid solubility, extravasation causes skin necrosis
Isoflurane	0.5% –1% v/v		NA			Respiratory depression, hypotension, arrhythmias, malignant hyperthermia, laryngospasm, coughing (due to pungent odor)
Lidocaine	2–3 mg/kg IV		2–6 mg/kg/h		1.5–2 h in adults	Sedation, cardiac arrhythmias

IV, Intravenous; *NA,* not applicable; *PE,* phenytoin equivalents; *PR,* rectal; *v/v,* volume per volume.
*Continuous infusion rates for ketamine are not well established in children; refer to institutional guidelines and experience.

Valproic Acid

Intravenous valproic acid may have a useful role in RSE, but relatively little evidence exists to support its use.[68] In one case series, the authors reported on the efficacy of intravenous valproic acid for generalized convulsive and nonconvulsive seizures in children. They recommended a loading dose of 20 mg/kg followed by an infusion at 1 to 4 mg/kg/h, depending on the patient's state of hepatic induction (1 mg/kg/h for noninduced, 2 mg/kg/h in the presence of polyanticonvulsant therapy, and 4 mg/kg/h for high-dose pentobarbital).[69] In a subsequent retrospective review of 40 children (18 with SE), the researchers reported on the safety and efficacy of valproic acid when administered at loading doses of 25 mg/kg (in valproate-naive patients) and infused at rates of 2 to 3 mg/kg/min.[70] No significant changes were noted in heart rate or rhythm, blood pressure, or liver enzymes. One patient reported a transient tremor after the infusion.

Inhalational Anesthetics

The efficacy of inhalational anesthetics for SE that is refractory to high-dose benzodiazepines and barbiturates is described in several reports.[71,72] Inhalational anesthetics have the advantage of being easily titratable; however, prolonged use (particularly of halothane) may cause organotoxicity. Hemodynamic compromise is seen with all of these agents, particularly halothane, and all patients in reported studies required vasopressors. In adults, achieving isoelectric EEGs has required isoflurane concentrations of 1.5% to 2%.[73] The use of inhalational anesthetics in the ICU setting is complicated by the need for a proper gas scavenging system and supervision by staff trained in the administration of anesthesia.

Ketamine and Lidocaine

Ketamine is a unique NMDA antagonist reported to have both anticonvulsant and neuroprotective properties. Because of its unique mechanism of action on NMDA receptors, ketamine is an attractive therapeutic option for refractory SE that has failed to respond to high-dose benzodiazepines and barbiturates.[74] Ketamine is commonly used for procedural sedation, but there is no consensus on its dosing for SE, particularly when given as a continuous infusion. Lidocaine, which is given as an intravenous bolus or a continuous infusion, is another treatment option, although it is not widely used in North America.[75]

Pyridoxine

Pyridoxine (vitamin B_6) is a cofactor for both glutamic acid decarboxylase and GABA transaminase, the enzymes required for the synthesis and metabolism of GABA in the brain. Pyridoxine dependency and pyridoxine deficiency are rare disorders (with a prevalence of ~1/300,000 in the United Kingdom) that usually present in the neonatal or infantile period but may present as late as age 2.5 years.[76] Patients with these disorders have intractable seizures that are refractory to conventional anticonvulsant medications but respond promptly to pyridoxine. Therefore a trial of pyridoxine should be considered in any child who is seen before age 3 years with recurrent seizures or SE, particularly if the seizures are refractory to conventional anticonvulsant agents.[76] Isoniazid poisoning is another clinical scenario in which pyridoxine may be the only effective anticonvulsant therapy.[77]

Surgical Treatment

When SE is refractory to multiple medical treatments, including high-dose barbiturates and benzodiazepines, surgical intervention can be considered by centers with experience in pediatric epilepsy surgery. This approach is most easily considered for but not limited to children with a large cortical malformation.[78] Focal cortical resections may be indicated if a focal structural abnormality can be identified on neuroimaging; however, the presence of a lesion on MRI is not sufficient to ensure that seizures are arising from that region. Seizures also may arise from regions remote from a lesion visualized by MRI. Furthermore, in children with prolonged RSE, secondary epileptogenic foci may develop. Typically, multiple investigations will be undertaken to ensure that seizures are arising from the area of potential surgical resection. At a minimum, there should be concordance between the structural lesion and the location of ictal and interictal EEG discharges. If the patient is medically stable, fluorodeoxyglucose positron emission tomography may be used to demonstrate interictal hypometabolism or ictal hypermetabolism of the epileptogenic focus, and magnetoencephalography may be used to support the identification of the epileptogenic focus.[79] Implantation of subdural electrodes allows for the most precise localization of the epileptogenic focus; however, this procedure usually is not feasible in the setting of RSE. The evidence for such surgical approaches is limited to case reports and smaller series.[78,80-82]

Corpus callosotomy also has been attempted for SE that is generalized or cannot be localized. Implantation of a vagal nerve stimulator may be another therapeutic option, although it is rarely considered in the acute situation.[83,84]

Investigations

Investigation of the cause of SE should proceed in parallel with treatment because the optimal treatment, including prevention of recurrent SE, requires an understanding of the underlying cause. A 2006 evidence-based practice parameter identified the lack of high-level evidence for many of the recommendations that are generally regarded as standard of care for children with SE.[85]

Box 60-2 outlines the spectrum of investigations that should be considered in patients with SE and their rationale.

Acknowledgment

We thank Angela Trope, MSc, RPh, for her contribution to Table 60-2.

References are available online at http://www.expertconsult.com.

Box 60–2 Investigation of the Patient with Status Epilepticus

To Be Performed in All Patients with Status Epilepticus

Serum glucose, electrolytes, calcium, magnesium
Blood gas, serum osmolality
Toxicology screen (serum and urine)
Antiepileptic drug levels
Complete blood count (RBC, differential WBC, platelet count)
Liver enzymes, serum ammonium
Blood culture
Lumbar puncture, including
- Opening pressure
- Cell count, Gram stain, smear for acid-fast bacilli
- Viral and bacterial cultures
- PCR for herpesvirus

EEG, preferably continuous monitoring with video
- To monitor for subtle or subclinical seizures
- To guide antiepileptic drug therapy
- To localize the epileptogenic brain region (focal slowing or epileptiform activity)

To Be Considered in Patients with Status Epilepticus

Structural neuroimaging (CT, MRI)
- To diagnose acute infarction, hemorrhage, vascular malformation, encephalitis, abscess, neurocysticercosis, neoplasm
- In nonlesional cases, may localize the epileptogenic zone by evidence of focal edema in the affected cortical region
- To assess the degree of cerebral edema and diagnose impending uncal or transtentorial herniation
- MR angiography may identify CNS vasculitis, especially in medium or large vessel disease

Functional neuroimaging (PET, SPECT)
- In nonlesional cases, may identify the epileptogenic zone

Cerebral angiography
- To identify small vessel CNS vasculitis, which may not be visible on MR angiography

Rheumatological workup for vasculitides
ESR, C-reactive protein, rheumatoid factor, serum complement levels, antineutrophil cytoplasmic antibodies
Brain biopsy
- To diagnose cerebral vasculitis (granulomatous compared with nongranulomatous)
- To identify malformations of cortical development

CNS, Central nervous system; *CT*, computed tomography; *EEG*, electroencephalography; *ESR*, erythrocyte sedimentation rate; *MRI*, magnetic resonance imaging; *PCR*, polymerase chain reaction; *PET*, positron emission tomography; *RBC*, red blood cell; *SPECT*; single-photon emission computed tomography; *WBC,* white blood cell.

Severe Traumatic Brain Injury in Infants and Children

Patrick M. Kochanek, Michael J. Bell, Hülya Bayir, Michael J. Forbes, Randall Ruppel, P. David Adelson, and Robert S.B. Clark

PEARLS

- Complete and rapid physiologic resuscitation is essential to the initial treatment of infants and children with severe traumatic brain injury.
- Recent data have begun to support age-dependent targets for cerebral perfusion pressure–directed therapy in the treatment of infants and children with severe traumatic brain injury.
- Monitoring and control of intracranial hypertension should begin with first-tier therapies and progress to less well established second-tier therapies in refractory cases.
- The choice of second-tier therapy is based in part on an in-depth knowledge of the physiologic derangements involved and the preferences of the treating team.
- Advanced neuromonitoring is providing additional insight into pathophysiology-guided treatment.
- Because pediatric patients with traumatic brain injury often sustain multiple insults, appropriate correction of physiologic derangements and complications in other organ systems is also important in creating an optimal environment for recovery.

The topic of severe traumatic brain injury (TBI) in infants and children has been the focus of many chapters and reviews, but it has been the focus of few clinical reports and even fewer randomized controlled trials (RCTs). The paucity of clinical trials in infants and children with severe TBI became apparent when a group of physicians and scientists (pediatric critical care medicine specialists, pediatric neurologic surgeons, pediatric emergency medicine specialists, and experts in the methodology of evidence-based medicine) met and published an evidence-based document outlining "Guidelines for the Management of Severe TBI in Infants, Children, and Adolescents" (henceforth referred to as "the pediatric guidelines" in this chapter).[1] While the document focused on evidence from pediatric studies, small controlled studies or even uncontrolled case series of specific therapies for severe pediatric TBI were scarce. Studies focused on the age-related effects of therapies in the pediatric population were largely absent, and therapeutic trials in key pediatric subgroups, such as victims of inflicted childhood neurotrauma (child abuse), were rare. Based on the existing literature, few recommendations at the guideline level could be made. Subsequent to these guidelines and the last edition of this textbook, a number of studies have contributed to improving evidence-based care of children with severe TBI, and this information is incorporated into this chapter. This chapter addresses a practical and contemporary approach to the management of patients with TBI based on several sources of information: (1) the pediatric data presented in the pediatric guidelines, (2) data from studies in adults with severe TBI, and (3) accepted principles of the physiology and pathophysiology of the cerebral circulation and cranial vault.

This chapter focuses on severe TBI, specifically on management in the pediatric intensive care unit (PICU). The evolution of PICU management has progressed from exclusively supportive care to strategies attempting to (1) optimize substrate delivery and cerebral metabolism, (2) minimize secondary insults that might worsen secondary damage and outcome, (3) prevent severe or intractable intracranial hypertension and/or herniation, and (4) target specific mechanisms involved in the evolution of secondary injury with novel therapies. The goal of contemporary neurointensive care is the prevention and/or amelioration of secondary injury. The role of newer technologies and the differences between adults and children are highlighted. For information on mild or moderate TBI, outcomes, or rehabilitation of pediatric patients with TBI, the reader is referred to other materials on these topics.[2,3]

Epidemiology

Traumatic brain injury remains a significant pediatric health problem, with an estimated incidence of approximately 230 cases per 100,000.[4] About 475,000 new cases of pediatric TBI are reported each year,[5] which corresponds to a frequency of approximately one case every 2 to 3 minutes.[6] TBI is the most important cause of death and disability in children.[6,7] Specifically, 3000 to 4000 pediatric deaths resulting from TBI are reported annually.[8] About 10% to 15% of TBI cases in infants and children are severe (Glasgow

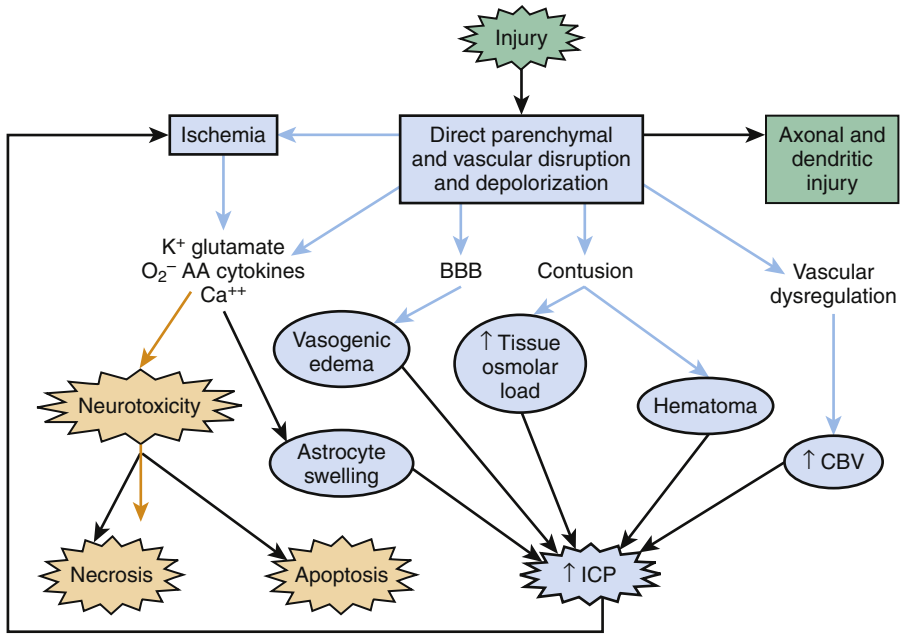

Figure 61–1. Categories of mechanisms proposed to be involved in the evolution of secondary damage after severe traumatic brain injury in infants and children. Three major categories for these secondary mechanisms are (1) ischemia, excitotoxicity, energy failure, and cell death cascades; (2) cerebral swelling; and (3) axonal injury.

Coma Scale [GCS] score <8), and these cases contribute most of the deaths or permanent brain damage observed.[9] The incidence of pediatric TBI is distributed evenly within three age groups (0 to 4 years, 5 to 10 years, and 11 to 15 years) based on data from the Traumatic Coma Data Bank.[10] Although children 5 to 15 years of age generally have favorable outcomes compared with adults, children aged 4 years or younger—particularly those younger than 2 years—have a worse outcome than older children and adults. Inflicted childhood neurotrauma is the leading cause of severe TBI in infants and is believed to be the key contributor to poor outcome in this younger subgroup, although other factors may play a role.[10,11] Penetrating injuries such as gunshot wounds, although not as common as either motor vehicle accidents or child abuse, also contribute significant morbidity and mortality in the pediatric population.[12]

Pathophysiology

Severe TBI involves a primary injury that includes direct and immediate disruption of brain parenchyma. However, not all of the effects of the primary injury are immediately apparent because damage also evolves over time and results from a cascade of biochemical, cellular, and molecular events involved in the evolution of the injury. In this chapter we define only the key factors involved. For detailed information on this topic, the reader is referred to other reviews.[13-15] Secondary injuries also result from extracerebral and intracerebral insults (e.g., hypotension, hypoxemia, ischemia, and refractory intracranial hypertension) at the injury scene and in the PICU. Three basic categories of secondary mechanisms can be defined (Figure 61-1): those associated with (1) ischemia, excitotoxicity, energy failure, and resultant cell death cascades; (2) secondary cerebral swelling; and (3) axonal injury. A constellation of mediators of secondary damage and repair are involved within each category. The contribution of each mediator to outcome and the interplay among them remain poorly defined. The biochemical and molecular responses to severe TBI resulting from child abuse often are unique and generally severe.[14]

Posttraumatic Ischemia

The early studies of Pickels[15] and Bruce et al.[16] on cerebral blood flow (CBF) in pediatric TBI focused on the role of hyperemia in secondary brain swelling. However, clinical studies in adults showed that CBF is reduced early after injury and suggested that early posttraumatic ischemia might be of special importance.[17,18] The devastating consequences of secondary extracerebral insults (i.e., hypotension and hypoxemia) early after TBI are consistent with this possibility, that is, contributing to an already compromised system. Adelson et al.[19] assessed CBF in 30 infants and children after severe TBI. Early posttraumatic hypoperfusion was common, and a global CBF less than 20 mL/100 g/min was associated with a poor outcome. After the initial 24 hours, CBF often recovered, in some cases to high levels. However, delayed increases in CBF were not associated with poor outcome. This finding shifted the emphasis toward the recognition and possible treatment of hypoperfusion early after TBI to avert secondary damage.

Numerous mechanisms may contribute to early posttraumatic hypoperfusion, including (1) an attenuated vasodilatory response to nitric oxide (NO), cyclic guanosine monophosphate, cyclic adenosine monophosphate, and/or prostanoids; (2) loss of endothelial NO production; (3) elaboration of endothelin-1[14]; and (4) production of other vasoconstrictor mediators.[20] Early after injury, increases in metabolic demands resulting from uptake of glutamate are reported.[21,22] Thus reduced metabolic demands coupled with CBF reduction in severely injured brain regions are an unlikely explanation for hypoperfusion. Work by Vavilala et al.[11] that was published after the pediatric guidelines identified a potentially

critical factor, that is, age at the time of injury, that could increase the importance of ischemic brain injury in pediatric TBI, particularly in infants and young children. These investigators reported that no difference exists in the lower limit of blood pressure autoregulation of CBF in children younger than versus older than 2 years.[11] This finding led them to conclude that the autoregulatory reserve (i.e., the difference between baseline mean arterial blood pressure [MAP] and the lower limit of autoregulation) is smaller in infants than in older children or adults; even modest MAP reductions may exacerbate ischemia in infants. The contribution of this finding to secondary ischemia in pediatric TBI will become apparent later in this chapter.

Excitotoxicity

Excitotoxicity is the process by which glutamate and other excitatory amino acids cause neuronal damage. Glutamate is the most abundant neurotransmitter in the brain, but exposure to toxic levels produces neuronal death.[23] Glutamate exposure produces neuronal injury in two phases. Sodium-dependent neuronal swelling quickly occurs,[24] followed by delayed, calcium-dependent degeneration. These effects are mediated through both ionophore-linked receptors, labeled according to specific agonists (*N*-methyl-D-aspartate [NMDA], kainite, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and receptors linked to second messenger systems (i.e., metabotropic receptors). Activation of these receptors leads to calcium accumulation via receptor-gated or voltage-gated channels or through release of intracellular stores. Increased intracellular calcium concentration triggers a number of processes that can lead to cell death. One mechanism involves activation of constitutive NO synthase, leading to NO production, peroxynitrite formation, and resultant deoxyribonucleic acid (DNA) damage. Poly(ADP-ribose) polymerase is an enzyme operative in DNA repair. In the face of excessive DNA damage, poly(ADP-ribose) polymerase activation leads to adenosine triphosphate (ATP) depletion, metabolic failure, and necrotic cell death.[25]

In cerebrospinal fluid (CSF) from adults with TBI, glutamate levels were about fivefold greater than in control patients (up to 7 μm/L).[26] These levels are sufficient to cause neuronal death in cell culture. Increased levels of glutamate also are seen in CSF of infants and children with TBI and correlate with poor outcome and child abuse as an injury mechanism.[27] Antiexcitotoxic therapies improve outcome after experimental TBI; pretreatment with NMDA antagonists (e.g., MK-801) attenuate behavioral deficits.[28] Other therapies that modify glutamate-NMDA receptor interaction and improve outcome after experimental TBI are magnesium, glycine site antagonists, hypothermia, and pentobarbital.[14] Despite this benefit, clinical trials with antiexcitotoxic therapies have been unsuccessful in adults, perhaps because of adverse effects of these drugs, delayed treatment, or the antiexcitotoxic effects of many current therapies (e.g., barbiturates, hypothermia, and sedatives).[29] Developing neurons are more susceptible to excitotoxic injury than are mature cells; however, concerns have been raised about use of NMDA antagonists in infants because these drugs may induce apoptotic neurodegeneration.[30] Investigating which specific NMDA receptor subunits may need to be targeted to produce antiexcitotic effects without triggering apoptosis is a key area for future research.

Apoptosis Cascades

Cells that die after TBI can be categorized on a morphologic continuum ranging from necrosis to apoptosis.[31,32] Apoptosis is a morphologic description of cell death defined by cell shrinkage and nuclear condensation, internucleosomal DNA fragmentation, and formation of apoptotic bodies.[33] In contrast, cells that die of necrosis display cellular and nuclear swelling with dissolution of membranes (see also Chapter 100).

Because apoptosis requires a cascade of intracellular events for completion of cell death, "programmed cell death" is the currently accepted term for the process that leads to apoptosis. In diseases with complex and multiple mechanisms, such as TBI, distinguishing clinical apoptotic from necrotic cell death as classically defined may be difficult,[34] and some cells have mixed phenotypes. In mature tissues, programmed cell death requires initiation via either intracellular or extracellular signals (Figure 61-2). Intracellular signaling appears to be initiated in mitochondria, triggered by disturbances in cellular homeostasis such as ATP depletion, oxidative stress, or calcium fluxes.[35] Mitochondrial dysfunction leads to egress of cytochrome c into the cytosol. Oxidation of the mitochondrial lipid cardiolipin may play a central role in cytochrome c release.[36] Cytochrome c release can be blocked by antiapoptotic members of the Bcl-2 family (e.g., Bcl-2, Bcl-xL, Bcl-w, and Mcl-1) and promoted by proapoptotic members of the Bcl-2 family (e.g., Bax, Bcl-xS, Bad, and Bid).[37] Cytochrome c in the presence of dATP and a specific apoptotic-protease activating factor in cytosol activates the initiator cysteine protease caspase-9.[38] Caspase-9 then activates the effector cysteine protease caspase-3, which cleaves cytoskeletal proteins, DNA repair proteins, and activators of endonucleases.[39] Extracellular signaling of apoptosis occurs via the tumor necrosis factor (TNF) superfamily of cell surface death receptors, which includes TNFR-1 and Fas/Apo1/CD95.[40] Receptor-ligand binding of TNFR-1–TNF-α or Fas-FasL promotes formation of a trimeric complex of TNF- or Fas-associated death domains. These death domains contain caspase recruitment domains, ultimately leading to caspase-3 activation, where the mitochondrial and cell death receptor pathways converge (see Figure 61-2). Both the intrinsic and extrinsic pathways may contribute to the evolution of cell death after severe TBI in infants and children. CSF levels of the anti-apoptotic protein Bcl-2 in pediatric patients after TBI were increased approximately fourfold in patients with TBI versus control subjects.[41] Similarly, CSF levels of sFas receptor and sFas ligand are increased in patients with TBI versus control subjects.[42] Apoptosis may be an important therapeutic target for new therapies in infants with severe TBI. Finally, current therapies likely attenuate both necrotic and apoptotic injury cascades.

Taken together, the currently available data strongly suggest that early after injury, severe TBI produces a state of hypoperfusion with simultaneous increased metabolic demands from excitotoxicity. This is a state of enhanced vulnerability to secondary insults (i.e., hypotension and hypoxemia). These processes are intimately linked with the evolution of neuronal death by either necrosis or apoptosis.

Cerebral Swelling

After the initial minutes to hours of posttraumatic hypoperfusion and hypermetabolism, a phase of metabolic depression occurs. Cerebral metabolic rate of oxygen ($CMRO_2$) decreases

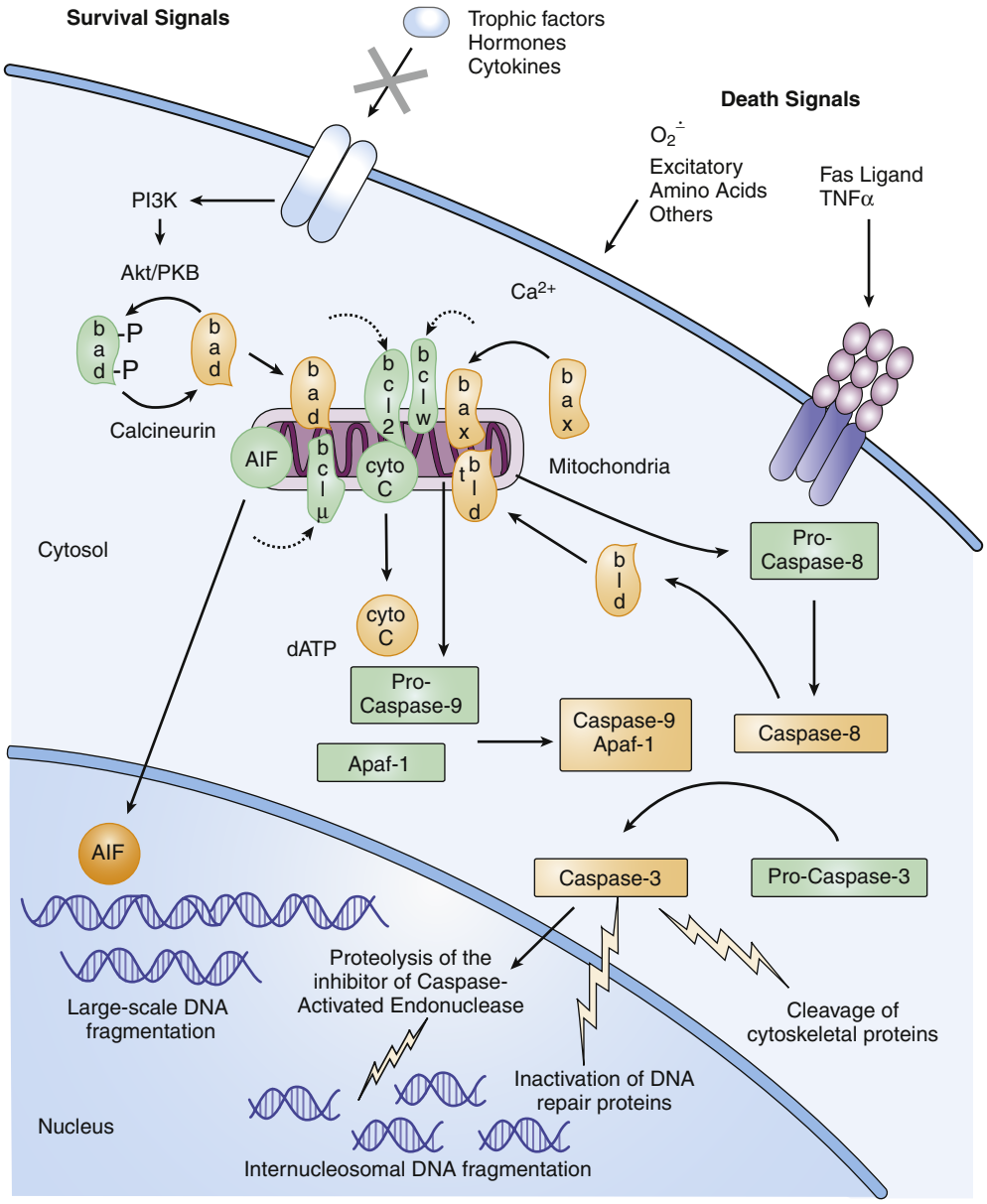

Figure 61–2. Cell death cascades involved in delayed neuronal death after severe traumatic brain injury. *AIF*, Apoptosis-inducing factor; *dATP*, deoxyadenosinemonophosphate; *DNA*, deoxyribonucleic acid; *PI3K*, phosphoinositide 3-kinase; *PKB*, protein kinase B; *TNF*, tumor necrosis factor.

to approximately one third of normal[43,44] and is maintained at that level for the duration of coma, unless perturbed by second insults such as seizures or spreading depression.[45] The exact etiology of this state remains to be defined; however, contributions from reduced synaptic activity and mitochondrial failure may be important.[46] Sustained increases in glycolysis are reported in some cases, possibly related to seizure activity or sustained increases in glutamate levels.[22] During the PICU phase, cerebral swelling develops and generally peaks between 24 and 72 hours after injury, although sustained increases in intracranial pressure (ICP) for 1 week or longer occasionally are observed.

Cerebral Blood Volume

Several mechanisms may contribute to intracranial hypertension in infants and children after severe TBI (see Figure 61-1). Brain swelling and accompanying intracranial hypertension contribute to secondary damage in two ways. Intracranial hypertension can compromise cerebral perfusion leading to secondary ischemia, and it can produce the devastating consequences of deformation through herniation syndromes. Bruce et al.[16] described the phenomenon of "malignant posttraumatic cerebral swelling" in children. CBF was measured in six children, and hyperemia was believed to be the major culprit. Muizelaar et al.,[47] in a series of 32 children, and Beyda[48] suggested similar findings. However, Sharples et al[49,50] suggested that hyperemia was uncommon after severe TBI in children; rather, reduced $CMRO_2$ was associated with poor outcome.

Suzuki[51] measured CBF in 80 normal children. He showed an age dependence of CBF, with rather high values in children ages 2 to 9 years, levels previously suggested to represent posttraumatic hyperemia. Nevertheless, in patients with TBI, after resolution of the aforementioned early posttraumatic hypoperfusion, CBF may increase to levels greater than metabolic demands in some children, producing a state of relative hyperemia.[14]

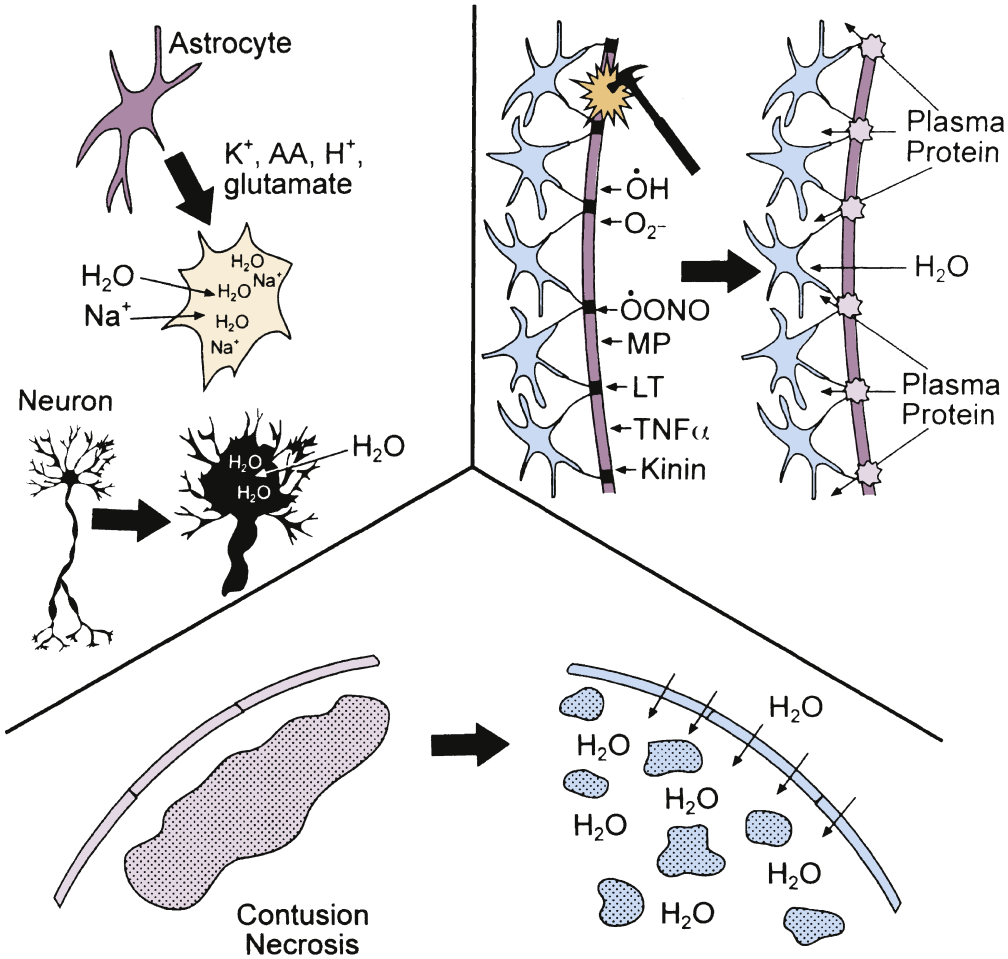

Figure 61–3. Schematic of three cascades leading to cerebral edema. *Top left*, Cellular swelling is predominantly seen in astrocytes and is stimulated by potassium, acidosis, glutamate, arachidonic acid *(AA),* and other factors. This key pathway is less representative of a toxic process and more consistent with a homeostatic or mediator-driven process. Neuronal swelling from pump leak probably is less important. *Bottom*, Osmolar swelling from contusion necrosis. In the hours after injury, reconstitution of the BBB or development of an osmolar barrier around a contusion sets the stage for marked local swelling as macromolecules in the contusion break down, increasing local osmolality. *Top right*, Vasogenic edema results from protein and water accumulation across the damaged BBB, which is formed by tight junctions (astrocyte foot processes). Direct vascular disruption by trauma, reactive oxygen species such as hydroxyl radical *(OH),* superoxide anion *(O_2^-),* and peroxynitrite *(ONOO),* metalloproteases *(MP),* kinins, leukotrienes *(LT),* cytokines, and other mediators contribute to BBB damage. *TNF,* Tumor necrosis factor.

Bergsneider et al.[22] posed the alternative hypothesis of "hyperglycolysis" to explain the increases in CBF in patients with severe TBI whose CBF is uncoupled from $CMRO_2$. Cerebral glutamate uptake is coupled to glucose utilization by glycolysis in astrocytes. Recent studies suggest two other potential contributors to increased glycolysis after TBI even in the absence of low CBF, namely mitochondrial falure[52] and nitration and inactivation of the enzyme pyruvate dehydrogenase, which is critical to the production of acetyl-CoA and thus oxidative metabolism.[53] Thus in injured brain regions with reduced $CMRO_2$, increases in CBF may be coupled to local increases in glucose utilization even in the absence of ischemia.

Local or global increases in glycolysis occur in adults with severe TBI.[22] The incidence and/or importance of secondary "hyperemia" or hyperglycolysis in pediatric TBI remains to be determined. It may occur in select cases, but secondary increases in CBF probably are not the major contributor to raised ICP. Increases in CBF were not associated with raised ICP in adults,[54] and hyperemia was not associated with poor outcome in children.[4] The contribution of hyperemia (increased cerebral blood volume [CBV]) to the development of raised ICP has been studied in adults with TBI.[55] Increased CBV was seen in only a small number of patients. These studies suggest that the importance of posttraumatic hyperemia may have been overstated, and edema rather than hyperemia may be the predominant contributor to brain swelling after TBI.[56]

Edema

Both cytotoxic and vasogenic edema may play important roles in cerebral swelling (Figure 61-3). However, the traditional concept of cytotoxic and vasogenic edema is evolving. There appear to be four mechanisms for edema formation in the injured brain. First, vasogenic edema may form in the extracellular space as a result of blood-brain barrier (BBB) disruption. Second, cellular swelling can be produced in two ways. Astrocyte swelling can occur as part of the homeostatic uptake of substances such as glutamate. Glutamate uptake is coupled

to glucose utilization via a sodium/potassium adenosine triphosphatase, with sodium and water accumulation in astrocytes. Swelling of both neurons and other cells in the neuropil can result from ischemia- or trauma-induced ionic pump failure. Finally, osmolar swelling may contribute to edema formation in the extracellular space, particularly in contusions. Osmolar swelling actually is dependent on an intact BBB or an alternative solute barrier. Cellular swelling may be of greatest importance.

Using a model of diffuse TBI in rats, Barzo et al.[57] applied diffusion-weighted magnetic resonance imaging to localize the increase in brain water. A decrease in the apparent diffuse coefficient after injury suggested largely cellular swelling rather than vasogenic edema in the development of raised ICP. Katayama et al.[58] also suggested that the role of BBB in the development of posttraumatic edema may have been overstated, even in the setting of cerebral contusion. An intriguing possibility is that as macromolecules are degraded within injured brain regions, the osmolar load in the contused tissue increases. As the BBB reconstitutes (or as other osmolar barriers form), a large osmolar driving force for local accumulation of water develops, resulting in the marked swelling so often seen in and around cerebral contusions. Thus in either diffuse injury or focal contusion, BBB permeability may play only a limited role in the development of cerebral swelling. If these results can be generalized, then hypertonic saline solution or mannitol seem to represent optimal therapies. This suggestion is in contrast to traditional recommendations, in which hyperventilation is suggested.[59,60] However, a role for BBB permeability in cases of severe TBI should not be dismissed. A recent study in adults with severe TBI by Polderman et al.[61] reported that prolonged use (>48 hours) of mannitol (a large molecule that does not cross the intact BBB) was associated with a progressive accumulation of mannitol in CSF, and in some cases, a reverse osmotic gradient was even established. This finding suggests that breaching of the BBB is important and that prolonged use of mannitol might create an iatrogenic secondary insult. Studies of the extent of BBB injury and the contribution of cellular swelling to intracranial hypertension in pediatric TBI are needed.

Axonal Injury

Traumatic axonal injury (TAI) encompasses the spectrum from mild to severe TBI.[62,63] The extent and distribution of TAI depend on injury severity and category (focal vs. diffuse). Its incidence and nature appear to be age independent,[64] but its consequences may be particularly devastating in children.[65] The effects of TAI in children during a period of developmental axonal connectivity remain unknown but likely are considerable. During development, numerous signaling molecules can function as attractants or repellents.[66] Clinical data on TAI after pediatric TBI are limited. However, strongly supporting the role for TAI in pediatric TBI, after publication of the guidelines, Berger et al.[67] reported that serum levels of myelin basic protein are markedly increased in infants and children after either accidental or inflicted TBI—in contrast to hypoxic-ischemic encephalopathy (Figure 61-4). In children affected by shaken baby syndrome, TAI may be highly prevalent.[68] The classic view that TAI occurs because of immediate physical shearing is represented primarily in patients with severe injury in whom frank axonal tears occur. Experimental studies suggest that TAI occurs by a delayed process termed *secondary axotomy*, which results from either calcium accumulation or altered axoplasmic flow.[69] What remains to be determined is how much of TAI results from a reversible evolution of damage to axons versus Wallerian degeneration of disconnected axons. The former but not the latter would be amenable to treatment. Nevertheless, TAI contributes to the morbidity after TBI.[69] Laboratory studies suggest that hypothermia, calpain antagonists, and cyclosporine A can attenuate TAI, but clinical data are lacking.

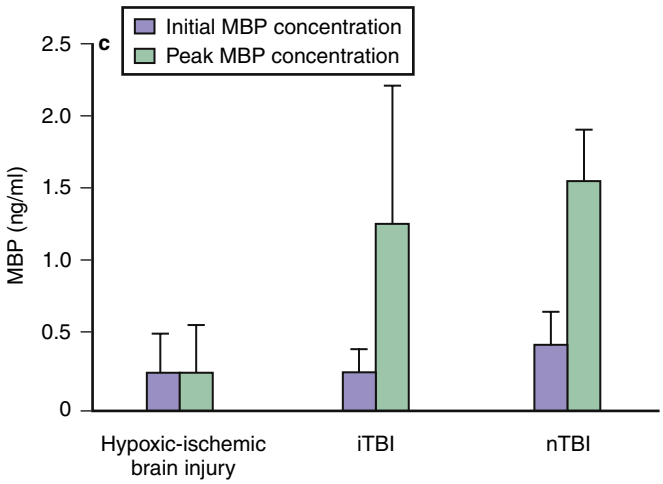

Figure 61–4. Initial (*solid bars*) and peak (*open bars*) serum levels of myelin basic protein (MBP) in infants and children after hypoxic ischemic insult from cardiorespiratory arrest, inflicted traumatic brain injury (*iTBI,* child abuse) or noninflicted TBI (*nTBI,* accidental). Axonal injury, reflected by increases in serum MBP levels, was seen only in the two forms of TBI, and in both cases the increase was delayed because it was not seen on initial presentation. *(Modified from Berger RP, Adelson PD, Richichi R et al: Serum biomarkers after traumatic and hypoxemic brain injuries: insight into the biochemical response of the pediatric brain to inflicted brain injury,* Dev Neurosci *28:327-335, 2006.)*

History

Unlike in adult TBI, where the history is generally straightforward, the special case of inflicted childhood neurotrauma contributes to increased importance of the history in pediatric TBI. For a discussion of the topic, the reader is referred to Duhaime[70] (see also Chapter 113). In cases of severe TBI resulting from child abuse, a history that is incompatible with the observed injury is often given.[71] Occult presentations of inflicted childhood neurotrauma can be particularly important because they may be recognized as cases of severe TBI relatively late in their treatment course.[72] In this setting, brain edema already may have evolved to life-threatening levels, and other superimposed secondary insults (e.g., seizures and apnea) may complicate management and worsen outcome.

Signs and Symptoms

The GCS score[73] (Table 61-1), first described in 1974, remains a valuable tool for grading and communicating severity of neurologic injury after TBI, although limitations remain with pediatric use. The verbal and motor components of the GCS score have been modified for assessment of infants,[74] but this modification has not been validated in infants and

Table 61–1 Coma Scales

Glasgow Coma Scale	Modified Coma Scale	Point Scale
EYE OPENING		
Spontaneous	Spontaneous	4
To speech	To speech	3
To pain	To pain	2
None	None	1
VERBAL		
Oriented	Coos, babbles	5
Confused	Irritable	4
Inappropriate words	Cries to pain	3
Grunting	Moans to pain	2
None	None	1
MOTOR		
Follows commands	Normal spontaneous movements	6
Localizes pain	Withdraws to touch	5
Withdraws to pain	Withdraws to pain	4
Abnormal flexion	Abnormal flexion	3
Abnormal extension	Abnormal extension	2
Flaccid	Flaccid	1

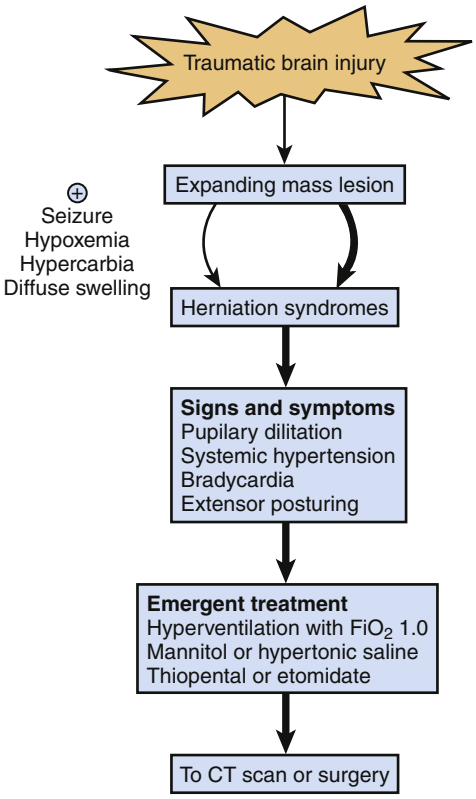

Figure 61–5. Treatment paradigm for management of signs and symptoms of acute herniation after severe traumatic brain injury in infants and children.

young children. The motor score has probably become the most important component of the GCS. A rapid "mini-neuroassessment" that allows evaluation of the patient's level of consciousness, pupillary size and light response, the fundi, extraocular movements, response of extremities to pain, deep tendon reflexes, and brainstem reflexes should all be part of the initial evaluation.[75] Until proven otherwise, an altered level of consciousness, pupillary dysfunction, and lateralizing extremity weakness in an infant or child should raise suspicion of a mass lesion that may require surgery.[76] These signs of impending herniation require an immediate response, as outlined in Figure 61-5.

Initial Resuscitation

The identification and correction of airway obstruction, inadequate ventilation, and shock take priority over a detailed neurologic assessment.[77] Thus the first step in managing a patient with a head injury patient is complete, rapid physiologic resuscitation.[1] Although raised ICP and cerebral herniation are the major complications, brain-specific interventions in the absence of signs of herniation or other neurologic deterioration currently are not recommended. Mannitol may be counterproductive for the management of malignant intracranial hypertension during initial resuscitative efforts. In the acute TBI resuscitation setting, hypertonic saline solution may be a better alternative (discussed later in this chapter). Studies have consistently shown that increased morbidity and mortality are associated with the secondary insults of hypotension and hypoxemia.[78,79] Gentleman[79] reported that the increased use of tracheal intubation and ventilation produced a concomitant reduction in episodes of hypoxemia and mortality rate and an increase in favorable outcomes. Although the basis for this improvement may be multifactorial, early correction of hypoxemia and hypovolemia must be the initial objective. However, specific recommendations for intubation at the scene are complex and likely are influenced by the expertise of caregivers in the field and by the transport distance, among other factors.[1]

Trauma patients with supraclavicular injury should be assumed to have cranial and cervical spine injuries until proven otherwise. The initial evaluation of a child after severe TBI begins by demonstrating the presence of a patent, maintainable airway; the patient must be conscious, alert, and breathing spontaneously. Unconscious patients must be assumed to have an obstructed airway requiring immediate evaluation. The relatively large head, occiput, and tongue and the short narrow epiglottis of the infant facilitate airway obstruction if the child's sensorium has been clouded. The rescuer must alleviate this situation (while protecting the cervical spine) to minimize secondary injury from hypoxia.

We previously outlined the use of the mnemonic SOAP to define the components for optimal preparation for securing the airway in the case of severe TBI requiring intubation in the emergency department or the PICU.[80] "S" represents suction; for most patients, a flexible 10 Fr catheter suffices. However, for school-age children (older than 5 years), we recommend the Yankauer rigid plastic suction catheter, which allows direct oropharyngeal suctioning. "O" represents oxygen; oxygen (a fraction of inspired oxygen [F_{IO_2}] of 1.0) should be delivered to the patient by face mask immediately before intubation. Optimal positioning of the patient requires immobilization of the neck to stabilize the cervical

Box 61–1 Criteria for Intubation of the Head-Injured Child

GCS score ≤10
Decrease in GCS of >3, independent of the initial GCS score
Anisocoria >1 mm
Cervical spine injury compromising ventilation
Apnea
Hypercarbia ($Paco_2$ >45 mm Hg)
Loss of pharyngeal reflex
Spontaneous hyperventilation causing $Paco_2$ <25 mm Hg

spine. Delivery of 100% oxygen facilitates nitrogen washout from the functional residual capacity, maximizing alveolar oxygenation. "A" represents airway; once the patient is positioned and ventilation and oxygenation are controlled, an age-appropriate laryngoscope blade and tracheal tube are selected. The tube is secured with adhesive tape that should not pass circumferentially around the neck because cerebral venous return may be reduced. "P" represents pharmacology; the medications chosen must be potent and rapid in their onset of action. The goals of analgesia, amnesia, and neuromuscular blockade must be met rapidly. Ideally, the patient never receives a preintubation positive-pressure breath.

Tracheal intubation of the child with severe TBI requires a cerebroprotective, rapid-sequence technique when possible (see also Chapter 42). Bag-valve-mask positive-pressure ventilation should be avoided. However, in cases of hypoxemia or impending herniation, positive-pressure ventilation should be instituted immediately.[81] Because the bag-valve-mask technique may cause unintentional cervical spine manipulation, care is advised.[82]

If a person who has sustained TBI meets any of the criteria listed in Box 61-1, assisted ventilation is indicated.[81,83] In children, the recommended route of initial airway control is orotracheal intubation under direct vision.[84] Nasotracheal intubation should be avoided. Blind passage of the endotracheal tube around the acute nasopharyngeal angle makes this procedure an unnecessary obstacle to rapid, physiologic resuscitation. Orotracheal intubation can be accomplished using a two-person strategy that protects the cervical spine from injury. A normal lateral cervical spine roentgenogram is reassuring but does not rule out cervical spine injury.[85] Spinal immobilization must be maintained,[86] which is accomplished via in-line cervical immobilization by one operator while the second intubates the trachea. Care must be taken to avoid pressing into the soft tissues of the submental region and strap muscles because inadvertent airway obstruction may ensue.

Rapid-Sequence Induction and Intubation

Tracheal intubation, although lifesaving, is a noxious stimulus. The technique of rapid-sequence induction and intubation secures the airway of an unprepared patient, who is at risk for aspiration of gastric contents, in an immediate and safe manner. No resistance is provided to direct laryngoscopy, and the normal responses to intentional placement of a foreign body into the trachea are eliminated. Rapid-sequence induction is documented to be a safer technique than either nasotracheal intubation or orotracheal intubation without neuromuscular blockade.[87,88]

Table 61–2 Drugs for Intubation of the Head-Injured Child

Situation	Drugs
Cardiopulmonary arrest	Resuscitation drugs
Hemodynamically unstable	Fentanyl 2–4 μg/kg
	Lidocaine 1 mg/kg
	Rocuronium 1 mg/kg or vecuronium 0.3 mg/kg
Hemodynamically stable	Fentanyl 2–4 μg/kg
	Lidocaine 1 mg/kg
	Midazolam 0.1–0.2 mg/kg
	Rocuronium 1 mg/kg or vecuronium 0.3 mg/kg
	or
	Thiopental 4–5 mg/kg
	Lidocaine 1 mg/kg
	Rocuronium 1 mg/kg or vecuronium 0.3 mg/kg

In the pediatric patient with TBI, a cerebroprotective rapid-sequence induction strategy should be used. The sequence involves preparation, preoxygenation, sedation, neuromuscular blockade, and orotracheal intubation. Pharmacologic adjuncts are used to prevent morbidity associated with hypotension, hypoxemia, intracranial hypertension, and gastric aspiration. The neurologic and hemodynamic status of the patient directs the choice of adjunctive pharmacologic strategy.

For a victim in cardiac arrest, cardiopulmonary resuscitation should begin immediately, accompanied by direct orotracheal intubation. No pharmacologic adjuncts are necessary to secure the airway. For a hemodynamically unstable patient, the combination of fentanyl, lidocaine, and rocuronium bromide is the first choice (Table 61-2). At Pittsburgh Children's Hospital use of etomidate has been eliminated in children with TBI because of concerns about adrenal suppression.[89] Either of these same sequences of drugs can be used in hemodynamically stable patients, for whom a rapidly acting benzodiazepine (midazolam) can be added.

An alternative in the hemodynamically stable patient is thiopental. Thiopental rapidly reduces cerebral metabolism,[90-93] which in turn blunts the ICP rise associated with laryngoscopy. The rapid cerebral uptake of these agents is matched by rapid washout. Thus these agents must be followed with another sedative or analgesic. Fentanyl, in combination with lidocaine, reduces the catecholamine surge associated with direct laryngoscopy.[81]

Circulatory Stabilization

Assessment of circulatory function after trauma involves the rapid determination of heart rate, blood pressure, central and peripheral pulse quality, capillary refill, and cerebral perfusion.[94] Posttraumatic hypoperfusion must be assumed to be hypovolemic (i.e., hemorrhagic) in nature, but it also

may have a secondary component of myocardial depression resulting from cardiac contusion. However, cardiac contusion is less common in children than in adults. In patients with severe TBI, fluid therapy for hypovolemic shock entails rapid replacement of vascular volume (see also Chapter 29). The choice of resuscitation fluid is controversial. The current recommendation is 20 mL/kg isotonic crystalloid (0.9% NaCl solution) given as soon as vascular access is obtained. Hypotonic fluid should not be used in the initial resuscitation of a patient with a brain injury. Subsequent doses of fluid should be isotonic crystalloid, colloid, or packed red blood cells and titrated based on serial assessment of blood pressure, perfusion, and hematocrit. Although concerns exist regarding the relative hypotonicity of lactated Ringer's solution,[95] evidence from studies in laboratory animals supports the safety of the use of lactated Ringer solution in patients with TBI.[96] Fisher et al.[97] reported the successful use of 3% saline solution as a maintenance fluid in children with TBI. Titration of 3% saline solution as an infusion to prevent development of intracranial hypertension is an acceptable first-tier strategy. Although its efficacy has yet to be proved in a clinical trial, inclusion of hypertonic saline solution should be considered in the setting of volume resuscitation of a child with TBI who has initial signs or symptoms of intracranial hypertension. Details of the approach to osmotherapy are discussed later in this chapter.

Herniation

The need to simultaneously address airway control, cardiovascular assessment and stabilization, treatment of extracerebral insults (hemorrhage and multiple trauma), and initial trauma survey in the field and emergency department makes management challenging. Although mass lesions are less common in children than in adults, they still occur in about 30% of children with severe TBI.[6] Although it happens infrequently, some of these patients, particularly those with rapidly expanding mass lesions (e.g., epidural hematoma), can present with signs and symptoms of herniation (i.e., pupillary dilatation, systemic hypertension, bradycardia, and extensor posturing). Because the devastating complications of herniation sometimes can be prevented or treated in the initial minutes of their progression, the importance of aggressively and presumptively treating signs and symptoms of herniation, which is a medical emergency, cannot be overemphasized until these signs and symptoms are proved not to represent herniation.

Appropriately, there has been a move away from prophylactic application of aggressive hyperventilation for the management of severe TBI. However, it is important to recognize that temporary use of hyperventilation with an F_{IO_2} of 1.0 is a therapy that can be immediately applied and can be life saving in the setting of impending herniation until other therapies can be instituted. Intubating doses of thiopental or pentobarbital and mannitol (0.25 to 1.0 g/kg) or hypertonic saline solution[97] also should be given emergently. One must recognize that factors other than a focal mass lesion may lead to herniation and that these situations may arise more commonly in children than in adults. Diffuse swelling is more common in children than in adults, and in this setting, inadvertent hypercarbia or hypoxemia, iatrogenic excessive fluid administration, or status epilepticus can precipitate herniation. Although discussed in this chapter in the context of acute therapy, herniation can occur at any time in the PICU course, and this approach to treatment also applies (see Figure 61-5).

Transition from the Emergency Department to the Pediatric Intensive Care Unit: Computed Tomographic Scan and Intracranial Pressure Monitoring

The transition of patients with severe TBI from the emergency department to the PICU includes computed tomographic (CT) evaluation of the head (and other anatomic regions, when clinically indicated) followed by placement of an ICP monitor, transport to the operating suite for surgical intervention, or both. In the initial resuscitation, sedation must be carefully titrated, maintaining the difficult balance that produces stability, analgesia, and anxiolysis during transport and scanning while allowing for rapid emergence for clinical assessment (as indicated) until a decision is made regarding surgery or ICP monitoring. Because the early period after injury generally reflects a state of increased vulnerability of the brain to second insults because of the brain's increased metabolic demands and compromised perfusion, providing adequate sedation and maintaining stable hemodynamics are important. An end-tidal CO_2 monitor also should be considered to avoid iatrogenic hyperventilation or hypoventilation. Clinical trials supporting definitive recommendations are not available. Nevertheless, the risks of intrahospital transport are well described;[98] therefore, when possible, a physician should accompany the infant or child upon transport to the scanner to direct care because serial assessment to titrate therapy is needed during the acute phase of injury.

Diagnostic Studies and Monitoring Modalities

Computed Tomography

Since becoming commercially available in 1973, CT has been of enormous benefit to neurointensive care.[99] Examples of classic findings in severe pediatric TBI are shown in Figure 61-6. Comprehensive classifications of CT findings in adults with severe TBI are reported. The Marshall classification is the most commonly used (Table 61-3).[100] A similar system specifically for pediatric TBI is not described, although several reviews characterize the spectrum of injury in infants and children as defined by CT.[101,102] Ewing-Cobbs et al.[101] compared acute CT findings in infants and children with inflicted and noninflicted injuries. Subdural interhemispheric and convexity hemorrhages and preexisting lesions were two to three times more common in the group with inflicted TBI. Epidural hematomas were more common in the group with noninflicted TBI.

Timing of repeat cranial CT scans has been investigated, including studies in children. Routine reimaging at 24 or 48 hours after injury has been suggested.[103] However, Tabori et al.[104] evaluated the impact of routine reimaging on 67 children after severe TBI and noted that although some new lesions were identified, reimaging did not lead to surgical or medical changes in therapy in any patient. A decision to reimage based on changes in ICP or clinical examination was

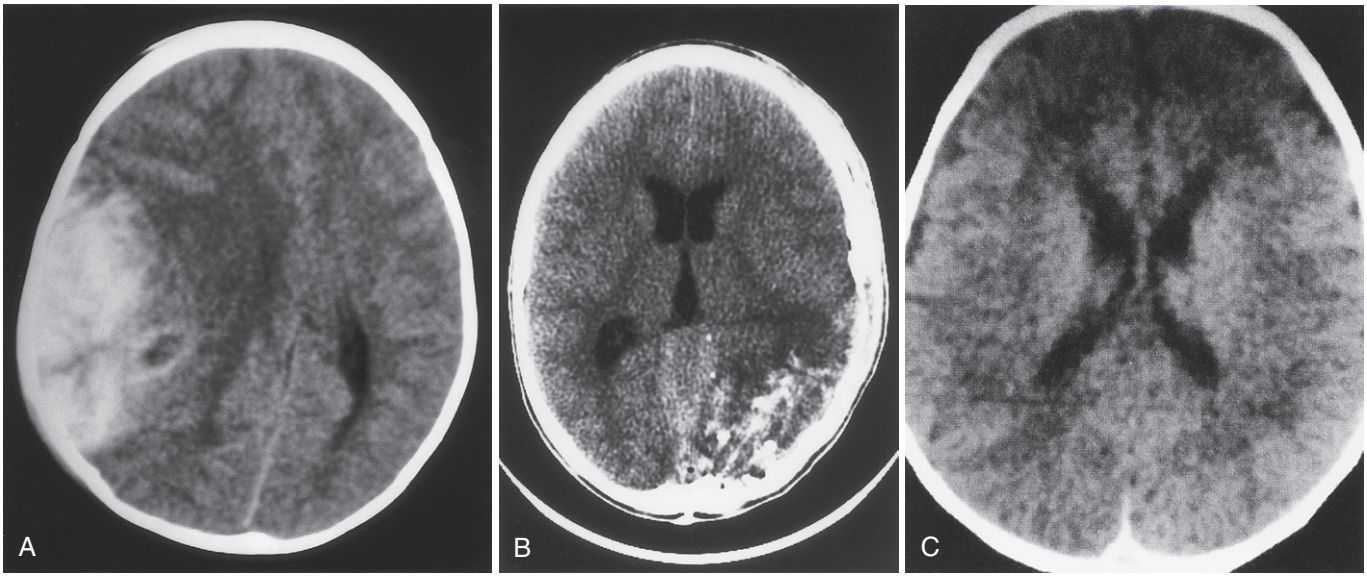

Figure 61–6. Axial cranial CT images of important lesions in pediatric traumatic brain injury including (**A**) acute epidural hematoma (**B**), penetrating brain injury resulting from a gunshot wound (with bullet fragments), and (**C**) inflicted childhood neurotrauma (shaken baby syndrome) with a subtle posterior subdural hematoma.

Table 61–3 Marshall Classification of Cranial Computed Tomographic Scans

Classification	Findings on Scan
Diffuse injury I (no visible pathologic change)	No visible intracranial pathologic change seen on computed tomography
Diffuse injury II	Cisterns are present with shift 0–5 mm and/or lesion densities present
	No high or mixed density lesion >25 mL
	May include bone fragments and foreign bodies
Diffuse injury III	Cisterns compressed or absent (swelling) with shift 0–5 mm
	No high or mixed density lesion >25 mL
Diffuse injury IV (shift)	Shift >5 mm
	No high or mixed density lesion >25 mL
Evacuated mass lesion	Any surgically evacuated lesion
Nonevacuated mass	High or mixed density lesion >25 mL, not surgically evacuated
Brain dead	No brainstem reflexes
	Flaccidity
	Fixed and nonreactive pupils
	No spontaneous respirations with a normal $Paco_2$
	Spinal reflexes permitted

recommended. Such an approach also is recommended in published pediatric guidelines.[1]

Studies in adults and children indicate that CT scans are not without limitations and must be used as only one, albeit important, piece of information. After severe TBI, in about 15% of adults with a normal CT scan, clinically significant intracranial hypertension develops. In contrast, in a study in 65 children, Hirsch et al.[105] reported that CT scans had a high false-positive rate in defining increased ICP. Finally, patients with normal initial head CT scans who also have hypotension or abnormal posturing have the same propensity to the development of intracranial hypertension as do their counterparts with an abnormal scan.[32,33]

Magnetic Resonance Imaging

MRI may have future applications salient to acute management in persons with TBI. The application of diffusion-weighted MRI for studying the evolution of cerebral edema,[55] the use of novel MRI methods for quantifying CBF,[106] and new methods such as susceptibility-weighted imaging to assess white matter damage increasingly are being applied (Figure 61-7).[107] The potential ability to couple these techniques with MR spectroscopy and functional MRI are beginning to yield unprecedented advances in our understanding of the brain's response to injury. However, MRI suites in most institutions are remote from the emergency department and PICU, introducing the risk of transport. Currently, hardware incompatibilities (e.g., ventilators and intravenous pumps) and long data acquisition times (relative to CT) limit the utility of this important tool.

Intracranial Pressure Monitoring

Unfortunately, clinical signs such as pupillary size, light response, and papilledema fail as early indicators of intracranial hypertension. Although the most reliable clinical signs are those associated with herniation, the introduction of ICP monitoring devices has allowed detection of intracranial hypertension before such changes are observed.[108,109] In the pediatric guidelines,[1] ICP monitoring was suggested as appropriate in children with an abnormal admission head CT scan and initial GCS score between 3 and 8. Also, ICP monitoring

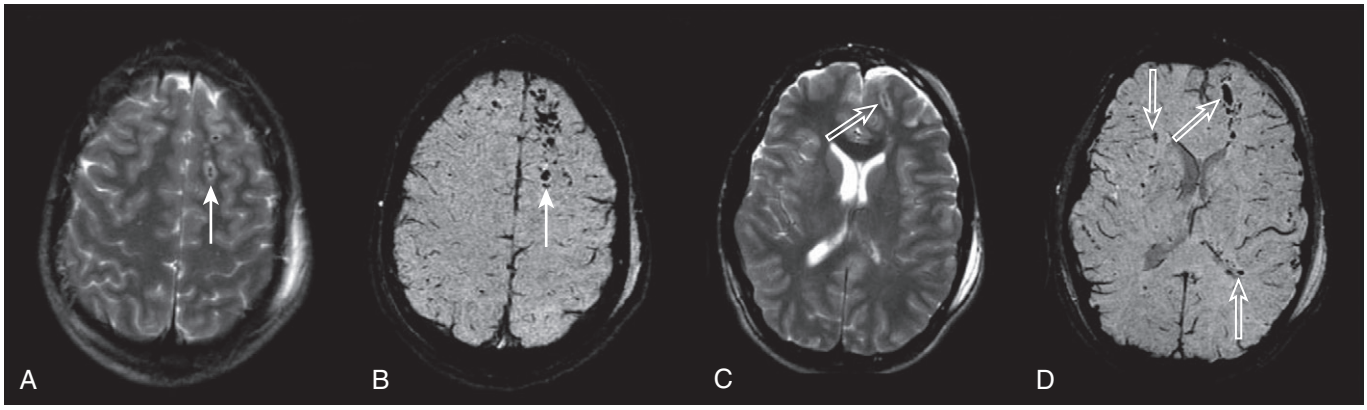

Figure 61–7. Detection of diffuse axonal injury is enhanced by susceptibility-weighted magnetic resonance imaging (SWI). **A,** Subtle hemorrhage in white matter is seen with conventional axial T2-weighted imaging. **B,** The diffuse white matter hemorrhages are much more readily detectible on SWI. *(From Tong KA, Ashwal S, Obenaus A et al: Susceptibility-weighted MR imaging: a review of clinical applications in children,* AJNR Am J Neuroradiol *29:9-17, 2008.)*

was suggested to be appropriate in adults with severe TBI and a normal head CT scan if the clinical course was complicated by hypotension or motor posturing. This modality is essential to implementation of a physiologically guided approach to management of cerebral perfusion pressure (CPP) in the infant or child with severe TBI.[110]

ICP monitoring has not been studied in an RCT to establish its efficacy in altering outcome after severe TBI in either adults or children. Since publication of the pediatric guidelines, however, several studies have contributed new insight. Forsyth et al.[111] recently examined the United Kingdom multicenter database of more than 500 cases of pediatric TBI and reported that both ICP >20 mm Hg and lack of ICP monitoring were independently associated with death before discharge. Given that raised ICP correlates with poor outcome, there is a strong rationale for identifying and treating this problem (see also Chapter 59).[112,113] As discussed in the section on CT, although CT is useful for identifying patients at high risk for the development of raised ICP (e.g., those with mass lesions), the finding of a "normal" cranial CT scan does not rule out the potential for raised ICP.[114] Despite this evidence, ICP monitoring in children with TBI, particularly in infants, is still not rigorously performed in clinical practice. Keenan et al.[115] surprisingly reported in 2005 that only 33% of infants and young toddlers (younger than 2 years) with severe TBI underwent ICP monitoring in the state of North Carolina. Consideration of risk versus benefit for ICP monitoring must be involved in the clinical decision in cases in which the complication rate is high, such as in patients with coagulopathy.

Currently, ICP monitoring by ventricular catheter is considered the most accurate, low-cost, reliable method.[1] The ventricular catheter also affords a key therapeutic option—CSF drainage. Other acceptable methods include parenchymal fiberoptic and microtransducer systems; subarachnoid, subdural, and epidural monitors of any type are less reliable.[116] The type of monitor (ventricular catheter or fiberoptic pressure transducer) used is dependent on the local preference of the neurosurgical staff.

The location of monitors in the hospital varies among centers and includes the emergency department/trauma bay, operating room, or PICU. Despite the flurry of activity that often surrounds the stabilization of a critically injured child with severe TBI, it is important to provide adequate anesthesia during placement of the monitor to prevent pain-induced spikes in ICP and/or herniation.

Monitoring and treatment of ICP are essential to contemporary management. Use of a ventricular catheter affords the added opportunity of CSF drainage as a therapy. Adult patients who have severe TBI with an ICP higher than 20 mm Hg have a poorer outcome than do those without increased ICP.[116] Similarly, although a large prospective RCT of children with and without both ICP monitoring and CPP management has not been performed, a prospective cohort study suggested a better outcome in adults monitored and treated with CSF drainage compared with those who did not undergo ICP monitoring.[117] However, this topic is controversial in the adult TBI literature,[118] and further study is needed.

Advanced Monitoring Techniques

Several techniques for assessing CBF, autoregulation of CBF, or metabolism can provide additional insight into the occurrence of cerebral ischemia during management and help guide therapy. However, information on the use of these techniques and their impact on outcome in infants and children with severe TBI is limited. Often, these methods are used only in clinical research or specialized trauma centers with particular interest in pediatric neurointensive care.

Techniques for measuring CBF after severe TBI include (1) stable xenon (Xe)-enhanced CT, (2) radioactive (inhaled or injected) ^{133}Xe methods, and (3) transcranial Doppler (TCD) methods. Stable Xe CT CBF measurement can aid in clinical decision making in children with TBI.[80,119,120] Although not a "monitor" in the sense that it does not provide bedside assessment of changes, stable Xe CT CBF measurement provides important information about regional CBF and its relationship to anatomic disturbances (Figure 61-8). This technique can be coupled to nearly all CT scans obtained in evaluation and follow-up, including the initial scan.[19,80,119,120] The procedure can be completed in less than 30 minutes. It is complicated when F_{IO_2} or MAP is high (because of the need for inhalation of 50% Xe gas and the effect of its inherently increased density) or if ICP is markedly increased. In those settings, careful monitoring of the patient is needed during the study. Serial stable Xe CT CBF measurements can be coupled to a physiologic manipulation, such as alteration of MAP or

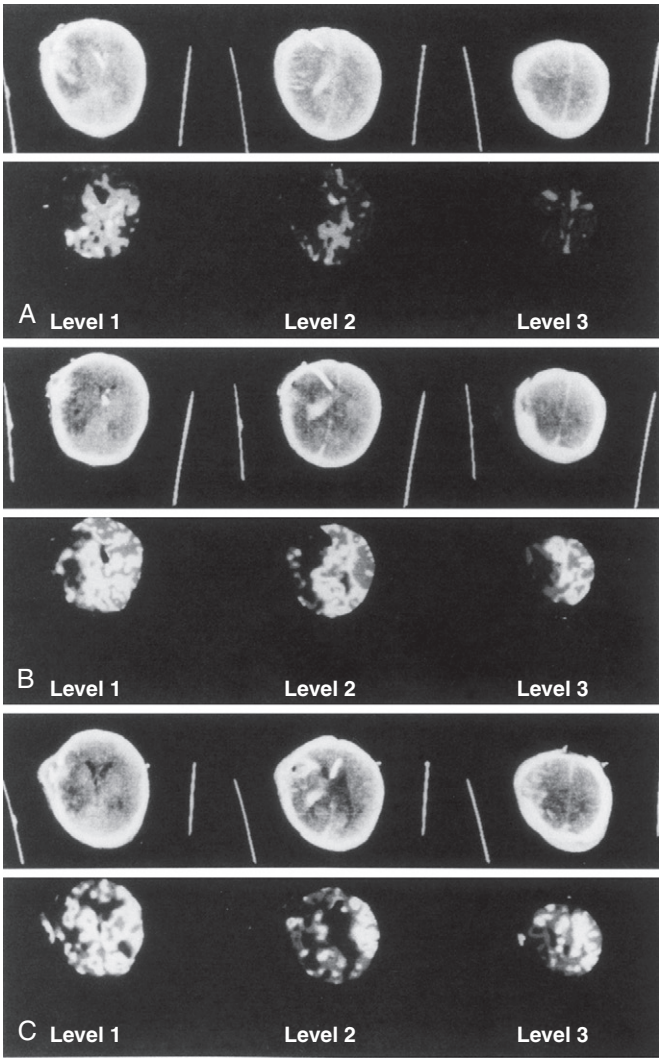

Figure 61–8. Time course of CBF measured by Xe-enhanced CT in a 2-month-old infant after severe traumatic brain injury from a motor vehicle accident. Standard CT images (*upper row*) and Xe-enhanced CBF maps (*lower row*) are shown from studies performed on admission (**A**) and at 2 days (**B**) and 5 days (**C**) after injury. Flow is severely reduced (*black*) on admission. Some recovery of CBF is seen at 2 days and 5 days after injury. CBF ranges from lowest (*darkest image*) to highest (*brightest image*).

$Paco_2$ (Figure 61-9).[80,121,122] These dynamic "pre and post" studies often provide additional insight into the optimal titration of bedside care such as $Paco_2$ levels and additional prognostic information.

Although titration of therapy to ICP or CPP is important, this technique shows that the response of the brain to an intervention such as manipulation of blood pressure or $Paco_2$ or administration of a specific drug often is not homogeneous and may be unpredictable. The response may be reflected by a change in ICP or CPP, as seen with focal losses of blood pressure, autoregulation of CBF, or reactivity to changes in $Paco_2$.

Stable Xe technique is a research tool in pediatric TBI. The ^{133}Xe method for assessment of patients with TBI was pioneered by Obrist et al.[123] By using multiple detectors, it can provide information on regional CBF, and it can be used in dynamic studies. The advantage of the ^{133}Xe method over the stable Xe CT method is that the ^{133}Xe method is a bedside technique. It has been used in children with TBI to define the time course and magnitude of changes in CBF and its regulation.[16,47-50] However, its inability to correlate flow with anatomic disturbances and radiation use is a limitation.

TCD is a method gaining acceptance in pediatric neurocritical care because it is noninvasive and is readily repeated at the bedside.[124,125] It can serve as an early warning monitor of the development of an unfavorable trend in cerebral perfusion; in addition, it can serve to assess autoregulation, define major alterations, identify vasospasm, and contribute prognostic information.[11,124-127] This method measures velocity rather than flow and usually is applied to assess the middle cerebral artery distribution. However, the inability of TCD to acquire regional information limits its utility in titrating care in TBI.[128]

Recently Brady et al.[129] have spearheaded considerable interest in continuous monitoring of blood pressure autoregulation of CBF with use of a pressure reactivity index that is calculated as a linear correlation between ICP and blood pressure. With use of this noninvasive adjunct to ICP monitoring, intact autoregulation was shown to be associated with survival in a study of 21 children with severe TBI. This method also may contribute to better definition of optimal CPP; further study is needed.

Monitoring Cerebral Metabolism

Jugular venous saturation has been used to monitor cerebral oxygen delivery in adults, but limited information on the utility of this technique in children is available.[47-50] Studies in adults suggest that therapies such as barbiturates and hyperventilation can be titrated according to jugular venous saturation.[128,130] Desaturations below the threshold value of 50% are associated with mortality in adults.[131] However, jugular venous desaturation below this level was rarely the sole indication that urgent intervention was needed, and false desaturations occurred. Nevertheless, this tool can assist in clinical decision making, and some persons have questioned its ability to monitor regional effects.[132]

Several other modes of monitoring cerebral metabolic rate may be helpful. Near-infrared spectroscopy has been used to track the oxidative state of cytochromes in brain. It reportedly aided in clinical decision making during treatment of brain-injured adults, warning of reduced cerebral oxygenation, sometimes with greater sensitivity than jugular venous saturation.[125] Near-infrared spectroscopy has been used to assess cerebral metabolic status in hypoxemic-ischemic neonates[133,134] and is beginning to be used in pediatric TBI.[135] Although its exact role remains unclear, it may prove valuable as a trend monitor.[136] Limitations with topographic resolution and the dominance of the superficial brain tissue in generating the signal are concerns.

Monitoring partial pressure of oxygen (PO_2) in brain parenchyma ($Pbto_2$) with a microelectrode implanted in the frontal lobe is feasible in adults.[137] A threshold value of about 8.5 mm Hg was associated with a reduction in CPP below 60 mm Hg, although in adults, thresholds anywhere from 10 to 30 mm Hg have been recommended. Stiefel et al.[138] recently reported on the utility of $Pbto_2$ monitoring in children and suggested a threshold of 20 mm Hg. We routinely use $Pbto_2$ in children with TBI, targeting a threshold of 20 mm Hg. Therapy is first targeted to optimize ICP and CPP. However, in some cases, $Pbto_2$ is less than 20 mm Hg despite control of ICP and it is necessary to evaluate other potential factors that might be affecting brain oxygenation.

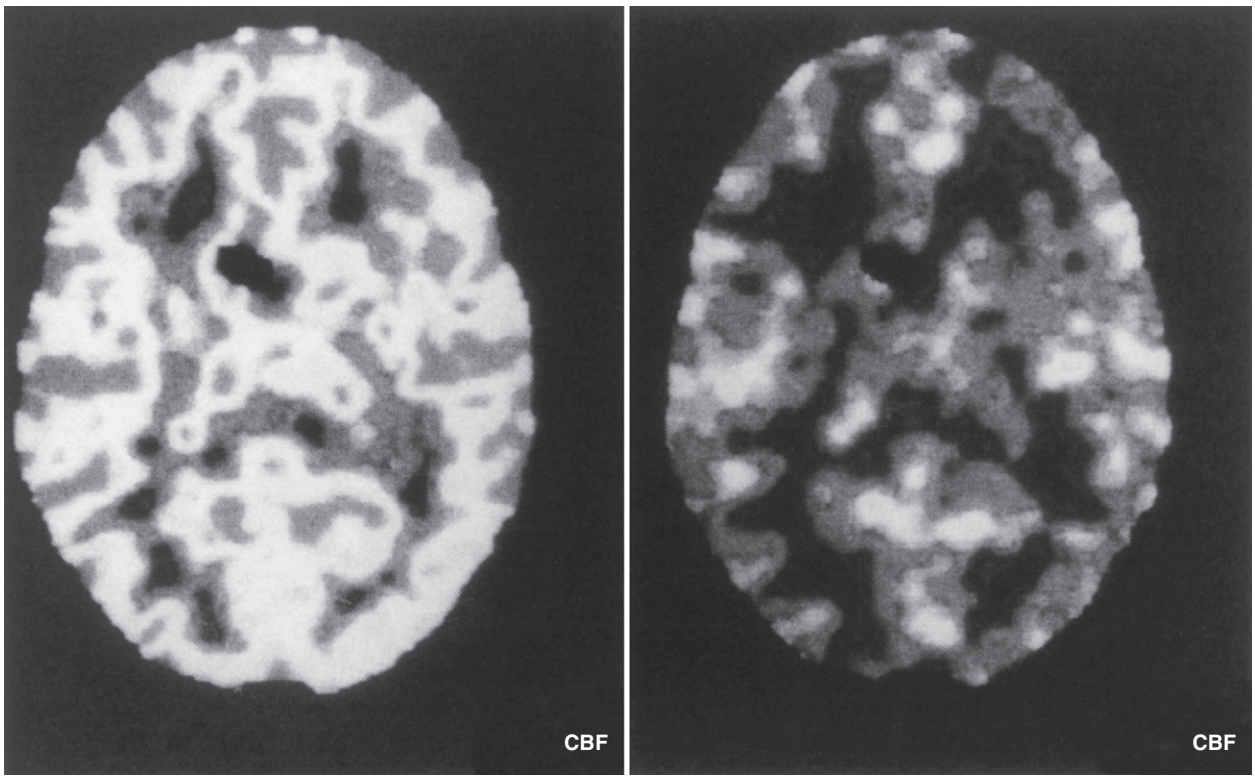

Figure 61–9. Xe-enhanced CBF maps from a child with severe traumatic brain injury before (*left*) and after (*right*) escalation of hyperventilation in the scanner. Intact reactivity of CBF to change in $Paco_2$ is demonstrated by an obvious reduction in flow. CBF ranges from lowest (*darkest image*) to highest (*brightest image*).

These factors could include inadvertant hyperventilation due to a ventilator change or a decline in Pao_2 due to lung disease—that should be addressed. If there is no extracerebral complication affecting $Pbto_2$, interventions such as increasing FIO_2 or raising $Paco_2$ or MAP/CPP to improve CBF may further augment $Pbto_2$. The major limitations of $Pbto_2$ are its invasiveness and provision of only focal data. In adults, $Pbto_2$ measurement has been coupled to cerebral microdialysis to provide metabolic data (i.e., glutamate levels).[139,140]

Finally, positron emission tomography (PET) has been used in adults with severe TBI.[22] Although limited by long acquisition times and the risk of intrahospital transport of critically ill patients, the metabolic maps generated provide much insight, particularly into cerebral glucose utilization after TBI. Diringer et al.[141] used PET to provide important insight into the effect of hyperventilation on $CMRO_2$ in adults with severe TBI (see the section on hyperventilation). Both PET and advanced MRI can provide insight into regional brain disturbances and the effect of therapy (Figure 61-10).

Treatment in the Pediatric Intensive Care Unit

Once the initial resuscitation is completed and evacuable intracranial masses have been addressed, maintenance of physiologic stability and recognition and management of raised ICP are the priorities. A flow diagram illustrating a general approach to first-tier treatments of the child with severe TBI was provided in the pediatric guidelines (Figure 61-11). The injured brain has complex metabolic requirements that are poorly understood.[142] Autoregulation of CBF may be disturbed, and metabolic demands may be either decreased or increased.[14,22,47-50,123] It is clear, however, that evidence of neuronal death from cerebral ischemia is a common finding on autopsy in patients who die after severe TBI. Control of ICP and maintenance of adequate CPP and $Pbto_2$ may limit the risk of developing secondary ischemia.[110,112,113] The goals of management are thus to optimize ICP, CPP, and brain oxygenation/perfusion, avoid secondary insults, and create the best possible environment for brain recovery.

Intracranial Pressure and Cerebral Perfusion Pressure Thresholds

Adult patients with severe TBI who have an ICP of 20 mm Hg have a poorer outcome than do those without increased ICP.[110,112,113,143] Although a prospective RCT in patients with and without both ICP monitoring and targeted management has not been performed, a prospective cohort study by Ghajar et al.[117] suggested better outcome in adults monitored and treated with CSF drainage versus those without ICP monitoring. Several studies suggest that optimal outcome is achieved when even more modest levels of ICP (i.e.,15 mm Hg) are the target.[117] Although no pediatric study has prospectively compared ICP treatment thresholds and their effect on outcome using a specific treatment regimen, review of the pediatric literature provides clues on the optimal ICP treatment threshold. Four of five major studies published before the guidelines, including a total of more than 230 cases of severe pediatric TBI, reported that poor outcome was associated with ICP higher than 20 mm Hg.[49,144-147] In a more recent study by Chambers et al.[148] in 99 children with head injuries (0-13 years of age) in the United Kingdom, an

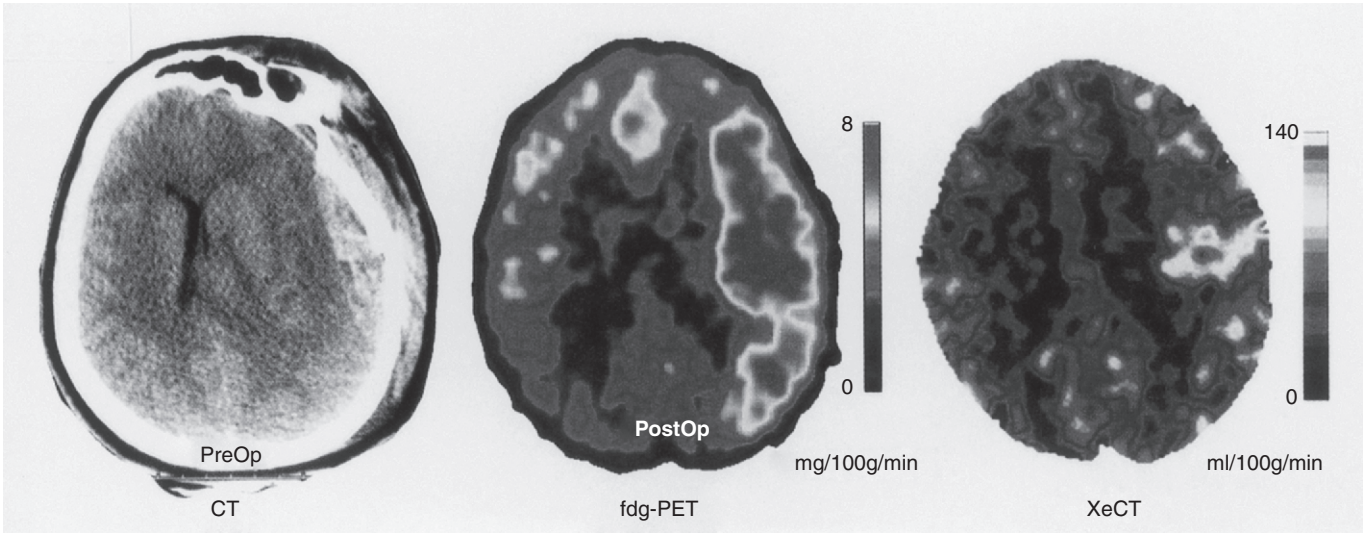

Figure 61–10. CT image (*left*) of an acute subdural hematoma with mass effect that was treated with surgical evacuation. ^{18}F-flurodexoyglucose positron emission tomographic (*PET*) map (*center*) obtained at 5 days after surgery shows marked local increases in cerebral glucose utilization in the brain regions underlying the hematoma. Stable Xe-enhanced CT CBF map also obtained at 5 days after surgery shows increased CBF in the same region, indicating that the increase in glucose utilization is not the result of hypoperfusion. This phenomenon, termed *hyperglycolysis*, is suggested to represent increased glucose utilization by astrocytes coupled to glutamate uptake and other mediator-driven processes. This highlights the complex regional metabolic demands of the traumatically injured brain.

ICP threshold of 15 mm Hg was used. However, it remains to be determined whether a lower ICP threshold is appropriate for infants in whom physiologic MAP is lower than in adults. This issue was viewed as one of the important unanswered questions in a recent survey on the pediatric TBI guidelines.[149]

As with ICP, no RCT has been conducted to define the optimal CPP for pediatric TBI, although its importance in patient management is recognized. Reductions in CPP below specific threshold values are associated with poor outcome. The guidelines' recommendation of 40 mm Hg was based on four studies that defined the CPP associated with poor outcome as between 40 and 65 mm Hg.[147,150-152] As discussed in two recent updates of the pediatric TBI guidelines,[153,154] a major limitation in the guidelines was the lack of data on optimal CPP targets. Based on normative data, lower optimal thresholds are likely in infants and young children versus older children and adults. However, because of limited available data, the Guidelines Committee could only conclude, at the guideline level, that a CPP greater than 40 mm Hg be maintained. This value, based largely on the work of Downard et al.[147] was believed to be the minimum acceptable value. This value differs from that indicated by adult data, which suggest a value of 60 mm Hg or possibly even higher. However, it was stated in the guidelines, at an option level, that a CPP between 40 and 65 mm Hg probably represented an age-related continuum for the optimal threshold.[1]

Since publication of the guidelines, Chambers et al.[155] published what is the largest study on this topic in pediatric TBI, and based on data from 235 children, they suggested minimum CPP values of 53, 63 and 66 mm Hg for children between the ages of 2 and 6 years, 7 and 10 years, and 11 and 16 years, respectively (Figure 61-12). However, that study considered only the first 6 hours of monitoring, and CPP and ICP were not addressed for infants younger than 2 years of age. In a follow-up study of 91 children, Chambers et al.[148] used a pressure-time index to determine critical CPP thresholds of 48, 54, and 58 mm Hg in children aged 2 to 6 years, 7 to 10 years, and 11 to 15 years, respectively. Based on these two reports since the guidelines, which are the most definitive work to date, thresholds of approximately 50, 55, and 60 mm Hg would seem reasonable for children in these age ranges.

In adults with severe TBI, the optimal CPP is also controversial.[156] The most definitive study in adults comes from Robertson et al.,[157] who compared CPP thresholds of 50 versus 70 mm Hg. Use of a CPP-directed treatment targeting a threshold of 70 mm Hg reduced the number of episodes of cerebral ischemia but led to an increased incidence of complications, likely associated with the increase in fluid given to raise MAP. This treatment resulted in no net difference in outcome between groups. Thus optimal CPP likely is directly correlated with age and overall is lower in children than in adults. For many years we have used a threshold of greater than 40 to 50 mm Hg in infants and toddlers, 50 to 60 mm Hg in children, and greater than 60 mm Hg in adolescents, which fortuitously are in agreement with the most recent data. Nevertheless, selection of an optimal CPP threshold is difficult in children with TBI.[158-161]

In addition to the methods described later for control of ICP, titration of vasopressor or inotropic support may be necessary to achieve an appropriate level of CPP once adequate filling pressure and hemoglobin are confirmed. In some situations, as with the development of neurogenic pulmonary edema, aggressive cardiovascular monitoring and optimal titration of cardiopulmonary support can be challenging and key determinants of outcome. Finally, not only are the optimal ICP and CPP targets likely to be important, but how one achieves these target values may be very important.

Treatment of Intracranial Hypertension: First-Tier Therapies

Ventricular Cerebrospinal Fluid Drainage

Ventricular CSF drainage has been used to manage raised ICP in adults for more than 40 years. Cerebrospinal fluid drainage for treatment of intracranial hypertension in children

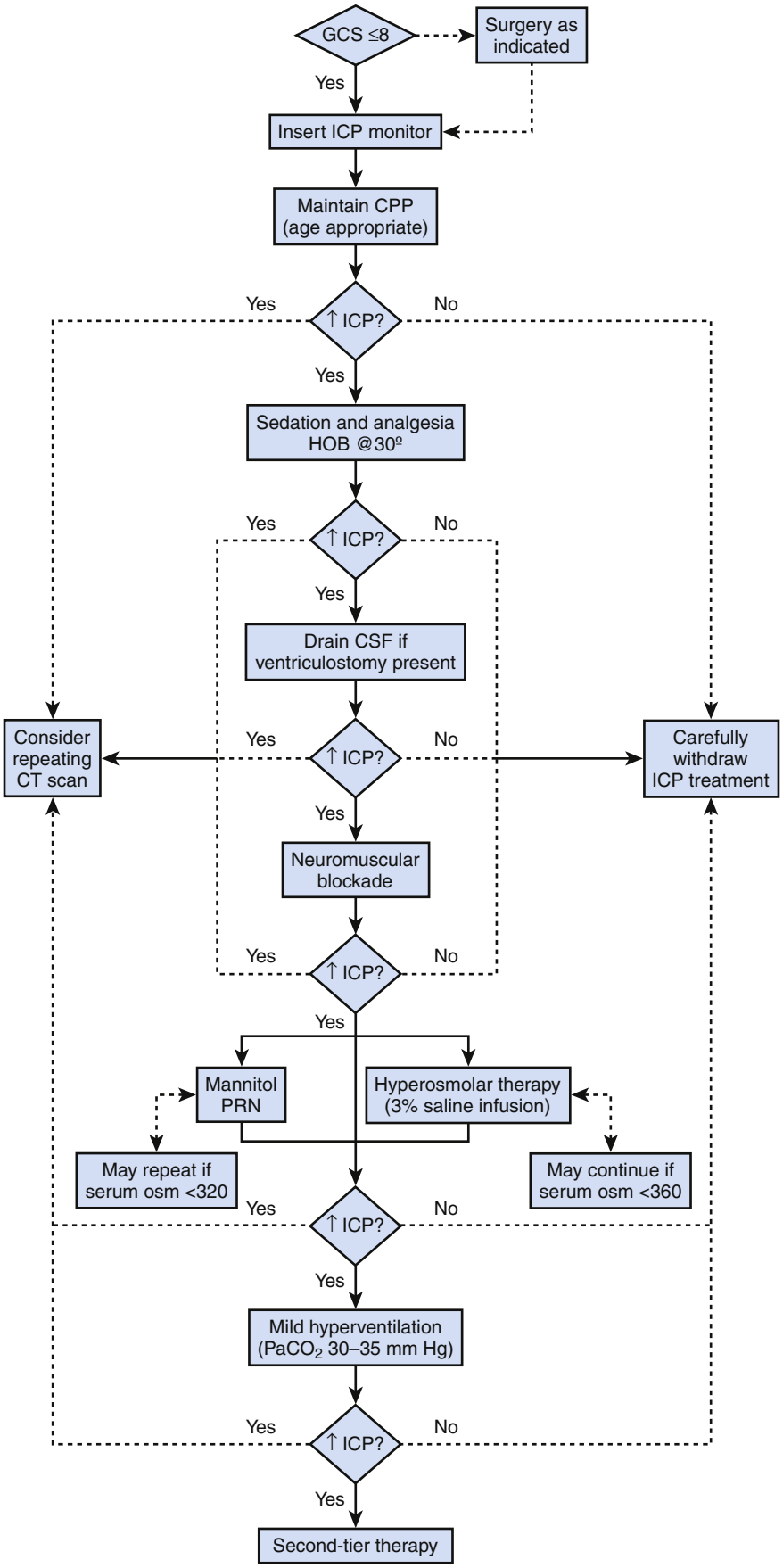

Figure 61–11. First-tier management approach based on the Guidelines for the Management of Severe TBI in Infants, Children, and Adolescents.[1]
HOB, Head of bed.

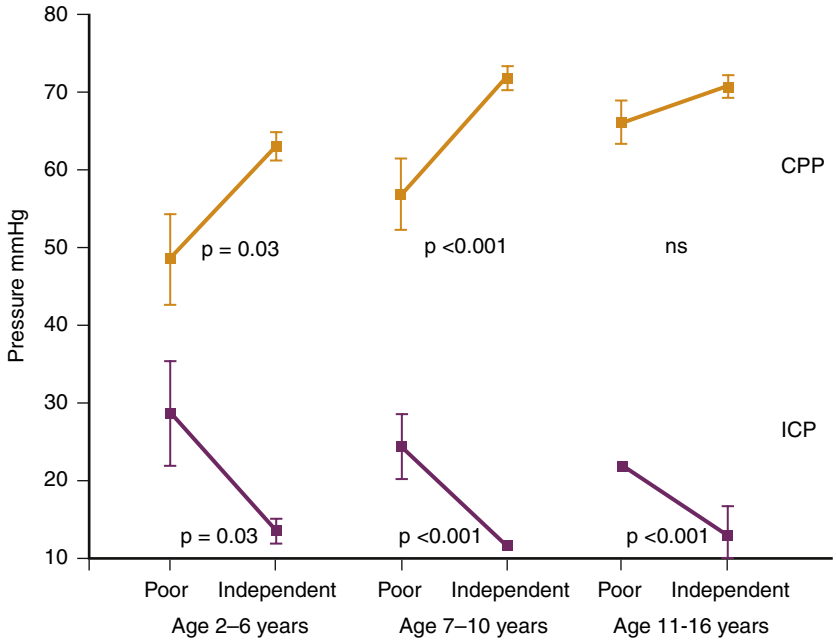

Figure 61–12. Mean ICP and CPP (mm Hg) after TBI for children with poor versus independent outcome for three age groups. Minimum CPP values of 53, 63, and 66 mm Hg were suggested for children between the ages of 2 and 6 years, 7 and 10 years, and 11 and 16 years, respectively. *(Modified from Chambers IR, Stobbart L, Jones PA et al: Age-related differences in intracranial pressure and cerebral perfusion pressure in the first 6 hours of monitoring after children's head injury: association with outcome,* Childs Nerv Syst *21:195-199, 2005.)*

was shown to improve CBF in 1971.[162] Fortune et al.[163] compared the effect of CSF drainage and mannitol in adults after severe TBI and noted similar effects on CBF and ICP. Use of CSF drainage was associated with a greater increase in jugular venous saturation than was mannitol therapy. CSF can be drained intermittently or continuously, with threshold values for drainage determined on the basis of the clinical indication. Since publication of the guidelines, in a small retrospective two-center comparison between continuous and intermittent CSF drainage approaches in children with severe TBI, Shore et al.[164] reported that continuous drainage was associated with removal of a substantially greater amount of CSF, markedly reduced CSF levels of biochemical mediators, and lower ICP. However, the efficacy of CSF drainage versus other treatments of intracranial hypertension remains unclear, and larger studies are needed. It is our clinical impression that CSF drainage reduces requirements for other therapies targeting ICP. However, this has yet to be proved. Recent studies from Pittsburgh Children's Hospital suggest that if continuous drainage is used, inserting a second parenchymal ICP monitor may be of value because continuous drainage limits the ability to continuously monitor ICP, and spikes of intracranial hypertension could be missed.[165] Finally, lumbar CSF drainage can reduce ICP in cases with discernible basal cisterns; this factor is discussed in the section on second-tier therapies.

Osmolar Therapy

Based on the hypothesis that BBB permeability and increases in CBV play only limited roles in the development of cerebral swelling and that tissue osmolar load may be more important, particularly in contusion, osmolar therapies (e.g., mannitol and hypertonic saline solution) seem to be logical. The BBB is nearly impermeable to both mannitol and sodium. This suggestion contrasts with traditional recommendations supporting the use of hyperventilation and avoidance of mannitol.[59,60] Despite its ubiquitous use and studies supporting its use for the management of TBI in adults, mannitol has been subjected to limited investigation in pediatric TBI. Even though mannitol is a cornerstone for management of intracranial hypertension in pediatric and adult TBI,[1,116] it has not been subjected to controlled clinical trials compared with placebo, other osmolar agents, or other mechanism-based therapies in children.

Mannitol reduces ICP by two distinct mechanisms.[116] First, it produces a rapid reduction in ICP by reducing blood viscosity with a resultant decrease in blood vessel diameter and CBV. This mechanism is dependent on intact viscosity autoregulation of CBF that is linked to blood pressure autoregulation of CBF. The effect of mannitol administration on blood viscosity and CBV is transient (lasting ~75 minutes).

The second mechanism by which mannitol administration reduces ICP is via an osmotic effect. This effect develops more slowly (over 15 to 30 minutes) and results from movement of water from parenchyma into the circulation. The effect persists between 1 and 6 hours and depends on an intact BBB. Changes in serum osmolality reduce brain water only in relatively normal brain regions. It has long been suggested that mannitol may accumulate in injured brain regions and a reverse osmotic shift may occur, with fluid moving from the circulation to the parenchyma, possibly exacerbating intracranial hypertension. Since publication of the pediatric guidelines, Polderman et al.[61] showed in adults that after 48 hours of therapy, mannitol levels in CSF increase and in some adults with severe TBI, a reverse osmotic gradient can be seen, explaining the lack of effect of this therapy or the need for escalating doses after several days of administration. They suggested that it might be optimal to measure CSF mannitol levels to guide therapy. Others have suggested titration of mannitol to osmolar gap.[166] Mannitol is excreted unchanged in urine, and a risk for development

of acute tubular necrosis and renal failure has been suggested for mannitol administration with serum osmolarity greater than 320 mOsm in adults. However, the literature supporting this finding dates from the late 1970s and early 1980s, an era when dehydration therapy in combination with mannitol use was common. Hyperosmolar euvolemia is targeted with contemporary mannitol use. High levels of serum osmolarity (365 mOsm) appear to be tolerated in children when induced with hypertonic saline solution, although one small case series suggests the possibility of renal impairment with these high osmolarity levels in children treated with hypertonic saline solution.[167,168]

Few data support the concomitant use of diuretics and mannitol to reduce ICP. James[169] performed a retrospective study of 60 patients (ages 1 to 73 years) treated with mannitol for increased ICP. After bolus mannitol administration, ICP decreased after 116 of 120 doses. The reduction in ICP in response to mannitol administration was dose dependent between 0.18 and 2.5 g/kg. In contrast, Marshall et al.[170] reported equivalence for doses between 0.25 and 1 g/kg in adults. Despite a remarkable track record for controlling ICP in TBI, clinical investigation of mannitol use in infants and children is lacking. Surprisingly, an epidemiologic study suggested that mannitol use was associated with prolonged PICU length of stay but no survival advantage.[156] Nevertheless, it remains a first-tier therapy in severe pediatric TBI.

Use of hypertonic saline for treatment of raised ICP was first described in 1919 but failed to gain clinical acceptance.[171] Interest in this treatment has undergone a resurgence. Penetration of sodium across the BBB is low. Sodium has a reflection coefficient higher than that of mannitol and shares with mannitol both the favorable rheologic effects on CBV and osmolar gradient effects. Hypertonic saline exhibits other theoretical benefits, such as restoration of cell resting membrane potential, stimulation of atrial natriuretic peptide release, inhibition of inflammation, and enhancement of cardiac performance.

Hypertonic saline was studied in more than 130 pediatric patients with severe TBI. There are two types of studies: (1) treatment of refractory intracranial hypertension and (2) comparison of hypertonic saline solution to maintenance fluid as a continuous infusion. Fisher et al.[97] compared 3% saline solution and 0.9% saline solution in children with severe TBI. During the 2-hour trial, hypertonic saline solution was associated with a lower ICP. The serum sodium level increased about 7 mEq/L after administration of 3% saline solution. Khanna et al.[172] reported a prospective study of 3% saline solution (514 mEq/L) given on a sliding scale to maintain ICP less than 20 mm Hg in children with resistant intracranial hypertension. A reduction in ICP and an increase in CPP were noted with 3% saline solution. The mean highest serum sodium level and osmolarity were approximately 170 mEq/L and approximately 365 mOsm/L, respectively. Sustained hypernatremia and hyperosmolarity were generally tolerated. Acute renal failure developed in two patients.

Peterson et al.[167] reported a retrospective study on the use of a 3% saline solution infusion titrated to reduce ICP to less than or equal to 20 mm Hg in infants and children with TBI. The mean daily doses of hypertonic saline solution ranged from between 11 and 27 mL/kg/day. A control group was not used, but only three patients died of uncontrolled ICP, and 73% of patients had a good or moderate outcome. Rebound in ICP or other adverse effects were not seen.

Theoretic concerns associated with use of hypertonic saline solution include development of extrapontine myelinolysis (EPM), rapid shrinking of the brain associated with mechanical tearing of bridging vessels leading to subarachnoid hemorrhage, renal failure, and rebound intracranial hypertension.[173] EPM is related to central pontine myelinolysis (CPM) but occurs with hypernatremia and/or its correction. It is characterized by demyelination of the thalamus, basal ganglia, and cerebellum.[174] Neither EPM nor CPM has been reported in human trials of hypertonic saline solution for treatment of TBI. EPM has been reported in dehydrated children with serum sodium levels of 168 to 195 mEq/L, and CPM has been reported with rapid correction of chronic hyponatremia.[162] Peterson et al.[167] performed MRI evaluations in 11 patients in their study, and none had evidence of CPM. However, rats with normal serum sodium levels subjected to increases of 39 mEq/L showed severe demyelinating lesions.[175] Similarly, subarachnoid hemorrhage has been reported with serum sodium concentrations from 149 to 206 mEq/L within 1 hour after injection of 9% hypertonic saline solution in normal kittens.[176]

Renal failure is a concern with use of hyperosmolar therapies. Use of hypertonic saline solution (vs. lactated Ringer solution) in the resuscitation of burn patients is associated with a fourfold increase in renal failure,[177] but this complication seems uncommon with hypertonic saline solution use in children after TBI.[167,168] Rebound intracranial hypertension has been described with use of hypertonic saline solution bolus therapy or after cessation of continuous infusion.[167,178] As with mannitol therapy, if the BBB is breached, one would also expect that CSF levels of sodium would gradually increase with prolonged therapy. Patients may require progressive increases in infusion rates to control ICP. Hypertonic saline solution, mannitol, and CSF drainage are first-tier therapies for raised ICP.

Sedation Analgesia and Neuromuscular Blockade

Sedation and neuromuscular blockade should be used as needed in the setting of raised ICP once appropriate monitoring has been established and thus are integrated into first-tier treatment. Narcotics, benzodiazepines, or small doses of barbiturates are generally recommended for routine use. To our knowledge, no controlled trial of varying sedation regimens has been performed in pediatric patients with severe TBI. Hsiang et al.[179] reported on 514 adults with severe TBI and suggested that prophylactic neuromuscular blockade was associated with increased length of ICU stay and nosocomial pneumonia. However, the study was not prospective and should not preclude the use of neuromuscular blockade in pediatric TBI. As with most therapies in this setting, careful assessment of indication and titration of therapy are essential. Finally, intermittent doses of barbiturates and/or lidocaine may be needed to blunt excessive rises in ICP resulting from routine patient care maneuvers such as suctioning. Additional studies are badly needed.

Head Position

Head position is an area of controversy. Feldman et al.[180] conducted a prospective RCT of the effect of head position on ICP, CPP, and CBF in 22 adults after severe TBI. Both ICP and mean carotid pressure were reduced in the 30-degree position versus the 0-degree position. CPP and CBF did not

change with this intervention. Thus, in general, the 30-degree head elevated position reduced ICP without deleterious effects on CPP and is preferred. Head elevation and midline position improve jugular venous and possibly CSF drainage and decrease the contributions of these components to ICP.

Treatment of Intracranial Hypertension: Second-Tier Therapies

Refractory intracranial hypertension occurs in 20% to 40% of cases of severe pediatric TBI and is associated with mortality rates of 30% to 100%.[144-147,150-152,156,157,181-183] Several second-tier therapies are available for treatment of refractory intracranial hypertension. These therapies were presented in the pediatric guidelines and are shown in Figure 61-13. Second-tier therapies include barbiturates, hyperventilation, hypothermia, decompressive craniectomy, and lumbar CSF drainage.

Barbiturates

Barbiturates produce a reduction in ICP via a decrease in cerebral metabolic rate. Although an RCT of barbiturate therapy for treatment of severe TBI in adults did not show an outcome benefit,[184] it can be effective in the setting of refractory raised ICP.[185] Goodman et al.[186] reported an improvement in brain interstitial concentration of lactate and glutamate accompanying a reduction of ICP in seven adults treated with barbiturates for refractory intracranial hypertension. In contrast, Cruz[128] reported that about one third of adults given barbiturates experience a deterioration (rather than improvement) in jugular venous saturation. If either frequent dosing or barbiturate infusion is used, an electroencephalogram (EEG) should be used to assess the response to treatment. The endpoint of barbiturate coma is generally burst suppression. Pentobarbital or thiopental often is infused to achieve a burst suppression response on EEG. However, that goal should only represent the maximal barbiturate dose used for ICP control because (1) smaller doses—those still associated with EEG activity—may be adequate to control ICP, and (2) indiscriminate use can be associated with undesirable adverse effects such as hypotension.[187] A lack of ICP response to barbiturates is associated with poor outcome. When barbiturates are used, hypotension should be avoided. Patients should be carefully monitored for reduced cardiac output or inadequate systemic perfusion, as clinically indicated. As the use of hyperventilation for the management of children with refractory ICP has waned, alternative therapies such as barbiturates appear to be increasingly used.

Hyperventilation

Hyperventilation has been used to manage pediatric patients with severe TBI since the 1950s.[188] Bruce et al.[16] suggested that hyperemia was the predominant mechanism involved in the development of raised ICP in children. Thus hyperventilation was recommended as first-line therapy. Until the mid 1980s, prophylactic hyperventilation was the standard of care. In addition to reducing postinjury hyperemia, hyperventilation was suggested to reduce brain acidosis and restore CBF autoregulation. Subsequently, studies in experimental models suggested hyperventilation had deleterious effects. Prophylactic hyperventilation depletes brain interstitial bicarbonate buffering capacity and is accompanied by gradual loss of local vasoconstrictor effects.[189]

In an RCT in adults after severe TBI, prophylactic hyperventilation for 5 days to a $Paco_2$ of about 25 mm Hg versus about 35 mm Hg was associated with worse outcome.[190] Skippen et al.[191] reported that hyperventilation to a $Paco_2$ of about 25 mm Hg reduced CBF to levels less than 18 mL/100 g/min in 73% of infants and children with severe TBI. Coles et al.[132] found similar results in adults. However, neither of these studies assessed the effect of hyperventilation on either regional cerebral metabolism or neurologic outcome. In experimental TBI in rats, aggressive hyperventilation ($Paco_2$ ~20 mm Hg) early after injury enhanced hippocampal cell death. The pediatric guidelines recommend that prophylactic hyperventilation not be used.[1] A $Paco_2$ of about 35 mm Hg was recommended.

Supporting this approach in infants and children, early after severe TBI, hypoperfusion rather than hyperemia was shown to be associated with poor outcome.[19] Zwienenberg and Muizelaar[56] questioned the occurrence of hyperemia in children after severe TBI, suggesting instead that normal CBF values previously were underestimated and are higher in children than in adults. However, the risks of hyperventilation are still somewhat controversial. Diringer et al.[141] reported that at between 8 and 14 hours after severe TBI in adults, hyperventilation ($Paco_2$ ~30 mm Hg) reduced CBF but did not further reduce cerebral metabolic rate for oxygen as assessed using PET. This finding suggests that in TBI, after the acute hypermetabolic phase, hypometabolism follows and hyperventilation may be a relatively safe means to reduce ICP in the PICU. This study did not evaluate outcome. In contrast, several reports in adults suggest deleterious effects of hyperventilation after TBI, including increases in brain interstitial levels of glutamate and lactate[192] and higher ischemic brain volumes.[193]

Based on these data, there is waning support for the use of hyperventilation. At Pittsburgh Children's Hospital, with the addition of $Pbto_2$ monitoring, when ICP is controlled but $Pbto_2$ is <20 mm Hg, we have found that careful limitation of even mild hyperventilation can, in some cases, promptly increase $Pbto_2$. Nevertheless, despite these concerns, hyperventilation surprisingly seems to remain a mainstay of care in pediatric TBI. Specifically, Curry et al.,[194] in a study of 375 children with severe TBI, reported a 52% to 60% incidence of substantial hypocarbia ($Paco_2$ <30 mm Hg) in the initial 48 hours that was significantly associated with poor outcome. This incidence was seen despite ICP levels less than 20 mm Hg in many cases. High frequency of hyperventilation also was reported by Morris et al.[195] in the United Kingdom database and, surprisingly, in the recent RCT of therapeutic hypothermia by the Canadian multicenter trials group (44%).[196] Some investigators have suggested that it may be time to set the alarm threshold for $Paco_2$ in management of severe TBI in children or for a practice bundle in TBI.[153] Nevertheless, its use as adjunct treatment of refractory raised ICP, particularly during the delayed postinjury phase, was supported as a second-tier therapy in the guidelines. Based on the current state of knowledge, if hyperventilation ($Paco_2$ ~30 mm Hg) is used to manage refractory ICP, advanced neuromonitoring such as assessment of $Pbto_2$, CBF, or jugular venous oxygen saturation is recommended to prevent iatrogenic ischemia. Finally, in the absence of signs and symptoms of herniation, there is no physiologic rationale for applying prophylactic hyperventilation.

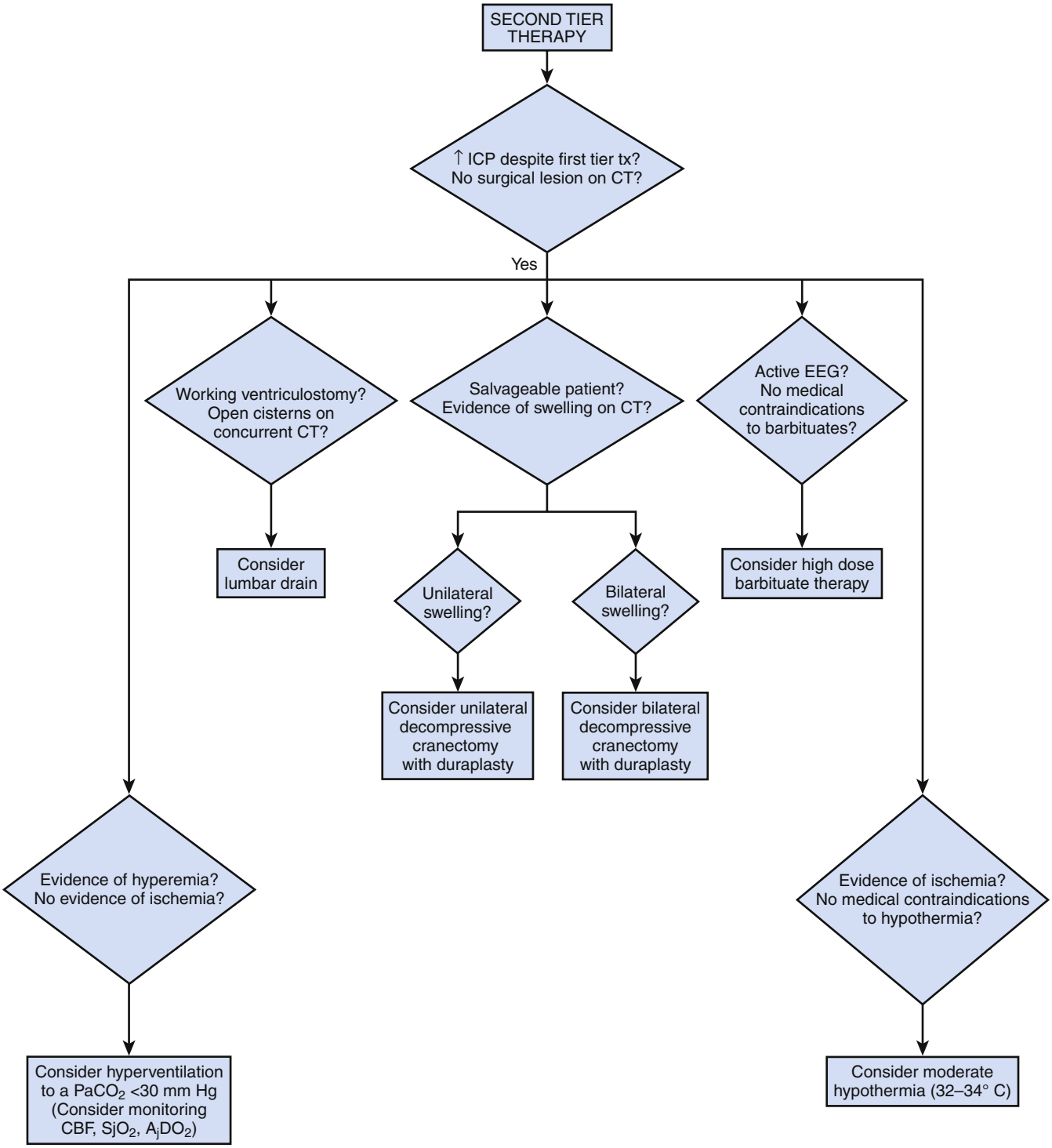

Figure 61–13. Second-tier therapies for the management of refractory intracranial hypertension based on the Guidelines for the Management of Severe TBI in Infants, Children, and Adolescents.[1] A_jDO_2, Arteriojugular venous oxygen content difference; Sjo_2, jugular vein oxygen saturation.

Hypothermia

In experimental models of TBI and in some clinical trials in adults after TBI, hypothermia improved outcome, presumably via multiple mechanisms, and meta-analyses supported its use in adults with severe TBI.[197-199] However, unlike the case in either cardiac arrest in adults or hypoxic ischemic encephalopathy (HIE) in newborns, RCTs of hypothermia targeting a temperature of about 33° C for 24 hours in adults[35] and more recently in children[196] failed to show benefit. Indeed, since publication of the pediatric guidelines, the most important published study is the work of Hutchison et al.[196] In that study, 225 children were randomly assigned to hypothermia versus normothermia for 24 hours with a mean time to target temperature of 6.3 hours. Surprisingly, there was a trend

toward worse outcome and increased mortality with hypothermia treatment. Delays in onset of cooling, short duration of therapy, frequent use of hyperventilation, and a rapid and unstable rewarming phase were suggested to represent limitations. However, this important trial certainly removes the prophylactic use of hypothermia from consideration as a first-tier therapy for severe TBI in infants and children. One might think that it even questions its use as a second-tier therapy; however, as evident in this chapter, other second-tier options also have important limitations.

Several important features of the trial may provide additional clues to the treatment of pediatric TBI. First, patients treated with hypothermia received less hypertonic saline solution than did those in the normothermia group. This protocol suggests a "trading of therapies" that is quite different from cardiac arrest and HIE where no other neurodirected therapies are generally used. It also suggests the possibility that hypertonic saline solution may represent a highly beneficial therapy (discussed previously). In addition, the major adverse effect observed was hypotension during rewarming. This complication, some persons have suggested, should have been prevented. However, hypotension was also seen in the recent RCT of magnesium in adults with TBI and was similarly associated with mortality.[200] Given the aforementioned narrow autoregulatory reserve in infants after TBI,[11] hypotension might represent an even greater concern in pediatric than in adult trials.

In contrast, hypothermia may still be useful for the management of refractory intracranial hypertension after severe TBI.[201,202] Unlike studies showing benefit from transient use (12-24 hours) of mild hypothermia (33° C) in adults after cardiac arrest,[203,204] a variety of temperature ranges are necessary to control ICP; thus a titrated approach to use of hypothermia in this setting is suggested.[201,202] Rewarming should be carried out carefully, at a rate no faster that 1° C every 4 hours—or even more slowly—and great care should be taken to monitor and treat hypotension that can occur with peripheral vasodilation during rewarming. Finally, hyperthermia is extremely deleterious in experimental models of TBI, exacerbating neuronal death. This effect is seen even when a brief 3-hour period of clinically relevant hyperthermia (39° C) is applied. Natale et al.[205] supported the clinical relevance of this work by showing that early hyperthermia (38.5° C within the first 24 hours of admission) occurred in 29.9% of pediatric TBI patients and was associated with poor outcome and increased length of stay. The most definitive clinical study on this matter is in the area of perinatal HIE, where just 1° C of hyperthermia after HIE was associated with a deleterious effect on long-term outcome.[206] Care should be taken to treat or prevent hyperthermia after severe TBI.

Decompressive Craniectomy

Another controversial area in the management of both adults and children with refractory intracranial hypertension is the use of decompressive craniectomy. Controlled studies on this modality are limited. Cushing[207] initially described this modality in 1905. There has been a resurgence of interest in this approach based on several case series and several small clinical trials, often involving children or young adults. Decompressive craniectomy is a controversial therapy that is based on the complex metabolic demands of the brain and the equally complex but poorly understood adverse effects of many of the therapies used to treat refractory intracranial hypertension (ischemia, hyperosmolality, metabolic suppression, and hypotension). However, this simplistic approach may have merit.

Several contemporary pediatric studies have been performed. Cho et al.[208] reported on the use of decompressive craniectomy versus medical management for treatment of infant victims of the shaken baby syndrome with refractory intracranial hypertension. Although the series was small, they reported an improved outcome compared with medical therapy, with some survivors showing good outcome. This study is one of the few specifically examining treatment of patients with severe TBI in whom child abuse is the injury mechanism. Polin et al.[209] reported on the use of extensive bifrontal decompressive craniectomy for the management of 35 adults and children with severe TBI and either refractory intracranial hypertension or diffuse edema on CT scan. They reported a favorable percentage of survivors with good or moderate disability (improved outcome vs. retrospectively matched cases from the Traumatic Coma Data Bank) and suggested a 48-hour time window for successful use. However, the patients in this report generally were not treated with either CSF drainage or barbiturates. Nevertheless, the best results were seen in the children in this study. Taylor et al.[210] reported on an RCT of early decompressive craniectomy versus standardized medical management alone. Although the sample size was limited (n = 27 children), strong trends toward reduction in ICP and improvement in long-term outcome were seen with decompressive craniectomy. More recently, Jagannathan et al.[211] reported 81% favorable outcome in 23 children with severe TBI treated with decompressive craniectomy.

Decompressive craniectomy is a second-tier therapy that is used with varying frequency depending on local experience and the discretion of the management team. Currently a large RCT (The RESCUEicp study) is underway in the United Kingdom.[212] This trial should contain a substantial pediatric component given that the entry criteria include children aged 10 years and older.

Lumbar Cerebrospinal Fluid Drainage

Lumbar CSF drainage can be effective in treating refractory intracranial hypertension in children. Levy et al.[213] reported that controlled lumbar CSF draining reduced refractory ICP in 14 of 16 pediatric patients and eliminated the need for barbiturates in their series. In adults with severe TBI, Munch et al.[214] reported an immediate and lasting reduction in ICP in 23 patients with very refractory intracranial hypertension. This modality is also a second-tier treatment option, but to avoid the risks of herniation, the patient must have open basal cisterns and no important mass effect or shift, and a functional ventriculostomy must already be in place.

Controlled Arterial Hypertension

Induced arterial hypertension is a controversial approach to the management of refractory raised ICP. Whether pressure autoregulation of CBF is intact or defective, arterial hypotension or inadequate CPP must be avoided. If pressure autoregulation is impaired, CBF is directly related to CPP and hypotension reduces flow. If pressure autoregulation is intact, then as CPP is reduced, reflex cerebral vasodilatation occurs (to maintain flow), which increases CBV and ICP.[215] This latter phenomenon occurs as CPP is reduced within the

autoregulatory range. Based on the relationship among CPP, vessel diameter, CBV, and ICP in selected adults with refractory intracranial hypertension, induced arterial hypertension (CPP increased to between 100 and 140 mm Hg via infusion of phenylephrine) produced a reduction in ICP.[215] However, arterial hypertension reduces ICP only when pressure autoregulation of CBF is intact because hypertension-mediated reduction in vessel caliber produces the reduction in CBV (to maintain a constant flow) and resultant reduction in ICP

Use of this intervention is complex in pediatric TBI because a single general threshold value of CPP is not applicable. Management must be tailored to each individual patient. It is possible that the aforementioned pressure reactivity index approach could help guide this intervention.[129] Also, the short-term and long-term effects of the greater hydrostatic pressure on the development of cerebral edema are unclear. Optimal management of blood pressure after severe TBI requires both monitoring of the involved factors and an in-depth understanding of the mechanisms.[215] Induced hypertension is a controversial "last-ditch" therapy that is not addressed in the pediatric guidelines.[1]

Finally, a few groups managing adults with severe TBI have adopted a very different therapeutic approach to blood pressure and ICP management termed the Lund Concept. This approach includes aggressive control of ICP with the unusual combination of β-blockade, α_2 receptor agonists, ergotamine, and barbiturates, with avoidance of systemic hypertension.[216] In some sense, this represents a form of chemical hyperventilation, that is, a pharmacologically controlled reduction in CBV. Remarkably, this approach has produced good outcome data and no exacerbation of ischemia, as assessed using intracerebral microdialysis in adults.[217] One report of this approach to ICP control in children with meningitis is available,[218] along with a recent report in children with TBI.[219] For additional insight into this approach, the reader is referred to the work of Stahl et al.[217] This approach merits additional study.

Is Rigorous Intracranial Pressure Control the Common Denominator in Studies with Exceptionally Good Outcome?

Whatever approach is selected to control ICP after severe TBI, the potentially deleterious and sometimes preventable consequences of secondary ischemia and herniation must be targeted. Interestingly, some of the best outcomes reported in clinical series of either adults or children with severe TBI have come from extremely divergent (albeit aggressive and protocol-based) approaches, namely, aggressive hyperventilation reported by Bruce et al.,[220] aggressive use of hyperosmolar therapy reported by Peterson et al.,[167] rigorous application of hypothermia with tightly controlled hemodynamics as reported by Marion et al.,[197] aggressive CPP management as described by Robertson et al.[157] and Rosner et al.,[221] and aggressive control of ICP using the Lund concept.[216] Perhaps the common denominator in these reports is the aggressive, meticulous, and protocol-driven control of ICP.

Miscellaneous

Seizures should be treated aggressively because excessive metabolic demands in the setting of hypoperfusion could result in a second insult to an already compromised brain. A recent study by Vespa et al.[222] in 20 adults with severe TBI showed that posttraumatic subclinical status epilepticus was associated with a considerable burden in raised ICP and long-lasting increases in brain interstitial lactate/pyruvate ratio—a marker of ischemia. This finding has heightened interest in this area and suggests the consideration of continuous EEG monitoring in pediatric TBI. However, the pediatric guidelines suggested use of prophylactic phenytoin only as a treatment option to prevent early posttraumatic seizures in severe TBI because it has not been shown to improve outcome either acutely or in the prevention of the late development of epilepsy.[1] Additional anticonvulsants are recommended to be given as needed to treat seizures. Finally, despite the fact that phenytoin has been the most commonly used anticonvulsant for acute seizure prophylaxis in pediatric TBI, recent studies in experimental TBI suggest that levetiracetam may be much more neuroprotective than fosphenytoin.[223] Clinical studies are needed.

Even if hypertonic saline solution is not used as a therapy, careful attention should be paid to the serum sodium level. It should be monitored at least twice daily in children with severe TBI. To prevent the development of hyponatremia, we recommend using 0.9% normal saline solution as the initial intravenous fluid for children with severe TBI. For infants, D_5 (5% dextrose) normal saline solution can be used. Hyponatremia that develops while only isotonic fluids are being administered generally can be attributed to either syndrome of inappropriate antidiuretic hormone secretion or cerebral salt wasting.[224] Care should be taken to determine the correct cause of hyponatremia because the management of syndrome of inappropriate antidiuretic hormone secretion involves fluid restriction, while that of cerebral salt wasting involves the administration of isotonic or hypertonic saline solution.

It has long been known that hyperglycemia exacerbates experimental ischemic brain injury, and threshold values greater than 200 mg/dL are generally considered as the target. Similarly, countless studies have shown associations between hyperglycemia and poor clinical outcome after various CNS insults, and most textbooks of adult neurocritical care recommend withholding glucose in intravenous fluids for at least 24 hours unless hypoglycemia is seen. Supporting this concept, Van den Berghe et al.[225] reported that insulin administration to control blood glucose at less than 110 mg/dL in 63 adults with isolated brain injury from various causes produced benefits with regard to ICP, CPP, and seizures. In contrast, Vespa et al.,[226] using intracerebral microdialysis in adults with severe TBI, reported that tight glucose control (serum glucose 90 to 120 mg/dL) produced a metabolic crisis in the brain (increases in glutamate and lactate/pyruvate ration) versus less rigorous glucose control (serum glucose 120 to 150 mg/dL). Great controversy remains as to the optimal management strategy for glucose administration and control after severe TBI.

The provision of adequate nutrition is essential during the catabolic response to critical illness, and beneficial effects of early feeding (either enteral or parenteral) in the critically ill or injured patient are well described. In critically ill adults, a cumulative deficit of 10,000 kcal was associated with increased mortality, and in the PICU this amount can be easily surpassed in less than 1 week.[227] Data in pediatric TBI, however, are lacking. In adults with severe TBI, Hadley et al.[228] reported that jejunal feeding within 36 hours of admission reduced septic complications and ICU days by 50% compared with delayed feeding (when gastric atony had resolved). Care must be taken to prevent the complications

of overfeeding (hyperglycemia with parenteral nutrition or hypoosmolality with enteral feedings). Frequent monitoring of blood glucose, electrolytes, and calorimetry may be useful.[229] Hyperalimentation formulations containing glutamate have been shown to increase glutamate levels, possibly exacerbating excitotoxicity.[230] Curiously, studies in experimental brain injury suggest that starvation for 48 hours dramatically reduces ultimate damage.[231] Ketosis is suggested to confer this benefit. The optimal nutritional approach in severe TBI needs to be addressed.

Routine use of glucocorticoids for treatment of patients with severe TBI is not recommended.[1] However, hypotension in the setting of severe TBI in rare cases is associated with pituitary failure, possibly from vascular disruption.[232]

Outcomes

Outcome from severe TBI generally has been assessed as a function of age at the time of injury and in relationship to three diagnostic categories: noninflicted (accidental) closed head injuries, inflicted childhood neurotrauma (child abuse), and penetrating injury (predominantly gunshot wounds). Accurate assessment of long-term outcome has been somewhat hampered in infants and children by the lack of validated outcome assessment tools. Application of modifications of adult outcome tools (e.g., the Glasgow Outcome Scale) has been the general approach; however, these tools have limitations when applied across the pediatric age spectrum.[233] In an important paper on pediatric outcomes, Levin et al.[10] highlighted the dramatic effect of age on outcome. About two thirds of children between the ages of 5 and 10 years had good outcome (i.e., normal or moderate disability), whereas more than 60% of children age 4 years or younger died. Rates of good outcome as high as 73% have been reported in clinical trials in pediatric TBI.[167] Specific studies of inflicted childhood neurotrauma and gunshot wounds generally have reported poorer outcome than results of series of accidental closed head injury. However, even within these two high-risk diagnostic categories, good outcome in some series has been as high as 35% in patients with severe TBI resulting from inflicted childhood neurotrauma and 24% in patients with severe TBI resulting from gunshot wounds.[208,234] Rehabilitation can have dramatic effects after a severe TBI is sustained, particularly in the setting of focal injury. Successful rehabilitation may require prolonged therapy (months or even years).[235]

Conclusion

Optimal care of the infant or child with severe TBI requires a multidisciplinary approach. Prompt and vigorous resuscitation, including stabilization and control of ventilation, is essential. After initial evaluation and surgical intervention, where appropriate, monitoring and carefully titrated management of raised ICP is essential to optimize cerebral perfusion and facilitate metabolic homeostasis. Meticulous and optimal neurointensive care is the basis on which future targeted therapies will be delivered as additional information on the evolution of secondary neuronal damage becomes available. The goal of contemporary pediatric neurointensive care is the prevention of secondary injury. Much of that care focuses on preventing secondary insults. The goal of future pediatric neurointensive case will be to overlay, on this therapeutic plan, strategies manipulating tissue injury in the evolution of secondary damage at a cellular level, along with strategies to foster regeneration and rehabilitation.

References are available online at http://www.expertconsult.com.

Hypoxic-Ischemic Encephalopathy: Pathobiology and Therapy of the Post-Resuscitation Syndrome in Children

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PEARLS

- Cardiac arrest in adult patients differs from cardiac arrest in pediatric patients in at least two important aspects: (1) cardiac arrest in pediatric patients is predominantly from asphyxial arrest, in contrast to adult patients, where it is predominantly from ventricular dysrhythmias, and (2) developmental differences exist between pediatric and adult patients including, ongoing synaptogenesis, lower cerebral blood flow in neonates and higher cerebral blood flow in toddlers and children compared with adults, neurotransmitter receptor maturation, and higher energy expenditure in pediatric patients.
- Although a multicenter, randomized clinical trial evaluating 48 hours of controlled hypothermia versus normothermia is ongoing, the International Liaison Committee on Resuscitation recommends consideration of 12 to 24 hours of moderate (32° to 34° C) hypothermia for comatose children after ventricular tachycardia/fibrillation cardiac arrest.[1]
- At present, there is no cure for hypoxic ischemic encephalopathy. It is likely that targeted therapies, spanning field interventions, intensive care, and rehabilitation, will be required to successfully prevent and treat hypoxic ischemic encephalopathy in infants and children after cardiac arrest.

In the past decade, important clinical trials demonstrating neuroprotective effects of therapeutic hypothermia in adults with cardiac arrest and neonates at risk for hypoxic ischemic encephalopathy (HIE) make this an exciting era for pediatric intensivists.[2-5] These trials (discussed later in this chapter) showing that induced hypothermia can prevent neurologic damage after cardiac arrest provide a window of opportunity for the application of pharmacologic or other interventions in what remains an important clinical problem with exceedingly high mortality and disappointingly high morbidity—cardiac arrest in children. At minimum, these trials have spurred renewed interest in determining whether therapeutic hypothermia is efficacious in infants and children after cardiopulmonary arrest, and were crucial in the implementation of a National Institutes of Health-funded multicenter clinical trial of therapeutic hypothermia after pediatric cardiac arrest in the United States. Although these "breakthroughs" and increasing depth and breadth of the understanding of mechanisms of HIE provide hope, challenges remain as by and large the likelihood of intact neurologic survival in children who suffer cardiopulmonary arrest remains unacceptably small.[6,7] A proven effective treatment protocol that reliably prevents HIE and improves neurologic recovery after cardiopulmonary arrest in infants and children remains elusive. Despite numerous advances in critical care medicine, the optimal supportive care to maintain neuronal function and maximize recovery after cardiorespiratory arrest is in and of itself controversial.

This uncertainty arises from the pathobiologic complexity of cerebral injury and from the limitations in our clinical ability to monitor key metabolic and physiologic parameters in the brain. Clinical stumbling blocks in the history of "brain resuscitation" have also slowed progress in our understanding of HIE after cardiopulmonary arrest. Historically, this entity was largely ignored as a specific disease process. Brain resuscitation was dealt with as a single therapeutic paradigm regardless of the etiology.[8] This resulted in the misguided application of results from studies of traumatic brain injury (TBI), stroke, Reye syndrome, and cerebral protection to patients suffering cardiopulmonary arrest. Second, within cardiopulmonary arrest etiologies and patient-relevant biologic factors such as genetic influences and comorbidities are lumped together. Factors influencing neurologic damage and recovery are clearly different depending on the cause (asphyxia, arrhythmia, hemorrhage, trauma, sepsis, etc.), age of the patient, interval between arrest and return of spontaneous circulation (ROSC), and effectiveness of cardiopulmonary resuscitation (CPR). Finally, the frustration encountered in dealing with the poor neurologic outcomes that often occur in this syndrome

has reduced the enthusiasm for clinical studies involving novel treatments or those with proven efficacy for other indications.

In this chapter, the pathobiology of HIE is reviewed with emphasis on cellular mechanisms, pathophysiology, and histopathology. Differences between the most prevalent etiologies of cardiopulmonary arrest in children (asphyxia vs. cardiac arrhythmia) are examined, and an appraisal of traditional and novel therapies is presented, including the reemergence of the potential for therapeutic hypothermia in children after cardiopulmonary arrest. Finally, any discussion of HIE in children is complicated not only by the specific mode of arrest in children but also by the unique nature of these young patients. The child's brain is still developing, adding another layer of variability in terms of age-specific pathological and reparative mechanisms, potential for therapies to afford benefit, evaluation of therapeutic effectiveness, and neurologic outcome. Thus the effect of the host's immaturity on the pathobiology of postarrest encephalopathy also is examined.

Epidemiology

In the United States, cardiac arrest occurs in 8 to 20/100,000 children per year in the out-of-hospital setting and in 1.06 of every 1000 pediatric hospital admissions.[6,9,10] Males have an increased frequency of cardiac arrest (~60 vs. 40% for females) but there are no sex differences in mortality.[7] Half of children with cardiac arrest have underlying comorbidities.[7,11]

Asphyxia is the most prevalent cause of cardiac arrests and the principal cause of HIE in children.[12,13] In asphyxial arrest, asystole or pulseless electrical activity is preceded and precipitated by a period of hypoxemic or anoxic perfusion.[14] Hypoxia most commonly results from submersion accidents, airway obstruction, pulmonary aspiration, severe asthma or pneumonia, inhalation injury, or apnea syndromes.[6,7,15] In contrast, ventricular fibrillation (VF) is the most frequent cause of out-of-hospital cardiopulmonary arrest in adults.[16] In VF-induced cardiac arrest, respiration ceases shortly after loss of perfusion pressure. VF also occurs in children, but at an estimated incidence of less than 10% of pediatric victims of cardiac arrest overall, more commonly in the in-hospital setting.[7]

Cellular and Molecular Pathobiology

Mechanisms of Hypoxic-Ischemic Brain Injury

Cerebral neurons in culture can tolerate hours of extreme hypoxia. Although it takes about 160 minutes of exposure to an anoxic gas mixture for oxygen tension in the culture medium to reach 1 mm Hg, cortical neurons tolerate 1 to 3 additional hours with little histologic change.[17] If 1 mmol/L sodium cyanide is used to simulate immediate anoxia, hippocampal neurons become swollen and vacuolated within 20 to 60 minutes and begin to disintegrate in 4 hours. Similarly, even 1 hour of complete global brain ischemia in monkeys is followed by electrophysiologic recovery of many neurons and significant recovery of some aspects of brain metabolism, such as protein synthesis.[18] Although the time limit for consistently normal outcome after normothermic primary cardiac arrest is unknown, it is certainly closer to 5 to 10 minutes than 1 to 3 hours. Restoration of integrated brain function, that is, "neurologic recovery," differs markedly from physiologic or metabolic brain recovery. In contrast to the relative cellular homogeneity in other organs, the functional specificity and interactions of neurons and glia in brain make patchy areas of cell death potentially devastating. This is evident in the neuropathology of dogs in persistent coma 1 week after a 10- to 15-minute cardiopulmonary arrest. Scattered neuronal death is evident, but the vast majority of neurons appear normal.[19]

Energy Failure

The brain depends on large amounts of substrate (glucose and lactate) because of its tremendous metabolic demands and paltry energy stores. Interruption of cerebral blood flow (CBF) results in loss of consciousness and electroencephalographic silence within seconds. Within 5 to 7 minutes, energy failure occurs, accompanied by disturbances of ion homeostasis in neurons and glial cells. Clinically this rapid depletion of brain high-energy phosphates has been demonstrated after hypoxia-ischemia in neonates using phosphorus magnetic resonance spectroscopy.[20] Influx of sodium and water and efflux of potassium occur because the cells cannot maintain their energy-dependent electrochemical gradients. When the extracellular potassium concentration reaches 10 to 15 mmol/L, voltage-gated channels open and extracellular calcium influx occurs.[21]

If CBF remains inadequate and energy failure persists, calcium-mediated events such as phospholipase and protease activation can lead to irreversible injury and neuronal cell death. Cerebral acidosis occurs, and intracellular pH decreases from 7 to 6.4.[22] If CBF is restored, however, recovery of basal cellular metabolism (ATP levels, protein synthesis, and oxygen consumption) and pH occurs. This has been shown in brain tissue samples and intact brain measurements after global ischemic insults that result in persistent vegetative coma.[18]

After anoxia or ischemia, the recovery of aerobic metabolism is essential for recovery, but is not in and of itself sufficient. The imbalance between aerobic and anaerobic metabolism and overdependence of neurons on lactate as a substrate[23] must be restored. Despite global metabolic recovery, certain neurons progress to cell death. After restitution of CBF and oxidative metabolism after energy failure in the brain cellular and molecular dysfunction progresses and cells may die via immediate necrosis (complete energy failure), programmed cell death (apoptosis, autophagic stress, or delayed necrosis), or a spectrum of these processes.[24-26] Brain magnetic resonance spectroscopy demonstrates early (during ischemia) and late (48 hours after reperfusion) depletion of high-energy phosphorous compounds and a corresponding lactate peak occurring in the face of normal vital signs, serum glucose, and arterial oxygen saturation after experimental hypoxia-ischemia.[27,28]

Selective Vulnerability

Certain neurons, such as those in the CA_1 region of the hippocampus; basal ganglia; cerebral cortical layers III and V; portions of the amygdaloid nucleus; the cerebellar Purkinje cells; and in infants, periventricular white matter regions and some brainstem nuclei, are known to be especially vulnerable to hypoxia-ischemia.[29,30] Five minutes of complete global brain ischemia produces cell death in these regions that begins to

appear between 48 and 72 hours, without apparent histological damage in other brain areas.

Transient calcium accumulation occurs in all cells during ischemia, but secondary irreversible accumulation occurs in the selectively vulnerable zones many hours later.[31] Electrophysiologic studies show that delayed neuronal death is preceded by neuronal hyperactivity. It is hypothesized that ischemic and early postischemic calcium accumulation leads to a complex sequence of derangements in cellular metabolism such as protease activation and oxygen-derived free radical formation.[32] These conditions, in concert with excessive release of excitatory neurotransmitters (glutamate, glycine, and aspartate) in these areas, lead to excitotoxicity and cell death. These findings are supported by work in neuronal culture showing that calcium influx accompanies cell death in the presence of anoxia or supraphysiologic levels of excitatory amino acids such as glutamate,[17,33] and that CA_1 cells are the most sensitive to glutamate-mediated injury.[34] Finally, delayed energy depletion, mitochondrial dysfunction, and infarction occur in concert, but are regionally distinct, suggesting that metabolic characteristics of brain regions affect recovery from ischemia.[35,36]

Of particular interest is that these intrinsically vulnerable cells do not have a unique vascular distribution.[37] They represent neither vascular watersheds nor hypoperfused zones. Death of these neurons after a threshold ischemic insult occurs in a delayed fashion after reperfusion and thus may be preventable, at least in part, by treatment.

Cell Death Mechanisms

Cell death can occur by at least three distinct pathways, necrosis, apoptosis or autophagy.[24,38] Cell death can also occur via a combination of one or all three of these pathways (see also Chapter 100). Necrosis, which is characterized by denaturing and coagulation of cellular proteins, is the basic pattern of pathological cell death that results from progressive reduction in the cellular content of adenosine triphosphate.[39] Necrosis involves progressive derangements in energy and substrate metabolism that are followed by a series of morphologic alterations, including swelling of cells and organelles, subsurface cellular blebbing, amorphous deposits in mitochondria, condensation of nuclear chromatin, and finally, breaks in plasma and organellar membranes.[39] Whereas necrotic cell death was traditionally felt to be entirely irreversible, recent studies showing that some degree of necrotic cell death responds to treatment after hypoxia-ischemia implicate "programmed necrosis," also termed "necroptosis."[40]

Cell death after hypoxic-ischemic insults can also occur by apoptosis.[41] Development of apoptosis usually requires new protein synthesis and the activation of endonucleases. Two distinct types of characteristic cleavage of DNA have been described. The most well described, *caspase-dependent* apoptosis, involves cleavage by caspase activated deoxyribonuclease at linkage regions between nucleosomes to form fragments of double-stranded DNA.[42] This produces a pattern of DNA cleavage observed on Southern blot analysis termed "DNA laddering." In contrast, *caspase-independent* apoptosis results in large-scale DNA fragmentation induced by the mitochondrial flavoprotein apoptosis-inducing factor.[43,44] The stimuli triggering apoptosis are complex and multifactorial, involving extracellular surface receptors, cell signaling pathways, protease cascades, and mitochondrial and other organelle

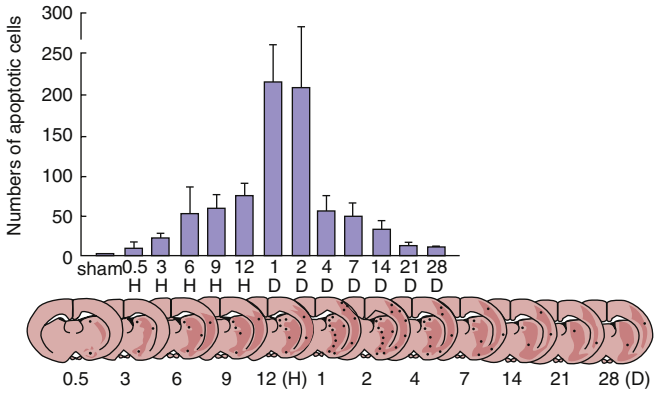

Figure 62–1. Apoptotic cells in coronal brain sections in rats subjected to 2 hours of middle cerebral artery occlusion and between 0.5 and 28 days of reperfusion. *Top,* Progressive increase in the numbers of apoptotic cells occurs with increasing reperfusion time to peak at 24 hours. However, apoptotic cells are still detectable even after 1 week of reperfusion. *Bottom,* Distribution of apoptosis (*dots*) and necrotic neurons (*hatched areas*). Apoptotic cells are localized predominately to inner boundary zone of infarction. *(From Li Y, Chopp M, Jiang N, et al: Temporal profile of in situ DNA fragmentation after transient middle cerebral artery occlusion in the rat,* J Cereb Blood Flow Metab *15:389, 1995.)*

dysfunction. Selective vulnerable cell death in brain regions such as the CA_1 region of the hippocampus after transient global brain ischemia appears to occur by apoptosis.[45] DNA extracted from the hippocampus of gerbils at 4 days after a threshold global ischemic insult exhibits a characteristic laddering pattern consistent with apoptotic cell death. Thus after a threshold ischemic insult, selective neuronal death in the highly vulnerably CA_1 region of the hippocampus occurs by apoptosis. Thalamic-delayed neuronal death was caused by Fas-mediated apoptosis in a model of neonatal hypoxia-ischemia.[46] Li et al.[47] reported that apoptosis in the postischemic brain is not limited to scattered neuronal death in what have been traditionally deemed to be "selectively vulnerable regions," but is seen even in penumbral regions around evolving cerebral infarcts (Figure 62-1). Finally, the proportion of apoptosis in the developing brain after ischemia appears to be a sex-dependent, because females but not males respond to antiapoptotic agents after neonatal hypoxia-ischemia.[48]

Recently, a new mode of cell death after brain ischemia has been implicated—autophagy. Autophagy is a homeostatic process that recycles cell resources during periods of nutrient stress.[49] Autophagy is upregulated after experimental brain ischemia,[50,51] which can be considered profound nutrient stress.[52] Studies show that blocking autophagy after hypoxia-ischemia can be protective or detrimental.[38,53,54] As such, autophagy's role after acute brain injury is controversial, and it may depend on stage of brain development and sex of the patient, animal, or cell.[52,55] Mouse pups lacking Atg7 (a necessary component for autophagy) or rat pups treated with an inhibitor of autophagy (3-methyladenine) are protected from focal hypoxia-ischemia.[50,51]

The proportion of neuronal cell death that occurs via apoptosis, necrosis, or autophagy after cerebral ischemia remains undetermined.[56,57] Moreover, it remains possible that treatments inhibiting apoptosis may simply convert cell death to necrosis or autophagy.[58,59] Although speculative, it is quite possible that after cardiopulmonary arrest and resuscitation, a continuum exists in neurons from recovery to necrosis[60] that

depends on the duration of the insult, the local milieu, and the given brain region.[61-63]

Nevertheless, in any given brain region, whether neuronal death is produced by necrosis, apoptosis, or autophagy, a highly complex series of events appears to be involved during the arrest and after ROSC. A theoretical scheme of the mechanisms involved is given in Figure 62-2, a scheme that remains remarkably contemporary despite being conceptualized almost two decades ago by Bellamy, Safar, and others.[64] Importantly, several molecular and pharmacological interventions that interrupt apoptosis have been reported to improve outcome after cerebral ischemia, including "pediatric" models. Although studies showing improved functional recovery with treatments inhibiting apoptosis after cerebral ischemia suggest that some salvaged neurons regain their integrative properties, it is also possible that some of the delayed apoptosis represents appropriate pruning of neurons that have lost their targets. These processes, coupled with the need to restore highly integrated function, explain the unfortunate clinical scenario of the persistent vegetative state despite restoration of normal function in other organ systems. The relationship of these distinct forms of cell death to selective vulnerability of neurons in brain is beginning to emerge.

Reperfusion Injury

Reoxygenation and reperfusion are essential to recovery of any organ after ischemia. Experimental evidence suggests, however, that certain aspects of reperfusion result in tissue injury.[65,66] Reperfusion injury is a complex series of interactions between parenchyma and microcirculatory elements, resulting in detrimental effects that negate some fraction of the benefits of reperfusion. The magnitude of reperfusion injury varies with the organ in question, the duration and type of hypoxic-ischemic insult, as well as the timing, duration and magnitude of reperfusion.[67,68]

In many organs and in the brain after focal insults, progressive microcirculatory failure is thought to be an important aspect of reperfusion injury.[69] However, as suggested by the nonspecific vascular distribution of selectively vulnerable neurons, the brain may display a second unique setting for the evolution of reperfusion injury, the evolution of selectively vulnerable cell death. Four key mechanisms hypothesized to be important to reperfusion injury in the brain include: (1) excitotoxicity and calcium accumulation, (2) protease activation, (3) oxygen radical formation, and (4) membrane phospholipid hydrolysis and mediator formation.

Excitotoxicity and Calcium Accumulation

Glutamate and aspartate are the major excitatory amino acid neurotransmitters in the mammalian central nervous system, but both also have neurotoxic properties. Pioneering studies by Rothman et al.[70] demonstrated in vitro that hypoxia-induced neuronal death is mediated by synaptic activity. Inhibition of synaptic glutamate release or blockade of glutamate receptors prevented hypoxia-induced neuronal injury. Glutamate is the major neurotransmitter in the selectively vulnerable zones and accumulates extracellularly at supraphysiologic levels in these regions after hypoxic or ischemic insults.[31]

Glutamate is released at the presynaptic terminal in response to neuronal stimulation and acts by binding to postsynaptic dendritic receptors. Two main classes of excitatory neurotransmitter receptors have been identified. One class consists of the ligand-gated ion channels ("ionotropic" receptors) and includes NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) or quisqualate, and kainate receptor subtypes. Toxicity caused by NMDA receptor activation is usually rapid, whereas AMPA or kainate receptor-mediated cell death is somewhat slower to develop.[71] The other class of excitatory neurotransmitter receptors includes the "metabotropic" receptors. These receptors are coupled with G proteins and modulate intracellular second messengers such as calcium, cyclic nucleotides, and inositol triphosphate.[72] When activated, the ionotropic glutamate receptors open sodium channels and may also have an important role in initiation and propagation of membrane depolarization and spreading depression.[73] With ionotropic receptor activation, rapid excitatory amino acid-mediated calcium accumulation occurs. In the face of ischemia this calcium accumulation is exacerbated by cellular energy failure, that disables the Na^+/K^+-ATPase membrane pump and results in further calcium accumulation.[31] Reestablishment of the energy supply can reverse these changes. Delayed glutamate-related neuronal injury is most likely the result of activation of ionotropic receptors and subsequent calcium influx. Calcium influx causes death of neurons in culture under anoxic conditions or in the presence of glutamate.[31] The intracellular accumulation of calcium: (1) activates proteases, lipases, and endonucleases resulting in the breakdown of membrane phospholipids; (2) activates neuronal nitric oxide synthase (nNOS), resulting in nitric oxide (NO) production and, in the presence of superoxide, peroxynitrite formation; (3) damages mitochondria; (4) disrupts nucleic acid sequences; and (5) ultimately mediates cell death via necrosis, apoptosis or autophagy (see Figure 62-2). The disturbance of the finely regulated intracellular calcium homeostasis is now recognized as a possible final common pathway of neuronal death.[25,31,64,72] NMDA receptor activation has also been shown to stimulate superoxide anion production, which may contribute to cellular injury.[74] The NMDA and AMPA-receptor subtypes have been suggested to play key roles in ischemic brain injury. The potential implications of these mechanisms in regard to therapeutic manipulation of glutamate receptors, as well as calcium and sodium channels, are discussed later.

Protease Activation

One of the candidates for a critical role in neuronal injury as a result of increases in intracellular calcium concentration is protease activation. Protease activation plays a central role in mediating both necrosis and apoptosis. With regard to necrosis, numerous calcium-dependent enzymes can become activated during ischemia and produce important structural injury to neurons. One class of calcium-dependent proteases, calpains, are cytosolic cysteine proteases that have a homeostatic role in cell-cycle regulation, differentiation, cell migration, and signal transduction.[75] After injury, calpain-mediated proteolysis of cytoskeletal proteins as well as activate protein kinase C and phospholipases can occur.[75] Calpains also hydrolyze the major plasma membrane sodium/calcium exchanger in neurons during excitotoxicity, allowing enormous secondary influx of calcium into the cell following NMDA receptor activation and creating a positive feedback environment.[76] In a model of oxygen-glucose deprivation in

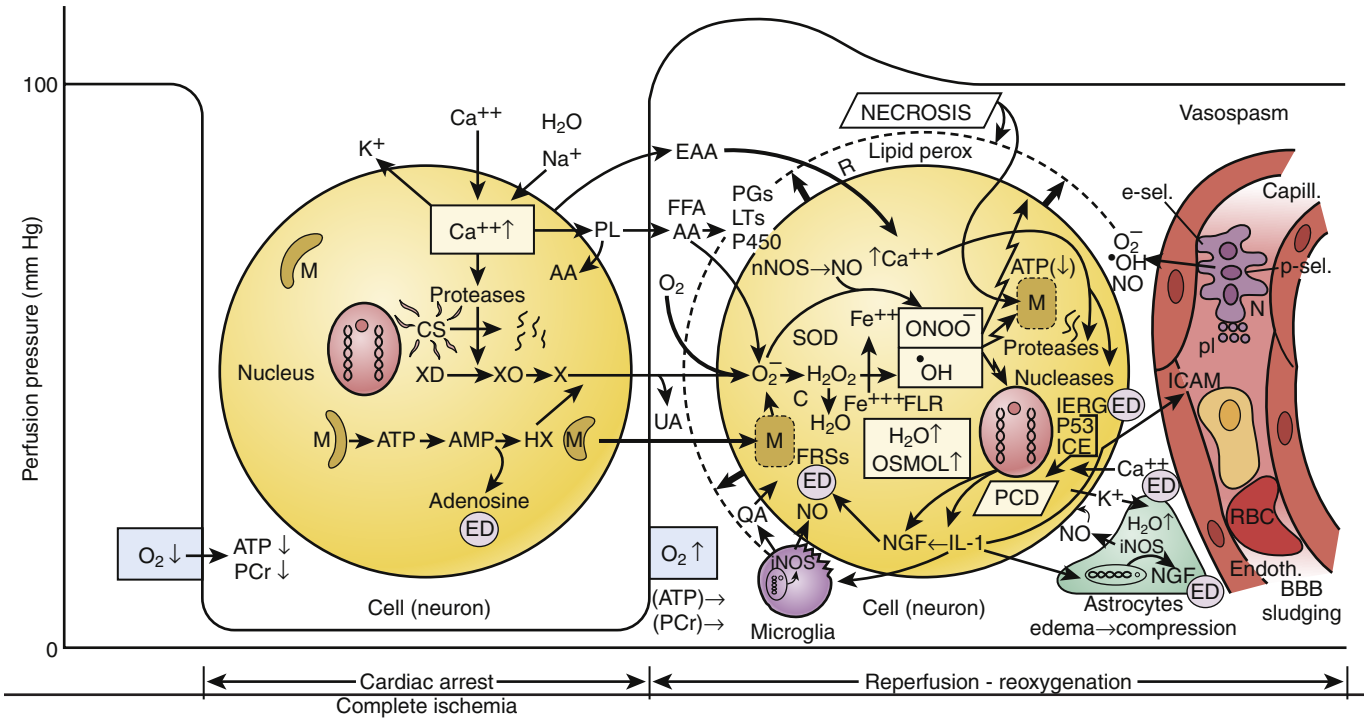

Figure 62–2. Death of cells after temporary ischemia. Diagram of complex, partially hypothesized biochemical cascades in neurons during and after cardiac arrest.[64] Normally intracellular ([Ca^{2++}]*i*) to extracellular ([Ca^{2++}]*e*) calcium gradient is 1:10,000. Calcium regulators include calcium/magnesium adenosine triphosphatase, the endoplasmic reticulum (ER), mitochondria, and arachidonic acid (*AA*). With stimulation, different cell types respond with an increase in [Ca^{2++}]*i* because of release of bound Ca^{2++} in the ER and influx of [Ca^{2++}]*e,* or both. During complete ischemic anoxia (cardiac arrest) *(left),* the level of energy (phosphocreatinine [*Pcr*] and adenosine triphosphate [*ATP*]) decreases to near zero in all tissues at different rates, depending on stores of oxygen and substrate; it is fastest in the brain (~5 minutes) and slower in the heart and other vital organs. This energy loss causes membrane pump failure, which causes a shift of sodium *(Na^+)* ions, water *(H_2O),* and calcium ions *(Ca^{2++})* from the extracellular into the intracellular space (cytosolic edema), and potassium *(K^{++})* leakage from the intracellular into the extracellular space. Increase in [Ca^{2++}]*i* activates phospholipase A_2, which breaks down membrane phospholipids (*PL*) into free fatty acids *(FFA),* particularly *AA*. Increase in [Ca^{2++}]*i* also activates proteolytic enzymes, such as calpain, which may disrupt the cytoskeleton (*CS*) and possibly the nucleus. In mitochondria (*M*) hydrolysis of ATP to adenosine monophosphate (*AMP*) leads to an accumulation of hypoxanthine (*HX*). Increased [Ca^{2++}]*i* may enhance conversion of xanthine dehydrogenase (*XD*) to xanthine oxidase (*XO*), priming the neuron for the production of the oxygen free radical superoxide anion (O_2) although this pathway is of questionable importance in neurons (*X,* xanthine; *UA,* uric acid). Excitatory amino acid neurotransmitters (*EAA*), particularly glutamate and aspartate, increase in extracellular fluid. Increased [EAA]*e* activates *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors (*R*), thereby increasing calcium and sodium influx and mobilizing stores of [Ca^{2++}]*i.* Increased extracellular potassium activates EAA receptors by membrane depolarization. Glycolysis during hypoxia results in anaerobic metabolism and lactic acidosis, until all glucose is used (in the brain, during anoxia after ~20 minutes). This lactic acidosis, plus inability to wash out CO_2, results in mixed tissue acidosis that adversely influences neuronal viability. The net effect of acidosis on the cascades during and after ischemia is not clear. Mild acidosis may actually attenuate NMDA-mediated [Ca^{2++}]*i* accumulation. Without reoxygenation, cells progress via first reversible, later irreversible structural damage, to necrosis at specific rates for different cell types. During reperfusion and reoxygenation (*right*), lactate and molecular breakdown products can create osmotic edema and rupture of organelles and mitochondria. Recovery of ATP and Pcr and of the ionic membrane pump may be hampered by hypoperfusion as a result of vasospasm, cell sludging, adhesion of neutrophils (granulocytes) (*N*), and capillary compression by swollen astrocytes, which also help to protect neurons by absorbing extracellular potassium. Capillary (blood-brain barrier [*BBB*]) leakage results in interstitial (vasogenic) edema. Increased concentrations of at least four oxyradical species that break down membranes and proteins, worsen the microcirculation, and possibly also damage the nucleus may be formed: Superoxide anion ($O_2.-$) leading to hydroxyl radical (⁻OH) (via the iron-catalyzed $Fe^{+++} \rightarrow Fe^{++}$, Haber-Weiss/Fenton reaction); free lipid radicals (*FLR*) and peroxynitrite (*OONO⁻*). O_2 may be formed from several sources: (1) directly from eicosanoid metabolism; (2) by the previously described XO system; (3) via quinone-mediated reactions within and outside the electron transport chain (from mitochondria [*M*]); and (4) by activation of NADPH-oxidase in accumulated neutrophils in the microvasculature or after diapedesis into tissue. Increased O_2 leads to increased hydrogen peroxide (H_2O_2) production as a result of intracellular action of superoxide dismutase (*SOD*). [H_2O_2] is controlled by intracellular catalase. Increased O_2 further leads to increased ·OH, because of conversion of H_2O_2 to ⁻OH via the Haber-Weiss/Fenton reaction, with iron liberated from mitochondria. This reaction is promoted by acidosis. ·OH and OONO⁻ damage cellular lipids, proteins, and nucleic acids. Also, AA is metabolized by the cyclooxygenase pathways to prostaglandins (*PGs*) including thromboxane A_2, or by the lipoxygenase pathway to produce leukotrienes (*LTs*); and by the cytochrome P-450 pathway. These products can act as neurotransmitters and signal transducers in neuronal and glial cells and can activate thrombotic and inflammatory pathways in the microcirculation. Inflammatory reactions after ischemia have been shown to occur in extracerebral organs, focal brain ischemia, or brain trauma; to date, they have not been demonstrated after temporary complete global brain ischemia. Neuronal injury can signal interleukin-1 and other cytokines to be produced and trigger endogenous activation of microglia, with additional injury (*QA,* quinolinic acid). In addition, tissue or endothelial injury—particularly associated with necrosis—can signal the endothelium to produce adhesion molecules (intercellular [*ICAM*], e-selectin [e-sel], p-selectin [p-sel]), cytokines, chemokines, and other mediators, triggering local involvement of systemic inflammatory cells in an interaction between blood and damaged tissue. Reoxygenation restores ATP through oxidative phosphorylation, which may result in massive uptake of [Ca^{2++}]*i* into mitochondria, which are swollen from increased osmolality. Thus mitochondria loaded with bound [Ca^{2++}] may self-destruct by rupturing and releasing additional free radicals. Increased [Ca^{2++}]*i* by itself and by triggering free radical reactions may result in lipid peroxidation, leaky membranes, and cell death. Neuronal damage can be caused, in part, by increased [EAA]*e* (excitotoxicity). During reperfusion, [Ca^{2+}]*i* and increased [EAAs]c normalize. Their contribution to ultimate death of neurons is more likely through the cascades they have triggered during ischemia. During ischemia and subsequent reperfusion, loading of cells and calcium maldistribution in cells are believed to be the key trigger common to the development of cell death. This calcium loading signals a wide variety of pathological processes. Proteases, lipases, and nucleases are activated, which may contribute to activation of genes or gene products (i.e., interleukin-converting enzyme, [*ICE*] or *P53*) critical to the development of programmed cell death (*PCD,* i.e., apoptosis, autophagy or necroptosis), or inactivation of genes or gene products normally inhibiting this process. Activation of nNOS by calcium can lead to production of NO·, which can combine with superoxide to generate peroxynitrite (*OONO⁻*). OONO⁻ and ⁻OH both can lead to DNA injury and PCD, or protein and membrane peroxidation and necrosis, respectively. Nerve growth factor (*NGF*), nuclear immediate early response genes (*IERG*) such as heat-shock protein, free radical scavengers (*FRSs*), adenosine, and other endogenous defenses (*ED*) may modulate the damage. *(Courtesy P. Safar, MD, and P. Kochanek, MD, with input from N. Bircher, MD, and J. Severinghaus, MD.)*

neuronal cell culture that mimics transient ischemia, calpains induced mitochondrial release of apoptosis-inducing factor, that translocates to the nucleus to initiate caspase-independent apoptosis.[77]

With regard to apoptosis, the caspase family of cysteine proteases plays an important role after cerebral ischemia, and may have a more prominent role in the developing versus mature mammalian brain.[78,79] After unilateral hypoxic-ischemic brain injury, neonatal rats had increased cytochrome c release and caspase-3 activation versus juvenile and adult rats.[55] Regulation of apoptotic machinery also appears to be sex dependent after neonatal hypoxic-ischemic brain injury.[80] Comparatively, female rats had more caspase-mediated apoptosis while male rats had more caspase-independent, apoptosis-inducing factor-mediated apoptosis.

Oxygen Radical Formation

Toxic oxygen radical species produced during postischemic reperfusion have been implicated as important contributors to reperfusion injury and delayed cell death.[66] The primary species of interest include superoxide anion, hydrogen peroxide, hydroxyl radical, and the reactive nitrogen species peroxynitrite.

The potential sources of oxygen radicals are many. Superoxide anion is produced by the electron transport chain during normal mitochondrial respiration. Mitochondrial dysfunction, as may occur under conditions of ischemia, produces increased generation of free radicals that may extend beyond the capacity of local endogenous antioxidants leading to oxidative stress. Metabolism of arachidonic acid via the cyclooxygenase pathway to form prostaglandins also produces superoxide anion as an enzymatic byproduct, and this also occurs to a lesser extent in the lipoxygenase and cytochrome P-450 pathways.[66,81] Accumulated neutrophils also can contribute superoxide anion via neutrophil reduced nicotinamide adenine dinucleotide (NADPH)-oxidase. Yet another potential oxygen radical source is xanthine oxidase (XO)-xanthine dehydrogenase (XD). Energy depletion is associated with conversion of ATP to adenosine diphosphate (ADP) and eventually to hypoxanthine. This ischemia- or anoxia-induced energy deprivation also causes conversion of XD to XO via calcium-activated proteases. In the presence of hypoxanthine and oxygen, that become available during reperfusion, XO produces superoxide anion. These XO-mediated reactions may occur in cerebral vascular endothelial cells, that are rich in XO.[66] However, the importance of XO in contribution to the generation of free radicals in human beings has been challenged.[82,83] Autooxidation of circulating catecholamines or of neurotransmitter catecholamines may represent another potential source of oxygen radicals.

Another possible contributor to free radical generation is delocalized iron. Iron is normally transported in the blood tightly bound to transferrin and stored inside the cell bound to ferritin. In ischemic conditions with accompanying acidosis, however, iron may be displaced from its normal binding sites and can catalyze reactions that promote oxygen radical formation.[84,85] Most commonly implicated is the Haber-Weiss/Fenton reaction, whereby the very potent hydroxyl radical is produced from superoxide anion and hydrogen peroxide in the presence of free iron. The iron-chelator, deferoxamine, has been shown to reduce neurologic injury after experimental neonatal hypoxia-ischemia.[86,87] Finally, NO is another free radical that contributes to both nitrosative and oxidative stress. NO increases during ischemia via increased NMDA receptor stimulation, mediated by release of excitatory amino acids and subsequent calcium-mediated activation of nNOS.[88] NO in the presence of superoxide produces peroxynitrite.[89] Free radicals have also been associated directly with an increase release of excitatory amino acids and vice versa.[74,90] Not only do they participate in each other's release and formation, but they also may act synergistically in causing tissue damage.

The brain may be particularly vulnerable to free radical injury for several reasons. One is the high concentration of polyunsaturated fatty acids, especially arachidonic acid. Release of free fatty acids (FFA) occurs throughout ischemia. On exposure to oxygen radical species, these FFA are vulnerable to autocatalytic lipid peroxidation.[91] Cerebrospinal fluid (CSF) has low concentrations of iron-binding proteins; therefore, iron released from injured neurons or glia is likely to contribute to these peroxidation reactions. Byproducts of these reactions, for example, malondialdehyde and conjugated dienes, have been used as markers of the extent of lipid peroxidation after brain injury (e.g., the thiobarbiturate assay). Lipid peroxides accumulate in the selectively vulnerable zones during reperfusion after transient forebrain ischemia.[84,92] The peroxides do not accumulate during the ischemic period itself or in areas that are not reperfused and thus are implicated in reperfusion injury.[93]

Investigators have also detected oxidative damage to brain proteins after reperfusion.[93] Pyruvate dehydrogenase, a key mitochondrial matrix enzyme that converts pyruvate into acetyl coenzyme A, undergoes oxidative protein modification after ischemia that impairs enzyme activity, possibly contributing to neuronal cell death.[94] However, others have argued that oxidized proteins detected in previous studies were oxidized during sampling and not as a result of ischemia.[91] Other investigators were also unable to detect oxidized nuclear material or mitochondrial DNA during cerebral ischemia.[95] These results were expected because of the compact structure of DNA and the presence of histones, which provide increased resistance to oxidative damage. However, there are two problems with these findings: (1) damage caused by oxidative stress can occur in the absence of lipid peroxidation[96] and (2) work investigating apoptosis suggests that oxidation of regulatory proteins of transcription and translation of DNA may be an important intermediate step in propagation of neuronal cell death.[97,98] Application of contemporary techniques to quantify oxidative stress should help clarify this issue,[99] and may assist in the evaluation of therapies to prevent oxidative stress-mediated brain damage produced during ischemia and reperfusion.

Developmental and sex differences exist in terms of the degree of oxidative stress and amount and function of antioxidant enzymes after brain injury. In mice, glutathione and catalase activity in brain is higher in adult female versus male mice, and discrepancies become more exaggerated with age.[100] Furthermore, neurons from male rats have less capacity to replenish glutathione levels after cytotoxic stress in vitro, and in vivo after asphyxial cardiac arrest.[101] A similar pattern occurs in adult patients after severe TBI with males demonstrating increased lipid peroxidation products in CSF compared with females.[102]

Membrane Phospholipid Hydrolysis and Mediator Formation

Membrane phospholipids modulate signaling cascades, affecting the development, differentiation, function, and repair of the nervous system, functions that become dysregulated with ischemia and oxidative stress.[103] FFAs are released from neuronal membranes during ischemia, and the amount of FFA released are proportional to the duration of ischemia. FFA release continues to change in proportion to duration of ischemia after the completion of energy failure.[104] FFA are released by two distinct but related processes. First, phosphatidyl inositol is hydrolyzed by phospholipase C with the production of diacylglycerol (DAG) and inositol phosphates.[105,106] Phospholipase C-mediated hydrolysis begins during the initial moments of the ischemic insult and is related to neurotransmitter receptor stimulation. DAG is then hydrolyzed by lipases to FFA, predominantly arachidonic and stearic acid. Second, other brain glycerophospholipids are hydrolyzed by phospholipase A_2, which is activated by increases in intracellular calcium concentration. FFA release and metabolism is not a generalized process in the neuronal membrane, but is concentrated in the synaptic regions and is thus related to excitotoxicity.[107]

The FFAs released then have potential detrimental effects during the postischemic period by three mechanisms: (1) arachidonic acid metabolism via the cyclooxygenase pathway contributes to oxygen radical production during reperfusion[81]; (2) FFA and DAG directly increase membrane fluidity, inhibit ATPases, increase neurotransmitter release, and uncouple oxidative phosphorylation; and (3) enzymatic oxidation of arachidonic acid during reperfusion by cyclooxygenase, lipoxygenase, or cytochrome P-450 produces a large number of bioactive lipids, including prostaglandins, thromboxanes, leukotrienes, and hydroxy fatty acids, many of which have detrimental effects (see Figure 62-2).

Endogenous Defenses

In response to the complex sequence of pathobiological events that evolve after brain injury, several endogenous neuroprotectants are produced, induced, or activated after ischemia, and their postulated or proven functions improve cell (specifically neuronal) survival in in vivo and in vitro models.

The heat-shock proteins are one family of candidate neuroprotectants that are highly conserved among biological species and are induced in cells after a variety of stimuli. Thermal stress is the classic example; however, any insult that damages protein structure, including ischemic[108] and TBI,[109] can produce a heat shock protein response. Simon et al.[108] showed that after global ischemia the 72-kDa heat shock protein (Hsp72) is temporally expressed in a pattern that mirrors the pattern of selective vulnerability in the model, seen first in the CA_1 region of the hippocampus, followed by CA_3, cortex, and thalamus, and finally in the dentate granule cells. Hsp72 is also induced in both gray and white matter of piglets after mild and severe hypoxia.[110] The heat shock proteins have generated major interest as potential neuroprotectants because their prior induction by a sublethal stress can afford protection from subsequent injury. Transient whole-body hyperthermia reduces subsequent ischemic brain injury in both adult[111] and neonatal rats.[112] Furthermore, exogenous Hsp72 reduces glutamate toxicity in neuronal cell cultures.[113] Importantly, overexpression of Hsp72 reduces ischemic damage and apoptosis after experimental stroke and global ischemia in vivo.[114-116]

Another potential mechanism for endogenous neuroprotection is the upregulation of genes that inhibit apoptosis and augment neurogenesis. The mammalian gene *bcl-2,* a proto-oncogene, can block apoptosis[97] and perhaps necrosis as well.[117] The *bcl-2* gene is expressed in neurons surviving both focal and global ischemia[118,119] and is reduced in degenerating neurons after cardiopulmonary arrest in rats.[120] Viral transfection of *bcl-2* reduces infarction after focal ischemia,[121] and upregulation of *bcl-2* via ceramide administered 30 minutes after hypoxia-ischemia reduced the number of cells with DNA damage in immature rat brain.[122] Forced overexpression of the *bcl-2* family member *bcl-xL* also reduces tissue damage after focal cerebral ischemia in adult rats.[123] After TBI in infants and children, CSF levels of *bcl-2* are increased in patients who survive compared with those who die.[124] Finally, *bcl-2* overexpression promotes neurogenesis in adult mice with and without ischemic injury.[125]

Adenosine is an endogenous biochemical mediator that may serve a protective role after cerebral ischemia, particularly early after injury. Adenosine is increased in brain tissue after experimental ischemia,[126] and in response to hypoxia,[127] hypotension,[128] and hypoglycemia.[129] The release of adenosine after ischemia could afford neuroprotection by a combination of several mechanisms. When bound to A2-receptors, adenosine is a potent cerebrovasodilator and inhibits platelet activation and neutrophil function.[130] Bound to A1-receptors, adenosine reduces neuronal metabolism and excitatory amino acid release and stabilizes postsynaptic membranes.[130] Thus the beneficial effects of adenosine after cerebral ischemia include improved regional blood flow, reduced local oxygen demand, attenuation of both excitotoxicity and calcium accumulation, and antiinflammatory and rheologic effects. Finally, adenosine agonists have been shown to improve survival of selectively vulnerable neurons after ischemia in many studies (reviewed in Rudolphi et al.[131]).

Clinical Pathophysiology

Cerebral Blood Flow and Metabolism After Resuscitation

The pioneering studies in which global CBF and cerebral metabolic rate for oxygen ($CMRO_2$) were measured in animal models of global ischemia or cardiac arrest focused on the early post-resuscitation period. In their classic study, Snyder et al.[132] showed that after 15 minutes of global brain ischemia in dogs, CBF transiently increased to levels well above baseline (Figure 62-3). Then, after 15 to 30 minutes, CBF progressively decreased to a level below normal for the remainder of the monitoring period (90 minutes). This pattern of early transient postischemic hyperemia and subsequent delayed postischemic hypoperfusion has been observed in many global cerebral ischemia models, including both VF and asphyxial arrest.[133,134] The level of hyperemia and subsequent hypoperfusion vary in relation to the duration of the insult.[135] Although these phases of increased and decreased CBF characterize the net global effect, regional CBF is often inhomogeneous, particularly during postischemic hypoperfusion, when areas of decreased and increased perfusion may coexist.[136]

Recently, the heterogeneous and duration dependent nature of post-arrest CBF was characterized using contemporary

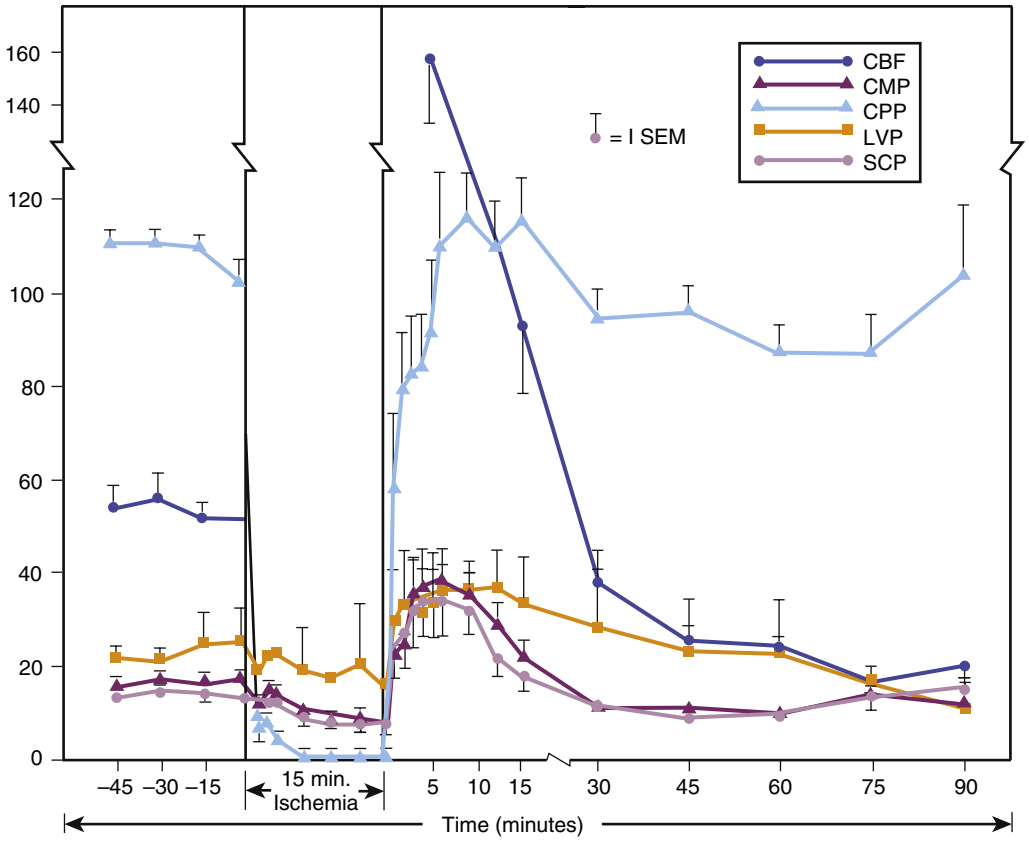

Figure 62–3. Global cerebral blood flow *(CBF),* cisterna magna pressure *(CMP),* cerebral perfusion pressure *(CPP),* lateral ventricular pressure *(LVP),* and supracortical pressure *(SCP)* measured before, during, and for 90 minutes after a 15-minute circulatory arrest in dogs. CBF data demonstrate that early postresuscitation hyperemia occurs, followed by hypoperfusion. *(Modified from Snyder JV, Nemoto EM, Carroll RG, et al: Global ischemia in dogs: intracranial pressures, brain blood flow and metabolism,* Stroke *6:21, 1975.)*

imaging techniques allowing for regional assessment and a clinically relevant model of pediatric asphyxial cardiac arrest.[137] Using arterial spin labeling magnetic resonance imaging, CBF was measured for the first 3 hours after 8.5, 9, or 12 minutes of asphyxial cardiac arrest in postnatal day 17 rats—approximating a 1- to 4-year-old human in terms of brain development (see also Chapter 57). Although the pattern of early global hyperemia followed by hypoperfusion similar to that observed by Snyder et al.[132] was seen after asphyxial arrests lasting 8.5 and 9 minutes, a pattern of global and persistent hypoperfusion was observed after a 12-minute arrest (Figure 62-4). Remarkably, CBF disturbances were also found to be region-dependent after asphyxial arrests lasting 8.5 and 9 minutes, with subcortical hyperemia but cortical hypoperfusion. After a 12-minute asphyxial arrest hypoperfusion was observed in both cortical and subcortical regions, and CBF was pressure passive, perhaps indicating loss of autoregulation after a prolonged arrest.

In patients with good outcomes, global CBF recovers over the subsequent 24 to 72 hours and CO_2 reactivity remains intact. Patients who do not regain consciousness or progress to brain death develop absolute or relative CBF hyperemia with impaired CO_2 reactivity.[138,139] A theoretical scheme of postarrest global CBF and its relation to neurologic outcome is presented in Figure 62-5. Most studies in experimental animal models of asphyxial arrest suggest a similar pattern of CBF and $CMRO_2$ to that observed after VF cardiac arrest and global ischemia in the early post-resuscitation period in humans.[134,138] However, there are some exceptions.[140] Results from clinical studies of pediatric asphyxial arrest are scarce and somewhat conflicting with regard to the prognostic implications of high or low values of postarrest CBF based on a single measurement; however, loss of CO_2 reactivity appears to be associated with poor outcome in all studies. In studies of children between 24 and 48 hours after near-drowning, Ashwal et al.[141] observed low CBF in the seven nonsurvivors and no relationship between CBF and $PaCO_2$ in these patients—again suggesting loss of CBF reactivity to changes in $Paco_2$. In this study, hyperemia was not routinely observed in either survivors in a persistent vegetative state or children who died, but only a single CBF measurement was made in these patients. Beyda[142] obtained serial measurements of postarrest ^{133}Xenon in a series of children who suffered asphyxial arrest from submersion accidents. Children with good neurologic outcomes had slightly decreased CBF values at 12 hours that increased to normal during the subsequent 24 to 60 hours. In these children, CBF reactivity to CO_2 was intact. Children with eventual vegetative outcome or brain death exhibited hyperemia with loss or attenuation of CO_2 reactivity. This hyperemia progressed to low or normal flow over the following 12 to 72 hours in children with vegetative outcome and progressed to low and then no flow with the development of brain death.

Brain metabolism, as assessed by $CMRO_2$, is reduced during the early postischemic period and then progressively recovers to a level that varies, depending on the model used

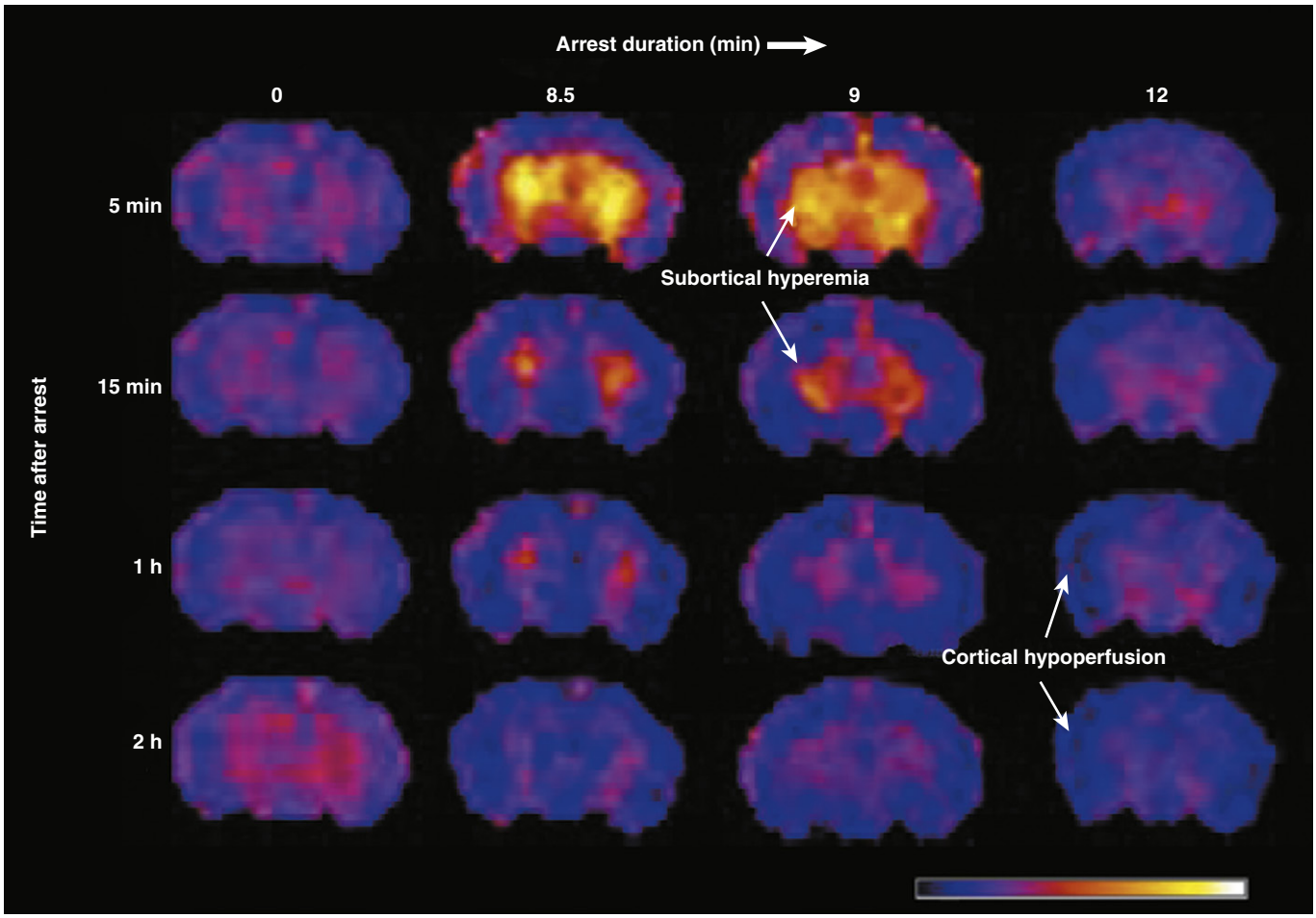

Figure 62–4. Duration and regional dependency of cerebral blood flow (CBF) disturbances acutely after asphyxial cardiac arrest in postnatal day 17 rats. CBF data demonstrate that early postresuscitation hyperemia occurs in subcortical regions after an 8.5- and 9-minute but not a 12-minute asphyxial cardiac arrest, and that duration-dependent hypoperfusion occurs in cortical regions. *(Modified from Manole MD, Foley LM, Hitchens TK, et al. Magnetic resonance imaging assessment of regional cerebral blood flow after asphyxial cardiac arrest in immature rats.* J Cereb Blood Flow Metab *29:197, 2009.)*

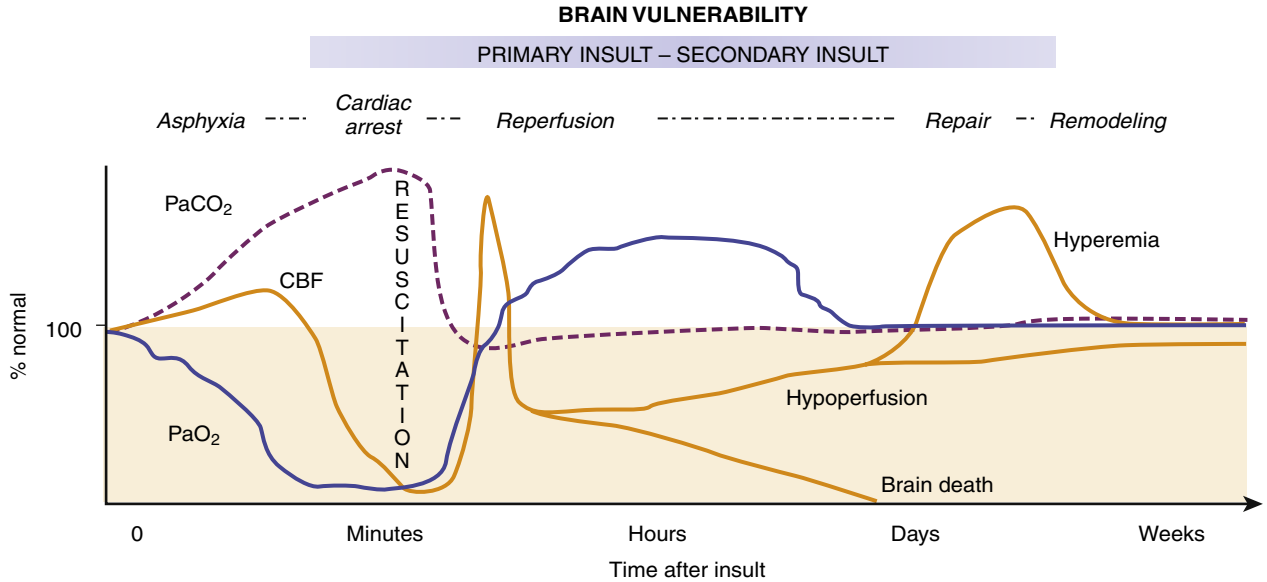

Figure 62–5. Hypothetical diagram illustrating the patterns of *global* cerebral blood flow (CBF) during and after cardiopulmonary arrest of moderate duration in humans. Immediately after resuscitation, "early postischemic hyperemia" occurs for about 15 minutes in subcortical brain regions. This is followed by patchy multifocal "delayed postischemic hypoperfusion" in cortical brain regions lasting from a few hours to days. Progressive return of CBF to normal is seen in patients with intact neurological outcome. In contrast, "delayed postischemic hyperemia" can be observed hours to days postarrest in patients with more severe insults.[139,142] This delayed hyperemia appears to be associated with disabled or vegetative outcome (where CBF gradually decreases to near normal or below normal) or brain death (where CBF decreases to no flow). It is unclear, however, if all patients with vegetative outcome or eventual brain death develop delayed hyperemia.

and on the duration of ischemia.[135,143] In some models, including VF arrest in dogs, significant recovery of $CMRO_2$ may occur during the first few hours, despite persistent postischemic hypoperfusion—creating the potential for a secondary ischemic insult during reperfusion. Whether this increase in $CMRO_2$ represents appropriate synaptic activity, seizures, or basal metabolism is not certain. In other models, global CBF and $CMRO_2$ are matched during the first few hours after ischemia.

It must be recognized that the measurements of metabolism in the studies have traditionally been $CMRO_2$. However, Bergsneider et al[144] used positron emission tomography in patients after TBI and reported the occurrence of delayed hyperglycolysis in some comatose patients, suggesting a shift to anaerobic metabolism in injured brain in some patients. Using microdialysis in a porcine model of cardiac arrest, increased lactate/pyruvate ratios were found during arrest, and again in a delayed fashion especially if kept normothermic versus hypothermic.[145] This same group found increased lactate/pyruvate ratios and glutamate using microdialysis in adult survivors after cardiac arrest, all of whom were treated with hypothermia.[146] Prolonged increases in brain lactate detected using proton magnetic resonance spectroscopy after global hypoxia-ischemia in children have also been reported.[28,147,148] Oxidative stress decreases the function of the pyruvate dehydrogenase complex, a key enzyme in oxidative metabolism, possibly contributing to the shift to anaerobic metabolism.[149] Although routine monitoring of CBF or CMR has not been applied extensively to the post-arrest setting in children, their routine assessment using contemporary methods would likely lead to an improved understanding of pathophysiology.

Drugs such as nimodipine can increase CBF during the early postischemic hypoperfusion phase after global cerebral ischemia. $CMRO_2$ recovery generally is not increased by treatment.[150] Although nimodipine has been shown to be beneficial in patients after subarachnoid hemorrhage,[151] but not ischemic stroke,[152] the testing of strategies targeting early post-arrest hypoperfusion deserves further study. Safar et al.[153] have reported that a multifaceted treatment strategy to increase CBF ("flow promotion") and reduce CMR or $CMRO_2$ early after VF in dogs improved outcome. This was accomplished by use of cardiopulmonary bypass (CPB), mild hypothermia, hemodilution, and transient hypertension.

Histopathology of Hypoxic-Ischemic Encephalopathy

Ischemic neuronal change (Figure 62-6), as first described by Sommer in 1880 and later by Spielmeyer, involves a progression from extensive cellular microvacuolation to a cell that resembles a naked shrunken nucleus.[18] As described by Brierley et al.,[37] "this type of neuronal damage is neither ubiquitous nor randomly distributed but is found in regions which exhibit selective vulnerability to hypoxic stress." As discussed previously, death of selectively vulnerable neurons (e.g., hippocampal CA_1) cannot be explained by vascular distribution. Remarkably, these clinical descriptions of cell shrinkage were consistent with apoptosis rather than necrosis. However, the connection between selective vulnerability and apoptosis was made 100 years later.[45] Neuronal death after cardiopulmonary arrest is seen not only in the selectively vulnerable neurons but also as a subtle histopathological finding in the arterial boundary zones. These neurons (not otherwise selectively vulnerable) are in the most poorly perfused areas during or after resuscitation.[34] Neuronal death in the arterial boundary zones was elegantly described by Nemoto et al. in a monkey model of 16 minutes of complete global brain ischemia followed by 7 days of intensive care.[154] Maximal damage appeared to be in the classically described selectively vulnerable zones, but neuronal death was also observed in the most distal distribution of the posterior cerebral artery and in the watershed zones of the anterior and middle cerebral arteries (Figure 62-7). With sufficient injury in the arterial boundary zone, more severe findings such as microinfarction or laminar necrosis can be seen.[19,154] As previously discussed, even in stroke, neuronal death in an ischemic penumbra can occur either by necrosis or apoptosis. Thus it appears that there may be a continuum between apoptosis and necrosis that may depend on a large number of factors, such as duration of the insult and brain region in question.[60] Whereas apoptosis in a given area often affects only a select percentage of neurons, infarction affects all neurons and glia. Obviously, if the arrest time is long or if the postischemic conditions are sufficiently poor, infarction of the entire brain can occur.

Vaagenes studied neuropathology after primary VF arrest of 10 minutes in dogs.[19] Despite vegetative outcome at

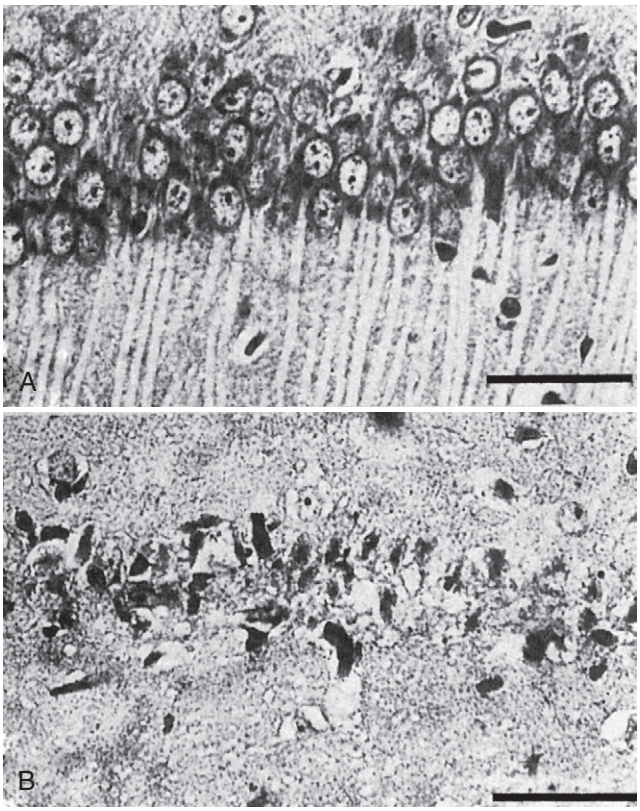

Figure 62–6. Light micrograph of dorsal hippocampus in gerbils 7 days after 5 minutes of sham ischemia (**A**) or global ischemia by carotid occlusion (**B**). Ischemic neuronal change is seen with CA_1 neurons appearing as dark, shrunken nuclei without cytoplasm (**B**) by contrast with the normal-appearing nonischemic neurons (**A**). Investigations by Nitatori et al.[45] indicate that neuronal death in selective areas, after threshold ischemia insults, occurs via apoptosis. *(From Kuroiwa T, Bonnekoh P, Hossmann KA: Therapeutic window of CA1 neuronal damage defined by an ultrashort-acting barbiturate after brain ischemia in gerbils,* Stroke *21:1489, 1990.)*

96 hours, only scattered ischemic neuronal changes in the selectively vulnerable neurons and to a much lesser extent in the vascular watersheds were observed. Microinfarct formation was seen in only 5 of 18 dogs, suggesting that patchy ischemic neuronal change is sufficient for vegetative outcome. They then compared this 10-minute VF arrest with an asphyxial episode (airway occlusion) resulting in cardiac arrest with 7 minutes of no flow. Related either to differences in the initial insult or to postischemic events, asphyxial arrest resulted not only in ischemic neuronal change in the selectively vulnerable regions but also in marked microinfarct formation (30 of 32 dogs) and scattered petechial hemorrhages. This more severe histological injury was seen despite significantly *easier* ROSC in the asphyxial arrest group (Figure 62-8). In addition, unlike VF arrest, asphyxial arrest caused some ischemic neuronal changes even after no flow of only 2 minutes. These findings may explain the poor outcome generally observed in cardiopulmonary arrest in children (usually asphyxial arrest) compared with that in adult series (VF arrest). After asphyxial cardiac arrest that results in long-term survival in both adult and pediatric-aged animals,[155-157] the pattern of neuronal death produced is similar to that reported in human studies[158] including that of the young victim of asphyxial cardiac arrest, Karen Ann Quinlan,[159] in which a predilection for basal ganglia injury resulting in a persistent vegetative state is observed.

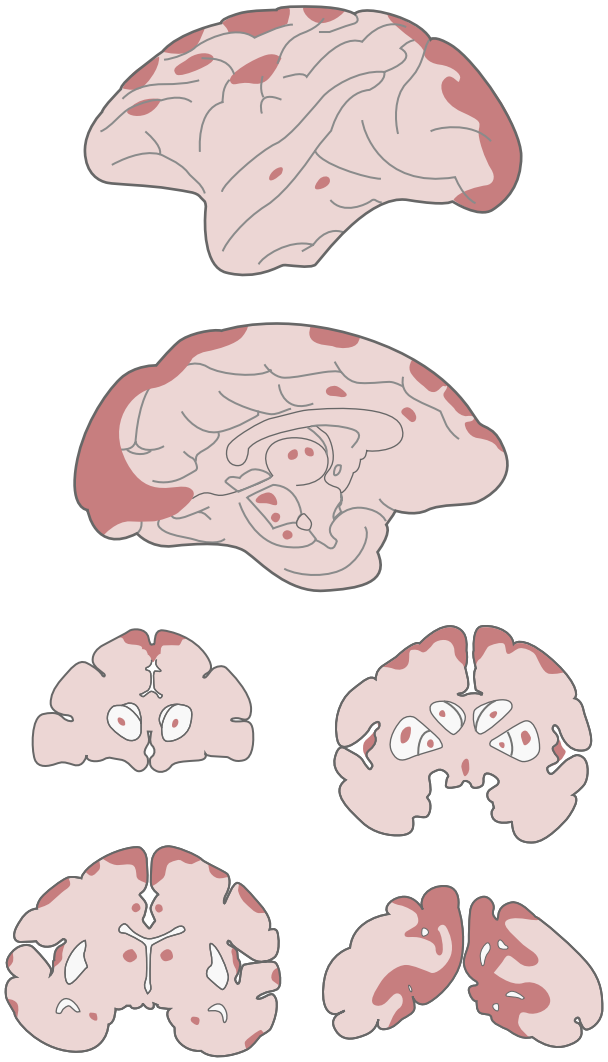

Figure 62–7. Topographic distribution of cortical lesions 7 days after 16 minutes of global brain ischemia in rhesus monkeys. Neuronal death in areas with intrinsic selective vulnerability was most apparent in the distal distribution of the posterior cerebral artery. Damage in the watershed distributions of the anterior and middle cerebral arteries was less consistent. *(Modified from Nemoto EM, Bleyaert AL, Stezoski SW, et al: Global brain ischemia: a reproducible monkey model,* Stroke *8:558, 1977.)*

Clinical Outcome After Pediatric Cardiopulmonary Arrest

Compared with results in adult series, survival and neurologic outcome after cardiopulmonary arrest in infants and children are remarkably poor.[6] Most published data examining out-of-hospital cardiopulmonary arrest in adults reveal about 11% to 12% "good" neurologic outcome at 6 months after arrest, with good outcome generally defined as the ability to function independently.[160] One review summarizing the results from 44 studies totaling 3094 pediatric patients after cardiopulmonary arrest showed favorable outcome at hospital discharge (generally defined as nonvegetative) in only about 6% of patients.[13] In addition, after asphyxial arrest in children, clinical outcomes somewhere between vegetative and good, such as moderate disability or severe disability, are uncommon.[141,161] Survival to hospital discharge after out-of-hospital arrest ranges from 8% to 25% and after in-patient arrest is 24% to 51% in several studies, with an overall survival of 13%.[7,9,10,13,15] However, if the child had a pulse by hospital arrival after out-of-hospital cardiac arrest, survival increases to 38%.[7] The most common cause of death is neurologic injury for out-of-hospital arrests and cardiovascular failure for in-hospital arrests.[7] Good neurologic outcome in pediatric patients surviving cardiac arrest is often overestimated using traditional categorical outcome measures such as the Glasgow Outcome Score and Pediatric Cerebral Performance Category Scale.[162-164] Furthermore,

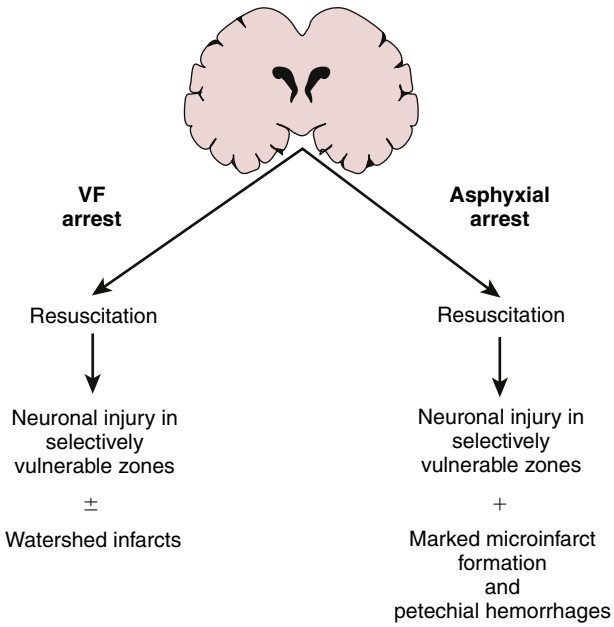

Figure 62–8. Schematic diagram based on the work of Vaagenes et al.[19] comparing the histologic outcome of VF cardiac (adult) and asphyxial (pediatric) arrest. *(From Holbrook P [ed]:* Critical care clinics, vol 4, *Philadelphia, 1988, WB Saunders, p 661.)*

contemporary longer-term outcome studies evaluating overall functional status, neuropsychological function, and quality of life do not exist. One observational study focusing on late improvements in functional outcome noted improved mobility in 22% of children after cardiac arrest versus 66% of children after TBI two years after the initial event.[165]

This high mortality and poor outcome after cardiorespiratory arrest in children generally represents out-of-hospital or unwitnessed full arrests. Recovery is much better in children who had witnessed arrests, cold water submersion, or isolated respiratory arrest, after which intact survival rates as high as 44% to 75% have been reported.[7,12,166-168] Nevertheless, these clinical data seem to bear out the severe neuropathology observed in asphyxia-induced arrest in animal models because asphyxial arrest is the most common mode of arrest in all of the clinical pediatric series.[12,13,162,166-168]

Such factors as initial pH, number of epinephrine doses, and arrest duration have been examined in an attempt to predict outcome from cardiopulmonary arrest. Although sometimes predictive, this information can be misleading. For example, the time delay before analysis of the first blood sample can vary, as can estimates of arrest duration. With asphyxial arrest, even controlled experimental animal studies show that the time from asphyxia until cardiac arrest varies considerably. Currently, the most powerful individual predictor of neurologic outcome after cardiorespiratory arrest is the neurologic examination or one of several scoring systems based on selected aspects of the neurologic examination. In 1985, Levy et al.[169] applied multivariate analysis to variables from the neurologic examination in a series of 210 adults in coma studied for at least 6 hours after a hypoxic-ischemic insult. None of the 15 patients who were in a vegetative state at 1 month regained independent function. In this retrospective study, the combination of scores is from 2 weeks. The oculocephalic response and the 3-day motor response were able to identify all patients who gained independent function. This was true even for the 2 of 57 patients who remained in eyes-closed coma for 3 days and then ultimately regained independent function. Edgren et al.[170] applied the Glasgow Coma Score (GCS) to assess outcome in 262 adult comatose survivors of cardiac arrest. GCS less than 6 at 3 days post-arrest predicted poor outcome (at 6 months) with no false-negative results. In a similar study of 216 adults after out-of-hospital cardiac arrest, Mullie et al.[171] found that a best GCS of less than 4 as early as 2 days post-arrest predicted death or vegetative outcome in all but one patient. The one exception progressed from vegetative state to severe disability. The addition of hypothermia as a post-resuscitative therapeutic option may delay attempts at early prognostication.[172]

Although a few patients survive relatively intact despite poor prognosis they likely represent cases of asphyxia without cardiac arrest, coma of an origin other than asphyxial arrest, unrecognized hypothermia, or an associated overdose of a cerebral protective drug. Two prospective trials examining predictors of outcome have been reported after cardiopulmonary arrest in pediatric patients. Robertson et al. in a series of 27 pediatric patients with hypoxic-ischemic encephalopathy found that a GCS of 3 and nonreactive pupils were predictive of adverse outcome.[162] Consistent with asphyxia as the predominant cause of cardiac arrest in infants and children, Sirbaugh et al. found that the only factor that was positively associated with ROSC was endotracheal intubation.[173] This would not support abandonment of the practice of ventilating infants and children found pulseless and apneic, and rather, suggests that it is crucial in this patient population.[174,175] Indeed a recent, prospective multicenter study done in Japan comparing conventional versus chest-compression only CPR for children after out-of-hospital cardiac arrest strongly supports this view.[176] In children requiring resuscitation from non-cardiac causes, conventional CPR resulted in favorable neurologic outcome in 45 of 624 children compared with "hands-only" CPR where favorable neurologic outcome was seen in only 6 of 380 (7.2 vs. 1.6%; odds ratio, 5.54; confidence interval, 2.52 to 16.99). Importantly, in children requiring resuscitation from cardiac causes, favorable neurologic outcome was not different between conventional CPR and compression only CPR, implying that unlike in adults, conventional CPR does not negatively influence outcome in children suffering arrests of cardiac origin.

The electroencephalogram (EEG) can also provide prognostic information for patients after cardiac arrest. Scollo-Lavizzari and Bassetti[177] retrospectively examined the relation between first post-arrest EEG and clinical outcome in 408 cases. A 5-grade classification was used to categorize EEGs. Although permanent severe neurologic damage was observed in some patients with grade I EEG, none of the 208 patients with grade IV or V EEGs had a good neurologic recovery. A recent single-center retrospective case series in children showed that after a 5-grade EEG score was collapsed into three categories, the score was associated with a positive predictive value of 90% and negative predictive value of 91% in determining poor outcome at hospital discharge.[178] Detailed quantitative EEG may also have a role in the prediction of neurologic outcome after cardiac arrest (see also Chapter 34).[179]

Adjunctive prognostic information also can be derived from brain-derived protein levels in serum or CSF. High serum levels of neuron-specific enolase (NSE) in comatose patients at 24 and 48 hours after cardiopulmonary arrest predict poor neurologic outcome.[180] Martens et al. found that serum concentrations of the astrocyte-derived protein S-100B were superior to serum NSE (as well as CSF S-100B and NSE) in predicting which adult patients would regain consciousness after cardiac arrest.[181] A study used a multimodal approach, combining serum concentrations of NSE, the astrocyte-derived protein S-100B, and somatosensory-evoked potentials (SSEPs), prospectively in 27 adult patients after cardiac arrest and were able to predict all patients that did not regain consciousness.[182] Serum NSE is increased in children after cardiac arrest and peaks at 24 hours.[183] NSE and other biomarkers may be useful in determining responsiveness to therapeutic interventions (e.g., it has been reported that decreasing serum NSE occurs mainly in hypothermic [vs. normothermic] adults after cardiac arrest and is predictive of outcome).[184] Other biomarkers showing promise in case series are procalitonin,[185,186] alpha II-spectrin breakdown products,[187] serum glial fibrillary acidic protein,[188] and brain natriuretic peptide.[189]

Studies have used SSEP monitoring in an attempt to provide early prognostic information about outcome after cardiopulmonary resuscitation. Madl et al. tested median nerve SSEPs in 66 adults after successful resuscitation from cardiac arrest. They reported that the presence or absence and the latency of the cortical N70 peak reliably differentiated between bad and favorable outcome with 100% predictive ability.[190] Testing was performed within 48 hours of resuscitation, which is a

clinically relevant time frame. Auditory evoked response testing has been used in children with cardiac arrest after a submersion accident.[191] Normal evoked responses were observed in all children who recovered neurologically intact. Children who recovered with significant handicaps demonstrated reduction in wave V amplitude over time, and prolonged wave I-V inter-peak latencies. In adults, bilaterally absent N20 waves at 24 and 48 hours have a reported specificity of 100% in predicting permanent coma after cardiac arrest.[192]

The utility of computed tomography (CT) of the head and other neuroimaging modalities after cardiac arrest is unknown (Figure 62-9). Head CT takes only a few minutes and is useful for evaluation of intracranial lesions contributing to the cause of arrest, but requires the critically ill subject to be transported out of the ICU and uses ionizing radiation. In a large retrospective case series of children with near-drowning, children with any abnormal CT findings (e.g., loss of gray-white differentiation, infarction) within the first 24 hours of admission died.[193] Ninety-six percent of children with an initially normal CT on the first day that had a subsequent abnormal CT either died or remained in a coma. Using a novel scoring system assessing primarily the cortex and basal ganglia, a good correlation between early magnetic resonance imaging score and neurologic outcome was reported.[194] Using magnetic resonance spectroscopy, decreases in the brain metabolite *N*-acetylaspartate and increases in lactate in the basal ganglia and cortex are can assist in outcome determination in children after near-drowning and cardiac arrest.[147,195,196]

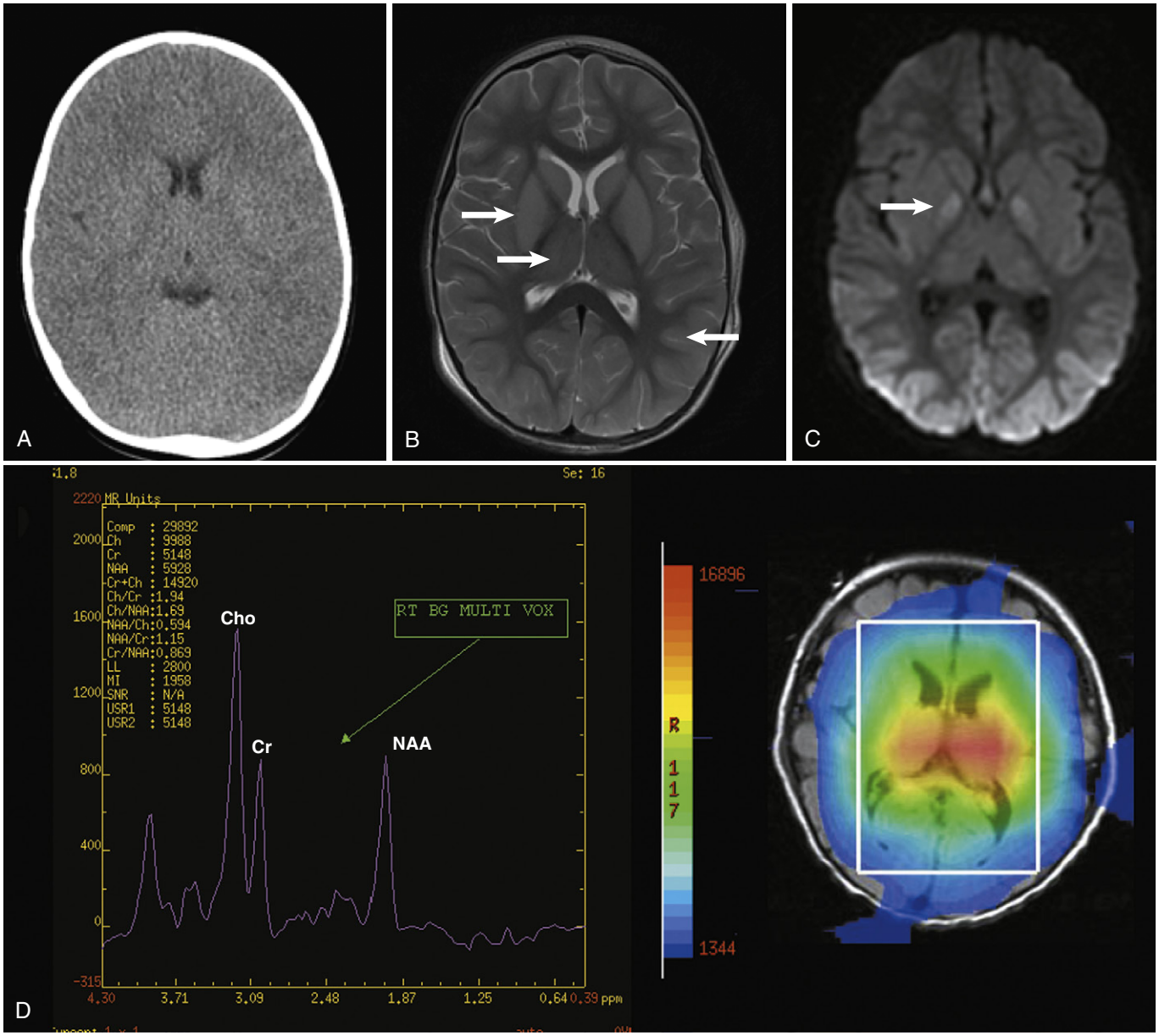

Figure 62–9. Neuroimaging after asphyxial cardiac arrest in children. **A,** Computed tomography scan of the head on day 1 showing decreased gray-white differentiation, consistent with cerebral edema. **B,** T2-weighted magnetic resonance image using a 3-Tesla magnet on day 10 showing enhancement of the basal ganglia, thalamus, and parietal lobes (*arrows*). **C,** Diffusion-weighted imaging shows corresponding edema of the globus pallidus (*arrow*). **D,** Multivoxel magnetic resonance spectroscopy showing the whole brain chemical analysis of N-acetylaspartate (*NAA*), choline (*Cho*) and Creatine (*Cr*). A regional color map for NAA is provided.

Response of the Immature Brain to Cardiopulmonary Arrest

Clinical and laboratory studies suggest that the neurologic outcome of newborn animals after a hypoxic-ischemic insult is favorable compared with that of adults; although this may be related to the ability of newborn animals to tolerate asphyxia systemically. This is most evident when neonatal and adult experimental models are compared. In newborn monkeys even 12 minutes of asphyxia did not result in cardiac arrest,[197] and in Beagle pups, 15 minutes of asphyxia produced hypotension but not cardiac arrest.[198] Asphyxial arrest in mature animal models generally occurs within 6 to 8 minutes.[19,133] Kirsch et al.[199] showed that newborn piglets had better recovery of SSEPs and less postarrest hypoperfusion than young adult pigs in the 2 hours after global cerebral ischemia. Thus not only does the cardiovascular response during asphyxia appear to be more robust in immature animals, but also the intrinsic sensitivity of the brain to a hypoxic-ischemic insult may be less. Studies suggest a selective vulnerability of the neonatal brain stem sensory nuclei to asphyxia.[197,200] This "selective vulnerability" may more correctly represent a relative lack of vulnerability of neonatal cerebral cortex to asphyxia because anoxic perfusion was tolerated for over 12 minutes in immature monkeys, most of which demonstrated no ischemic neuronal change.[197] However, some mechanisms of secondary damage, such as excitotoxicity, appears to be more injurious in the immature.[201,202] Further complexity is added to processes such as excitoxicity when the immature brain is involved, as some degree of excitatory stimulation is essential for neuronal survival and normal development.[203] Finally, greater plasticity in the immature brain may also allow for improved long-term recovery of function, although this may be more important in focal insults.[204,205]

The poor clinical outcome of infants and children presenting in cardiopulmonary arrest is probably related to specific mechanisms operating in the special setting of the asphyxial arrest. As the asphyxial arrest is developing, cardiac standstill is preceded by a variable period of severe hypoxia with increased CBF. During this period, severely hypoxic perfusion, a form of incomplete ischemia is produced, which can markedly increase cerebral lactate production.[206] The initial phase of asphyxia can also be accompanied by extreme stress during struggling, which could increase $CMRO_2$ and may be accompanied by systemic hyperglycemia.[141] The combination of hypoxic perfusion or incomplete hypoxia-ischemia and hyperglycemia can increase cerebral lactate concentration to 30 to 35 μmol/g tissue and decrease tissue pH to levels as low as 6.05.[207-209] These lactate levels are much higher than those observed during even 30 minutes of complete ischemia (11 to 14 μmol/g tissue) and are above the threshold of 20 to 25 μmol/g tissue, at which lactic acid can produce local coagulation necrosis.[210] As suggested by the histopathological outcome studies previously discussed,[19] cardiac arrest or reperfusion may be particularly devastating to the brain in this milieu. Also, because of the relative resistance of the immature myocardium to asphyxia, it is easier to restore cardiovascular function in younger patients after longer durations of cardiac arrest than would be possible in adults. Total insult time (hypoxia plus anoxia plus cardiac arrest) is often very long. In adults with asystole or a pulseless bradycardia rather than VF, outcome is also poor.[211] Thus although pediatric intensivists have the apparent luxury of dealing with a somewhat resistant brain with more plasticity for functional recovery, this advantage is often trivial compared to the devastating pathobiology of the asphyxial arrest.[157,212]

Treatment of Cardiopulmonary Arrest

Adequate understanding of the pathobiology of HIE after cardiopulmonary arrest in children is possible given the development of contemporary models of pediatric asphyxial arrest. These models in juvenile rodents and piglets will hopefully lead to more etiology-specific evaluation of the post-resuscitation syndrome in terms of mechanisms and relevant therapies.[156,157]

Field Interventions

Pediatric cardiac arrests are usually not sudden in onset as in adults and thus a window of opportunity exists during which interventions could potentially prevent cardiac arrest and subsequent poor outcome. As discussed, children sustaining isolated respiratory arrest have a mortality rate as low as 25%, whereas patients with cardiac arrests as a result of hypoxia have a high mortality rate.[6,13] Thus, the sooner the recognition and interventions, the better are the chances for a good outcome. Aside from witnesses with knowledge of CPR or the capacity to follow instructions provided by telephone emergency services, prehospital emergency medical services are capable of providing the earliest medical interventions and hold the greatest promise for improving outcome from prehospital pediatric cardiopulmonary arrest. Emergency medical services have developed sophisticated methods for dispatch and transport, but there are logistical limits to the rapidity with which they can provide basic interventions. Nationwide the average response time is well over 8 minutes, greater than the time required for an infant to progress from apnea to cardiac arrest. As a result, more advanced, traditionally hospital based and investigational interventions must also be administered in the prehospital setting in attempts to optimize outcome. Toward this end, use of medical simulation has greatly improved both the understanding of the mechanics of quality CPR, as well as teaching and training (see also Chapter 34).

High-dose epinephrine therapy has been shown in many animal models to improve resuscitation rates.[213] However, a more recent study in a piglet model of asphyxial cardiac arrest showed no improvement in survival or neurologic outcome when high-dose epinephrine was used for resuscitation versus standard-dose.[214] Vasopressin and terlipressin may also be of value after cardiac arrest in pediatric patients, as vasopressin alone and in combination with epinephrine increases CBF during resuscitation from VF compared with epinephrine alone.[215-217] However, the effects of high-dose epinephrine, vasopressin, or terlipressin on long-term survival and neurologic outcome in pediatric patients have not been firmly established. A small study in children using historical controls demonstrated a beneficial effect on resuscitation and outcome in patients receiving high-dose epinephrine.[218] In contrast, a large multicenter trial with concomitant controls in adults was unable to demonstrate a beneficial effect of high-dose epinephrine.[219] Further, a recent meta-analysis of adult studies favored high-dose epinephrine in terms of ROSC, but a trend toward favoring standard-dose epinephrine in terms of survival to hospital discharge.[220] Recently,

the use of bolus calcium during resuscitation was found to be associated with poor neurologic outcome and mortality.[221] The efficacy of pharmacological therapy during CPR is probably limited by the minimal perfusion provided by standard CPR (see also Chapter 34). Development and implementation of improved perfusion techniques for cardiac arrest victims in the prehospital environment would provide an increased "therapeutic window" and thus a better chance of benefiting from advanced therapeutic techniques.

Controlled experimental or prospective clinical studies of intracranial pressure (ICP) monitoring or treatment after asphyxial arrest have not been performed. It could be predicted that ICP elevation would be more common after asphyxial arrest than after isolated global brain ischemia or VF arrest, given the severe histopathology seen after asphyxial arrest and the long insult times from which the myocardium can recover in children. Sustained elevation of ICP (>20 mm Hg) has been shown uniformly to predict poor outcome in four series of pediatric submersion accidents.[222-225] Unfortunately, as in VF arrest, the threshold for poor outcome from asphyxial arrest appears to be below the threshold for the occurrence of intracranial hypertension because some patients experience poor outcome despite normal ICP.[225] Although anecdotal cases of asphyxial arrest in patients with intact neurologic outcome despite elevated ICP are occasionally discussed, in the series cited previously the ability to control ICP elevation did not result in meaningful survival.[223,225] Routine ICP monitoring and ICP-directed treatment are not currently recommended after asphyxial arrest[161,223,225]; however, studies using ICP-directed therapy in the era of contemporary neurointensive care have yet to be performed.

The blanket use of hyperventilation for cerebral resuscitation after cardiac arrest is currently out of favor. Only one laboratory study of cardiopulmonary arrest has demonstrated a beneficial effect of hyperventilation. Vanicky et al.[226] reported that 8 hours of hyperventilation reduced neuronal damage after cardiac arrest in dogs. However, histology was examined at 3 hours after arrest, and no long-term outcome was studied. The blind application of hyperventilation early after severe TBI in adults worsened outcome.[227] The failure of ICP-directed therapy to improve outcome after cardiopulmonary arrest and the commonly observed period of hypoperfusion in the first hours to days after arrest seriously question the application of an intervention with the potential to further reduce CBF.[228,229] Although irreversible ischemic brain damage has never been demonstrated with hyperventilation,[230] these data suggest that it is probably not wise to intentionally or unintentionally hyperventilate patients routinely after arrest, particularly during the period of postischemic hypoperfusion.[132,142,154] Clinical studies suggest that postischemic hyperemia is accompanied by loss or severe attenuation of CBF response to alterations in $Paco_2$ resulting from severe ischemic insult.[139,142] However, some post-resuscitation patients with delayed hyperemia but intact CBF response to $PaCo_2$ have been observed (Figure 62-10).

The traditional approach to cerebral resuscitation has also recommended the use of hyperosmotic agents in the post-arrest period,[231] although similar to hyperventilation, the blanket use of hyperosmotic agents after cardiac arrest is currently not in favor. Again, studies in the setting of cardiopulmonary arrest are lacking. In dogs subjected to 6 minutes of global ischemia, mannitol (2 g/kg) further reduced CBF during the postischemic hypoperfusion phase.[232] This unwanted effect of mannitol likely represents a result of dehydration because with more conventional doses, decreased blood viscosity after mannitol administration lowers cerebral blood volume but maintains

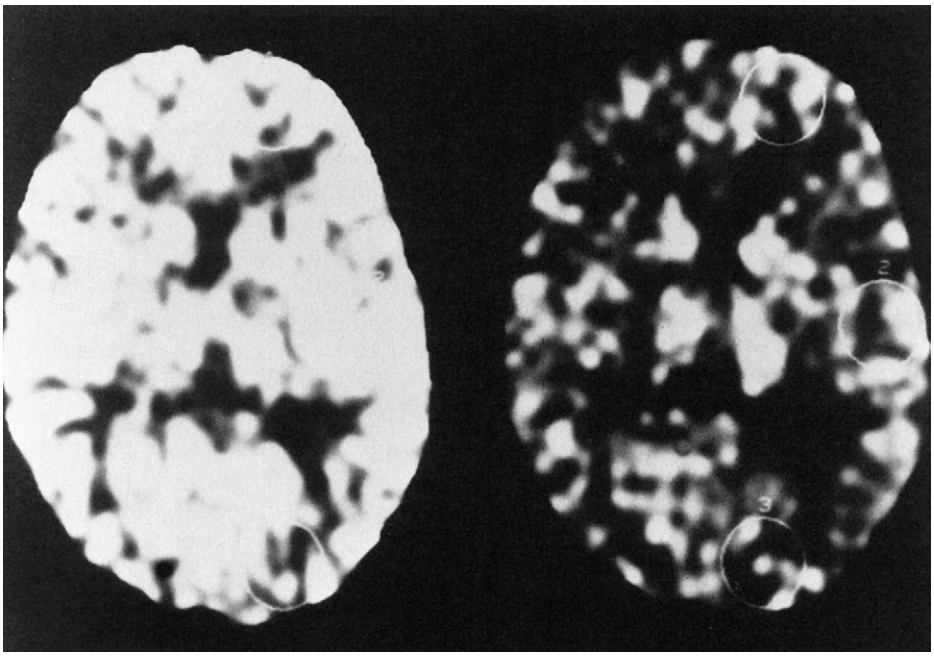

Figure 62–10. Stable-xenon computed tomography (CT) cerebral blood flow study in a comatose 6-year-old 3 days after cold-water submersion accident with asphyxial cardiorespiratory arrest. Delayed CBF hyperemia is represented as high-density white areas through the CT brain section shown on the left ($PaCO_2$ ~40 mm Hg). Flows (calculated from this scan) are in excess of 100 mL/100 g/min throughout the brain. Normal values are ~60 to 70 mL/100 g/min. Despite diffuse hyperemia, CBF reactivity to changes in $Paco_2$ remain intact. CBF values ranged from 50 to 60 mL/100 g/min *(right)* in areas sampled when $Paco_2$ was reduced to 29 mm Hg with hyperventilation. Six months after the arrest, the child was moderately disabled but not in a vegetative state.

CBF.[233] A few anecdotal reports in support of the use of albumin as an osmotic agent after cardiac arrest exist,[234,235] supported by several more recent experimental studies in models of global ischemia.[236] Administration of hypertonic saline improves myocardial blood flow and survival versus standard resuscitation after VF in pigs.[237] These studies suggest that clinical trials examining the effect of hypertonic solutions on outcome after cardiopulmonary arrest are warranted.

In clinical practice, patients are encountered who have been successfully resuscitated from an arrest of unknown etiology, have a clinical history suggestive of trauma, or demonstrate focal pupillary findings. In this setting it is appropriate to hyperventilate and/or to administer mannitol until CT and clinical examination confirm the absence of trauma or a mass lesion.

Supportive Care in the Intensive Care Unit

A hypothetical algorithm for the management of infants and children after cardiopulmonary arrest is provided in Figure 62-11. In addition to maintenance of normal ventilation, arterial oxygenation, and blood pressure, several other aspects of supportive care are important to discuss because suboptimal treatment might adversely affect outcome.

Although transient hyperglycemia commonly occurs after resuscitation from cardiac arrest,[238] the optimal therapy or need for controlling blood glucose after resuscitation has not been established. Current recommendations are for the use of glucose containing solutions during newborn resuscitations[239] because of evidence that hypoglycemia has synergistic deleterious effects coupled with perinatal asphyxia.[240] Glucose containing solutions are generally avoided in the resuscitation of the older child, given the association between hyperglycemia and poorer outcome after near-drowning and TBI in pediatric patients.[141,241] Although a cause and effect relationship between hyperglycemia and outcome in humans has not been established, it is curious to note that in one of the clinical trials showing beneficial effects of hypothermia in adults after cardiac arrest, hyperglycemia was associated with hypothermic treatment.[5] However, reports of tight glucose control versus standard care in adults with VF arrest showed no difference in outcome.[242] The optimal resuscitation fluid has not been established, particularly in pediatric patients beyond the

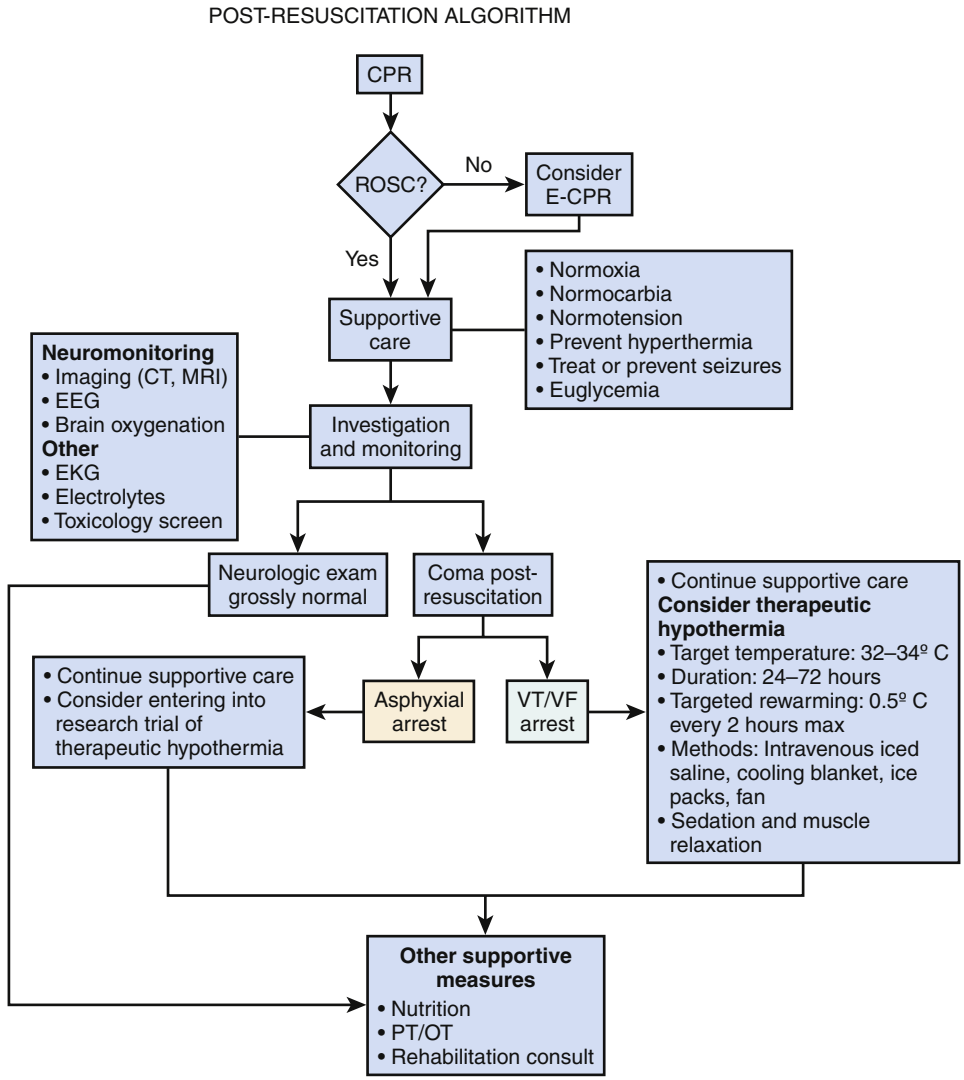

Figure 62–11. A hypothetical algorithm for the management of infants, children, and adolescents after cardiopulmonary arrest.

neonatal period and before adolescence, but is likely to be age- and perhaps mechanism-dependent.

Although the optimal cerebral perfusion pattern for neuronal recovery remains to be defined,[231] blood pressure fluctuations, both high and low, adversely affect outcome. In their classic study of the neuropathology of systemic circulatory arrest in immature monkeys, Miller and Myers[197] found that systolic blood pressures at or below 50 mm Hg during the reperfusion period had devastating effects on survival and neuropathology. This occurred even when the ischemic time was less than the 12-minute minimum that caused brain injury in their model. In contrast, Bleyaert et al.[243] showed that intermittent episodes of hypertension (mean atrial pressure 150 to 190 mm Hg) induced with norepinephrine during the first 24 hours after 16 minutes of global brain ischemia in monkeys worsened neurologic outcome. A beneficial effect of transient hypertension during the immediate postresuscitation period has been suggested,[8] hypothesizing that this improves flow in areas with microvascular sludging. Safar et al.[153] suggested that transient hypertension was beneficial after cardiac arrest in dogs. However, it was applied as part of a multifaceted treatment protocol and its specific benefit remains controversial.

While seizures may be seen in 30% to 50% of children after cardiac arrest, the use of prophylactic antiepileptics is also controversial. A recent prospective study showed that 9 of 19 children who received therapeutic hypothermia and continuous EEG monitoring had seizures, many occurring near or during the rewarming period.[244] A small case series in children surviving cardiac arrest observed how a seven-channel EEG test evolved from the first few hours to days after resuscitation.[245] EEGs were grouped into normal, impaired, grossly impaired, and "death of the brain," and the authors posited that the first EEG may not be valid for outcome prediction. The independent association between poor outcome and the presence and severity of seizures after birth asphyxia is better established.[246] There is strong rationale for treating clinical seizures postarrest; however, whether or not to aggressively treat subclinical seizures and/or use antiepileptics prophylactically remains to be determined.

Current and Novel Therapies

Postresuscitative Hypothermia

The effectiveness of hypothermia as a cerebral protective intervention (i.e., prearrest) is unquestioned. The beneficial effects of hypothermia applied immediately before and during cardiopulmonary arrest are also clearly demonstrated by the clinical experience with cold-water submersion (near-drowning) accident victims.[161] By contrast, complications from the use of moderate hypothermia (30° to 34° C) postarrest and the apparent lack of a beneficial effect led to the abandonment of its routine application in the 1980s.[247] In the last decade, however, two independent randomized clinical trials in adults remaining comatose after resuscitation from ventricular-arrhythmia induced cardiac arrest showed a beneficial effect of mild (30° to 34° C) whole-body hypothermia.[4,5] These studies prompted the International Liaison Committee on Resuscitation to recommend 12 to 24 hours of mild hypothermia (34° C) for adult victims of VF or VT cardiac arrest.[248]

Although hypothermia after cardiac arrest has relatively recently been recommended, therapeutic hypothermia has been used to treat acute brain injury for over a century.[249] Classically, the beneficial effect of hypothermia was thought to be primarily related to a reduction in oxidative metabolism. Rosomoff and Holaday demonstrated that with each decrement of 1° C, brain oxidative metabolism slows by 6.7%,[250] a finding also seen in immature rats.[251] Moderate hypothermia (31° C) during neonatal hypoxia-ischemia maintains brain glucose and ATP concentration and reduces lactate production compared with normothermia (37° C) or mild hypothermic (34° C).[251] Taken together with the well-documented effects of hypothermia on neurologic outcome in experimental models, at least a partial contribution of the effect of hypothermia on cellular energetics in affording neuroprotection after cardiac arrest is supported. However, given that mild hypothermia, which does not significantly lower oxygen consumption, provides some degree of neuroprotection, it seems more likely that hypothermia affects multiple mechanisms that influence outcome after cardiac arrest. These mechanisms include, but are not limited to, excitotoxicity, calcium fluxes, oxidative stress, and inflammation.[252]

Although the composition of mechanisms by which hypothermia confers neuroprotection after cardiopulmonary arrest is still under debate, numerous experimental studies support further preclinical and clinical studies designed to optimize its application in humans. For instance, both applied mild hypothermia, reducing temperature by as little as 2° C,[253] and delayed spontaneous hypothermia[254] reduce neuronal death seen after cerebral ischemia in rats. Leonov et al.[255] reported improved neurologic recovery in dogs subjected to ice-water immersion of the cranium beginning 3 minutes after the onset of 12.5 minutes VF arrest, using CPB to maintain core temperature at 34° C for 1 hour. In this same canine VF arrest model, mild (34° C) or moderate (30° C) hypothermia was found to be protective whereas deep (15° C) hypothermia worsened cerebral and cardiac outcome.[256] Relevant to pediatric cardiopulmonary arrest, posttreatment with brief (1 hour) and prolonged (24 hour) hypothermia improved neurologic outcome in a juvenile rat model and piglet model of asphyxial cardiac arrest, respectively.[156,257]

Raising the question as to the need for further clinical trials in pediatric cardiopulmonary arrest in the era of contemporary intensive care, are the two multicenter, randomized trials demonstrating beneficial effects of hypothermia after cardiac arrest in adult patients.[4,5] In the European study by the Hypothermia After Cardiac Arrest Study Group, 137 of 275 patients were assigned to the hypothermic group. Mild hypothermia (32° to 34° C) was instituted with a median interval to target temperature of 105 minutes after ROSC. Patients were maintained at target temperature for 24 hours. Passive rewarming to a temperature above 36° C occurred over a median of 8 hours. Mortality rate at 6 months after arrest was 41% in the hypothermic group compared with 55% in the control group. The hypothermic group also had more patients with better neurologic outcome assessed by the cerebral performance category (55% vs. 39% in the control group). In the Australian study by Bernard et al.,[5] cooling was initiated in 77 patients in the field after ROSC. Mild hypothermia (33° C) was maintained for 12 hours, followed by active rewarming over 6 hours. Improved survival to discharge was observed in patients in the hypothermic group compared with patients in the normothermic group (49% vs. 26%). Although somewhat different from a pathophysiologic standpoint, studies in neonates at risk for HIE from birth asphyxia have similarly shown that local head or whole-body mild hypothermia applied for 72 hours improves survival and neurologic outcome.[2,3,258]

The main question is whether or not hypothermia will benefit infants (outside the neonatal period) and children with asphyxial cardiac arrest? Lesser questions and a few caveats remain. For instance, the timing, duration and degree of hypothermia warrant further optimization, as well as which patients stand to benefit from treatment. Extrapolating from experimental studies, hypothermia should be initiated as soon as possible after resuscitation. However, even when delayed for a few hours, mild hypothermia has been shown to be beneficial in animal models of cardiac arrest.[254] Consequently, prehospital induction of hypothermia is being implemented in a few centers for emergency services, but barriers exist for its implementation in this setting.[259] Consideration should be paid to proper monitoring of transport patients undergoing hypothermia to prevent overcooling and other known side effects of cooling such as fluid and electrolyte depletion.[260] Current guidelines recommend a duration of 12 to 24 hours of moderate (32° C to 34° C) hypothermia for adult victims of cardiac arrest instituted as quickly as possible.[248] While this duration and degree of hypothermia does not appear to have any untoward effects, more profound depth and duration of hypothermia (28° to 32° C) increase the risk for complications such as arrhythmias, coagulopathy, and infection.[261] Intra-arrest cooling is more neuroprotective than postresuscitative hypothermia in experimental models and may also improve rates of ROSC.[262,263]

Other important issues include the method and rate of cooling. In both the European and Australian studies, mild hypothermia was achieved by surface cooling over a period of hours. Other modalities that achieve target temperatures more rapidly deserve further investigation, such as peritoneal lavage, venovenous or arteriovenous bypass, or novel internal cooling devices.[264,265] There are important differences in cooling rate and precision of temperature maintenance found in cooling devices and also in different patient populations.[266-268] Studies in adults and children demonstrate that caregivers must be cognizant of overcooling below target temperature.[269,270] Bernard et al.[271] reported that administering a bolus of 30 mL/kg of ice-cold (4° C) lactated Ringers solution intravenously safely and effectively decreased core temperature from 35.5° C to 33.8° C in 22 adult patients after cardiac arrest. In a group of healthy volunteers, mild hypothermia (34.9° to 35.5° C) was attained after 40 mL/kg of ice-cold (4° C) normal saline was infused through an antecubital vein.[272] This method of core cooling might be the fastest, most practical way of inducing hypothermia in the field immediately after ROSC. Rapid rewarming and hyperthermia[273,274] should be avoided, and based on available data, active rewarming of patients after cardiac arrest that present with mild-moderate spontaneous hypothermia (33° C-35° C), should be discouraged.

Finally, the efficacy of hypothermia for neuroprotection in neonates with birth asphyxia and in adults with VF arrest prompted some clinicians to treat pediatric victims of asphyxial or arrhythmia-induced cardiac arrest with hypothermia.[275] Two retrospective studies found that clinicians were applying hypothermia to patients with historically poor outcomes—out-of-hospital and unwitnessed arrests that required multiple doses of epinephrine for ROSC.[270,276] Whether or not hypothermia is beneficial, detrimental or has no impact in pediatric cardiac arrest remains to be determined. Currently, a multicenter, randomized prospective trial is underway in the United States (Therapeutic Hypothermia after Pediatric Cardiac Arrest; THAPCA).

Inhibition of Postischemic Excitotoxicity

The observation in animal models that hypermetabolism accompanies postischemic hypoperfusion formed the basis for early clinical cerebroprotective strategies in the postarrest setting. Therapies directed at attenuating active cerebral metabolism ($CMRO_2$ resulting from synaptic transmission) were applied in the hope of reducing this secondary insult of hypoperfusion plus hypermetabolism. The cerebral protective effects of interventions that decrease cerebral metabolic rate *before* the onset of ischemia, such as barbiturates and hypothermia, are well established and clinically important.[277,278] The selective inhibitory effect of barbiturates on active $CMRO_2$ was particularly attractive. However, therapeutic reductions in brain metabolism when applied *after* the insult, as in the "HYPER" therapy of the 1970 and 1980s, did not improve outcome.[247,279] This may have been the result of the relative lack of post-arrest hypermetabolism in human beings.[138] In addition, adverse hemodynamic consequences of barbiturates and the ill effects of sustained hypothermia on immune function and blood rheology may have counteracted any beneficial effects.

Death of selectively vulnerable neurons is mediated by local release of excitatory neurotransmitters with hypermetabolism and calcium accumulation. This has led to attempts to attenuate postischemic excitotoxicity more selectively by administering specific receptor antagonists. The failure of barbiturates to block NMDA-mediated excitotoxicity in vitro emphasized the need to test more specific agents. Many animal models of focal and global brain ischemia have been used to test the efficacy of both competitive and noncompetitive NMDA receptor antagonists. Most studies have demonstrated beneficial effects on histological severity of ischemic damage (especially in the hippocampus) and several have shown benefits in survival.[280] After asphyxial arrest in piglets, alterations in NMDA receptor potentiation within the striatum may participate in striatal neuron degeneration.[281] An important consideration is the finding that beneficial effects of NMDA antagonists in the earlier rodent models of ischemia may have been related to mild systemic hypothermia induced by a central effect of these agents.[282] Blockade of non-NMDA receptors (i.e., AMPA and kainate receptors) with selective receptor-antagonists have shown the most consistent prevention of delayed neuronal cell loss in the hippocampal CA_1 region in models of global cerebral ischemia. However, a report by Brambrink et al.[283] suggests that treatment with the AMPA antagonist NBQX in piglets worsened outcome after asphyxia. The exact role of excitatory neurotransmitter receptor and sodium channel blockade in both the selectively vulnerable zones and other areas of the brain remain to be more clearly defined,[284] particularly in established models of cardiac arrest. Clinical trials using anti-excitotoxic strategies to treat adult stroke patients have been terminated for both futility and the possibility of adverse side effects.[285]

Voltage-Operated Calcium Channel Antagonists

Calcium accumulation in neurons and release of stored intracellular calcium are pivotal events leading to irreversible cellular damage during the reperfusion phase after an ischemic insult. Calcium accumulation occurs via receptor-operated channels such as the NMDA receptor-activated channels,

voltage-operated calcium channels, nonspecific membrane channels, and release of intracellular calcium via the inositol second-messenger pathway. Conflicting results have been obtained regarding the ability of the voltage-operated calcium channel antagonists (lidoflazine, nimodipine, nicardipine) to attenuate calcium accumulation in neurons after ischemia.[286] The contribution of the voltage-gated channels to postischemic calcium accumulation is apparently less than that of the agonist-operated channels in selectively vulnerable zones.

After encouraging animal investigations, Abramson and colleagues conducted a multicenter study of the effect of lidoflazine treatment in a blinded, randomized protocol in 505 adult patients after cardiopulmonary arrest. Lidoflazine did not significantly improve neurologic outcome, which was normal in about 12% of patients.[219] Nimodipine increased CBF in humans at 3 hours after cardiac arrest in a blinded, randomized study.[287] However, a subsequent multicenter, placebo-controlled, randomized, double-blind trial of nimodipine after out-of-hospital cardiac arrest in adults failed to demonstrate a beneficial effect on cognitive function in the survivors.[288] Adults suffering a stroke also did not benefit from nimodipine.[152] Although clinical studies of nimodipine in asphyxial arrest have not been done, Ment et al.[198] observed hypotension and decreased CBF with nimodipine in a perinatal asphyxia model.

A limitation of these studies is that they target only one of several redundant pathways contributing to cell death. Thus some investigators argue for trials targeting multiple mechanisms or final common pathways.

Inhibitors of Oxygen Radical Mediated Injury

As previously noted free radicals can damage membrane lipids, cellular proteins/enzymes and DNA. The importance of damage to each brain component and subsequent contribution to triggering or mediating the final pathway of neuronal death remains to be defined. Studies with superoxide dismutase (SOD) to reduce injury from ischemia have met with mixed results.[289,290] Manipulation of glutathione metabolism has also shown some promise.[291,292] Interestingly, females may have more intrinsic antioxidant activity and benefit less from exogenous treatment.[101,293]

Antioxidant enzymes and water-soluble free radicals scavengers do not easily penetrate the blood-brain barrier.[294] As a result, multiple strategies have been devised to modify these agents to improve availability and efficacy in the brain. Conjugation of polyethylene glycol (PEG) to both SOD and catalase improves drug half-life and reduces cerebral damage caused by ischemia.[295] Liposome-encapsulated SOD has also been shown to be beneficial.[296] Analogs of glutathione, YM737 and γ-glutamylcysteine ethyl ester, have been developed to allow for better penetration of the blood-brain barrier and have been shown to reduces brain injury caused by cerebral ischemia, oxidative stress, and trauma, respectively.[297-299] Ascorbic acid has been combined with α-tocopherol to form the compound EPC-K1. EPC-K1 has both protective and resuscitative effects on the brains of gerbils sustaining cerebral ischemia and reperfusion.[277]

Lipid-soluble agents rapidly cross the blood-brain barrier, a beneficial property for cerebral resuscitation. Administration of α-tocopherol after cerebral ischemia reduces ischemic neuronal damage in gerbils.[300] Lipid-soluble compounds termed "Lazaroids" have been developed to reduce iron-dependent lipid peroxidation after cerebral ischemia. The 21-aminosteroid Trilizad (U74006) has been most extensively investigated and is efficacious in reducing brain damage when given before both focal and global cerebral ischemia.[301] Edaravone is a powerful blood brain barrier-permeable free radical scavenger that that reduces lipid and DNA peroxidation after experimental neonatal hypoxic-ischemic injury.[302-304]

Hydroxyl starch-conjugated deferoxamine that penetrates the blood-brain barrier and chelates transitional metals can reduce free radical production and brain injury.[305] An additional mechanisms of action for deferoxamine is activation of hypoxia-inducible factor-1α, a transcription factor activated by hypoxia that upregulates gene expression including erythropoietin.[306,307] α-phenyl-*N*-tert-butyl-nitrone (PBN), a spin trap commonly used for quantitating free radical production may have therapeutic use during ischemia and reperfusion.[308] However, PBN has been shown to paradoxically increase DNA fragmentation in neurons after TBI.[309] The antioxidant Tempol, provides benefit above and beyond deep hypothermia in a dog model of hemorrhagic shock induced cardiac arrest that produces cerebral ischemia.[310] The antioxidant allopurinol has shown promise in newborns with birth asphyxia,[311,312] and thus may warrant testing in pediatric cardiac arrest.

Although hyperbaric oxygen has been shown to reduce histologic damage after transient forebrain ischemia in rodents,[313] two recent clinical studies have shown that resuscitation outcomes are similar between neonates resuscitated with 100% oxygen versus room air[314,315]; however, in one of these studies, the incidence of cerebral palsy was nonsignificantly higher in the group treated with room air compared with the 100% oxygen group (12% vs. 9%, respectively) as well as the incidence of neurologic abnormalities reported (15% vs. 10%, respectively).[315] Increased oxygen concentration administered during resuscitation also appears to increase the degree of oxidative stress[316-318] Therefore the optimal Fio_2 for resuscitating victims of cardiac arrest needs to be further examined.

Multifaceted antioxidant therapeutic strategies have also been used in experimental asphyxial arrest. Cerchiari et al.[133] produced an asphyxial arrest in mature dogs with a 5- to 8-minute period of airway obstruction followed by 7 minutes of cardiac standstill. Dogs treated with deferoxamine and SOD showed improved recovery of SSEPs, but functional neurologic outcome was not evaluated. Rosenberg et al.[319] showed improved CBF and $CMRO_2$ at 2 hours after prolonged hypoxia (without arrest) in newborn lambs pretreated with PEG-SOD and PEG-catalase. The Thiringer group[320] produced asphyxia in fetal lambs by umbilical cord clamping and studied two insults: severe asphyxia (until asystole) or moderate asphyxia (10 minutes). Treatment with the radical-scavenging compounds methionine and mannitol and the calcium antagonist lidoflazine increased survival and improved postischemic CBF. A pilot randomized clinical trial comparing ascorbic acid plus ibuprofen therapy in neonates with birth asphyxia failed to show neurologic benefit.[321] Long-term follow-up studies with antioxidant therapies in asphyxial arrest models and clinical studies are lacking.

Interventions targeting pathways indirectly related to free radical generation may be beneficial for reducing oxidative stress in the brain. Hypothermia reduces lipid peroxidation and maintains endogenous antioxidant activity during reperfusion from global brain ischemia[322] and is a promising

therapy for improving neurologic outcome after cardiac arrest. Acidosis during ischemia increases free radial production[22] and may inactivate endogenous antioxidants[323]; however, the role of buffer therapy is controversial.

Phospholipid-Derived Mediator Manipulation and Antiinflammatory Therapies

Although many avenues exist for manipulation of phospholipid-derived mediator formation after global cerebral ischemia or cardiorespiratory arrest, most studies have focused on the arachidonic acid cascade. Prostaglandins potentiate the effects of excitatory amino acids, and inhibition of this effect may explain the protection afforded by these agents. Similarly, inhibition of superoxide anion synthesis during the metabolism of arachidonic acid also may be an important mechanism for this effect. Alternatively, cyclooxygenase metabolites of arachidonic acid are important regulators of normal CBF, especially in the immature brain,[324] and cyclooxygenase inhibitors increase CBF after global ischemia.[325] Pretreatment with cyclooxygenase inhibitors (indomethacin, piroxicam, diclofenac, or flurbiprofen) before 5 minutes of global brain ischemia in gerbils attenuated selectively vulnerable cell death.[326] In contrast, inhibition of the lipoxygenase pathway did not prevent selectively vulnerable cell death.[327] However, cyclooxygenase inhibitors (indomethacin or diclofenac) are not protective when given before 10 minutes of global ischemia,[328] and indomethacin administration *after* ischemia does not increase CBF,[329] and the effect of resuscitation with cyclooxygenase inhibitors on CBF after cardiorespiratory arrest has not been studied. A limit to the clinical effectiveness of cyclooxygenase inhibitors may be that a burst of cyclooxygenase product formation occurs within seconds of reperfusion.[330] Nevertheless, Kuhn et al.[331] showed improved 24-hour neurologic outcome in dogs treated with ibuprofen after a 6-minute VF arrest. The 46% mortality rate in vehicle-treated dogs after 6 minutes of VF was excessively high, however, and affected outcome scoring. Jastremski et al.[332] retrospectively assessed the impact of steroid use in the 262 patients who did not receive thiopental in the Brain Resuscitation Clinical Trial I. Four groups (no, low-, medium-, or high-dose steroid) were compared. No effect on mortality or neurologic outcome was seen.

Identification of and agents targeting specific cyclooxygenase isoforms has led to a resurgence of investigation in this area. The inducible form of cyclooxygenase is formed after tissue injury (cyclooxygenase II, COX-2).[333] Thus COX-2 may be a more appropriate therapeutic target, if prostanoids or arachidonic acid metabolites play an important role in ischemic brain injury. Currently, their use as a neuro-resuscitative therapy after cardiopulmonary arrest is unsupported.[328,334] However, recent data suggesting that COX-2 is upregulated after asphyxia in neonates[335] support further testing of more specific and safe agents as they are developed.

Futuristic Approaches

Anti–Cell Death Strategies

Apoptosis occurs over days to weeks after injury and thus may represent an especially important therapeutic target in the developing brain.[46,55,63] Pharmacologic caspase inhibitors have been shown to reduce apoptosis in a sex-dependent manner in a model of neonatal hypoxia-ischemia.[48,336] In a model of VF-induced cardiac arrest in adult rats, intracerebroventricular treatment with a relatively selective caspase-3 inhibitor improved neurologic outcome and reduced apoptosis and histological damage compared with vehicle treatment.[337] Taken together, these studies support testing of antiapoptotic strategies in models of pediatric cardiac arrest.

Minocycline is a blood-brain barrier permeable derivative of the antibiotic tetracycline that has anti-inflammatory properties including inhibition of microglia activation and cytokine production, that also inhibits poly(ADP-ribose) polymerase-1 mediated cell death.[338] Minocycline was effective in reducing microglial activation and CA_1 hippocampal neurodegeneration after asphyxial cardiac arrest in juvenile rats.[339] Of note, preliminary clinical studies suggest that minocycline treatment may benefit adults with acute ischemic stroke.[340]

Statins are 3-hydroxy-3methylglutaryl-coenzyme A reductase inhibitors that act on the endothelium to promote NO release, and have potent antiinflammatory and antioxidant properties. Atorvastatin may protect humans from stroke after transient ischemic attacks.[341] Because Atorvastatin and other statins are currently in clinical trials, timely preclinical testing in models of pediatric cardiac arrest appears warranted.

Erythropoietin (EPO) is a glycoprotein hormone that is upregulated after hypoxia-ischemia. In addition to stimulating erythrocyte production, EPO has neuroprotective effects including preservation of endothelium, inhibition of apoptosis, and prevention of cellular swelling mediated by aquaporin 4.[342-344] Clinically, the efficacy of EPO after adult stroke is mixed and complicated by potential adverse effects of EPO such as hypertension and thrombosis, but neonates with birth asphyxia appear to benefit.[345-347] Similar to the other strategies discussed above, urgent preclinical studies in clinically relevant models and timely clinical trials appear warranted.

Neuronal Regeneration and Replacement

Several trophic factors are synthesized by neurons and other parenchymal cells and are critical to cellular maintenance and regeneration. Nerve growth factor,[348] brain-derived neurotrophic factor,[349] and neurotrophin-3[350] have all been shown to be neuroprotective in models of neonatal hypoxia ischemia. Many others, including vascular endothelial growth factor, have been found to be upregulated after cerebral ischemia.[351] D'Cruz et al.[352] found that hypothermia increases brain-derived neurotrophic factor after asphyxial cardiac arrest in adult rats, implicating enhancement of trophic factors as one possible mechanism behind the protective effects of hypothermia seen in this model. Several of these trophic factors are now commercially available. Augmentation of neuronal regeneration either via trophic factor replacement or augmentation via other means after cardiopulmonary arrest is an unexplored area for future research.

Transplantation of specialized cells to improve neurologic outcome after cerebral ischemia is under investigation. Embryonic, mesenchymal, and cord blood stem cells have been tested in various experimental models of brain injury using systemic (intravenous, intraarterial) and local

(intracerebroventricular) delivery.[353-355] Other groups are looking to enhance the natural production of neural stem cells that occurs after insult by supplementing key growth factors or signaling molecules.[356,357] Phase I clinical trials administering mesenchymal stem cells to patients with stroke have begun and early findings are promising.[358]

Extracorporeal Support

As previously suggested, CPB initiated immediately after VF arrest in dogs (with cannulae already in place) improves outcome when compared to standard ACLS-guided resuscitation.[359] CPB produced 64% survival after even 20 minutes of VF arrest, although all dogs were neurologically impaired. This supports the concept that cerebral and coronary perfusion during CPR extends tolerated insult time, although studies with vascular cannulation during resuscitation have not been reported. These studies would be important in light of the difficulty in obtaining this type of vascular access during arrest in children. Nevertheless, extracorporeal support allows control of postarrest blood flow and temperature, and the cardiovascular support provided might allow use of otherwise contraindicated therapies. Chen et al.[360] reported a 32% survival rate in adult patients rescued with extracorporeal membrane oxygenation (ECMO) or "E-CPR" after prolonged cardiac arrest. A strikingly favorable 5.6% incidence of severe neurologic deficit was reported in survivors within this study. Analysis of 682 pediatric patients placed on ECMO during CPR from the Extracorporeal Life Support Organization registry found that overall survival to discharge was 38%, but there were no data on neurologic outcomes for survivors.[361] The number of reported E-CPR cases increased each year. A meta-analysis of studies in children found a 40% survival rate (total 288 patients).[362] Complications were common after E-CPR and the presence of complication(s) increased risk of mortality. These included neurologic complications (27%), renal failure (25%), and sepsis (17%). Given the enormous resources required for quality E-CPR, institutions providing this service may benefit from having guidelines for inclusion and exclusion patient criteria. Obviously, a highly skilled and dedicated team prepared to provide the service at a moment's notice is also required (see also Chapter 53).

A multimodality approach, combining hypothermia with extracorporeal modalities in pediatric patients after cardiopulmonary arrest, particularly refractory or prolonged arrest, appears to be the next logical step. This is not a new concept. In 1984, Dr. Peter Safar and colleagues recommended research into "suspended animation for delayed resuscitation" for situations where conventional resuscitation attempts were not successful. Recently, they reported survival without brain damage after clinical death of 1 to 2 hours in dogs using suspended animation.[363] In their canine exsanguinations-cardiac arrest model, deep hypothermia (10° to 20° C) was induced by infusion of ice-cold saline via abdominal aorta. Postarrest resuscitation and hemodynamic support was provided by CPB. Mild hypothermia was subsequently maintained at 34° C. Using this protocol, they reported good neurologic outcome based on overall performance category score, neurologic deficit score and brain histologic damage score. The histological differences between groups were striking, with little evidence of neuronal damage in dogs treated with the suspended animation strategy (Figure 62-12). The use of CPB allows ROSC after a prolonged down time, as well as control of postarrest blood flow and temperature, providing the cardiovascular support that many patients might require, particularly under conditions of more profound hypothermia. Nagao et al.[364] reported a 92% ROSC in 50 adult patients that failed standard CPR, rescued with CPB followed by mild hypothermia (34° C) for a minimum of 2 days. These investigators also reported "good outcome" in 12 of the 23 long-term survivors. In the study by Chen et al.,[360] hypothermia was not used with ECMO. Interestingly, much of the mortality was attributed to multiple-organ failure (MOF) in this study. After a prolonged cardiopulmonary arrest, MOF is a common finding, sometimes ignored as the focus is generally on neurologic status. Treatment of MOF will likely become necessary in the

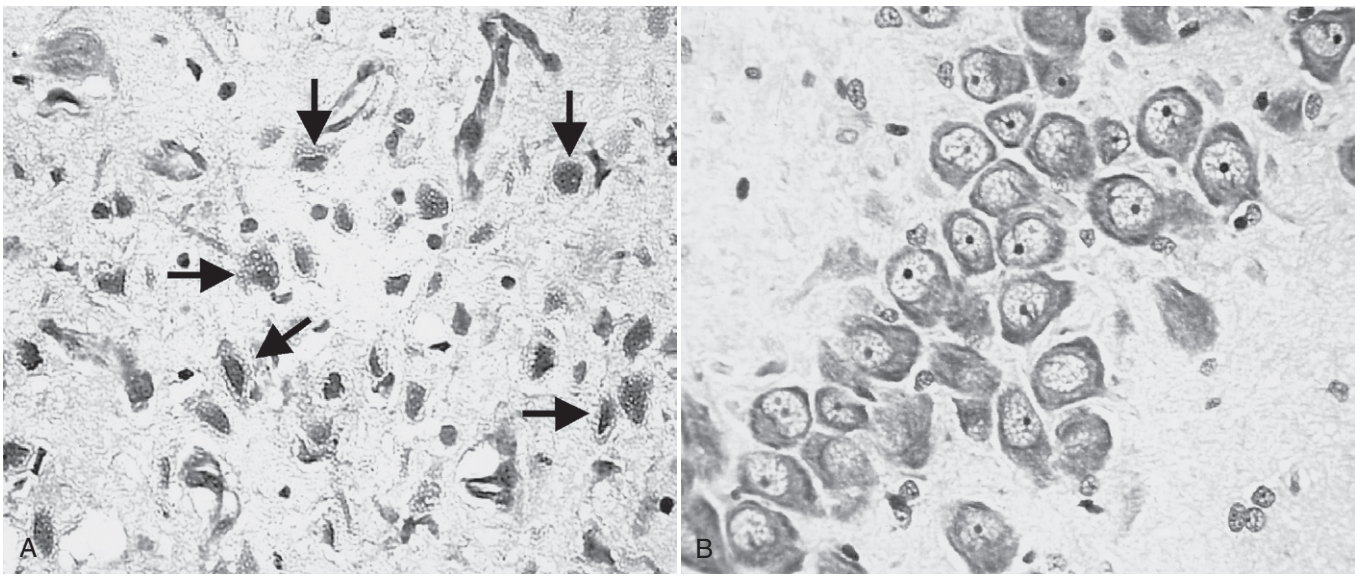

Figure 62–12. Using a "suspended animation" paradigm envisioned by Dr. Peter Safar, neuropathologic damage typically produced by 60 minutes of no flow is dramatically reduced. The hippocampal region of dogs treated without (**A**) versus with hypothermic intraaortic flush (**B**) are shown. Note extensive neuronal damage with evidence of DNA fragmentation (*arrows*) in **A**.

post-resuscitation phase, particularly as effective cerebroprotective strategies are developed.

For patients at risk for the development of HIE with MOF and coagulopathy, plasma exchange might be beneficial. Plasma exchange has been shown to reverse sepsis-induced MOF and effectively correct coagulopathy be removing cytokines and inflammatory mediators and restoring clotting homeostasis.[365] Granted, further clinical studies are needed; however, combining CPB, mild hypothermia, and plasma exchange would provide maximum therapeutic support after cardiopulmonary arrest, and all of these therapies are clinically utilized in pediatric patients. This concept of "therapeutic hibernation and plasma exchange" (HIBERPLEX) was introduced for recalcitrant shock in the pediatric population.[366] This approach could potentially provide neuroprotection, hemodynamic support, and reversal of MOF, thus targeting the major management challenges after prolonged cardiopulmonary arrest.

Summary

The social and economic impact of children left with persistent neurologic injury after cardiopulmonary arrest is unacceptable. Preventive approaches to this problem are unlikely to reduce significantly the occurrence of these multifactorial and largely unanticipated events. However, it is worthwhile for the general public to become more knowledgeable of child CPR and safety measures (e.g., pool and road safety), enormous benefit of quality CPR,[176] and to consider implementation of systems that recognize a hospitalized child in distress before an arrest is imminent, such as pediatric medical emergency teams.[367] Improvements in prognostication after cardiopulmonary arrest are on the horizon with a more concerted application of existing methods and new techniques. The successful application of novel brain-oriented therapeutic approaches is somewhat more speculative, but is likely to require intervention beginning in the prehospital setting or emergency department. Improved, pathophysiologic guided stratification of post-arrest patients is essential to determine which patients have resuscitable insults and, with optimal supportive care and prevention of secondary neuronal deterioration, potential for good rather than vegetative outcome. Unfortunately, this group is unlikely to include most patients with prolonged asphyxial arrest and in any single institution represents a small number of cases per year. Biochemically and physiologically guided, multifaceted pharmacological and mechanical approaches will almost certainly be required, with their application based on the temporal sequence of pathological events.

Acknowledgment

This chapter is dedicated to Peter J. Safar, the "father of modern-day CPR," who passed away August 3, 2003—*Rest in Peace.*

References are available online at http://www.expertconsult.com.

Stroke and Intracerebral Hemorrhage

Stuart Friess and Rebecca Ichord

PEARLS

- Childhood stroke encompasses a wide spectrum of disease that can be categorized into three groups: arterial ischemic stroke, cerebral venous sinus thrombosis, and intracranial hemorrhage.
- The adult classification of arterial ischemic stroke (AIS), which is based on mechanism, is not applicable to childhood stroke. Dividing AIS into broad pathophysiologic groups of cardiac-aortic embolism, vascular disease, and coagulation disorders is more appropriate.
- Regardless of the etiology of AIS, management should focus on optimizing perfusion and oxygenation, neuroprotection (minimizing the ischemic core and rescuing the penumbra), rehabilitation, and prevention of recurrence.
- In children who have had a stroke, endotracheal intubation and mechanical ventilation should be performed in patients with severe hypoxemia, loss of respiratory drive, or respiratory insufficiency, or to facilitate advanced neuroimaging.

Stroke and intracerebral hemorrhage are significant causes of morbidity and mortality in children. In recent years, childhood stroke has become more commonly recognized. Because of the heterogeneous etiologies, risk factors, and presentations in children, the diagnosis, treatment, and management of stroke present many challenges compared with the adult population. Previous studies have found the incidence of pediatric stroke to be between 2.3 and 13 per 100,000 children per year.[1-4] Boys have been observed to be at higher risk than girls, and children of African descent are at higher risk than white or Asian children.[5] Peak incidence of stroke and intracerebral hemorrhage occurs during the first year of life except in the case of subarachnoid hemorrhage, which peaks in adolescence.[5] Childhood stroke encompasses a wide spectrum of disease and can be categorized into three groups: arterial ischemic stroke, cerebral venous sinus thrombosis, and intracranial hemorrhage. The pediatric intensivist must be familiar with the various etiologies of childhood stroke and be facile in integrating a complete diagnostic and treatment approach to prevent further brain injury and minimize morbidity and mortality.

Arterial Ischemic Stroke

Arterial ischemic stroke (AIS) can be defined as an acute-onset neurologic deficit conforming to an arterial distribution associated with infarction in a vascular territory corresponding to the clinical deficit. AIS can be the result of a myriad of mechanisms and risk factors, and the presentation of pediatric AIS can be subtle. Pediatric AIS requires extensive diagnostic investigation to determine the cause, and in most thoroughly investigated cases outside the neonatal period, one or more risk factors can be identified.

Pathophysiology

The pathophysiology of ischemic stroke is initiated when circulating blood supply to the brain is decreased or absent, resulting in the deprivation of necessary substrates for metabolism (see also Chapter 62). The brain does not have extensive glucose stores, which results in a fairly rapid pathologic cascade after the onset of ischemia.[6] Brain tissue has limited capacity for anaerobic metabolism, which exacerbates substrate deprivation. The decrease in arterial blood supply is the result of thrombus formation, embolus, arterial stenosis, or in many cases a combination of these factors.

The extent and progression of ischemic injury is related to a multitude of factors (Box 63-1). Cerebral perfusion pressure plays a major role, and the maintenance of a steady and adequate cerebral perfusion pressure is critical to minimizing the extent of ischemia. The extent of collateral circulation in the area of affected brain and the duration of the ischemia influences outcome as well. Ischemia of shorter duration or slower onset is better tolerated by the brain, and regions with extensive collateral circulation are at less risk for infarction. Hypercoagulable states can increase the rate of progression and size of thrombus formation, and elevated temperature following brain injury has been associated with poorer outcomes in animal models and humans.[7-10] Disturbances in serum glucose levels (hyperglycemia or hypoglycemia) can increase the extent of ischemic injury.[11]

Cerebral blood flow (CBF) is coupled to the cerebral metabolic rate, which changes with age in the immature brain. Infants have similar CBF rates compared with adults (50 to 60 mL/100 g brain tissue/min). CBF rises in children and peaks between the ages of 3 to 8 years at 80 mL/100 g/min.[12]

It then decreases to the adult level by mid to late adolescence. In response to ischemia, cerebral autoregulation mechanisms increase CBF by local vasodilation (in collateral vessels), and brain tissue responds by increasing the oxygen extraction rate.

Following a decrease in CBF, energy failure at the cellular level leads to a phase of neuronal hyperexcitability. The loss of membrane ion gradients and the failure of glutamate reuptake with widespread neuronal depolarization results in further increases in extracellular glutamate and excitotoxicity. Excitotoxicity results in a cascade of oxidative stress, failure of cellular systems, and ultimately cell death. The perfusion threshold below which infarction occurs has been reported to be 5 to 8 mL/100 g/min within the first few hours of onset.[13,14] In regions of focal ischemia, the central area of lowest perfusion is defined as the ischemic core and is beyond therapeutic rescue when ischemia is of sufficient severity and duration to cause cell death. Surrounding the ischemic core is an area of decreased perfusion above the threshold of ion pump failure and irreversible damage but below the threshold of functional impairment, known as the ischemic penumbra, first described in experimental models.[14] The ischemic penumbra varies with duration of the interruption of blood flow, and the threshold for infarction in the penumbra rises with time, which emphasizes the need for timely intervention to promote recovery. Interventions that promptly restore flow at the site of vascular occlusion and optimize reperfusion of the ischemic penumbra are currently the most effective therapies for stroke in adults.[15]

Box 63–1 Factors Affecting Extent and Progression of Arterial Ischemic Stroke

Rate of onset and duration
Cerebral perfusion pressure
Collateral circulation
Hypercoagulable states
Temperature
Glucose disturbances

Epidemiology

The incidence of pediatric AIS has been estimated at two to three per 100,000 children per year in the United States, but it has been reported to be as high as 13 per 100,000 children in France.[1,4,5,16]

A classification system based on mechanism has been developed for adult AIS, but this system is not applicable for neonatal strokes or for the vast majority of childhood strokes. An alternative conceptual framework for classifying stroke in childhood begins by separating neonatal from childhood stroke, and then subdividing the causes into broad pathophysiologic groups: cardiac-aortic embolism, vascular disease, and coagulation disorders (Figure 63-1). About half of children with first-time stroke have conditions known to be associated with risk of stroke (symptomatic AIS), and about half are previously healthy children at the time of stroke presentation (cryptogenic stroke). After completion of a comprehensive risk factor evaluation, 80% to 90% of children are found to have at least one risk factor, and many children have multiple risk factors.[18,19] Risk factors for neonatal stroke differ significantly from those for childhood stroke. For a detailed review of neonatal stroke, including a discussion of definitions and risk factors, the reader is referred to a recently published summary of a National Institute of Health workshop on this topic.[18] The risk of recurrent AIS in children has been reported to be from 6% to 14%.[19,20] In a study from the United Kingdom, moyamoya syndrome and low birth weight

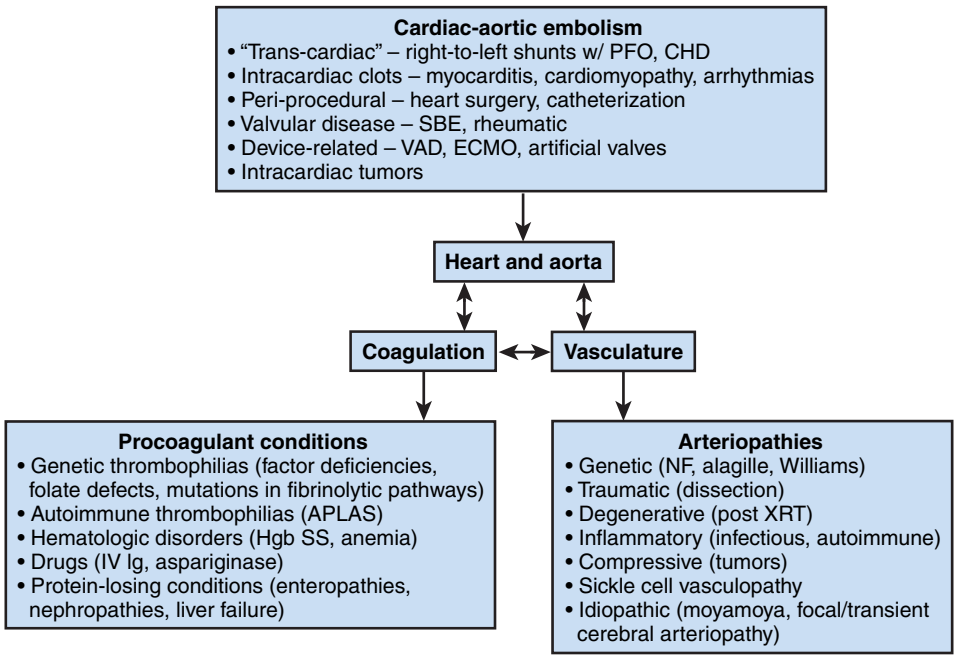

Figure 63–1. A conceptual framework for the classification of childhood arterial ischemic stroke. *PFO,* Patent foramen ovale; *CHD,* congenital heart disease; *SBE,* subacute bacterial endocarditis; *VAD,* ventricular assist device; *ECMO,* extracorporeal membrane oxygenation; *APLAS,* antiphospholipid antibody syndrome; *IV Ig,* intravenous immunoglobulin; *NF,* neurofibromatosis; *XRT,* radiation therapy.

were found to be the most important predictors of recurrent pediatric stoke.[19]

Etiologies and Risk Factors

Sickle Cell Disease

Incidence of stroke in children with sickle cell disease (SCD) has been reported to be 200 times higher than in the general pediatric population.[21] High blood flow velocity on transcranial Doppler (TCD), silent brain infarction, low hemoglobin, hypertension, and history of acute chest syndrome all have been identified as stroke risk factors in children with SCD.[22] A familial predisposition to stroke in SCD also has been reported.[23] Approximately 20% of patients will have silent brain infarcts on magnetic resonance imaging (MRI). Stroke in SCD is associated with the development of large vessel stenosis in the middle cerebral or distal internal carotid artery (moyamoya syndrome), the mechanism of which is unclear (also see Chapter 84).[24]

Moyamoya Disease and Syndrome

Moyamoya syndrome is a condition characterized by progressive stenosis of the distal intracranial internal carotid arteries and their proximal branches that predisposes patients to stroke. It was first described in 1957 in Japan. Moyamoya is a term in Japanese meaning "something hazy or a puff of smoke," representing the characteristic finding on angiography (Figure 63-2).[25,26] Patients with no known associated comorbidity are categorized as having moyamoya disease. The highest incidence has been reported in Japan at three cases per 100,000 children, and much lower rates have been reported in Europe and the United States (0.086/100,000).[27,28] Moyamoya syndrome in children usually presents as ischemic stroke or transient ischemic attacks. Ischemic strokes can be repetitive and are commonly found in watershed territories. Presentations can vary from infrequent, intermittent attacks to a rapid and fulminant course.

Arterial Dissection

A spontaneous or traumatic tear in the intimal layer of an arterial vessel can lead to arterial occlusion and artery-to-artery embolism. Arterial dissection is a significant cause of pediatric stroke and has been reported to be the cause for 7.5% of ischemic strokes.[29] Traumatic vertebral artery dissections in children are usually the result of sports injuries, and symptoms may appear quickly or can be delayed up to days (Figure 63-3). In many cases, the precipitating injury does not seem severe enough to result in vertebral artery dissection. Recurrence in cases of arterial dissection is highest in the first 4 to 6 weeks after the initial presentation, and thereafter it falls to less than 1% per year. Factors associated with recurrence are incompletely understood but may include predisposing conditions such as pro-thrombotic conditions, fibromuscular dysplasia, Marfan syndrome, autosomal-dominant polycystic kidney disease, coarctation of the aorta, and Ehlers-Danlos syndrome type IV.[30]

Congenital and Acquired Heart Disease

Among children with cardioembolic causes for stroke, those with complex congenital heart disease with right-to-left shunts are at greatest risk, but stroke has been observed in children with other heart defects. Children with uncorrected congenital heart disease are at highest risk, and emboli can arise at the atrial, ventricular, and arterial level. Prosthetic heart valves increase the risk for endocarditis and stroke. Patients with left-sided endocarditis have neurologic complications rates of 20% to 40%, with half of these events being strokes.[31] Cardiac surgery and catheterization also can be complicated by thromboembolic stroke (Figure 63-4). Stroke secondary to cardiac arrhythmias or acute myocarditis is uncommon in children but has been reported. Cardiomyopathy and congestive heart failure place children at higher risk for stroke and are associated with muscular dystrophy, mitochondrial disorders, and other metabolic disorders.

Focal and "Transient" Cerebral Arteriopathy

Focal cerebral arteriopathy refers to a group of childhood cerebral arteriopathies of uncertain cause; they manifest most typically as arterial ischemic stroke in the middle cerebral artery territory and are associated with findings on vascular imaging of focal stenosis or occlusion in the proximal middle cerebral artery.[32] The natural history is variable, with spontaneous remission and normalization of the vessel in some children, stable chronic partial occlusion in others, and progressive stenosis involving other areas of the circle of Willis in other children. In some children there is a period of progression over months to a year and eventual stabilization, often referred to as "transient cerebral arteriopathy."[33] This pattern is typical of that seen in children with stroke and vasculopathy attributed to prior varicella (postvaricella vasculopathy),[33] and it is among the childhood arteriopathies associated with significant risk of recurrence.[3]

Vasculitis

Vasculitis of intracranial vessels in children can be due various etiologies and affect a wide variety of vessel sizes (Box 63-2). Cerebral vasculitis should be considered in children with stroke and fever, elevated markers of inflammation (c-reactive protein or sedimentation rate), skin findings, or renal dysfunction. Primary vasculitis of the intracranial vessels in children is rare and usually presents with headache and altered mental status but without elevation in the sedimentation rate. Intracranial infections can cause a secondary vasculitis leading to AIS. Bacterial meningitis, mycotic infections, and tuberculous meningitis all have been associated with stroke. Lyme disease and rickettsial infections can involve intracranial vessels, leading to stroke. Varicella infections have been reported to cause a cerebral vasculopathy in children.[34] Takayasu's arteritis should be considered in older children, especially girls of Asian descent. Patients with systemic lupus erythematosus are at higher risk for stroke. Direct intracranial vasculitis in persons with systemic lupus erythematosus is rare, but stroke also can occur as a result of embolism from Libman-Sacks endocarditis and a hypercoagulable state (antiphospholipid antibodies) (also see Chapter 98).[35]

Hypercoagulable States

Various pro-thrombotic states are common in children with stroke, and often are combined with other major stroke risk factors such as congenital heart disease (Box 63-3).[36] Elevated lipoprotein a and deficiencies in antithrombin III, protein C, and protein S have been identified in children with AIS.

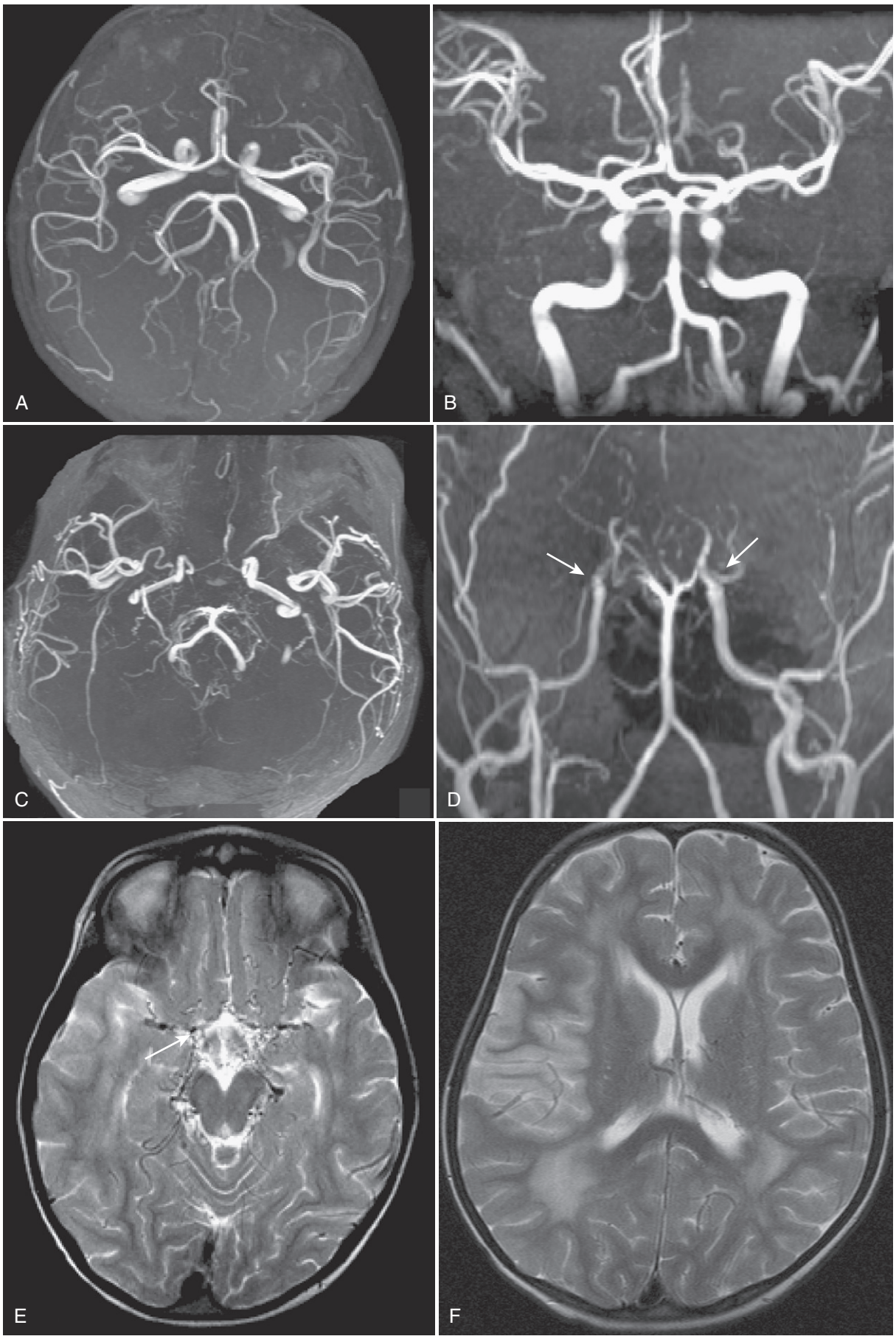

Figure 63–2. Normal MR angiogram, axial (**A**) and coronal (**B**). Bilateral terminal carotid artery occlusion (**C, D,** *arrows*) in a 4-year-old boy presenting with acute left hemiparesis, typical of advanced moyamoya disease. T2 sequence shows multiple small collaterals in basal cisterns (**E**, *arrow*) and large acute right middle cerebral artery infarct and chronic white matter ischemic changes (**F**).

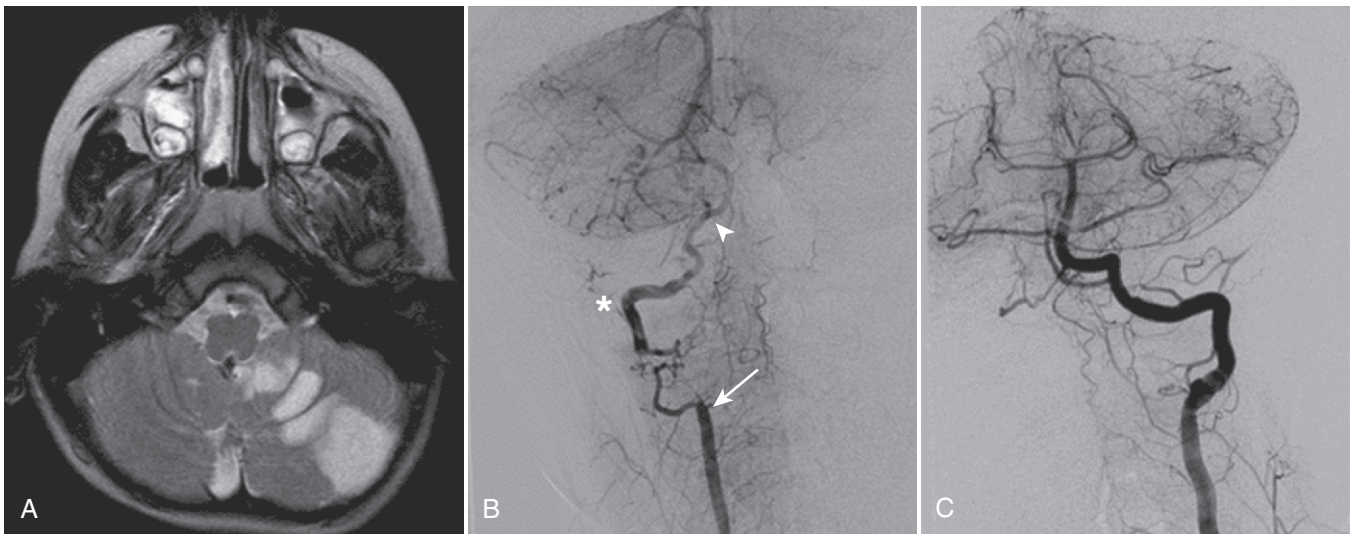

Figure 63–3. Sudden onset of headache, ataxia, and complaint of dizziness developed in a healthy 3-year-old boy after a fall from a slow-moving vehicle. One week later MRI showed cerebellar stroke (**A**). Angiogram shows right cervical vertebral artery occlusion (**B**, *arrow*) with distal reconstitution (*) from collaterals, reocclusion at junction with basilar artery (*arrowhead*). Compare to normal left vertebral artery (**C**).

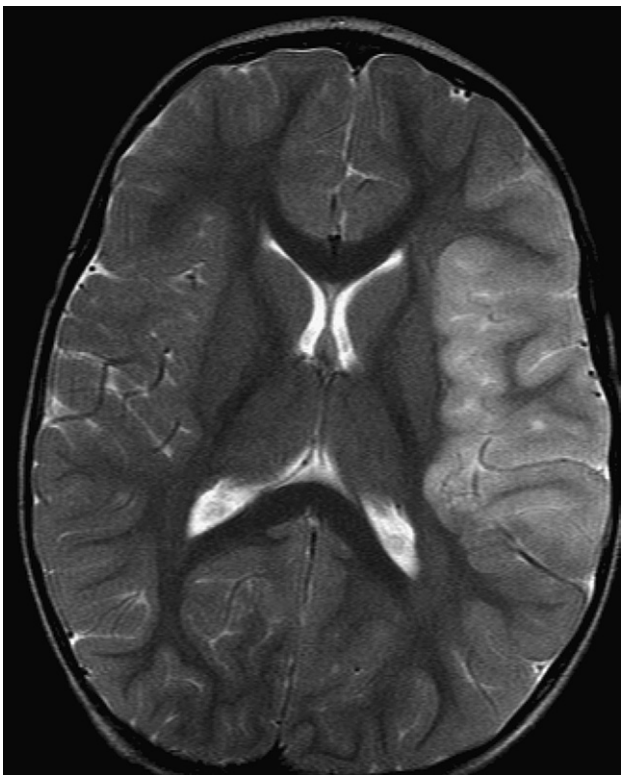

Figure 63–4. Presumed cardioembolic stroke. A 2-year-old with sudden onset of hemiparesis, loss of speech, and seizures 4 days after atrial septal defect closure.

Antiphospholipid antibody syndrome has been associated with recurrent fetal loss, thrombocytopenia, and cardiac valve disturbances, but its association with increased AIS in children is unclear.[37] Homocystinuria is an uncommon condition but can cause arterial ischemic stroke. Clinical manifestations include marfanoid features, mental retardation, seizures, and arteriosclerotic vascular disease. The spectrum of microangiopathic hemolytic anemias including hemolytic-uremic syndrome and thrombotic thrombocytopenia purpura can present with various neurologic manifestations including ischemic infarction. In adolescent girls both pregnancy and use of oral contraceptives must be considered risks factors for AIS.[38] The importance of pro-thrombotic risk factors is further evidenced by the observation that certain pro-thrombotic conditions are associated with higher recurrence risk.[20]

Box 63–2 Causes of Cerebral Vasculitis

Primary Cerebral Vasculitides

Takayasu arteritis
Primary cerebral vasculitis
Polyarteritis nodosa

Secondary Vasculitides

Immune Disorders

Systemic lupus erythematosus
Wegner granulomatosis
Kawasaki syndrome
Sarcoidosis
Henoch-Schönlein purpura

Primary Intracranial Infections

Bacterial meningitis (especially *Diplococcus pneumoniae)*
Tuberculous meningitis
Mycotic infections
Cat-scratch disease
Human immunodeficiency virus/acquired immunodeficiency syndrome
Malaria
Lyme disease
Rickettsial infections
Brucellosis

Metabolic Disorders and Toxins

Metabolic disorders are rare causes of stroke-like syndromes or lesions that are not the result of vascular-occlusive infarcts but, for the purposes of this chapter, will be discussed here. Chief among these disorders is MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke).[39] The exact mechanism of ischemia in MELAS is likely multifactorial,

Box 63–3 Conditions Associated with Thrombophilia

Inherited Factor Deficiencies or Cofactor Deficiencies

Protein C or S deficiency
Antithrombin III deficiency
Homocystinuria
Factor V Leiden mutation
Prothrombin mutation

Acquired Circulating Pro-thrombotic Factors

Anticardiolipin antibodies
Lipoprotein a elevation

Systemic Disorders Causing Defective Synthesis or Excess Consumption or Loss of Fibrinolytic Pathway Factors

Chronic liver disease
Protein-losing enteropathy
Protein-losing nephropathy
Sepsis
Disseminated intravascular coagulation

Pro-thrombotic Hematologic Disorders

Hemoglobinopathies
Iron-deficiency anemia
Thrombocytosis

Drugs and Toxins

Oral contraceptives
Smoking
Pregnancy
Intravenous immunoglobulin infusion

including direct cytotoxicity from mitochondrial failure and glutamate toxicity, as well as loss of normal coupling of cellular metabolism and CBF.[40] Illicit drug use has been associated with stroke. Cocaine use has been associated with both ischemic and hemorrhagic stroke, and there have been reports of stroke in young adults using amphetamines and ecstasy (3,4-methylenedioxymethamphetamine).[41-43]

Clinical Manifestations

AIS in infants and children can be difficult to correctly diagnose. Stroke typically is not high on the practitioner's differential diagnosis in the pediatric population, and the presenting symptoms are attributed to more common conditions such as a viral syndrome, migraine, or oppositional behavior. Compared with adults, children may not articulate their symptoms well. Infants usually fail to display localized deficits and typically present with seizures or altered mental status. Many stroke "mimics" exist in childhood that require advance imaging for accurate diagnosis, including migraines, demyelinating disorders, tumors, hypertensive encephalopathy, psychogenic, postictal paralysis, infections, and metabolic disorders.[44] These factors can lead to delays in presentation as well as delay in diagnosis.[45]

AIS usually presents with acute neurologic deficits in an arterial distribution and typically conforms to a pattern of ischemia in either the anterior (carotid) or posterior (vertebrobasilar) circulations. Deficits associated with each are related to the regions of brain supplied by the affected artery or arteries. The anterior circulation includes the internal carotid, anterior cerebral, and middle cerebral arteries. Ischemia in anterior circulation produces unilateral motor and sensory deficits.[46] The location of the lesions can influence presentation. Typically cortical infarcts will affect both motor and sensory function in the face and upper extremity more than in the lower extremity. Subcortical infarcts will produce the same density deficits in the face and upper and lower extremities. Many patients will have visual field cuts with a gaze preference. If the stroke occurs in the dominant hemisphere, patients can present with aphasia. Extinction and neglect are seen when the infarction occurs in the nondominant hemisphere. The posterior circulation includes the vertebrobasilar arteries that supply the brainstem, cerebellum, and the occipital lobe.[46] Cerebellar strokes closely resemble acute cerebellitis, typically including severe headache, lethargy, vomiting, ataxic gait, unilateral limb ataxia, and dysarthria.[47,48] Unilateral brainstem deficits include pure motor deficits without cortical symptoms, oculomotor deficits, diplopia, vertigo, tongue deviation, or dysarthria/dysphagia.[49] Infarcts in the distribution of the posterior cerebral artery present typically with visual field deficits and gaze preference. Seizures herald the onset of stroke in 10% to 20% of childhood-onset AIS and in the vast majority of neonatal cases of AIS.

Imaging and Laboratory Evaluation

The goals of initial investigation are to verify the occurrence of AIS and the location to determine the likely causative stroke mechanisms so a specific treatment plan can be initiated.[10] If AIS is suspected, strict attention to maintenance of adequate airway, breathing, and circulation and close monitoring of neurologic status should be performed throughout the acute evaluation process.

Neuroimaging typically starts with a head computerized tomography scan (CT) because it is widely available and can quickly demonstrate hemorrhage as the cause of symptoms. The major disadvantages of CT, in addition to exposure to ionizing radiation, are that it is insensitive and nonspecific and does not provide information about vascular disease. Ischemic changes on CT typically are not visible until 12 to 24 hours after onset and are indistinguishable from lesions that mimic stroke such as tumor and demyelinating disease. MRI with diffusion weighting is far superior for the diagnosis of AIS and the differentiation of stroke from other diagnoses such as acute disseminated encephalomyelitis or methotrexate toxicity.[50] Moreover, vascular imaging can be obtained readily with the initial diagnostic brain imaging using MRI, and it should be obtained for both the head and the neck in all children suspected of having a first ischemic stroke (see Figure 63-3). When a metabolic stroke-like syndrome is suspected, such as MELAS, magnetic resonance spectroscopy may be helpful. If MRI is not available, vascular imaging can be achieved with CT angiogram.[51] Diagnostic imaging can be challenging for the pediatric patient, and care must be taken not to compromise oxygenation, ventilation, and perfusion to at-risk tissues with sedation or general anesthetics. Careful planning and coordination of diagnostic imaging is necessary to obtain optimal imaging in a timely and safe manner. This coordination is best accomplished through direct consultation and dialogue involving the primary team caring for the patient, the sedation team, and the radiology technicians and physicians responsible for specifying and executing the imaging protocol (also see Chapter 56).

Box 63–4 Laboratory Evaluation of Suspected Stroke in Infants and Children

Screening Studies on Admission for Children with Acute Neurologic Deficit

Complete blood cell count with differential and platelet count
Coagulation parameters (prothrombin time, partial thromboplastin time, international normalized ratio)
Electrolyte panel
Blood glucose level
Comprehensive metabolic panel (kidney function, liver function, total protein, albumin, calcium, phosphorus)

Definitive Thrombophilia Studies for Children with Confirmed Arterial Ischemic Stroke

Protein C—functional†
Protein S—functional and free†
Antithrombin III*
Factor V Leiden mutation
Prothrombin mutation
Anticardiolipin antibodies
Anti-β_2 glycoprotein antibody
Dilute Russell viper venom time
Plasma homocysteine level
Lipoprotein(a)
Factor VIII level

Supplementary Studies for Children with Atypical Infarcts or Suspected Metabolic Stroke

Plasma amino acids
Plasma and cerebrospinal fluid lactate and pyruvate
Brain spectroscopy (including interrogation of regions not involved with infarcts)
Muscle biopsy for mitochondrial enzymes
Deoxyribonucleic acid studies for mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke
Serum and urine toxicology

*Sample must be drawn before patient receives heparin.
†Results not applicable if patient is taking warfarin.

Box 63–5 Treatment in Pediatric Arterial Ischemic Stroke*

Perfusion: Restore and Maintain Cerebral Circulation and Energy Substrate Delivery (Glucose, Oxygen)

Maintain circulating volume with intravenous fluids
Eliminate postural perfusion fluctuations (keep head of bed flat)
Respiratory support, oxygenation
Correct anemia (ideal hemoglobin for cerebral perfusion ~10–12 mg/dL)
Blood pressure: aim for upper limit of normal for age, do not overtreat hypertension
Prevent clot propagation—antithrombotic drugs (antiplatelet, anticoagulation)*
Thrombolysis—evidence lacking on safety, dose, efficacy in children; see American Heart Association guidelines*

Neuroprotection: Limit the Extent of Infarction, Salvage the Penumbra

Temperature: target intervention to keep temperature ≤37.5° C
Glucose control: target intervention to keep serum glucose >50, <150 mg/dL
Assess for and treat seizures
Prevent complications: deep venous thrombosis prophylaxis, aspiration precautions

Rehabilitation: Promote Recovery and Plasticity

Start rehabilitation in pediatric intensive care unit or acute care ward
Be aggressive —"time is brain" also during rehabilitation and plasticity is use dependent
Greatest long-term morbidity is neurocognitive and psychosocial—take care of the whole child and the family unit within the family, neighborhood, and school

Secondary Prevention: Prevent Recurrence*

Antiplatelet Agents, Commonly Used for:
Idiopathic stroke (no risk factor after complete evaluation)
Cerebral arteriopathy for low-grade stenosis
Congenital heart disease with no intracardiac thrombus or cardiac failure
Mild pro-thrombotic states

Systemic Anticoagulation, Commonly Used for:
Dissection of cervical/extracranial cerebral arteries
Intra-cardiac thrombus or severe ventricular dysfunction
Stroke or transient ischemic attack while taking antiplatelet agents
High-grade stenosis of cerebral artery
Major pro-thrombotic state

*Use of antithrombotics in neonatal arterial ischemic stroke is not usually recommended because of very low recurrence risk. An exception would be to consider systemic anticoagulation where intracardiac or systemic thrombosis is identified or a major pro-thrombotic defect is identified.

Laboratory evaluation in the early screening stage should include a complete blood cell count, comprehensive metabolic panel, and coagulation profile (Box 63-4). If AIS is confirmed, a thrombophilia workup should be performed and consultation with a hematologist should be considered. It is critical that blood samples be taken for key tests prior to the initiation of anticoagulation therapy (see Box 63-4). If stroke symptoms are associated with an acute febrile illness, a lumbar puncture should be considered as well as serologies for other infectious etiologies (e.g., mycoplasma infection and Lyme disease). Lumbar puncture may need to be delayed if intracranial hypertension as a result of stroke and peri-infarct edema are suspected, particularly for patients with large strokes. When an embolic etiology of AIS is suspected, urgent cardiac evaluation is warranted, including an echocardiogram with a bubble study and an electrocardiogram (ECG). Although uncommon, AIS has been reported in children with cardiac arrhythmia.[52]

Treatment

Regardless of the etiology of AIS, management should focus on optimizing perfusion and oxygenation, neuroprotection (minimizing expansion of the ischemic core and secondary injury and rescuing the penumbra), rehabilitation, and prevention of recurrence (Box 63-5). Specific therapies should be tailored based on the stroke mechanism. Reviews of existing evidence and summaries of evidence-based and consensus-based management guidelines have been published recently.[10,53]

Supportive Measures

Interventions aimed at optimizing perfusion to ensure adequate oxygen delivery and protection of the ischemic penumbra should begin immediately. Evidence for the effectiveness

of supportive measures in childhood AIS is lacking, and thus these measures are largely based on adult trials and consensus guidelines. Airway patency and adequate breathing should be assessed and maintained and supplemental oxygen provided to maintain normal oxygenation. Currently no strong evidence exists to support administration of supplemental oxygen in the absence of hypoxemia.[10] Endotracheal intubation and mechanical ventilation should be performed in children with severe hypoxemia, loss of respiratory drive or respiratory insufficiency, or obtundation with loss of airway protective reflexes. The need for early advanced neuroimaging (e.g., MRI and magnetic resonance spectroscopy) in the pediatric stroke patient raises additional challenges of sedation. Endotracheal intubation and mechanical ventilation may be necessary to ensure adequate oxygenation, ventilation, and perfusion during neuroimaging.

The head of the bed should remain flat to maximize perfusion and eliminate postural fluctuations during the initial 12 to 24 hours until the hemodynamic status and neurologic deficits stabilize. Blood pressure should be monitored closely, and isotonic intravenous fluids should be administered to maintain circulating intravascular volume. Adult stroke guidelines recommend permissive hypertension, and the most recent pediatric guidelines suggest controlling systemic hypertension, but to what degree or how quickly is unclear.[10] Symptomatic hypertension should be controlled, a reduction in blood pressure should be performed slowly, and neurologic status should be monitored closely during this process. Treatment of asymptomatic hypertension in the patient who has had a stroke must be tailored to the specific status of the individual patient, including the perceived risk or demonstrated occurrence of hemorrhagic transformation or infarct progression, presence of anticoagulation, and the potential complications of overtreating or undertreating the hypertension.

Hyperthermia increases metabolic demand and, in the presence of impaired substrate delivery, can increase neuronal injury. It has been demonstrated that fever following brain injury in animal models worsens outcomes.[8,9] In children with traumatic brain injury, hyperthermia has been associated with longer hospital stays, but currently no studies have been performed that assess the role of fever in childhood AIS.[54] Adult stroke guidelines recommend aggressive treatment of fever, and current pediatric consensus statements support the treatment of fever.[7,10] Experimental studies also have demonstrated possible benefits of neuroprotection with therapeutic hypothermia after brain injury, but to date efficacy and safety has not been studied in the pediatric stroke population.[55,56]

Clinical and electrographic seizures should be controlled with antiepileptic medications. In the absence of seizures, little evidence exists that prophylactic antiepileptic medication administration is beneficial.[10] In adult AIS, hyperglycemia and hypoglycemia have been associated with worse outcomes.[57,58] Although hypoglycemia should always be treated, glycemic control after pediatric AIS has not been extensively studied; however, based on adult evidence, pediatric guidelines currently recommend treatment of hyperglycemia.[10]

Thrombolytic Therapy

Randomized controlled trials have demonstrated the efficacy of intravenous and intraarterial thrombolysis in adult patients with AIS.[15,59] Evidence regarding thrombolysis for acute AIS in children is scarce, resulting in a lack of consensus on the role of this therapy for children. Published studies on the use of tissue plasminogen activator (tPA) in children with AIS is limited to only a few case reports and small case series.[60-63] In the largest case series published to date, Amlie-Lefond et al.[64] described the clinical features, dosing and timing, and short-term outcome in all children treated with tPA for acute AIS who were enrolled in the International Pediatric Stroke Study between 2003-2007. Among 677 children in the International Pediatric Stroke Study with acute AIS, 15 (2.2%) received tPA. Time intervals and dosing often deviated from adult guidelines. Intracranial hemorrhage was seen after tPA treatment in four of 15 patients, though none were judged acutely symptomatic, and functional outcome was poor in most patients. Consensus is strong that tPA should not be used in children with neonatal stroke because of uncertainty regarding the stroke onset. In older children and adolescents data on safety and efficacy are very limited, and to date consensus among experts is limited. Lower dose tPA has been reported to be effective in children, but further investigation and clinical trials are needed.[65] The current American Heart Association Guidelines suggest that tPA be used in children (preadolescents) only in the context of a clinical trial,[11] and if it is considered for children or adolescents, its use should adhere strictly to adult guidelines.

Antithrombotic Therapy: General Principles

In some centers it is common practice to begin anticoagulation initially in children with acute AIS while studies of risk factors are undertaken. This approach is based on the assumption that children with AIS may be more likely to benefit from anticoagulation compared with adults because of the greater prevalence of hypercoagulable states and lower incidence of hypertension. Typically, decisions regarding therapy for secondary prevention are finalized at 7 to 10 days after symptom onset, when results of comprehensive risk factor evaluation (cardiac, vascular, and thrombophilia) are available and the clinical course has stabilized (see Box 63-5). Because a significant risk of recurrent ischemic stroke exists, it is reasonable to provide most children with some form of antithrombotic therapy for secondary stroke prevention for 1 to 2 years. The decision to use anticoagulation vs. antiplatelet therapy takes into account stroke mechanism, presence of thrombophilia, and comorbid diseases that may be affected by the use of antithrombotic agents. Anticoagulation is commonly used in patients with presumed cardioembolic stroke, cervical artery dissection, and certain high-risk thrombophilias (such as antiphospholipid antibody syndrome). Antiplatelet therapy, usually with aspirin, is commonly used for all other stroke subtypes or in children with contraindications for chronic anticoagulation therapy. A thorough review of antithrombotic treatment strategies and of the relevant literature can be found in the American Heart Association's Scientific Statement on the Treatment of Childhood Stroke[10] and the *Chest* guidelines for the use of antithrombotic therapies in children.[66]

Antiplatelet Therapy

Aspirin inhibits platelet activity by irreversibly inhibiting cyclooxygenase-1, which results in impaired platelet activation. Two adult multicenter trials examining the role of aspirin administration within 48 hours of onset of stroke symptoms demonstrated an absolute risk reduction for in-hospital AIS recurrence of seven per 1000 patients.[67-69] The

risk of hemorrhagic transformation was only increased by two per 1,000 patients. Currently no studies have been conducted in children with AIS, but pediatric consensus statements recommend initial treatment with aspirin, 3 to 5 mg/kg/day for acute pediatric AIS, excluding patients with sickle cell disease, intracranial hemorrhage, or recent thrombolytic therapy.[10,53]

Aspirin also is used for long-term secondary prevention of stroke. Adult studies have demonstrated no difference in the prevention of stroke recurrence between aspirin and anticoagulation. A nonrandomized single-center prospective study of 135 children with AIS comparing low-molecular weight heparin (LMWH) and aspirin demonstrated no difference in recurrence rates and bleeding risks between the two drugs.[70] Dosing of aspirin is usually 3 to 5 mg/kg/day. Because of the association of aspirin use and Reye syndrome, patients taking aspirin for secondary stroke prevention need to be monitored closely during flu-like illnesses.[10] Varicella and annual influenza vaccination is recommended for these patients as well.

Anticoagulant Therapy

Heparins are the mainstay of acute anticoagulation for AIS. By enhancing the activity of antithrombin, they effectively inhibit thrombin, a key player in the coagulation cascade. Antithrombin levels vary with age. Infants have lower levels of antithrombin, and as a result they require higher doses of heparin to achieve anticoagulants effects that are similar to those in adults.[71] LMWH offers both advantages and disadvantages for acute coagulation compared with unfractionated heparin (UFH). LMWH offers more predictable pharmacokinetics, fewer blood tests to ensure therapeutic dosing, and subcutaneous administration, but it is cleared renally, which may pose problems for patients with renal insufficiency or failure. UFH advantages over LMWH include rapid reversibility with protamine sulfate or fresh frozen plasma and the fact that kidney dysfunction does not alter clearance. For long-term anticoagulation, the practitioner has the choice of LMWH or oral vitamin K antagonists such as warfarin. LMWH can be administered in doses of 1 mg/kg every 12 hours through a subcutaneous catheter that is replaced weekly to minimize needle injections.[72] Therapy is monitored with anti-factor Xa levels sampled 4 to 6 hours after injection with a therapeutic range of 0.5 to 1 U/mL. Dosage of warfarin is tailored to target an international normalized ratio between 2 and 3. The risk of major hemorrhage in children with AIS being treated with warfarin has not been studied but has been reported to be less than 3.2% in children receiving warfarin for mechanical heart valves.[66]

Special Circumstances

Sickle Cell Disease. The primary acute treatments for AIS in patients with sickle cell disease are hydration and exchange transfusion. Exchange transfusion avoids the risk of increasing blood viscosity that may occur with increases in hematocrit with simple transfusions.[73] Typically, sickle hemoglobin reduction to less than 30% is targeted during exchange transfusion therapy. A randomized trial comparing periodic blood transfusions with standard treatment in children with sickle cell disease and high risk for stroke determined by TCD demonstrated a reduction in stroke risk from 10% to less than 1% per year.[74] Periodic transfusions are now recommended for children ages 2 to 16 years with sickle cell disease and abnormal TCD results.[10]

Moyamoya Syndrome. Moyamoya syndrome affects the internal carotid artery and its branches while leaving the external carotid artery unaffected. Surgical revascularization using the external carotid artery as a new blood supply to the affected hemisphere has become a viable option for pediatric patients with moyamoya syndrome.[75,76] There are two general approaches to surgical revascularization: direct and indirect. Direct revascularization involves taking a branch of the external carotid artery and directly anastomosing it to a cortical artery.[77] This technique can be technically difficult in the pediatric population because of the small size of the vessels that need to be manipulated.

Indirect revascularization such as pial synangiosis involves placement of external carotid artery branch or vascularized tissue in direct contact with the brain, leading to growth of new blood vessels to the underlying brain tissue (Figure 63-5). A review of 143 pediatric patients with moyamoya syndrome treated with pial synangiosis demonstrated marked reduction in stroke rate from 67% before surgery to 3.2% in the first year of follow-up.[78] Forty-six patients who had 5 years or more of follow-up had a stroke rate of only 4%. Pediatric patients with moyamoya syndrome undergoing revascularization procedures have additional challenges in the immediate postoperative period of ischemic events. Crying and hyperventilation can reduce partial pressure of carbon dioxide, inducing cerebral vasoconstriction and ischemia. Adequate pain control and sedation during the postoperative period as well as avoidance of hypotension and hypovolemia is warranted.[79]

Rehabilitation

Introduction of rehabilitation relatively early in the stroke course has the potential to reduce long-term morbidity. A multidisciplinary approach to rehabilitation including physical medicine and rehabilitation physicians, occupational, speech, and physical therapists, child life specialists, and psychologists has been recommended.[80] Constraint-induced movement therapy (CIMT) has been introduced to improve recovery from pediatric stoke.[81] CIMT is based on the theory of forced use that was originally investigated with primate models.[82,83] Forced use theorizes that the affected or paretic arm can be retrained by restricting movement of the unaffected or less affected arm. A trial in adults with subacute AIS randomly assigned to a 2-week period of intensive physical therapy with or without CIMT demonstrated a significantly greater improvement in function of the affected arm in the CIMT group compared with the control group at 1 year.[84] Observational studies in pediatric stroke patients and patients with hemiplegic cerebral palsy have reported mixed results.[85-87] A randomized controlled trial in children with cerebral palsy who had asymmetric motor impairment reported improvement in acquisition and quality of motor skills following CIMT.[88]

Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis (CVST) is a relatively rare disease in the overall pediatric population, but with advances in neuroimaging, recognition of this condition has increased.

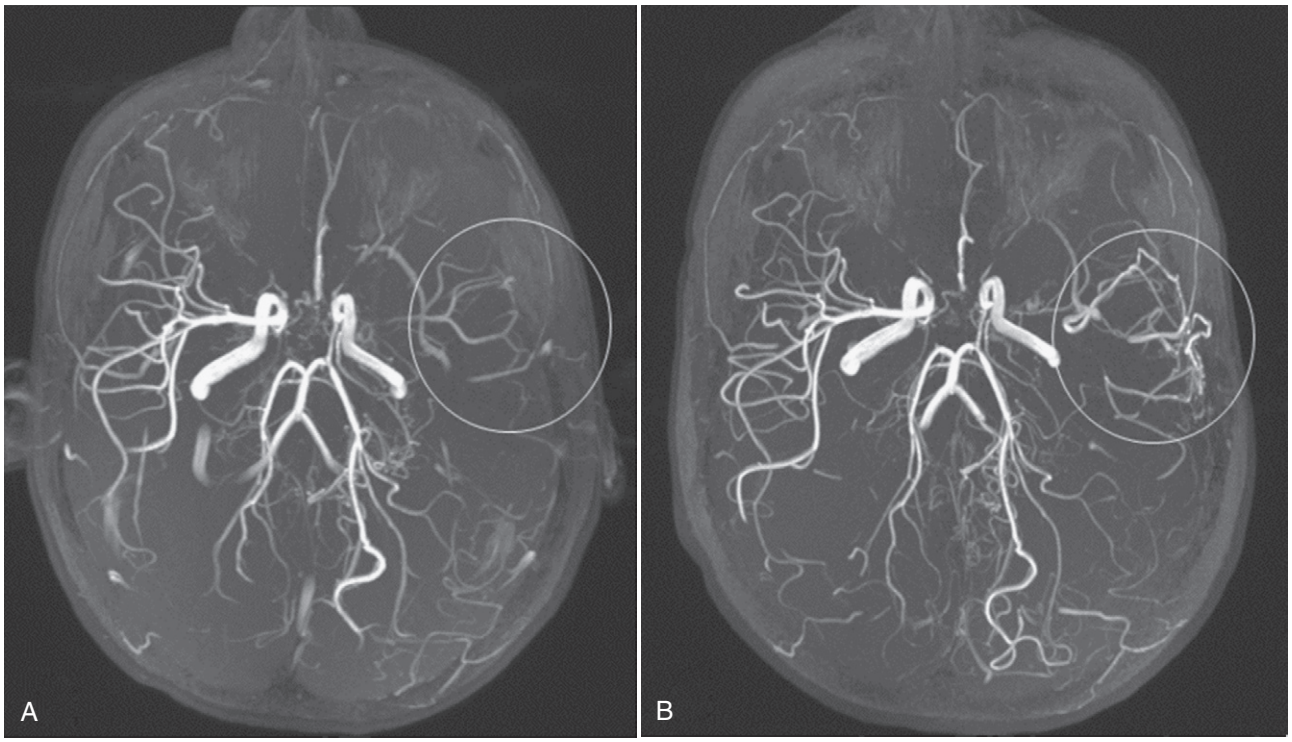

Figure 63–5. A 16–year-old with unilateral moyamoya syndrome presenting with left carotid territory transient ischemic attack (right face, arm, and hand weakness and numbness with headache). MR angiogram at onset (**A**) and 1 year after pial synangiosis (**B**). Note increased vascularity in middle cerebral artery territory at site of surgery (*circle*).

CVST can be the result of a variety etiologies, and the presentation can be nonspecific and subtle, making early diagnosis challenging.

Pathophysiology

Thrombosis of the cerebral venous sinuses can be the result of various processes. Venous stasis, hypercoagulable states, dehydration, hyperosmolality, and disruption of the vessel wall due to regional pathology (such as infection or trauma) all can result in CVST. The lower velocity of blood flow in the venous sinus system provides optimal conditions for thrombus propagation. Venous infarction may occur if the venous sinus system pressure rises above the arterial perfusion pressure resulting in venous congestion, leakage of fluid and blood into the brain parenchyma, and hemorrhagic infarction. In the most severe cases of venous outflow obstruction from thrombotic occlusion, extensive venous infarction, hemorrhage, and cerebral edema progress to herniation and death. Occlusion of the venous sinuses with thrombosis may impede cerebrospinal fluid absorption and produce intracranial hypertension without ventricular enlargement via a process resembling pseudotumor cerebri. If untreated, intracranial hypertension can lead to papilledema and vision loss.

Epidemiology

CVST is rare in the pediatric population, with an estimated incidence of 0.67 per 100,000 children per year.[89] Neonates have the highest incidence of CVST. The majority of neonates (84%) are observed to have a systemic illness, most commonly dehydration or perinatal complications (e.g., hypoxia at birth, premature rupture of membranes, or maternal infection).[89] Other disorders in neonates known to be associated with CVST include bacterial sepsis, meningitis, and hypercoagulable states.

In infants with CVST, head and neck disorders are common, with otitis media and mastoiditis being the most frequent pathology. Chronic systemic illnesses (e.g., malignancy, inflammatory bowel disease, and nephrotic syndrome, among others) are frequently found (40% to 60%) in older children with CVST. CVST in older children also has been associated with anemia and hemoglobinopathies, including iron deficiency, hemolytic anemia, sickle cell disease, and β-thalassemia.[90-93] Pro-thrombotic disorders have been observed in one third to two thirds of children with CVST, which can be congenital or acquired.[89-90]

Clinical Manifestations

Presenting symptoms of CVST in children can be variable and nonspecific. Infants may present with a wide spectrum of clinical manifestation from nonspecific findings such as irritability and a decrease in feeding to lethargy and coma. Older children may present with the triad of unremitting headache, vomiting, and altered level of consciousness.[94] Commonly associated findings include seizures and signs and symptoms of increased intracranial pressure (papilledema and sixth nerve palsy).[89,94] Because of the association with meningitis, mastoiditis, and otitis media, the presence of these signs and symptoms should prompt the practitioner to pursue further laboratory evaluation of CVST.

Imaging and Laboratory Evaluation

When CVST is suspected, strict attention to maintenance of adequate airway, breathing, circulation, and close monitoring of neurologic status should be performed

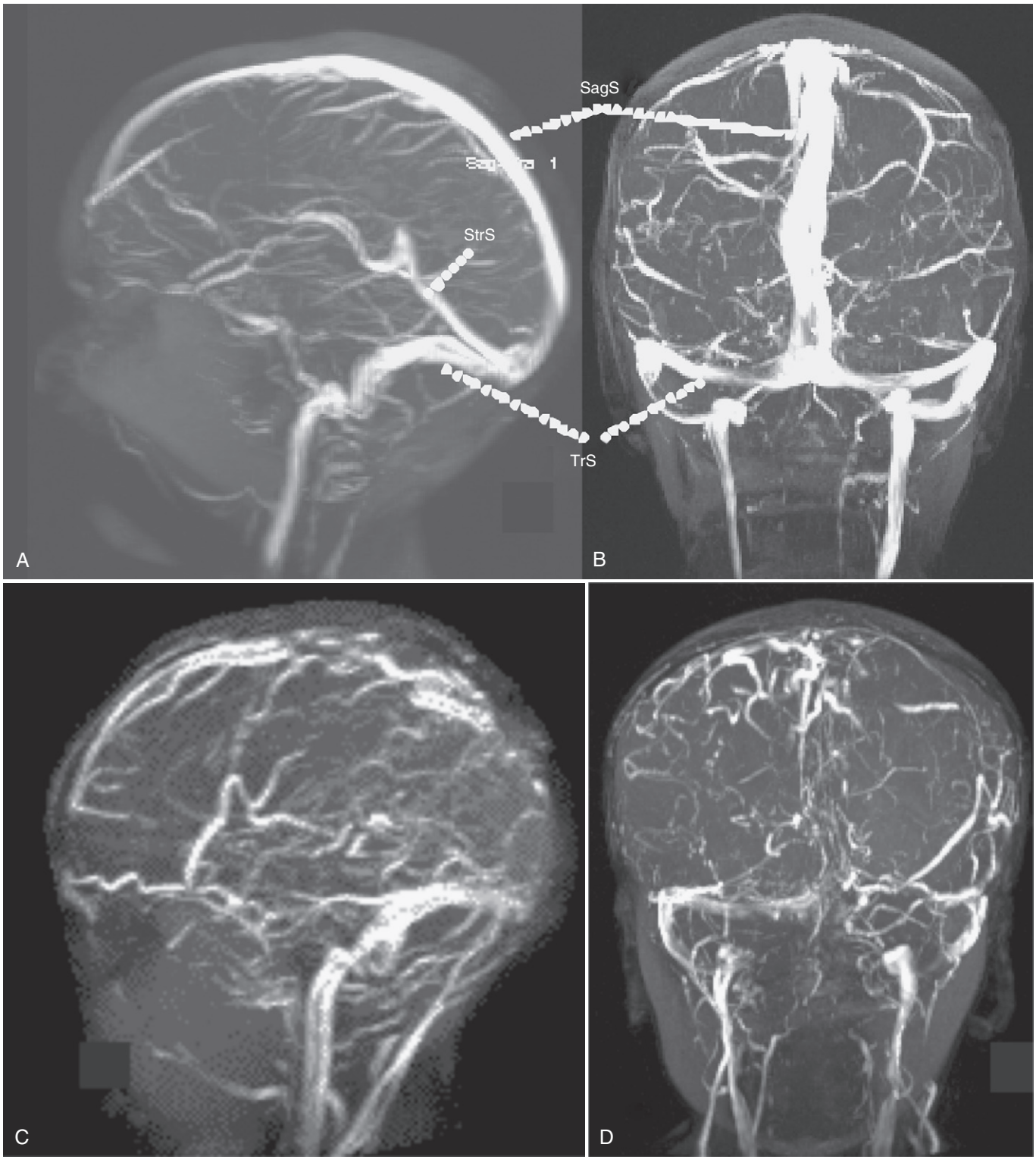

Figure 63–6. Normal MR venogram in a child, sagittal (**A**) and coronal (**B**) views. MR venogram (**C, D**) in an 18-month-old boy with iron deficiency anemia presenting with lethargy, vomiting, and quadriparesis shows absence of flow-related signal in sagittal sinus (*SagS*), straight sinus (*StrS*), and both transverse sinuses (*TrS*).

throughout the acute evaluation process because there is risk of rapid progression and death.[90] With the advent of contrast-enhanced CT and MRI, early diagnosis of CVST in children has become possible. Nonenhanced CT imaging commonly discloses hyperdense venous sinuses, whereas contrast-enhanced CT may demonstrate filling defects in the sagittal sinus. Imaging via head CT alone, however, is associated with a high rate of false positives, and CVST may be missed in up to 40% of patients.[89,95,96] MRI with magnetic resonance venography is more sensitive but may require the use of sedation in younger patients (Figure 63-6). CT venography is a sensitive and specific alternative to

MRI, but it has the disadvantage of radiation exposure. Laboratory evaluation for CVST should include a complete blood cell count and thrombophilia studies. In one cohort of children with CVST, 52% were found to be anemic.[10,90] If a bacterial etiology is suspected, cultures should be taken and appropriate imaging should be performed. Previous studies have observed pro-thrombotic abnormalities in a significant number of children with CVST (32% to 45%).[10,89,90]

Treatment

Supportive measures should be started immediately. Airway patency, oxygenation, and ventilation need to be maintained at all times. If endotracheal intubation is indicated, it should be performed with caution because there maybe on going intracranial hypertension. Dehydration should be treated with intravenous fluids and anticonvulsants should be administered for control of seizures.[97] If a bacterial etiology is suspected, appropriate broad-spectrum antibiotics should be administered as soon as possible.

Anticoagulation in adult patients with CVST has been shown to be safe and provide clinical benefit.[98,99] Smaller studies in children with CVST have demonstrated that anticoagulation with heparin can be safely administered with monitoring of activated partial thromboplastin time when using UFH or anti-factor Xa levels when using LMWH.[90,100] In a small prospective study of 30 children with CVST, three of the eight children who did not receive anticoagulation therapy died compared with no deaths in the 22 children who did receive anticoagulation therapy.[90] In patients with CVST, venous infarcts with hemorrhage may develop, and small studies in adults have shown that anticoagulation for CVST in the presence of intracerebral hemorrhage is safe.[99,101] The pediatric literature is sparse, with case reports of anticoagulation with intracerebral hemorrhage, but consensus statements conclude that anticoagulation is reasonable in these cases.[10,90,102] Close monitoring in the intensive care unit during initial anticoagulation in these patients would seem to be prudent. Thrombolysis, thrombectomy, and surgical decompression have been reported to be successful in small case series of severely affected adults and children.[103-106] The duration of anticoagulation can vary, but 3 to 6 months is recommended.[10]

Prognosis

In the Canadian Pediatric Ischemic Stroke Registry study, the mortality rate for children with CVST was 8%.[89] Other studies have reported higher mortality rates (13%), with neonates having the highest death rates (25%).[97] Seizures at presentation and the presence of infarcts (nonhemorrhagic or hemorrhagic) have been observed to be predictors of adverse neurologic outcome.[89] In a prospective study of 42 patients, older age, lack of parenchymal abnormalities, anticoagulation, and lateral and/or sigmoid sinus involvement were all independent predictors of good outcome.[90] Long-term follow-up of children with CVST has found that they may have residual mild cognitive deficits.[107] Children with CVST are at risk for recurrence, and one multicenter database reported that in 6% of children recurrent thrombosis developed during an average of 36 months of follow-up.[108] Half of these children's recurrent thrombosis was intracranial.

Spontaneous Intracranial Hemorrhage

Spontaneous intracranial hemorrhage (ICH) is customarily broadly defined to include intraparenchymal hemorrhage, hemorrhagic transformation of ischemic stroke, and intraventricular and subarachnoid hemorrhage (SAH) of nontraumatic origin. Each of these subtypes of ICH differs in terms of underlying causes, treatment approaches, and prognosis. A variety of conditions and risk factors predispose children to ICH and carry a variable risk of recurrence. Many of these patients can present with a sudden and rapidly deteriorating clinical picture, requiring emergent stabilization by the intensivist and rapid diagnosis to implement lifesaving treatment.

Epidemiology

The incidence of spontaneous intracranial hemorrhage in children has been reported to be equal if not higher than AIS, at 1.1 to 1.5 per 100,000 children per year.[1,2,4] The peak age for incidence is in the first year of life with the exception of SAH, which peaks in adolescence.[5] Arteriovenous malformations (AVMs) account for 14% to 46% of hemorrhagic stroke and almost 50% of intraparenchymal hemorrhages.[2,109-111] More than 75% of symptomatic AVMs present with hemorrhage, and the majority of them are supratentorial in location. The risk of hemorrhage in children with known AVMs is 2% to 4% per year, and 25% of these hemorrhages will be fatal.[112,113] Cavernous malformations are reported to be the cause of up to 25% of cases of pediatric intraparenchymal hemorrhage.[111] They may increase in size over time because of repeated bleeding and calcification, producing a typical "bull's eye" appearance on MRI (Figure 63-7).[114] For untreated cavernous malformations, the risk of recurrent hemorrhage has been reported at 4% to 5% per year.[115-117]

Congenital and acquired coagulation disorders are also risk factors for spontaneous ICH. In one series of 68 children, 10 children had coagulation disorders including factor VIII deficiency, coagulopathy due to hepatic failure, or vitamin K deficiency.[118] In this same series, an additional eight children were found to have thrombocytopenia. The risk of spontaneous (nontraumatic) ICH correlates with the severity of the coagulation disorder or thrombocytopenia.[119,120] Platelet counts higher than 20,000 appear to minimize the risk of nontraumatic ICH with thrombocytopenia.[121,122] Systemic hypertension, a common cause of spontaneous ICH in adults, has rarely been observed to be a risk factor in children.[118]

Intracranial aneurysms causing ICH are relatively rare in the pediatric population. Symptoms are most common before the age of 2 years or after the age of 10 years. Like adults, children with ruptured aneurysms usually present with SAH, but they also may present with intraparenchymal or intraventricular hemorrhage. Children are more likely to have giant aneurysms and posterior circulation involvement compared with adult patients. Up to 20% of adult patients with an aneurysm will be found to have more than one aneurysm, compared with 5% of pediatric patients. Pediatric aneurysms can be associated with various congenital conditions including

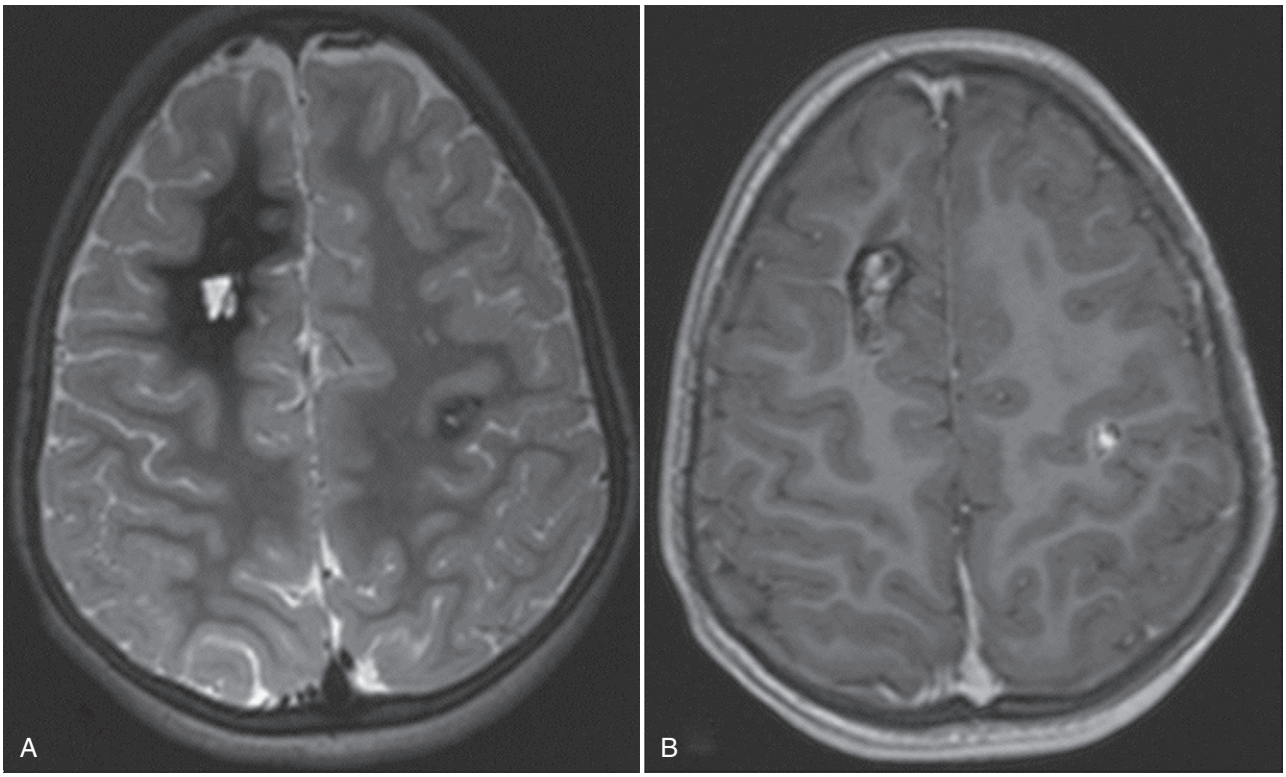

Figure 63–7. T2 (**A**) and T1 (**B**) MR images of a large right frontal cavernous hemangioma and an additional small cavernous hemangioma in the left perisylvian region.

coarctation of the aorta, Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease, and fibromuscular dysplasia.[123-127]

Clinical Manifestations

ICH in the infant can present with subtle and nonspecific findings unless the hemorrhage involves the motor pathways or the brainstem.[10] Infants with arterioventricular fistula or vein of Galen malformation may present with high output cardiac failure or hydrocephalus.[128] If a vein of Galen malformation is suspected, a bruit maybe auscultated by placing the bell of stethoscope on the child's head. Older children with ICH have a presentation similar to that of adults, with repeated forceful vomiting and sudden headache, often described as the worst headache the patient has ever experienced. They also can present with seizures (focal or generalized), hemiparesis, and coma.[118] Signs and symptoms can progress quickly with rapid deterioration in neurologic status to coma, herniation, and death unless promptly recognized and treated.

Evaluation

Rapid stabilization and diagnostic imaging to determine the presence of ICH and its etiology is essential. Unenhanced CT has good sensitivity and specificity in identifying the presence and location of ICH (intraventricular and intraparenchymal vs. SAH) and associated mass effect and shift, such as subfalcine and uncal herniation. A complete blood cell count and a coagulation profile should be ordered to evaluate for hematologic risk factors. Vascular imaging is usually necessary to determine the etiology of intraparenchymal hemorrhage. MR angiography, brain MRI, and CT angiography are often performed and can provide specific and complementary information in identifying underlying lesions. MRI is the most specific and sensitive modality for identifying cavernous malformations. In cases where an AVM or aneurysm is suspected, catheter angiography is necessary for diagnosis and surgical planning. Repeat catheter angiogram is typically performed in the immediate postoperative period and again at 1- to 5-year intervals through late adolescence in children with ICH due to AVMs, because these lesions are known to recur and cause recurrent hemorrhage (Figure 63-8).

Treatment

Initial treatment should include optimization of oxygenation and ventilation. Systemic hypertension should be controlled to prevent further intracranial bleeding. Seizures should be controlled with antiepileptic drugs, and fever should be treated aggressively. Intracranial hypertension should be managed with hyperosmolar therapy (i.e., mannitol or hypertonic saline solution), titration of $Paco_2$ to 35 to 40 mm Hg, and elevation of the head of the bed to 30 degrees. Ventriculostomy drain placement can be both diagnostic and therapeutic. It allows for the drainage of fluid to relieve intracranial pressure due to intraventricular hemorrhage and hydrocephalus as well as intracranial pressure monitoring. If central venous access is needed for hyperosmolar therapy or circulatory stabilization, care should be taken in choice of insertion site, because cerebral angiography and endovascular interventions may be necessary.

Children with ICH should have treatable hematologic abnormalities corrected to prevent further bleeding. The

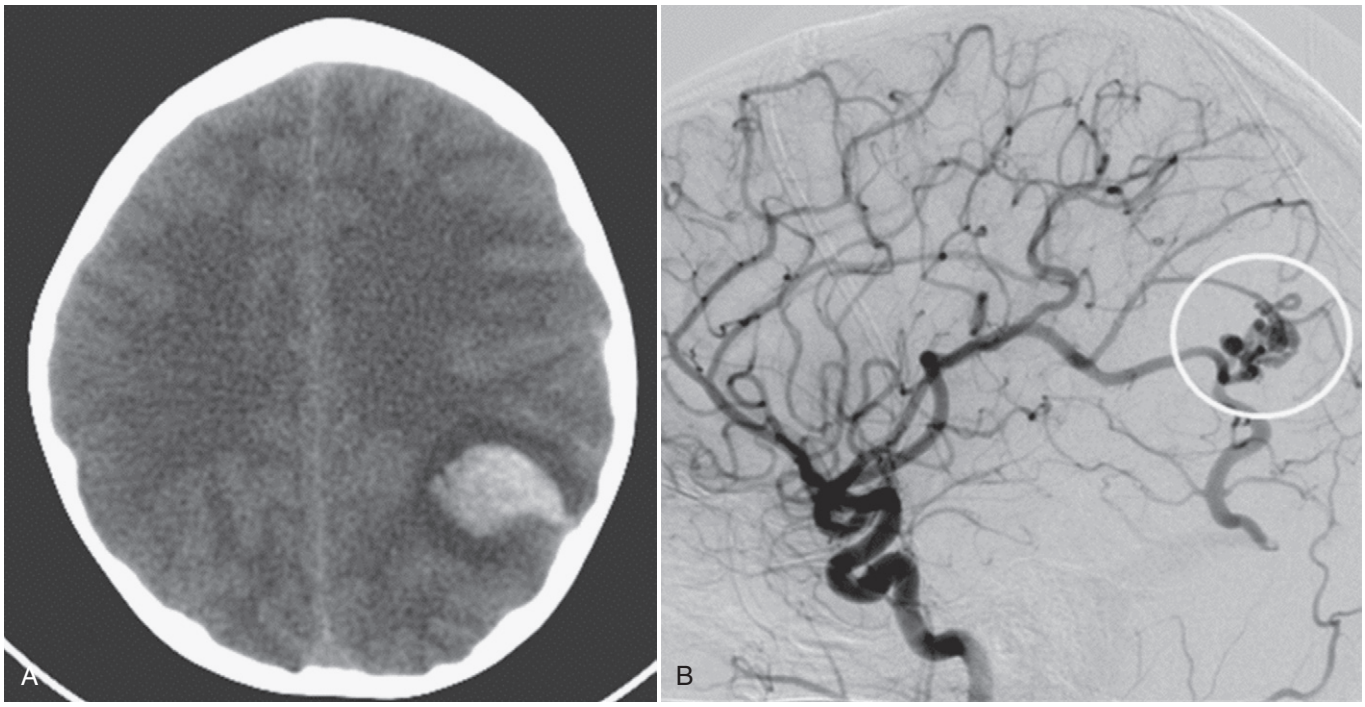

Figure 63–8. Severe headache, vomiting, and confusion develops in a 9-year-old healthy boy. **A,** A head CT scan shows left parietal parenchymal hemorrhage. **B,** An angiogram shows arteriovenous malformation (*circle*) being supplied by the left middle cerebral artery in nidus of hemorrhage.

efficacy of recombinant activated factor VII (rFVIIa) administration in adults with acute hemorrhagic stroke is unclear. A phase IIb trial in adults demonstrated reduction in ICH growth and improvements in mortality and functional outcomes when rFVIIa was administered within 4 hours of onset.[129] A larger follow-up study did not reproduce the improvements in survival and function.[130] The role of rFVIIa in children with ICH has not been determined, and currently it is only recommended in children with severe factor VII deficiency.[10]

Because of the years of cumulative risk of hemorrhage in children with AVMs, removal and/or embolization of the lesion with endovascular embolization, surgery, stereotactic radiotherapy, or a combination of these procedures is usually performed. Cavernous malformations have similar cumulative risk for hemorrhage in children and have been successfully treated with surgical removal or stereotactic radiotherapy.[131-133] Although clinical trials in adults have not proved a benefit for early hematoma evacuation, this approach has not been well evaluated in children. It is widely accepted that acute hematoma evacuation, sometimes combined with decompressive craniectomy, may be life saving in selected children with large lesions in the cerebral hemisphere and cerebellum resulting in impending herniation.[134-136] Intracranial aneurysms are treated with both surgical microvascular and endovascular techniques.[137,138]

Prognosis

Overall prognosis is heterogeneous and is highly dependent on the etiology of the hemorrhagic stroke and the risk of recurrence. The mortality rate for children with cerebral aneurysms is 20%, and poor outcomes are related to delay in diagnosis and rebleeding prior to endovascular or microsurgical treatment.[137,139] Approximately two thirds of patients will have good outcomes (Glasgow Outcome Score of 5) following treatment.[139] A long-term follow-up of 56 children with hemorrhagic stroke of all etiologies found that 13 children died during the initial phase and seven additional children died during long-term follow-up.[140] Of the remaining survivors, only 25% were without physical or cognitive deficits, but almost all were functionally independent.

References are available online at http://www.expertconsult.com.

Acute Neuromuscular Diseases and Disorders

Maria B. Weimer, James J. Reese Jr., and Ann H. Tilton

PEARLS

- **Some causes of acute flaccid paralysis in childhood**
  - Guillain-Barré syndrome (GBS)
  - Botulism
  - Tick paralysis
  - Periodic paralyses
  - Organophosphate poisoning
- **Risk factors for respiratory failure in GBS**
  - Elevated cerebrospinal fluid protein in first week of disease
  - Short time interval between prodrome and onset of GBS symptoms
  - Cranial nerve involvement
  - Myasthenia gravis symptoms
  - Ptosis
  - Diplopia
  - Pupillary sparing
  - Weakness that waxes and wanes
- **Asbury criteria for GBS**
  - Required criteria
    - Progressive motor weakness of more than one limb
    - Areflexia
  - Supportive criteria
    - Symmetry of symptoms
    - Mild sensory changes
    - Cranial nerve involvement
    - Autonomic symptoms
  - Recovery begins 2 to 4 weeks after symptom progression discontinues
- **Differential diagnosis in hypokalemic periodic paralysis**
  - Bartter syndrome
  - Corticosteroids
  - Diuretics
  - Hyperaldosteronism
  - Laxatives
  - Licorice
  - Renal tubular acidosis
  - Amphotericin B
  - p-Aminosalicylic acid
  - Alcoholism
  - Villous adenoma
- **Acute management of hypokalemic periodic paralysis**
  - Oral potassium is preferred unless there is an inability to swallow or there are cardiac symptoms
  - Avoid intravenous fluids with dextrose or physiologic saline solution
  - Vigilant cardiac monitoring
  - Serial potassium levels
  - Serial muscle strength examinations
- **Botulism symptoms**
  - Weak cry
  - Poor suck and swallow
  - Decreased tone
  - Decreased reflexes
  - Weakness in descending pattern
  - Constipation
  - Autonomic symptoms
  - Tachycardia
  - Fluctuating blood pressure
  - Urinary retention
  - Decreased tears and saliva
  - Flushed skin or pallor

Neuromuscular diseases, which encompass the entire motor unit, may have similar presentations initially and must be deciphered in a methodical manner. The motor unit consists of the anterior horn cell, which is located in the spinal cord and terminates in a motor nerve; the myelin associated with the nerve; the neuromuscular junction; and the muscle that the nerve innervates. Any disruption of function in this pathway may produce weakness of some variety. Neuropathies and myopathies have similar clinical findings, including weakness and decreased or absent reflexes. These disease processes may be distinguished, however, by sensory abnormalities and the distribution of the weakness. Neuromuscular junction defects may have reflexes present, as in myasthenia gravis, or absent, as seen in tick paralysis. The clinician can narrow the etiologic possibilities by considering the clinical presentation, family history, recent illness, travel history, inciting factors, and the clinical course.

This chapter is devoted to acute neuromuscular diseases that may be seen in a pediatric intensive care unit (PICU). Although

clinicians may encounter a variety of neuromuscular illnesses, this chapter begins with the most common disorders seen in the PICU. Weakness due to spinal cord or other central nervous system abnormalities are discussed in a separate chapter.

Guillain-Barré Syndrome

The most common acute neuromuscular disease seen in the intensive care unit is Guillain-Barré syndrome (GBS). When given the history of an ascending paralysis, a clinician can easily place GBS in the differential diagnosis; however, this history may be difficult to obtain, particularly if the patient is a small child or an infant. GBS is the most common cause of acute flaccid paralysis in children. The incidence is estimated to be 0.38 to 1.1 per 100,000 in a population younger than 15 years.[1,2] A prodromal respiratory or gastrointestinal illness is commonly found in the history. The prodromal illnesses may include *Campylobacter jejuni* and cytomegalovirus. In one study, 70% of patients reported an illness before the onset of symptoms, with 26% having documented cytomegalovirus.[3]

The neurologic symptoms typically present with progressive paralysis that is relatively symmetrical and may evolve to all extremities. Other symptoms include varying degrees of hyporeflexia or areflexia, or even respiratory embarrassment. Other presentations may include acute ataxia, pain, or cranial neuropathies.[4,5] In one study, risk factors for patients requiring ventilation included cranial nerve involvement, elevated cerebrospinal fluid (CSF) protein during the first week of illness, and a short period between antecedent illness and onset of symptoms.[6]

Autonomic symptoms, which may be overlooked, also are present in some cases. Autonomic instability, particularly cardiac arrhythmias, increase the morbidity of this disease. Cardiac monitoring of the R-R interval with reduction of beat-to-beat variability may possibly identify patients at risk for fatal arrhythmia.[7] Cardiac arrhythmias induced by tracheal tube manipulation have been reported.[8]

Asbury and Cornblath[9] have established criteria for the diagnosis of GBS. Per their criteria, the features that are required for the diagnosis include progressive motor weakness of more than one limb and areflexia. Symptoms that are strongly supportive of GBS include the relative symmetry of symptoms, mild sensory symptoms, cranial nerve involvement, autonomic symptoms, and recovery that usually begins 2 to 4 weeks after symptom progression discontinues. Sphincter disturbances rarely occur early in the course of GBS and are usually transient.[10]

Diagnostic studies include examination of the CSF and nerve conduction studies. The CSF reveals elevated protein amid a relative paucity of white blood cells, usually less than 10 cells/mL, with the protein increasing after the first week of symptoms.[9] Electrodiagnostic testing reveals motor conduction velocities in the demyelinating range, conduction block, temporal dispersion, and prolonged F waves. Bradshaw and Jones[4] reported that conduction block and temporal dispersion occurred in 74% of patients.

If the symptoms are severe, treatment options for GBS include plasmapheresis and administration of intravenous immunoglobulin (IVIg). In 2003 the American Academy of Neurology published a practice parameter after reviewing the adult literature and made several recommendations.[11] First, plasmapheresis and IVIg both hasten recovery, and neither is more efficacious. Using these two treatments sequentially is not superior to using either treatment alone. Finally, steroids do not seem to help. The decision of which therapy to apply to children is controversial because a large randomized study has not been performed. Plasmapheresis may be technically difficult to perform in young or very small children; therefore immunoglobulin may be used with more ease. Results from one adult study in which the two methods were compared showed that 53% of the patients treated with immunoglobulin improved by one or more grades on the functional scale at 4 weeks compared with 34% of the patients treated with plasmapheresis.[12] Favorable improvement in pediatric patients treated with immunoglobulin has been reported in several small series.[13-16] More recently, a randomized trial in children showed that fewer relapses occurred if 2 g/kg of IVIg were divided over 5 days instead of 2 days.[17] If additional courses of IVIg are necessary, a 2-day protocol is often well tolerated.

Several GBS variants exist. The best known are the Miller-Fisher variant and acute inflammatory axonal polyneuropathy, the axonal form of GBS. The neurologic triad found in the Miller-Fisher syndrome includes ataxia, areflexia, and ophthalmoparesis. Miller-Fisher syndrome has been linked to immunoglobulin G antibodies against ganglioside GQ1b.[18] In some *C. jejuni* strains, molecular mimicry exists between the surface epitopes and ganglioside GQ1b.[19] The GQ1b ganglioside is thought to cross-react in the brainstem area of the ophthalmic cranial nerves.[20] The axonal form of GBS has been associated with a more prolonged recovery than the classic form of GBS, which is attributed to axonal involvement. Early research suggests that CSF levels of neurofilament correspond to levels of axonal damage on electromyographic (EMG) testing and may help complement EMG studies to help predict patients who will have more prolonged recoveries.[21,22]

Myasthenia Gravis

Myasthenia gravis (MG) has many forms that may present in the pediatric population. The juvenile form of MG is the most common and is clinically identical to the autoimmune adult form of MG. Overall, however, juvenile MG is rare and comprises 10% of all cases of MG in Western populations. Antibodies directed toward the acetylcholine receptor (AchR) at the postsynaptic neuromuscular junction cause this form of the disease. These antibodies result in blockade of the AchR, increase the degradation of the AchR, and also result in complement damage to the AchR.[23] Fenichel[24] reported that 75% of cases occur after age 10 years; however, this age of onset has been debated in recent years.[25,26] AchR antibodies are found less frequently in juvenile MG compared with adult autoimmune MG and are more easily shown in the postpubertal patient population.[27] Anticholinesterase antibody levels should be determined, however, in all patients with suspected MG. Newer assays are finding antibodies previously missed in older anticholinesterase antibody assays, including binding, blocking, and modulating, but these assays may need to be ordered separately.[28-30]

The most common heralding symptoms of weakness in MG include ptosis (with pupillary sparing) and diplopia (from restricted eye movements). These symptoms wax and wane, and the weakness may generalize to the extremities. The two clinical forms of juvenile MG are ocular and generalized. In

ocular MG, symptoms include ptosis and diplopia, but the weakness does not progress to other areas of the body. Generalized MG may begin with ocular symptoms and progress to generalized weakness, usually within 1 year of onset; however, generalized weakness may be the initial presentation. The exact prevalence of generalized compared with ocular forms of juvenile MG is disputed. As in adults with MG, pediatric patients have the fewest symptoms in the morning or after rest, with increasing fatigability with exercise being a hallmark of this disease. The most troublesome symptoms seen in generalized MG are those involving bulbar and respiratory muscles, which may result in difficulty chewing or swallowing and exercise intolerance.

When a patient is suspected to have MG, the classic diagnostic bedside test is the edrophonium (Tensilon) challenge. Edrophonium is an intravenous short-acting anticholinesterase preparation that is no longer available in many hospitals. The dosing is 0.15 mg/kg in infants and 0.20 mg/kg in older children. Only 10% of the entire dose is given initially so that the clinician can observe for muscarinic adverse effects. Atropine (0.015 to 0.040 mg/kg) should be available for these possible adverse effects, which include bradycardia and respiratory distress resulting from bronchial secretions and bronchospasm. After the trial dose is tolerated, the entire dose is then given. In lieu of edrophonium, neostigmine is given at a dose of 0.025 to 0.050 mg/kg intramuscularly. The patient should be observed during the trial for changes in ptosis or fatigability. The onset of action with edrophonium is approximately 30 to 90 seconds after intravenous delivery and remains for approximately 5 minutes. Neostigmine has an onset of action within 15 minutes, and effects may last for 1 hour. Many clinicians also perform a blinded placebo trial of normal saline solution.

The neurodiagnostic study used in patients with suspected MG is repetitive nerve stimulation. This study is best performed on proximal muscles, although distal muscles are often studied. The confirmatory finding on repetitive nerve stimulation is a 10% decrement in amplitude of the compound muscle action potential.

Antibodies have been found that can block, bind, or modulate AChR. Approximately 80% of patients will have antibodies to AChR found in standard assays. Antibodies directed against muscle specific kinase (MuSK) appear to account for some of the remaining 20%.[28] Newer, more sensitive assays can also find antibodies with low affinity for AChR.[30] Clinically, MuSK-positive patients tend to have more frequent bulbar involvement and respiratory crises than do AChR-positive patients and require larger doses of maintenance corticosteroids, although there is no clear difference in clinical outcomes.[31] Seronegative (AChR-negative and MuSK-negative) patients have a disease severity between the other two groups but appear to have better clinical outcomes.[31]

Treatment of MG begins with anticholinesterase medications. The symptoms of MG usually respond to pyridostigmine bromide (Mestinon), the most common oral form of anticholinesterase medication. The dosage of pyridostigmine bromide is 7 mg/kg/day divided four to six times daily as needed for symptoms. Immunosuppressant agents, including prednisone, azathioprine, cyclophosphamide, and tacrolimus, may be added to the regimen for pyridostigmine nonresponders.[32] Mycophenolate also may be prescribed, although it has not proved more efficacious than placebo in two randomized trials of patients already taking prednisone.[33,34] Prednisone is usually initiated at 1 to 2 mg/kg/day. Clinicians must be careful when using prednisone because it may exacerbate weakness on initiation.

Many studies have suggested that the beneficial effects of thymectomy are best when it is performed early in the course of MG.[27,35,36] Because of the spontaneous remission rate of 22.4 per 1000 person-years reported by Rodriguez et al.,[37] as however, many clinicians are reluctant to proceed with early thymectomy, particularly with young children.

Myasthenic crisis is an exacerbation of myasthenic symptoms requiring ventilatory assistance. In adults with MG, myasthenic crisis has been reported to occur in 15% to 20% of patients, with 74% having their first crisis within 2 years of disease presentation.[38,39] Anlar et al.[40] reported that one third of patients with juvenile MG had at least one episode of crisis. Crisis duration in adults has been reported as having a median duration of 13 days by Thomas et al.[39] Initial therapy during crisis includes mechanical ventilation, which provides rest for the weakened patient. Two retrospective studies suggest that the use of biphasic positive airway pressure) may prevent intubation and shorten hospital stay.[41,42] In each study, hypercapnia was a predictor of biphasic positive airway pressure failure.[41,42]

Anticholinesterase medications should be discontinued because they increase secretions that could lead to mucous plugging. Myasthenic crisis is most commonly heralded by infection in 38% of patients; however, 30% of patients have no obvious trigger for their crisis other than respiratory or bulbar weakness.[39] A thorough investigation for the cause of the crisis should be undertaken. The mortality rate has fallen with improvements in health care; however, Thomas et al.[39] recently reported a 10% mortality rate in patients with myasthenic crisis.

Plasmapheresis and IVIg (2 g/kg over 2 to 5 days) also play a role in the treatment of myasthenic crisis and acute exacerbations of myasthenic symptoms. In cases of adult crisis, plasmapheresis has been shown to be more efficacious than IVIg; however, plasmapheresis has more deleterious adverse effects, including cardiovascular and infectious complications.[43] In the first randomized adult trial between plasmapheresis and IVIg, no significant difference was found between the two treatments; however, this study also included myasthenic exacerbations, as well as crisis.[44] Only small numbers of juvenile MG exacerbations or crisis treated with IVIg have been reported.[45,46] These reports have been favorable for IVIg in acute exacerbations of MG.[45,46] IVIg has been shown to be superior to placebo in a randomized controlled trial, with significant improvements seen as early as 14 days after infusion and lasting through 28 days.[47] Several dosing regimens have been used. The previous study used 2 g/kg divided over 2 days; another study failed to find a difference between a 1 g/kg dosage of IVIg given over 1 day and a 2 g/kg dosage given over 2 days.[48] Evidence supports the use of IVIg to treat patients experiencing myasthenic crisis or to treat an exacerbation in patients in whom plasmapheresis is not feasible.

Cholinergic crisis must also be a consideration in a patient with an MG exacerbation. Cholinergic crisis occurs with an overdose of anticholinesterase drugs in patients with MG. The overdose causes depolarization of skeletal muscles and muscarinic adverse effects, including increased secretions, diarrhea, lacrimation, sweating, and bradycardia. These symptoms will

improve upon withdrawal of the anticholinesterase medications. Some authors argue that cholinergic crisis is rarely the cause for worsening myasthenic symptoms.[38,49]

The clinician must always be cautious when initiating new medications in patients with MG. Many drugs interfere with the neuromuscular junction; the drugs best known for doing so are the aminoglycoside medications. Steroids can exacerbate weakness in a patient with MG, although this potential is not well recognized. For this reason one must be cautious when initiating the use of prednisone in a patient with refractory MG; it is necessary to observe the patient closely for any initial increased weakness. Antibiotics that have been implicated in the worsening of myasthenic symptoms include ampicillin, ciprofloxacin, clindamycin, erythromycin, sulfonamide, tetracycline, and the peptide antibiotics (polymyxin A and B and colistin). Cardiovascular medications including antiarrhythmic agents (e.g., quinidine, procainamide, and lidocaine) and β-blockers (e.g., propranolol, timolol, and others) also have been reported to worsen symptoms. Thyroid replacement medications and phenytoin also may cause problems. The neuromuscular junction blockers, including vecuronium, rocuronium, and pancuronium, as well as succinylcholine, should be used with caution because the effects of these medications are prolonged in patients with MG.[49,50] The Myasthenia Gravis Foundation of America maintains a list of medications to avoid and to use with caution on their Web site at www.myasthenia.org.

Additional immune diseases have been associated in approximately 16% of patients with juvenile MG.[37] The autoimmune diseases may include asthma, rheumatoid arthritis, juvenile diabetes mellitus, hyperthyroidism, chronic inflammatory demyelinating polyneuropathy, and central nervous system demyelination.[25,37,51,52] Seizures have occurred in 4% to 12% of patients with juvenile MG, although the exact cause is not known.[25,37]

Congenital and Transient Neonatal Myasthenia Gravis

The other forms of MG are congenital MG and neonatal transient MG. Neonatal transient MG is unique in neonates who are born to mothers with autoimmune MG. Neonates can manifest symptoms of neonatal transient MG even if the mothers were symptom free during pregnancy and delivery. Neonatal transient MG occurs in approximately 12% of infants born to mothers with MG.[53] If a mother with MG gives birth to an infant with neonatal MG, her subsequent neonates are also at increased risk of having this transient disorder. Neonatal MG usually resolves in the first few weeks after birth, when the maternally derived antibody level diminishes in the neonate. Results from several studies have shown that even symptom-free infants born to mothers with MG have elevated titers of AchR antibodies.[54] Additionally, the same phenomenon has been reported in infants born to mothers with anti-MuSK.[40] It is not known why some infants appear to be more susceptible than others for having transient neonatal MG. The antibody concentration of the symptom-free neonate rapidly decreases when compared with the antibody concentration of a neonate with symptoms.[55] The symptoms of neonatal transient MG usually include hypotonia, feeding problems (particularly fatigue), weak cry, and respiratory difficulty. These symptoms are treated with supportive care, and anticholinesterase medications are used for severe symptoms.

Congenital MG usually presents in childhood, with symptoms similar to those of juvenile MG. Many defects are responsible for causing symptoms in congenital MG, including congenital abnormalities resulting in presynaptic, synaptic, or postsynaptic defects of the neuromuscular junction.[56] Congenital MG is always negative for Ach antibody, and a family history of congenital MG may or may not be present. The inheritance of congenital MG may be autosomal recessive or dominant, or sporadic.[56] Treatment of congenital MG is different from the treatment of juvenile MG because immunosuppression obviously does not play a role. Symptoms of congenital MG may or may not respond to anticholinesterase medications.

Tick Paralysis

The clinician must always entertain the possibility of tick paralysis in the differential diagnosis of acute flaccid paralysis in children. On presentation, patients with tick paralysis may be mistakenly diagnosed with GBS. The treatment of the two diseases is distinct; therefore a high index of suspicion for tick paralysis should be maintained.

Affected patients are usually between the ages of 1 and 5 years. A review of 33 patients with tick paralysis reported that 82% were younger than 10 years, and 76% were female patients.[57] Longer hairstyles have been speculated to be the cause of this female preponderance. A thorough search of the patient should ensue because more than one tick may be attached. The ticks most commonly implicated in North America are *Dermacentor andersoni* (wood tick) and *Dermacentor variabilis* (dog tick)[58]; however, other types of ticks have been documented. In Australia, the most common tick variety to cause paralysis is *Ixodes holocyclus*.[58] The cause of the weakness is a neurotoxin that is secreted in the saliva of the gravid female tick. The neurotoxin is produced during the engorgement phase of feeding after mating. The neurotoxin inhibits the release of acetylcholine at the presynaptic terminal.[58]

The symptoms in North American hosts begin with vague complaints of fatigue, irritability, and pain. Vague symptoms may not begin until approximately 5 days after tick attachment, but they progress rapidly.[59] Symptoms may include cerebellar signs, such as ataxia.[59] If the tick remains attached, a symmetrical ascending flaccid paralysis with areflexia develops. Subsequently, bulbar and facial weakness as well as respiratory involvement occur. No systemic features are seen in tick paralysis. Patients are afebrile with normal vital signs, erythrocyte sedimentation rate, CSF, and mental status. The removal of the tick results in the rapid reversal of symptoms, usually within 24 hours.

Upon discovery, the tick needs to be promptly removed. Removal of the tick is performed with blunt curved forceps or tweezers. The tick should be grasped at the point of attachment, as close to the skin as possible. The tick should be pulled upward with steady pressure. Twisting or jerking motions may cause parts of the tick to break off, particularly the mouth parts. The tick should not be handled with bare hands. Needham[60] evaluated various methods of tick removal including fingernail polish, petroleum jelly, 70% isopropyl alcohol, and a hot kitchen match. None of these passive techniques induced tick detachment.

Tick paralysis is more severe in Australia than in North America. The presenting symptoms are similar to those in

the North American cases; however, ocular involvement with nonreactive pupils has been described.[61] Flaccid paralysis may take days to evolve, unlike in North American hosts. The major difference in Australian tick paralysis occurs after the tick is removed. Australian patients must be carefully observed because maximal weakness may not occur until 48 hours after tick removal.[61] Another distinguishing feature of Australian tick paralysis is the possible use of an antitoxin for treatment. The antitoxin, a canine hyperimmune serum, is used cautiously in humans because of potential reactions, including serum sickness.[61] Efficacy of the antitoxin remains uncertain because no controlled studies have been performed.[61]

Periodic Paralyses

Clinicians may encounter several forms of periodic paralysis (PP), including hypokalemic, hyperkalemic, and normokalemic. Persons with most forms of the periodic paralyses have a family history of the disease. The weakness, which eventually results in paralysis, is associated with potassium response as demonstrated in hyperkalemic PP (HyperPP) or potassium serum levels in hypokalemic PP (HypoPP). PP also may be accompanied by cardiac abnormalities, as in Andersen-Tawil syndrome, and thus checking an electrocardiogram may be prudent, regardless of the serum potassium level.[62]

Hypokalemic Periodic Paralysis

HypoPP is the most common form of the periodic paralyses. The presentation of HypoPP usually occurs within the second decade of life. The number of attacks, which may be frequent, usually decrease as patients get older. The rate of occurrence of HypoPP is 1 in 100,000 people. The inheritance pattern of HypoPP is autosomal dominant, with boys/men more frequently affected, but one third of cases are sporadic.[63,64] The most common mutation in familial HypoPP is the dihydropyridine receptor in the voltage sensitive Ca channel, located on chromosome 1q.[65] Another common mutation is a voltage-sensitive sodium channel, SCN4A.[64,66] In a minority of cases no mutation is found.[67]

The onset of symptoms in persons with HypoPP usually occurs after the consumption of a high-carbohydrate meal or after vigorous exercise followed by rest. Other provoking factors include cold temperature, emotional stress, menses, and pregnancy.[64,66,68] In one study of a large affected family, Chinese food was specifically cited as a specific provocative factor.[68] Weakness usually begins during sleep with the patient noticing weakness upon awakening. The weakness usually begins proximally in the legs and then progresses distally before the upper extremities become involved; it may progress to flaccid paralysis of all limbs with areflexia and normal sensation. Cranial nerve function remains normal, and swallowing and respiratory function are rarely affected. The patient remains alert with a normal mental status during the attack, and sensation remains intact. Weakness usually lasts a few hours but may last several days. Upon noticing the initial symptoms of mild muscle cramping or "heaviness," however, some patients are able to abort an attack with light exercise.[69] Sudden death from cardiac arrhythmias or respiratory failure has been reported.[70,71] During paralytic attacks, patients have minimal urine output, with decreased potassium excretion and absent defecation.[68,72] In persons with HypoPP, myotonia confined to the eyelids has been described.[73] Before this report, myotonia was described as occurring only with hyperkalemic periodic paralysis.

Diagnosis of HypoPP can be confirmed with the identification of hypokalemia during an attack. Laboratory testing during HypoPP reveals a markedly diminished potassium level. Although serum potassium levels are decreased, the total body amount of potassium remains normal. The decreased potassium level is due to a shift of the potassium into the muscle cells, resulting in inexcitable muscle cells.[74] During an attack, potassium levels usually fall below 3, but levels below 2 have been reported.[75] Secondary causes of hypokalemia such as Bartter's syndrome, use of corticosteroids and diuretics, hyperaldosteronism, ingestion of laxatives and licorice, renal tubular acidosis, amphotericin B, p-aminosalicylic acid, alcoholism, and villous adenoma must be ruled out.[76]

The paralytic attack may be reversed with normalization of the potassium level. The clinician must be careful when correcting the potassium level, remembering that the total body amount of potassium remains normal. Correction with orally administered potassium (0.2 to 0.4 mmol/kg every 15 to 30 minutes) should be considered. Patients with cardiac symptoms or an inability to swallow, however, require parentally administered potassium.[63] While the potassium level is corrected, vigilant cardiac monitoring, monitoring of serial potassium levels, and muscle strength examinations should be used. Administration of intravenous fluids with dextrose or physiological saline solution should be avoided because they may prolong an attack or even induce cardiac arrhythmias.[76,77] Griggs, Resnick, and Engel[76] reported that a 5% mannitol solution should be considered as a diluent for intravenous potassium replacement.

Links et al.[68] studied a large kindred with HypoPP and showed that all family members older than 50 years had permanent muscle weakness. Muscle biopsy specimens from patients with HypoPP reveal vacuoles in the muscle fibers.[71] Vacuolar changes in the muscle also have been shown in family members of persons with HypoPP who have not had any paralytic attacks.[68] Links et al.[68] concluded from their study that all patients eventually exhibit permanent muscle weakness but that only 60% may have paralytic attacks.

Once a patient is known to have HypoPP, prophylactic medications should be initiated. Acetazolamide has been shown to prevent future attacks in patients with and without a family history of the disease when they take daily doses of 250 to 750 mg.[78] Some patients, however, have been reported to have an exacerbation of attacks when taking acetazolamide.[79] Another report revealed that acetazolamide prophylaxis improved strength between attacks in 80% of patients who displayed persistent weakness between paralytic attacks.[78] Daily oral ingestion of potassium chloride shortens the duration of the attacks but does not appear to prevent attacks.[78] Other medications used for prophylaxis of attacks include triamterene and spironolactone in patients who are not responsive to acetazolamide.[78,79] Other considerations for the prevention of attacks include avoidance of high-sodium, high-carbohydrate meals as well as arduous exercise followed by prolonged rest.

Thyrotoxic periodic paralysis is another entity of weakness with concomitant hypokalemia. As the name implies, a thyrotoxic state is the impetus of this disease. It is mostly found in adult Asian boys/men, although it has been reported in the Asian-American pediatric population.[80] The purpose of

treatment of this disease is to alleviate the hyperthyroid state (also see Chapter 77).

Hyperkalemic Periodic Paralysis

The term *hyperkalemic periodic paralysis* (HyperPP) may be misleading because high, normal, and low levels of potassium have been reported in these attacks.[81] The name "HyperPP" actually correlates to the response these patients have to potassium. HyperPP is also referred to as potassium-sensitive PP, a term that may be more appropriate and less confusing. HyperPP is autosomal dominant with a common gene located on chromosome 17q, affecting the alpha subunit of the sodium channel, but other sodium channels also may be affected.[64,82,83] Sporadic cases have been reported.[64,84] HyperPP usually presents in the first decade of life.

Rest after exercise is the most common provoking feature of HyperPP. Other provoking factors include cold temperatures and skipping meals. The pattern of weakness is similar to that of HypoPP: the legs are usually affected before the arms, with symmetrical weakness. The sensory examination is normal during an attack. Weakness during the attacks varies from mild to flaccid quadriplegia with areflexia, but respiratory weakness rarely occurs. The usual length of attacks is shorter than that of HypoPP attacks; HyperPP attacks usually resolve in a few hours, but they may persist for days. Myotonia and Chvostek's sign are often found in these patients.

Light exercise can prevent an attack. Attacks may be provoked by potassium intake and relieved by glucose intake. Most attacks do not require treatment. In the rare severe attack, however, glucose can be administered intravenously.[85] Cardiac monitoring is important if medical intervention is needed because cardiac arrhythmias may occur.[86] Prophylactic therapy should be considered in these patients because permanent muscle weakness develops over time.[87] Muscle biopsy specimens reveal vacuoles in the muscle cells.[81] Acetazolamide and thiazide agents have been used for prophylaxis of this disease.[88]

Normokalemic Periodic Paralysis

Normokalemic periodic paralysis (NormPP) is a disputed phenomenon. Patients with NormPP have normal potassium levels during an attack and have been shown to be sensitive to potassium.[89] Provoking factors include cold temperatures, alcohol intake, and stress.[89] The kindred described by Poskanzer and Kerr[89] also displayed autosomal dominant inheritance. Therefore it has been argued that this is actually HyperPP, which also is known to display normal values of potassium during an attack. Molecular testing has revealed NormPP mutations in genes associated with HyperPP and HypoPP.[90,91] Treatment of this disease is similar to the treatment of HyperPP.

Botulism

Infantile botulism is a syndrome predominately found in infants ages 6 days to 12 months.[92] In infantile botulism, *Clostridium botulinum* enters the body as a spore through ingestion, germination occurs, and the organism begins to produce the neurotoxin that is the cause of the symptoms.[93] Infant botulism differs from foodborne botulism, in which the preformed toxin is actually ingested. In mouse models, the relationship of the gut and the spores are important, with the pH of the gut and the transient lack of competitive intestinal flora being essential in allowing the spores to germinate.[92] Infants appear to be susceptible, as are adults who have abnormal intestinal flora from abdominal surgery, gut abnormalities, or antibiotic use.[94-97]

Most cases of infantile botulism occur in California, Pennsylvania, and Utah. In one report, more than 75% of the patients with botulism had *C. botulinum* in their home environment.[98] Other sources include soil disruption from cultivation or construction and parental occupations that involve soil exposure.[99] The consumption of honey and corn syrup is a risk factor; these products should not be fed to children who are younger than 12 months. The role of breast-feeding in botulism remains controversial.[100] In one study of 44 patients with botulism, 100% of the patients were breast-fed.[99] Nevertheless, breast milk has been cited as a protective influence against botulism. Arnon et al.[101] reported that of the 10 patients who died of sudden infant death syndrome that was linked to *C. botulinum* infection, eight were fed formula exclusively, and the remaining two patients had not received breast milk 10 weeks before their death. They concluded that breast-fed infants are not completely protected from botulism but appear to have diminished severity of the disease at onset.[101]

The botulinum toxin irreversibly binds at the presynaptic segment of the neuromuscular junction, inhibiting acetylcholine release and causing neuromuscular weakness. The autonomic system is also affected because the toxin binds the acetylcholine-mediated preganglionic parasympathetic and sympathetic synapses, as well as the postganglionic parasympathetic synapse.[102]

The most common symptoms include weak cry, poor suck and feeding, decreased tone with decreased reflexes, weakness in a descending pattern, and constipation.[102] Autonomic symptoms, which often are the first to appear, include constipation, tachycardia, fluctuating blood pressure, urinary retention, decreased tears and saliva, and flushed skin or pallor.[92,103] L'Hommedieu and Polin[103] proposed an algorithm of symptoms beginning with tachycardia and constipation progressing to loss of head control, difficulty feeding, and weak cry. A depressed gag reflex is followed by peripheral muscle weakness and, finally, diaphragmatic weakness. Because of the combination of autonomic and neuromuscular symptoms, the infant with botulism may mistakenly be thought to be septic or dehydrated. Enlarged, sluggishly reactive pupils also may be present but are less common than the other autonomic symptoms.[104]

The consequence of botulism that is of greatest cause for concern is respiratory embarrassment. Schreiner, Field, and Ruddy[102] reported that only 24% of the patients reviewed did not require ventilation or an artificial airway. Patients with botulism also have become apneic during certain procedures, including lumbar puncture and placement of an intravenous catheter.[102] Hypoxic ischemic encephalopathy resulting from respiratory arrest also has been described.[104] Other complications that have been described include syndrome of inappropriate secretion of antidiuretic hormone, urinary tract infections, pneumonia, and autonomic instability.[102] Aminoglycosides exacerbate the neuromuscular blockade and should be avoided in persons with botulism.[105] L'Hommedieu et al.[105] reported that in five patients with

botulism who received aminoglycosides, clinical deterioration was apparent in all of them.

The diagnosis of botulism is clinical but confirmed by isolation of the organism or toxin in stool. EMG in patients with botulism reveals decreased compound motor action potential amplitude and facilitation of the compound motor action potential amplitude with high-frequency repetitive motor nerve stimulation.[106]

The management of patients with botulism has advanced in recent years. Previously, clinicians could offer only supportive care until axonal sprouting could reestablish the neuromuscular junction. The median length of hospital stay was 27 to 37 days, and patients typically required mechanical ventilation for a median of 13 to 16 days.[98,104,107] In patients with respiratory compromise, mechanical ventilation should be instituted until the patient regains protective reflexes and respiratory strength. If patients are unable to tolerate eating orally, nasogastric or nasojejunal feeding should be initiated. Human botulism immune globulin (BIG) has provided the first direct pharmacologic treatment. A randomized, controlled trial has shown that BIG decreased mean hospital stay (5.7 weeks to 2.6 weeks), mean duration of mechanical ventilation, mean duration of feeding through a tube or intravenously, and mean hospital charges with no adverse effects related to BIG.[108] A retrospective article spanning 30 years complemented the randomized trial.[109] Resolution of symptoms occurs in the reverse pattern of presentation, with return of head control appearing to be a reliable measure of improving muscle function.[103]

Diphtheria

Although diphtheria was the leading killer of children in the early 20th century, the United States currently reports fewer than 10 cases of diphtheria annually. Epidemics have occurred in developing countries. Recently the former Soviet Union had a dramatic resurgence of diphtheria, with approximately 48,000 cases reported in 1994.[110]

Although several forms of diphtheria exist, the most common in children is the upper respiratory tract infection. Initial mild infection of the pharyngeal area is followed by tonsillar pseudomembrane formation. The pseudomembrane consists of necrotic epithelium and fibrin, as well as numerous colonies of the bacterium, and may cover the airways and pharynx to the main bronchi down into the smaller bronchi. It can lead to aspiration and ultimately complete obstruction of the airway. Extensive soft tissue edema and lymph node enlargement occur.[111]

Toxic myocardiopathy is estimated to occur in 10% to 25% of patients and is responsible for 50% to 60% of the deaths.[112] Toxic myocardiopathy often arises in the second to third week of illness when the affected individual is improving. Abnormalities of the myocardium, the conductive system, and the pericardium occur. The conductive disturbances are in response to the toxin.[113] Cardiac ectopy is 100% sensitive and specific to predict fatal outcome in children with severe diphtheria.[112]

When severe disease is present, neuropathy is seen in approximately three fourths of the patients.[111] In a classic case of diphtheria, local paralysis of the soft palate occurs 2 to 3 weeks after the beginning of the oropharyngeal infection. Weaknesses of the pharyngeal, facial, and ocular nerves follow. The symmetrical polyneuropathy has a varied onset from 10 days to 3 months following the oropharyngeal infection. The axonal and demyelinating neuropathies are based on the circulating toxins and range from motor weakness to sensory abnormalities in a stocking-glove distribution.[111,112]

The distal ascending weakness and spinal fluid findings are described as being "indistinguishable" from GBS.[112] Additionally, dysfunction of the autonomic function may occur with associated hypertension and cardiac failure, although this phenomenon is rare. Typically the patient recovers completely.

Diagnostically, cultures should be obtained from the nose, throat, and the infected mucocutaneous area. Giving the antitoxin is critical even when there is only a presumptive diagnosis. If the antitoxin is administered on the first day, the mortality rate is 1% compared with a rate of 20% if administration is delayed until the fourth day.[112] Immunoglobulin preparations also have been hypothesized as helpful. The only antimicrobial agents that have been the subject of prospective studies proving efficacy are penicillin and erythromycin.[112]

Airway complications should be anticipated, as should the probability of congestive heart failure and, ultimately, malnutrition. Studies have revealed no difference in the occurrence of carditis, neuritis, or death in patients receiving steroids. Additionally, use of digitalis is associated with an increased occurrence of arrhythmias. Overall prognosis depends on multiple variables, including the delay in the administration of the antitoxin along with the immunization status and age of the individual. The fatality rate of 10% for respiratory tract diphtheria has not changed in 50 years.[112]

Acute Intermittent Porphyria

The most common of the four types of porphyria is acute intermittent porphyria (AIP). Clinical symptoms in acute attacks span multiple medical subspecialties and may be precipitated by numerous medications, hormonal variations, calorie restrictions, and alcohol. AIP most commonly occurs in girls/women with the age of onset between 15 and 40 years, and it rarely occurs before puberty.[114]

An acute neuropathy is found in approximately 40% of acute AIP attacks.[115-117] The neuropathy typically follows the onset of the attack by 1 to 4 weeks but may do so as late as 11 weeks afterward. Although paresthesias and distal sensory changes may be a prodromal finding, the motor signs are much more prominent. Typically the patient has proximally symmetrical upper extremity weakness, but it may advance to involve the lower extremities. Generalized weakness is documented in approximately 42% of patients.[115] In AIP's most dramatic setting, the patient can have a rapid progression of weakness that leads to a flaccid involvement of all four extremities and respiratory compromise. When cranial nerves are involved, nerves VII and X are the most frequently affected. Vascular compromise has been documented in persons with vision loss, which may be monocular or total. Although this vision loss is usually transient, it can be permanent.[115]

AIP is often difficult to diagnose. The patient's chief complaints are typically nonspecific abdominal and back pain. This colicky pain often leads to the consideration of surgical intervention. Notably, AIP is not associated with temperature elevation, leukocytosis, or rebound tenderness.[115] Neurologic and psychiatric symptoms often accompany the onset of attack.

Another important issue is significant hyponatremia and associated seizures, which may be further precipitated by the use of intravenous fluids containing dextrose and water. Cardiovascular complications include hypertension and tachycardia. In its most extreme case, significant hypertension may be present with associated hypertensive encephalopathy and ischemic changes. Intravenous infusion of magnesium sulfate may be helpful.[114] Nutritional support is important to avoid a catabolic state, which will further complicate the clinical picture. In the event that nutrition is required intravenously, high-glucose solutions with dextrose are recommended. Enteral feeding is preferred, with carbohydrates providing 50% to 60% of the energy needs.[114]

Diagnostically in persons with AIP, urine and stool can be tested for alpha aminolevulinic acid. In addition, a marked elevation of urinary porphobilinogen (PBG) is seen. Checking PBG deaminase levels in the blood is helpful because they are abnormal even between the acute attacks.[114]AIP should be a consideration in the differential diagnosis of progressive weakness. It is most often confused with GBS. The ascending qualities, which are classic in GBS, are rare in acute porphyria. Additionally, persons with acute porphyria do not have elevation of the CSF protein or abnormalities of the cellular contents. The associated abdominal discomfort and tachycardia that are seen in porphyria would not be anticipated in GBS. Differential considerations should include lead intoxication and hereditary tyrosinemia as well.[115]

Elder and Hift[114] provided a review of AIP therapy. The two recommended approaches are carbohydrate loading and administration of heme. If the patient has severe symptoms such as seizures, hyponatremia, and initial signs of neuropathy, aggressive therapy is begun as early in the crisis as possible. In mild attacks it may be possible to wait 24 hours to determine if the attack will spontaneously reverse. Carbohydrate loading is delivered as a 20% glucose solution provided via a central venous catheter. Studies that support the use of heme are primarily noncontrolled and have difficulty reaching statistical significance, but the overall consensus is that it does provide benefit. Daily measurements of urinary alpha aminolevulinic acid or PBG may be a helpful monitor.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA), a disease of the anterior horn cell, is most commonly inherited in an autosomal recessive manner. The responsible gene is the survivor motor neuron gene on chromosome 5q13.[118,119] SMA has three subtypes that present in childhood, and both autosomal dominant and X-linked inheritance have been reported. The combined incidence of all forms of SMA has been estimated as 1 case in 6000 to 25,700 live births.[120,121] After cystic fibrosis, SMA is the next most common fatal disease with an autosomal recessive pattern of inheritance.[120] The most severe form is previously known as Werdnig-Hoffmann disease but is now more commonly referred to as SMA type I. It usually presents shortly after birth but should be apparent before age 6 months and is defined by the patient never being able to achieve independent sitting. SMA type II usually presents between ages 6 and 18 months and is characterized by the patient sitting but never standing or walking. In SMA type III, patients do stand independently and walk.

In SMA type I, the examination reveals a floppy baby with proximal weakness greater than distal weakness. The lower extremities are more affected than the upper extremities, and the only spontaneous movement in these infants may be in the hands and feet. When supine, the infant will assume a frog-legged position. Polyminimyoclonus, a fine tremor most easily visualized in the hands, also may be present in these patients. Areflexia, tongue fasciculations, facial weakness, and normal sensation are also found.[122,123] Retrospectively, some mothers will report decreased fetal movement during the pregnancy with the affected infant. Death usually occurs before age 2 years as a result of respiratory problems.[120] In patients with clinical symptoms within the first day of life, life expectancy was between 2 and 6 months, with a mean age at death slightly before 4 months.[124]

Patients with SMA type II usually have delayed motor milestones after having normal motor development in infancy. Polyminimyoclonus is also present in these patients. Life expectancy is variable, with many patients not surviving past adolescence.[120] Life expectancy can be enhanced, however, with fastidious respiratory care.[125] Not surprising was the correlation that patients with an earlier onset of the disease had an earlier death.[126]

In SMA type III, weakness is again more proximal than distal, with the lower extremities being more severely affected. The gait exhibited in these patients has a waddling quality, and lumbar lordosis is also prominent. Once the patient loses the ability to ambulate, the inability to raise the hands above the head also occurs.[127] If symptoms begin after age 2 years, ambulation may continue to a median age of 44 years.[127] If symptoms begin before age 2 years, ambulation continues to a median age of 12 years.[127] Life expectancy for patients with SMA type III may be the same as in the normal population because muscle weakness appears to stabilize in these patients.

Electrodiagnostic studies on these patients reveal normal motor conduction velocities. Over time, the amplitude of the compound muscle action potential may be decreased. Results from sensory nerve conduction studies are normal. EMG reveals evidence of acute denervation with spontaneous activity and chronic denervative changes with polyphasic motor units. Muscle biopsy specimens reveal angulated fibers suggestive of denervation. The creatine phosphokinase (CPK) level may or may not be increased. Genetic testing may be performed to confirm the diagnosis.

Respiratory complications are the most aspect of this disease that cause the most concern and include aspiration, pneumonia, and respiratory failure. Respiratory failure may even be the presenting symptom in SMA type I.[128] Respiratory muscle weakness results in restrictive lung disease with a weak cough and hypoventilation.[123] Hypercapnia is also a consequence of restrictive lung disease, so supplemental oxygen may have devastating consequences, including apnea and death.[123] If supplemental oxygen is needed, conventional ventilation or noninvasive ventilation should be instituted.

Other complications may occur over time. Scoliosis complicates pulmonary function over time because of chest wall alterations. Contractures, particularly in the lower extremities, are also common. In addition, feeding difficulties play a prominent role, particularly in the developing infant with SMA type I. If concerns arise, a feeding evaluation should be performed to rule out aspiration. Supplemental feeding through a nasogastric tube or gastrostomy may be necessary.

Aggressive symptomatic treatment, including more frequent use of ventilation and gastrostomy, has been associated with longer life spans. Specific pharmacologic treatments have not been successful.[129] Phenylbutyrate was ineffective in a randomized, controlled trial.[130] Although riluzole (which blocks glutamatergic neurotransmission in the central nervous system) is effective in persons with amyotrophic lateral sclerosis, it has not been adequately tested in children.[131]

Poliomyelitis

The paralytic form of polio represents only 1% to 2% of the actual infections. Aseptic meningitis represents less than 10% of infections and is often thought to be a nonspecific illness. The remaining 90% to 95% of those affected have no apparent infection. Patients who will have paralytic disorder show very high fevers and significant muscle pain with the lack of reflexes. Paralysis rapidly progresses to complete loss of motor use asymmetrically in one or more extremities over a few hours. The distribution of weakness is classically proximal and in the lower extremities. Cranial nerve abnormalities have been reported in 5% to 35% of the patients. Loss of function peaks at 5 days. The disorder can be associated with bowel and bladder problems over the initial 3 days. Sensory abnormalities are rare. Physical examination reveals meningeal findings with changes in the reflexes both superficially and deep. One of the classic signs described in the early reports is the "head drop." As the examiner lifts the patient's shoulders and raises the trunk, the head often falls backward in a limp fashion. It is thought that this phenomenon is not due to paralysis of the neck muscles because it can occur in the nonparalytic form. The clinical course may include significant respiratory muscle weakness. Involvement of the bulbar muscles, brainstem, the respiratory center, and cranial nerve pose difficulties in breathing and paralysis of the pharynx and vocal cords. Respiratory compromise leads to most deaths in the paralytic form.[132] Typically, 50% of patients with any paralysis exhibit some degree of residual deficits, although most do improve. A 10% mortality rate is now reported in the patients with the paralytic from. Before the use of mechanical ventilation, 60% died.[132]

A throat and stool culture may reveal the poliovirus, which is shed early in the course of pharyngeal infection and later from the stool. It is difficult to isolate from the spinal fluid in affected patients. Usually the results of routine laboratory tests are unremarkable. CSF findings are characteristic of aseptic meningitis. A white blood cell count between 20 and 300 cells is expected with a predominance of lymphocytes and a normal glucose level. Normal or slightly elevated levels of protein may be found. In the first few hours after the onset of symptoms, polymorphonuclear leukocytes may predominate, but within 12 hours the predominance of lymphocytes is seen.[132]

This disorder has numerous clinical manifestations. In the viral myocarditis, the heart is extremely sensitive, and thus very small doses of digoxin have been suggested. Hypertension is well recognized and can be severe enough to cause encephalopathy. In the child with poliomyelitis, analgesics, including opiates, may be required for pain relief. Hot packs have been noted to be effective when applied every 2 to 4 hours. Constipation and bladder paralysis are major issues early in the course and should be monitored closely. Because of the risk of aspiration and airway compromise, a high level of vigilance must be maintained. If the patient demonstrates respiratory compromise, then a tracheostomy is indicated with accompanying mechanical ventilation.[132] Use of antiviral agents is debated. Additionally, some authors argue that steroids are not indicated in enteroviral infections.[132]

Children who experience mild weakness generally have a full recovery. If paralysis is present, the recovery is ongoing for 2 years, with 80% realized by 6 months.[132] Adults may have new symptoms later in life after paralytic poliomyelitis, including weakness and muscle atrophy that is related to continued normal attrition of anterior horn cells.[133]

Polio-like Syndromes

Polio-like syndromes have been reported, and antiviral intervention has been advocated.[134] Interferon-α therapy within 24 hours of admission has been recommended on the basis of information from small case studies. The authors thought that this intervention altered the course and that improvement was evident within 1 to 2 days. West Nile Virus is now recognized as a possible etiologic agent for a polio-like syndrome.[135] Magnetic resonance imaging and proton magnetic resolution spectroscopy have been recommended to monitor the functional activity of the neurons. It is difficult to determine without further study whether the natural course would have been almost complete recovery or if it was in the fact the interferon-α intervention that was responsible.[136] Overall prognosis in patients with nonpolio enteroviral infections is very good.[132]

Organophosphate and Carbamate Poisoning

The clinician must always maintain a high index of suspicion and consider poisoning in the differential diagnosis in patients with altered mental status, respiratory symptoms, or weakness (also see Chapter 105). In their study of 37 children with organophosphate or carbamate poisonings, Zweiner and Ginsburg[137] reported that 43% of these patients were evaluated by their primary care doctor, and pesticide toxicity was not suspected. Patients commonly do not have a known history of exposure. Exposure to these substances may occur as inhalation, ingestion, or dermal contact. In one study of 37 infants and children with organophosphate and carbamate poisonings, 76% of these patients ingested these substances (which were improperly stored), 16% had transcutaneous exposure (through contact with treated carpets, linens, and lawns), and 8% were poisoned by an unknown etiology.[137] Cholinesterase, which is present in the neuromuscular junction, is irreversibly inhibited by organophosphates and reversibly inhibited by carbamate compounds. Therefore, a constellation of muscarinic, nicotinic, and central nervous system symptoms may occur.

Symptoms may originate from various systems. Muscarinic symptoms include miosis, excessive salivation, sweating, lacrimation, diarrhea, urination, and bradycardia. In severe poisonings, flaccid paralysis with areflexia is common. In moderate poisonings, muscle fasciculations may be present. Central nervous system symptoms include coma and seizures; however, seizures are less common in persons with carbamate toxicity.[138] Pulmonary symptoms including bronchoconstriction, increased pulmonary secretions, and wheezing have been reported.[139] In one study of 52 children with organophosphate or carbamate poisoning, 100% of these patients exhibited hypotonia, stupor, or coma.[140] With further analysis

of the 16 patients with organophosphate poisoning, the other common symptoms included miosis (56%), salivation (37%), pulmonary edema (37%), diarrhea (30%), and bradycardia (25%).[140] Various cardiac rhythms may occur with pathologic signs of cardiotoxicity.[141] Overall, carbamate poisonings are usually less severe and shorter in duration, although the symptoms are essentially the same as those found in organophosphate poisonings.[142]

If organophosphate and carbamate compounds are ingested, gastric lavage and activated charcoal should be initiated. If contaminated, the patient's skin and hair should be rinsed and cleansed thoroughly with soap, and the clothes should be changed to reduce further exposure.[138]

In both forms of poisonings, atropine is used as an antidote for the muscarinic symptoms. Treatment with atropine, however, does not reverse the nicotinic symptoms, which include muscle weakness and respiratory failure. Atropine should be administered as quickly as possible and in adequate doses. In children older than 12 years, the dosing is 1 to 2 mg intravenously every 10 to 30 minutes.[139] In children younger than 12 years, the initial dose is 0.05 mg/kg with maintenance doses of 0.02 to 0.05 mg/kg over 10 to 30 minutes.[139] In organophosphate and carbamate poisonings, the atropine dose is 5 to 10 times greater than conventional atropine dosing.[139] Atropine should be continued until the muscarinic symptoms begin to abate. The signs of atropinization include mydriasis, tachycardia, and xerostomia, and they help provide parameters for adequate dosing.[143] Atropine should be continued for at least 24 hours after severe exposures and then tapered if symptoms are improving.[139]

Pralidoxime chloride, the only cholinesterase reactivator in the United States, is an antidote for only the nicotinic symptoms of organophosphate poisonings; therefore atropine must be used concomitantly. Pralidoxime chloride does not help in carbamate exposures. Various doses have been reported for pralidoxime in patients older than 12 years. A conservative dose is 0.5 to 1 g administered intravenously over 15 to 30 minutes, repeated every 10 to 12 hours, beginning 1 to 2 hours after the initial dose. More recently, another study suggests a 2 g loading dose with a continuous infusion of 1g/h for 48 hours.[144] These doses have not been directly compared with each other. In patients younger than 12 years, the dose is 25 to 50 mg/kg administered intravenously over 15 to 30 minutes, repeated every 10 to 12 hours, beginning 1 to 2 hours after the initial dose.[139] Further studies appear warranted because a meta-analysis showed either no benefit or possible harm of pralidoxime compared with best medical therapy.[145]

After the antidotes are given, the mainstay of treatment is supportive. If necessary, ventilation should be provided until the patient regains respiratory strength. Suctioning of secretions in both the oropharynx and in the respiratory tree is essential. Seizures should be treated with diazepam or lorazepam. Cardiac monitoring should be implemented because complex ventricular arrhythmias may occur.[146,141] Early feeding may prolong the hospital stay.[147] Death usually occurs as a result of respiratory arrest and pulmonary complications, including excessive secretions, edema, and bronchoconstriction.[139]

Diagnosis is based on clinical findings and response to antidote medications. Serum and red blood cell cholinesterase levels should be obtained to assist in the diagnosis of organophosphate poisoning. Treatment should be initiated immediately and not be delayed while waiting for cholinesterase level results. Cholinesterase levels do not assist in the diagnosis of carbamate exposure because the reversal of the enzyme occurs too rapidly to be quantified.

Rhabdomyolysis

Rhabdomyolysis refers to a process in which myoglobin is liberated from injured or damaged skeletal muscle into the blood and urine, resulting in myoblobinemia and myoglobinuria. Evidence of chronic rhabdomyolysis, the most common form in children, may be discovered incidentally during routine blood laboratory workups that include CPK levels.[148] Acute episodes of rhabdomyolysis also may result from a myriad of causes. The history of the patient is extremely important in determining the exact cause. Acute episodes of rhabdomyolysis may be fatal because of electrolyte abnormalities, cardiac arrhythmias, and renal damage, which occur during this process.

Potential causes of rhabdomyolysis include environmental factors (extreme cold or heat); viral and bacterial infections; and metabolic abnormalities, including hypokalemia, hypernatremia, nonketotic hyperosmolar coma, and diabetic ketoacidosis.[149,150] Less common causes include excessive muscle activity as seen in convulsive seizures, extreme exertion, drugs, toxins, venoms, physical trauma, malignant hyperthermia, and metabolic myopathies.

Muscle-related symptoms found in rhabdomyolysis include severe weakness, hypoactive reflexes, tenderness, edema, cramps, and localized pain.[150,151] Muscle symptoms make the diagnosis more obvious; however, if the patient has decreased level of consciousness from metabolic abnormalities, trauma, drugs, or seizures, these muscle symptoms may be obscured.

Abnormal laboratory results include myoglobinuria and profound elevation of serum CPK. Muscle cell destruction results in the release of potassium and phosphorous into the blood, with consequential hyperkalemia, hyperphosphatemia, and eventually hypocalcemia.[151,152] Elevations of aldolase, uric acid, lactic dehydrogenase, and transaminase (serum glutamate oxaloacetate transaminase and serum glutamate pyruvate transaminase) levels also occur.[151,152]

Complications from rhabdomyolysis may affect the heart, kidneys, and ventilation. The severe myoglobinuria in rhabdomyolysis may result in acute tubular necrosis, which can be fatal. Alkalinization of the urine, hydration, and osmotic diuresis have been used to prevent renal damage.[152] Hypocalcemia, which results from the elevated potassium and phosphorous levels, may lead to cardiac arrhythmias. In the review by Robotham and Haddow,[151] several types of cardiac disturbances were reported, including ventricular arrhythmias, intraventricular conduction delays, abnormal axis deviation, sinus bradycardias and tachycardias, ischemic changes, nonspecific ST segment and T wave changes, and T wave changes associated with hyperkalemia. Compartment syndrome also may occur because of severe muscle edema, and fasciotomy may be required to prevent neurovascular compression.[152] If the diaphragm and intercostal muscles are affected, mechanical ventilation may be required. Bulbar weakness necessitating mechanical ventilation in rhabdomyolysis is rare.[152] Overall, it is unusual for muscle weakness to be permanent, with full muscle strength usually returning in 1 to 6 weeks.[152]

Several diseases may result in recurrent rhabdomyolysis. McArdle's disease, a metabolic myopathy that also goes by the names type V glycogenosis and myophosphorylase deficiency,

is predominantly autosomal recessive. Patients with this disease exhibit exercise intolerance, muscle stiffness, and myalgia.[153] Vigorous activity, including squatting, sprinting, and carrying heavy objects, may precipitate an episode of muscle rigidity with cramping and myoglobinuria resulting in rhabdomyolysis. Recognition of these symptoms will help achieve a timely diagnosis, prevent morbidity, and avoid recurrent rhabdomyolysis. Tarui's disease, also known as glycogenosis type VII and phosphofructokinase deficiency, is also autosomal recessive. The clinical picture is similar to that found in McArdle's disease and may also result in rhabdomyolysis.[153] Carnitine palmitoyltransferase deficiency is an autosomal recessive disease that also may lead to rhabdomyolysis. Carnitine palmitoyltransferase catalyzes carnitine and fatty acid for transfer into the mitochondria. Rhabdomyolysis may be precipitated by prolonged exercise and fasting and may be prevented by eating frequent meals of low-fat, carbohydrate-rich foods with avoidance of both fasting and prolonged exercise.[153]

Malignant Hyperthermia

Malignant hyperthermia (MH) is a disease that is associated with certain anesthetic agents, including inhalation anesthesia such as halothane and depolarizing muscle relaxant agents such as succinylcholine (also see Chapter 12). MH occurs in approximately 1 in 12,000 children with anesthesia.[154] MH has a variable clinical presentation as described by Kaus and Rockoff.[155] In classic MH, the symptoms include tachypnea, tachycardia, blood pressure abnormalities, cyanosis, mottling, and diaphoresis. Hypoxia, hypercapnia, metabolic acidosis, and muscle rigidity resulting in severe rhabdomyolysis also occur. The severe hyperthermia, which denotes the disease, may exceed more than 42° C. A second presentation of MH occurs after the administration of succinylcholine and results in an abrupt onset of generalized muscle rigidity, cardiac arrest, and rhabdomyolysis. An additional presentation is masseter muscle spasm, which occurs after the administration of halothane and succinylcholine, and results in severe contracture of the jaw that lasts 5 to 20 minutes.[155]

Recent advances have been made in understanding the genetics of MH. The ryanodine receptor appears to be involved, and first- and second-degree family members of patients who have or are suspected of having MH should be considered at risk for MH until a gene test or muscle biopsy is performed.[154,156] As more causative mutations are found, fewer patients will have unexplained causes of their MH. In addition to cases caused by mutations of the ryanodine receptor, some muscle diseases have been associated with MH, including Duchenne muscular dystrophy, Becker muscular dystrophy, central core disease, myotonia congenita, King-Denborough syndrome, Schwartz-Jampel syndrome, and other muscular dystrophies.[155]

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome occurs in 0.5% to 1.4% of patients exposed to antipsychotic medications.[157,158] Neuroleptic malignant syndrome has a constellation of signs and symptoms including hyperthermia, muscle rigidity, autonomic instability, tachycardia, tachypnea, diaphoresis, hypertension, and altered mental status (also see Chapter 124).[159] Rhabdomyolysis may be a component of this syndrome, which includes elevated CPK levels and myoglobinuria; therefore, MH may be in the differential diagnosis of severe acute-onset weakness.

Inflammatory Myopathies

Dermatomyositis and Polymyositis

Dermatomyositis and polymyositis are inflammatory myopathies with symmetrical proximal muscle weakness that progresses over weeks to months (see also Chapter 98, Autoimmune Diseases and Their Treatment). The incidence ranges from 2.5 to 4.1 per million children in the United States and comprised 5% of all rheumatologic referrals in one review.[160,161] Five major criteria exist for the diagnosis of polymyositis/dermatomyositis as described by Bohan and Peter.[162] Of the five criteria, one clinical criterion is symmetrical proximal weakness that may include respiratory muscles. Another clinical criterion is dermatological, which includes the heliotrope rash and Gottron's sign. In addition, a scaly erythematous rash of the face, neck, upper torso, knees, elbows, and median malleoli is also present. The two laboratory criteria include elevation of skeletal muscle enzymes, including CPK and adolase, and a muscle biopsy specimen with evidence of necrosis of type I and II fibers, phagocytosis, and inflammatory exudates. The electrodiagnostic criterion includes EMG findings of spontaneous activity, myopathic motor units, and bizarre high-frequency repetitive discharges. Definitive diagnosis must include three or four criteria and the rash for dermatomyositis, and four criteria without the rash for polymyositis.

Systemic symptoms such as fatigue, lethargy, irritability, arthralgias, myalgias, weight loss, gastrointestinal discomfort, and low-grade fever may herald the onset of weakness.[163] Complications of dermatomyositis and polymyositis include respiratory problems such as chronic interstitial pulmonary fibrosis and pneumothorax; gastrointestinal involvement with decreased esophageal motility, gastric ulceration, and bleeding; and cardiac problems such as arrhythmias, abnormal electrocardiograms, and pericarditis.[163,164] The initial treatment of polymyositis and dermatomyositis is corticosteroids. The mortality of juvenile dermatomyositis is 3% in the United States.[165]

Benign Acute Childhood Myositis

Benign acute childhood myositis (BACM) is a self-limited process that usually affects boys more often than girls.[166] The presentation of muscular symptoms occurs after a prodrome of viral upper respiratory illness. An acute onset of severe muscle pain usually involving the calf muscles, difficulty walking, and increased CPK levels usually follow the prodrome. Mackay et al.[168] describe the prodromal symptoms of fever, cough, headache, rhinorrhea, sore throat, and vomiting as being the most common symptoms. In the 41 episodes of BACM that Mackay et al.[166] reported, 42% of those tested were confirmed to be caused by a virus, with 50% of those cases confirmed as being caused by influenza B. The mean CPK level was 14 times normal, but resolution of symptoms occurred within 1 week. BACM resolves rapidly. Bed rest may be necessary until the pain resolves; otherwise, no treatment is needed. This disease process rarely progresses into a severe life-threatening form.

References are available online at http://www.expertconsult.com.

IV Chapter 65

Central Nervous System Infections Presenting to the Pediatric Intensive Care Unit

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PEARLS

- While the term *meningitis* implies that the meninges are primarily involved, *encephalitis* indicates brain parenchymal involvement. The presence or absence of normal brain function is important in distinguishing between meningitis and encephalitis.
- An exception is when intracranial hypertension develops in a patient with meningitis. Prompt administration of an effective bactericidal antimicrobial regimen potentially reduces neurologic sequelae.
- The diagnosis of primary amebic menigoencephalitis should be considered in southern-tier states in the United States.
- The most common origin of central nervous system abscesses in children is direct or indirect extension from the middle ear, paranasal sinus, or dental abscesses, which occurs in up to 10% of untreated cases.

Life-threatening infections in the pediatric population are an all too common occurrence in the pediatric intensive care unit (PICU). These infections can come from a myriad of sources and can affect any organ system. Extremely young age, poor nutritional status, incomplete development of both innate and adaptive immune responses, and underlying disease processes all contribute to the increased risk for severe infections in the pediatric population. Infections of the central nervous system (CNS) are frequently encountered by the pediatric intensivist and often pose life-threatening challenges to the individual.

Understanding infections of the CNS entails more than a comprehension of the appropriate antimicrobial agents and laboratory tests. Recently it has become clear that CNS infections in childhood may have long-term consequences. Earlier studies focused on risk exposures of congenital infections of the CNS acquired during the fetal period. However, the human brain continues to develop well into early adulthood, and infections of the CNS during infancy and childhood may increase the risk of neuropsychiatric problems later in life. A study from South America of persons who had "epidemic meningitis" during childhood (mainly of bacterial origin) demonstrated a fivefold increase in the prevalence of psychotic disorders.[1] Additionally, in a recent Swedish study of over 1 million pediatric patients, serious viral CNS infections during childhood, specifically mumps virus and cytomegalovirus (CMV), appeared to be associated with the later development of schizophrenia and other psychoses.[2] The exact pathophysiology of these long-term insults is currently the focus of clinical interest. Use of new immunohistochemical staining, such as amyloid precursor protein (β-APP), along with biomarkers of axonal injury such as c-tau and α-II spectrin, may offer insight into the axonal and neuronal injury that occur both with and following CNS infections.[3,4]

Bacterial Meningitis

Bacterial meningitis remains a common cause of morbidity and mortality in the pediatric population. It is not infrequent for many children with bacterial meningitis to be admitted to a PICU for initial supportive care.

Many microorganisms have the ability to cause meningitis. Most microorganisms are acquired through a hematogenous route, and others through direct extension from nasal cavities, paranasal sinuses, mastoids, or the middle ear. Other microorganisms are associated with trauma or surgery with or without the placement of foreign materials. In certain instances, the age and the immune status of the host, the exposure history, and the virulent characteristics of the organism directly influence the likelihood of the development of meningitis.

Epidemiology

The use of conjugate vaccines against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* have significantly decreased the incidence of Hib as a meningeal pathogen and *S. pneumoniae* as a cause of invasive disease.[5] Even as nonvaccine serotypes have emerged as "newly recognized" pathogens, *S. pneumoniae* remains an important adversary.[6,7] The isolation of nonvaccine serotypes such as 19A, 22F, and 35B has increased since the introduction of the seven-valent vaccine. It is of great therapeutic concern that approximately 28% of these invasive isolates are resistant to penicillin and 11.8% are resistant to cefotaxime. *Neisseria meningitidis* is the second most common cause of sepsis and meningitis beyond the neonatal period. In a recent study of children with bacterial

meningitis, one third of cases were by *S. pneumoniae*, while *N. meningitidis* was responsible for 28% of cases. Sixty-two percent of typed pneumococcal isolates were caused nonvaccine serotypes.[8]

In young infants in the first few months of life, *Escherichia coli* has become the main cause of sepsis and meningitis and is responsible for 22% of cases. Because of the use of intrapartum prophylaxis, *Streptococcus agalactiae* (group B *Streptococcus* [GBS]) is being observed less frequently.[9] Other organisms such as *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Cronobacter* spp. (formerly known as *Enterobacter sakazakii*),[10] and *Citrobacter koseri* (formerly known as *C. diversus*) have been reported as causes of meningitis in young infants.

Listeria monocytogenes continues to be listed as a cause of sepsis and meningitis in the newborn. However, because the frequency of its occurrence in this age group is so low, most clinicians have never seen a case. A known association with specific dietary habits in the mother such as the consumption of unpasteurized soft cheeses, dairy products, and cold meat cuts has been recognized for years.

Children with asplenia, humoral immunodeficiencies, cochlear implants, human immunodeficiency virus (HIV), and cerebrospinal fluid (CSF) leakage resulting from trauma are at high risk of pneumococcal meningitis. Asplenic children and those with complement deficiencies are at risk for meningococcal meningitis. On rare occasions, *Streptococcus pyogenes* has been responsible for meningitis, with concurrent otitis media being a major risk factor.[11] *S. pyogenes* was responsible for close to 2% of cases. Less frequent meningeal pathogens in young infants are *Salmonella* species and *Capnocytophaga canimorsus*, an organism associated with exposure of the mucous membranes to dog saliva.[12]

Rare causes of pediatric meningitis, such as *Cryptococcus neoformans*, *Coccidioides* spp., rickettsiae, ehrlichiosis, *Mycobacterium tuberculosis*, and *Baylisascaris procyonis* (raccoon roundworm) are well recognized for their high degree of morbidity and mortality. Meningoencephalitis also can result from tick bite–associated transmission of rickettsial pathogens such as *Rickettsia rickettsii* and ehrlichia. Infections by *Staphylococcus aureus* and coagulase-negative staphylococci are generally associated with neurosurgical surgery and trauma.

Pathogenesis

Prior to bloodstream invasion, intravascular multiplication, and penetration of pathogenic bacteria through the blood-brain barrier (BBB), in most instances the nasopharynx becomes colonized. Organisms in the nasopharynx penetrate through or between respiratory epithelial cells as a preamble to disease. A lack of immune defenses in the subarachnoid space allows for the rapid multiplication of bacteria in the CNS.

Clinical Manifestations

The classic features of bacterial meningitis such as fever, nuchal rigidity, and altered mental status may not always be observed in young infants and children. Seizures, irritability, decreased appetite, vomiting, poor perfusion, hypotension, coma, and respiratory distress may indicate a serious bacterial infection. Paleness and skin mottling may be observed in severely ill infants. Nuchal rigidity and bulging fontanelle are usually late manifestations of meningitis. Kernig and Brudzinski signs are frequently unrecognized or are absent. The presence of petechiae and purpura may suggest meningococcus as the causative agent. However, similar findings have been observed in children with *S. pneumoniae* and *H. influenzae* (type a) sepsis.[13] Anisocoria, poorly reactive pupils, bulging fontanelle, diplopia, papilledema, and uncontrollable vomiting are signs of increased intracranial pressure (ICP) (see also Chapter 59, Intracranial Hypertension and Brain Monitoring).

Diagnosis

When clinically feasible, the diagnosis of meningitis requires the examination of CSF. In most cases of bacterial meningitis, the diagnosis relies on the isolation of bacteria from a CSF specimen. Cell count and differential, along with protein and glucose determinations, Gram stain, and cultures, are essential tests to be performed. The use of blood cultures alone as an initial screening test is not appropriate. Approximately 80% of patients with bacterial meningitis will have a positive blood culture. This approach alone would result in a large number of cases being missed.

Lumbar puncture should be postponed in children with an ongoing coagulopathy, elevated ICP, or cardiorespiratory difficulty, and in patients with suspected mass-occupying lesions as demonstrated by focal neurologic signs. However, it is critical to remember that antimicrobial therapy and other supportive measures should not be delayed while waiting for results of CSF analysis. Routine end-of-treatment lumbar punctures are no longer recommended.[14] Patients with multidrug resistant *S. pneumoniae* or Gram-negative bacilli meningitis should have a repeat lumbar puncture at 48 hours after initiation of therapy to document sterilization.

Although a computed tomography (CT) scan is not required in all children with suspected meningitis, it is indicated prior to lumbar puncture in patients with focal neurologic findings and signs of ICP. It is important to remember that even when CT scans are normal, herniation may still occur.[15] Similar findings have been confirmed in adults with meningitis.[16]

CSF with pleocytosis (usually greater than 1000/μL) and a predominance of polymorphonuclear leukocytes is highly suggestive of bacterial meningitis. High protein and low glucose (usually < ½ serum value) concentrations also support the diagnosis. A predominance of lymphocytes and monocytes suggests a viral pathogen. A predominance of lymphocytes and monocytes also can be observed in patients with rickettsial and tuberculous meningitis. CSF eosinophils are frequently observed in patients with CSF shunt devices, but this also can be observed in persons with parasitic infections that result in meningoencephalitis, such as baylisascariasis and infections by *Angiostrongylus* species.

Clinicians must remember that a polymorphonuclear leukocyte predominance may be observed early in the course of enteroviral meningitis as well. Frequently, patients with this disease have normal CSF protein and glucose concentrations. However, hypoglycorrachia can be observed with certain viral pathogens such as enterovirus and mumps virus. On occasion, a small percentage of patients may have an initial "normal appearing" CSF analysis, especially with *N. meningitidis*.

Gram stains have been reported to demonstrate organisms in 50% to 75% of specimens. The impression of most clinicians is that it is not that high. The clinician is cautioned not to

make significant changes in antimicrobial therapy based solely on a Gram stain result. CSF cultures remain the ultimate gold standard.

In most instances, prior oral antimicrobial therapy will not significantly alter CSF cell counts, differential, and chemistries in children with bacterial meningitis. In contrast, Gram stain and culture positivity are greatly reduced. Clinicians frequently are faced with the question of how to treat these patients and/or if there is a need for prophylaxis of household members if the infection happens to be caused by *N. meningitidis*.

Routine use of rapid bacterial antigen detection assays have been shown to be of limited clinical relevance because on most occasions therapy typically is not altered based on the result.[17] However, in a multisite study from Asia and Africa, an immunochromatographic test for pneumococcal antigen was found to have high sensitivity and specificity. This assay may be useful in previously treated children with a negative CSF Gram stain and culture.[18]

Real-time fluorescent quantitative polymerase chain reaction (PCR) amplification of the bacterial 16S ribosomal ribonucleic acid (RNA) gene may become a useful clinical tool for the rapid diagnosis of bacterial meningitis. It would be particularly beneficial in patients who have taken antibiotics prior to undergoing a lumbar puncture. Compared with bacterial culture controls, sensitivity was 100% in one study; in another study it was 86% overall.[19,20] This assay also may be useful for the prompt identification of *S. pneumoniae* and *N. meningitidis* as the etiologic agents.[21] In a clinical setting, a real-time PCR for *N. meningitidis* was found to have a high sensitivity, specificity, and predictive values.[22]

Serum procalcitonin assays have been used to differentiate between bacterial and aseptic meningitis. In a small study, procalcitonin determination had 99% sensitivity and 83% specificity.[23] A larger prospective study will be needed to assess the ultimate clinical role for this assay.

Susceptibility testing of most bacterial isolates is of clinical importance. In certain pathogens, however, it may not be required. Unless penicillin G is being considered for the treatment of meningococcal meningitis, susceptibility testing for this pathogen is not required. Similarly, penicillin or cephalosporin resistance is not currently recognized for *S. pyogenes*.

Treatment

An effective antimicrobial agent for the treatment of bacterial meningitis must be bactericidal and must achieve high concentrations in the CSF. In addition, initial empiric therapy should take into consideration antimicrobial resistance among the most likely meningeal pathogens. Once meningitis is suspected, antimicrobial therapy must be initiated promptly.

The Infectious Disease Society of America has published practice guidelines for the management of bacterial meningitis. All critical care clinicians should be familiar with their recommendations.[24] Tables 65-1, 65-2, and 65-3 provide a listing of most frequent meningeal pathogens and recommended antimicrobial regimens along with dosage information.

In the neonate with meningitis, empiric antimicrobial agents used initially should consist of ampicillin, an aminoglycoside, and cefotaxime. In infants older than 1 month, vancomycin and a third-generation cephalosporin (cefotaxime or ceftriaxone) is recommended. Alterations to these regimens may be influenced by Gram stain, culture, and drug susceptibility results. Additional empiric agents could be added according to epidemiologic exposures, underlying conditions, and the presence of resistant organisms in the community or hospital.

Table 65–1 Initial Empiric Antimicrobial Therapy for Bacterial Meningitis Based on Presumptive Pathogen(s)

Age and/or Predisposing Condition	Pathogen	Antimicrobial Therapy
<1 mo	*Escherichia coli, Streptococcus agalactiae, Klebsiella* spp., *Listeria monocytogenes*	Ampicillin + cefotaxime ± aminoglycoside
1–2 mo	*Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae, Haemophilus influenzae, E. coli*	Vancomycin + third-generation cephalosporin*
2 mo–5 y	*S. pneumoniae, N. meningitidis, H. influenzae*	Vancomycin + third-generation cephalosporin*
>5 y	*S. pneumoniae, N. meningitidis*	Vancomycin + third-generation cephalosporin*
Humoral immunodeficiency, human immunodeficiency virus, asplenia	*S. pneumoniae, N. meningitidis, H. influenzae, Salmonella* spp.	Vancomycin + third-generation cephalosporin*
Complement deficiencies	*N. meningitidis, S. pneumoniae*	Vancomycin + third-generation cephalosporin*
Basilar skull fractures	*S. pneumoniae, N. meningitidis, Streptococcus pyogenes*	Vancomycin + third-generation cephalosporin*
Cerebrospinal fluid, shunt related	Coagulase-negative staphylococci, *Staphylococcus aureus* (methicillin-susceptible, methicillin-resistant), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*), *Propionibacterium acnes*	Vancomycin + ceftazidime or vancomycin + cefepime or vancomycin + meropenem†
After neurosurgery	Coagulase-negative staphylococci, *S. aureus* (methicillin-susceptible, methicillin-resistant), aerobic gram-negative bacilli (including *P. aeruginosa*), *P. acnes*	Vancomycin + ceftazidime or vancomycin + cefepime or vancomycin + meropenem†
Cochlear implants	*S. pneumoniae*	Vancomycin + third-generation cephalosporin*

*Cefotaxime or ceftriaxone.
†The choice of anti–gram-negative bacillary agent should be based on the institution's susceptibility patterns.

Once a specific pathogen has been identified and susceptibility data are available, antimicrobial therapy could be "narrowed" to specifically target the offending pathogen. It is the opinion of many clinicians that ampicillin or penicillin G plus gentamicin are the agents of choice for GBS meningitis in the young infant. Unless susceptibility is provided for penicillin, a third-generation cephalosporin is the agent of choice for patients with *N. meningitidis*. Because drug-resistant *S. pneumoniae* (DRSP) has become a problem in the United States, vancomycin plus cefotaxime or ceftriaxone, possibly with rifampin, may be indicated for the full course.

The duration of antimicrobial therapy will vary according to causative pathogen. Neonates with group B streptococcal meningitis require 14 to 21 days of antimicrobial therapy, and those with *S. pneumoniae* require 10 to 14 days; for neonates with *N. meningitidis*, most clinicians prescribe therapy for 7 days, and for those with *H. influenzae*, 7 to 10 days of therapy is required. Children with Gram-negative bacillary meningitis require a minimum of 3 weeks of antimicrobial therapy.

Table 65–2 Antimicrobial Therapy for Specific Meningeal Pathogens

Pathogen	Antimicrobial Therapy
Streptococcus agalactiae	Penicillin G ± gentamicin or ampicillin ± gentamicin
Hemophilus influenzae, β-lactamase–negative	Ampicillin
H. influenzae, β-lactamase–positive	Third-generation cephalosporin*
Streptococcus pneumoniae, penicillin-susceptible	Penicillin G or ampicillin†
S. pneumoniae, penicillin-resistant, cephalosporin-susceptible	Third-generation cephalosporin*
S. pneumoniae, drug resistant (multiply resistant)	Vancomycin + rifampin
Neisseria meningitidis	Third-generation cephalosporin*
N. meningitidis, penicillin-susceptible	Penicillin G or ampicillin†
Escherichia coli, other aerobic enteric gram-negative bacilli (not including *Pseudomonas aeruginosa*)	Cefotaxime or ceftriaxone (if >1 mo of age) + aminoglycoside‡§
P. aeruginosa	Meropenem + aminoglycoside or cefepime + aminoglycoside or ceftazidime + aminoglycoside§
Coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus*	Vancomycin ± rifampin
Methicillin-susceptible *S. aureus*	Nafcillin

*Cefotaxime or ceftriaxone.
†Some clinicians prefer ampicillin because of less frequent dosing.
‡The choice of aminoglycoside will depend on the institution's susceptibility patterns.
§The choice of antipseudomonal regimen is influenced by the institution's susceptibility patterns.

Supportive Care

The correction of hyponatremia and hypotension (which is key to maintaining adequate cerebral perfusion) and the treatment of ICP are just as important as the selection of an effective antimicrobial regimen. The presence of hyponatremia, hypotension, or ICP along with a delay in CSF sterilization is associated with poor outcomes and neurologic sequelae.

In the patient who is dehydrated or in shock, administration of intravenous fluids is critical for the maintenance of normal blood pressure and proper perfusion; in addition, it potentially reduces the risk of central venous or sagittal sinus thrombosis. Some patients may require vasoactive-inotropic agents such as dopamine and dobutamine. Routinely restricting fluids in patients with CNS infection as a way to prevent inappropriate antidiuretic hormone secretion should be limited. Patients may have elevated ICP as a consequence of CNS inflammation or obstruction by purulent debris of their lateral, third, or fourth ventricles. Treatment of elevated ICP is discussed in Chapter 59, Intracranial Hypertension and Brain Monitoring. Anticonvulsant therapy is indicated in patients with seizures. Generalized seizures are present in ~20% to 30% of patients in the first 3 to 4 days of illness. The presence of focal seizures and an onset past the third day of illness are associated with long-term neurologic sequelae.

Table 65–3 Dosages of Commonly Used Antimicrobial Agents for Bacterial Meningitis*

Antibiotic	Neonates 0–7 Days, >2000 g†	Neonates >7 Days, >2000 g	Infants and Children	Maximum Daily Adult Dose
Ampicillin	150 (8)	200 (6)	300–400 (6)	12 g
Cefepime	–	–	150 (8)	6 g
Cefotaxime	150 (8)	200 (6)	200-300 (6)	12 g
Ceftriaxone	–	–	100 (12–24)	4 g
Gentamicin	5	7.5	7.5	5 mg/kg
Meropenem	–	–	120 (8)	6 g
Penicillin G	150,000	200,000	300,000	24 million units
Rifampin	–	10–20 (12–24)	10–20 (12–24)	600 mg
Vancomycin	30 (12)	45 (8)	60 (6)	45 mg/kg

*Total daily dose based on mg/kg/day. Exception: penicillin G is expressed as units/kg/day. Numbers in parenthesis represent dosing intervals.
†Dosages of agents for neonates <2000 g can be obtained from Lexi-Comp, Inc. online or from Bradley JS, Nelson JD: *2008-2009 Nelson's pocket book of pediatric antimicrobial therapy*, ed 17, Buenos Aires, Argentina, 2009, AWWE.

Adjunctive Therapy

Two agents, glycerol and dexamethasone, have been evaluated as candidates for possible adjuvant therapy in persons with meningitis. In various studies, orally administered glycerol had been shown to reduce neurologic sequelae in children with bacterial meningitis. It has been postulated that through an increase in serum osmolality, enhanced movement of water back into plasma would result in a reduction of CSF volume and an increase in cerebral blood flow.[25,26] However, in a recently published multicenter trial, it was found that glycerol did not prevent hearing loss, which is a frequent neurologic sequelae.[27]

Corticosteroids such as dexamethasone (DXM) have a discernible effect on inflammatory markers in the CSF in persons with bacterial meningitis.[28] Use of DXM in children remains a topic of controversy among clinicians. In adults with pneumococcal meningitis, the early administration of DXM (15 to 20 minutes before or with the first dose of an antibiotic) was associated with a reduction in mortality and unfavorable outcomes.[29]

In early studies in children with Hib meningitis, children treated with DXM had a lower incidence of moderate-to-severe hearing deficits when compared with placebo.[30] However, one of the antimicrobial agents used in the study, cefuroxime, was later shown to be associated with increased neurologic sequelae. This single factor may have influenced the results for the placebo group. In a study by Peltola and Roine, DXM did not prevent neurologic sequelae in children with Hib meningitis; however, glycerol performed in a favorable manner.[31] On the other hand, in a recently published multicenter study, neither agent was found to prevent hearing loss.[27]

In children with pneumococcal meningitis, DXM has not demonstrated the same magnitude of benefit as in adults. In one study, DXM use was associated with an increase in moderate or severe hearing loss and other neurologic deficits.[32] As a consequence, some clinicians may elect not to administer DXM. However, many experts would agree to administer DXM if Hib meningitis was suspected (e.g., in an unimmunized child, in a child living in an endemic region with known Hib transmission, or in a child whose Gram stain shows pleomorphic gram-negative bacilli).[33]

In summary, studies of adjuvant corticosteroid therapy in children have not unequivocally demonstrated beneficial effects. Study design flaws and the fact that most studies were done in the era of Hib disease bring into question the applicability of these results to today's practice. Meta-analysis and retrospective studies have demonstrated beneficial effects in persons with Hib and pneumococcal meningitis. However, these effects were demonstrated at a time when DRSP was not a serious problem. The data could support a beneficial effect in persons with Hib meningitis, but because this organism is an uncommon pathogen at this time, empiric therapy would not be warranted in most cases. In the era of DRSP, when an isolate may be resistant to the third-generation cephalosporin, it has been suggested that DXM may impair the diffusion of vancomycin through the BBB, delaying CSF sterilization. Thus the use of caution has merit. Some clinicians recommend the addition of rifampin under these circumstances. Further studies are needed in this patient population. Lastly, because maximal beneficial effect would be gained by administering DXM prior to antibiotic therapy, infants and children previously treated with antibiotics should not receive DXM.

There is no evidence that corticosteroids are beneficial in patients with viral or meningococcal or neonatal meningitis.[34,35] In contrast, patients with tuberculous meningitis who are treated with steroids have an improved survival rate compared with those who are not treated with steroids. However, the severity of disability commonly observed in those with tuberculous meningitis is not altered.[36]

Prevention

Persons such as household members, caregivers, and day care center playmates who have significant prolonged and close exposures to children with *N. meningitidis* meningitis should receive antimicrobial prophylaxis with either ceftriaxone, ciprofloxacin, or rifampin.[37] Recently ciprofloxacin resistance was reported in Minnesota and North Dakota. Clinicians should be familiar with resistance rates in their communities.[38] Young children exposed to a person with Hib meningitis also may require prophylaxis with rifampin to eradicate potential nasopharyngeal colonization and prevent secondary infections.[39]

A quadrivalent conjugate meningococcal vaccine is now recommended for all children at 11 to 12 years of age and for high-risk individuals as young as 2 years of age. *N. meningitidis* groups B, C, and Y account for most cases in the United States, with group B being responsible for most *N. meningitidis* disease in young infants.

Outcomes

With aggressive support and appropriate antimicrobial therapy, the mortality rate of bacterial meningitis remains low. Unfortunately, neurological sequelae still occur. When compared with other pathogens, pneumococcal, tuberculous, and Gram-negative bacillary meningitis are commonly associated with neurological sequelae. Seizures, hearing deficits, hydrocephalus, and motor and intellectual deficits are the most common sequelae reported.

No single laboratory factor is entirely predictive of outcome in children with meningitis. In pneumococcal meningitis, antimicrobial resistance was not associated with death, ICU admission, need for mechanical ventilation, focal neurologic deficits, seizures, secondary fevers, or duration of hospital stay.[40] However, the presence of shock, hyponatremia, or coma upon admission to the ICU was associated with a higher use of invasive medical devices and higher mortality.[41,42] The presence of low leukocyte blood cell and platelet counts also was associated with increased mortality.[43] In another study, no child with a leukocyte blood cell count greater than 16,000/μL died.[44]

Subdural Empyema

Subdural collections complicating meningitis are common in young infants, and they occur in 40% of infants with proven pyogenic meningitis.[45] However, these fluid collections are typically sterile and cause no long-term sequelae. Subdural empyemas (SDE) are serious CNS infections defined as purulent fluid collections outside the brain parenchyma but contained under the dura. They usually are encapsulated and often loculated. Historically, otorhinolaryngeal infections were an important predisposing factor to SDE in older children. However, a recent study demonstrated that only 10% of episodes

were related to otorhinolaryngeal infections. The decrease in the incidence of SDE after sinus infections is presumed to be from increased antibiotic use for this disease process. Meningitis, head trauma, or neurosurgeries are now more common predisposing conditions for SDE.[46]

In adolescents and adults, subdural empyemas usually result from infection of the paranasal sinuses, middle ear, and face or, less frequently, from a penetrating skull fracture. In young infants, SDE is rare and is usually a complication of purulent meningitis wherein the infection extends through the arachnoid and into the subdural space.[47] The sequelae of SDE may be more severe in young infants than in any other age group.[48] The clinical symptoms can mimic mild meningitis, followed several days later by rapidly progressive drowsiness, neurologic deficits, and seizures. Prolonged fever (90%), seizures (70%), and focal neurologic signs (60%) are the most common clinical signs noted in the pediatric population.[46]

In children, SDE is commonly secondary to Hib *or S. pneumoniae* meningitis. SDE also occurs with *Salmonella, N. meningitidis, E. coli,* and neurotuberculosis. The most common pathogen in infants younger than 4 months of age is GBS.[46]

The diagnosis is often made with radiologic assistance and evaluation of the subdural fluid collection. Distinguishing an SDE from a sterile reactive subdural effusion (RSE). is often difficult.[49] The differentiation of SDE from sterile RSE may not be possible if contrast enhancement of the inner membrane is not seen at CT. Magnetic resonance imaging (MRI) is superior to CT in the demonstration of both the extra-axial fluid and the enhancement of the inner membrane with a paramagnetic contrast medium. Still, there are no MRI characteristics that are specific for SDE compared with a nonpurulent RSE. Analysis of the subdural fluid often is required to establish the diagnosis of SDE. Serial cranial ultrasounds may be the modality of choice for the evaluation of response to medical management.[48]

The goal of treatment is evacuation of pus and eradication of the source of infection. Management choice should be related to the clinical condition. Medical treatment may be adequate if the empyema is small. A surgical approach is suggested in patients who are not responding well to medical treatment or in those who have large subdural pus accumulation with evidence of midline shift or elevated ICP. In infants whose anterior fontanelles are still wide open, transcutaneous subdural tapping may be another option but should be performed by an experienced clinician.

The keys to an optimal outcome in SDE are early, accurate diagnosis, timely intervention, and appropriate antibiotic therapy. The reported mortality rate of SDE is approximately 10%.[46] Age, level of consciousness, timing and aggressiveness of treatment, and the rapidity of disease progression all influence outcome.

Meningoencephalitis

As more children are successfully immunized with vaccines to prevent bacterial meningitis, a greater proportion of children with CNS infections present to the PICU with viral meningoencephalitis. The initial signs and symptoms are often indistinguishable from bacterial meningitis, and a diagnosis of a viral rather than bacterial CNS infection does not decrease the chance of a patient becoming critically ill.

While the term *meningitis* implies that the meninges are primarily involved, *encephalitis* indicates brain parenchymal involvement. The presence or absence of normal brain function is important in distinguishing between aseptic meningitis and encephalitis. Patients with meningitis have fever, meningeal symptoms, and CSF pleocytosis but no evidence of bacterial or fungal infection and no associated neurologic dysfunction.[50] Abnormal neurologic function, such as focal neurologic signs, cranial nerve involvement, motor deficits, sensory deficits, or speech difficulties, implies brain parenchymal involvement and encephalitis. Both meningitis and encephalitis may result in increased ICP, and patients may present with coma as a result of increased ICP or partial or complete brainstem herniation. Patients presenting with seizures may have meningitis or encephalitis. Making the distinction between meningitis and encephalitis is often difficult, and patients may present with both a parenchymal and meningeal process. Therefore, some clinicians prefer the term *meningoencephalitis* to recognize the inherent overlap between the two clinical entities.

Epidemiology

A survey of hospital discharge records from 1988 to 1997 showed approximately 19,000 hospitalizations per year (7.3 hospitalizations per 100,000 population), 230,000 hospital days, and 1400 deaths annually due to viral encephalitis in the United States.[51] Children younger than 1 year had the highest risk for hospitalization as a result of encephalitis. Between the years 1989 to 1998, approximately 1100 deaths were attributed to encephalitis in children younger than 19 years in the United States. The highest rate of death occurred in children younger than 1 year (9.3 per 100,000 population).[52] Nonviral causes of encephalitis are extremely rare.

Although the causative agent in many cases of encephalitis can be difficult to isolate, most cases are attributed to enteroviruses, herpesviruses, and arboviruses. Table 65-4 lists some of the common pathogens associated with meningoencephalitis. The enteroviruses and arboviruses in particular display seasonality in infection, being seen most frequently in the summer and autumn months. Herpesviruses, CMV, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) often show a predilection for the winter and spring. Herpes simplex virus (HSV), on the other hand, does not demonstrate any seasonality. With this epidemiology in mind, the evaluation of children with suspected viral meningoencephalitis is guided by many factors, including age, geographic location, season of the year, vaccination status, chronic conditions or immunosuppression, history of tick or mosquito exposure, and travel history.

Pathophysiology/Pathogenesis of Viral Meningoencephalitis

The current understanding of how viral pathogens infect the CNS holds that most neurotropic viruses initially multiply at the port of entry (mucosal surfaces of the skin, gastrointestinal tract, or respiratory tract) and then travel to extraneural sites in the body. They then migrate to vascular tissue, further multiply, and finally infect the CNS. Viruses may reach the CNS by several mechanisms. Whereas most directly invade across cerebral capillary endothelial cells that comprise the

Table 65–4 Causes of Meningoencephalitis and Available Laboratory Testing and Treatment

Virus	Available Laboratory Testing	Treatment
COMMON CAUSES		
Enterovirus		No specific therapy
Poliovirus (three serotypes)	Cell culture; isolates sent to CDC via state laboratories	
Nonpoliovirus	CSF PCR	
Echovirus (28 serotypes)	Cell culture, CSF PCR	
Coxsackievirus A (23 serotypes)	CSF PCR	
Coxsackievirus B (six serotypes)	Cell culture, PCR	
Parechovirus (six serotypes)	None	
Herpesvirus		
Herpes simplex virus-1, -2	CSF PCR	Acyclovir, foscarnet (if resistant to acyclovir in immunocompromised patients)
Cytomegalovirus	CSF PCR	Ganciclovir, Foscarnet
Ebstein-Barr virus	CSF PCR	
Varicella zoster	CSF PCR	Acyclovir
Human herpesvirus-6	CSF PCR	
Arbovirus	Viral isolation, serology done by state and research laboratories, detection of virus-specific IgM in CSF + Ab in serum specimen; CSF PCR in reference laboratories	
Flavivirus		
St. Louis encephalitis		
West Nile virus		
Togavirus		
Eastern equine encephalitis virus		
Western equine encephalitis virus		
Bunyavirus		
California encephalitis virus		
La Crosse virus		
Jamestown virus		
Snowshoe virus		
LESS COMMON CAUSES		
Mumps	Cell culture, mumps-specific IgM Ab, PCR	
Adenovirus	CSF PCR, cell culture	None
Respiratory syncytial virus	Viral isolation from nasopharyngeal secretion in cell culture, PCR	
Influenza A and B	Viral culture, PCR	Oseltamivir, zanamivir, amantadine or rimantadine if susceptible
HIV	HIV-1 nucleic acid detection by PCR	Multiple drug regimens
Lymphocytic choriomeningitis virus	Viral isolation from CSF, virus-specific IgM Ab in serum or CSF	
Rabies	Antemortem diagnosis via fluorescent microscopy of skin biopsy specimen, isolation of virus from saliva, detection of Ab in CSF or serum, detection of viral Ag and nucleic acid in infected tissue; postmortem diagnosis by immunofluorescent or immunohistochemical examination of brain	None

Ab, Antibody; *Ag,* antigen; *CDC,* Centers for Disease Control and Prevention; *CSF,* cerebrospinal fluid; *DNA,* deoxyribonucleic acid; *IgM,* immunoglobulin M; *PCR,* polymerase chain reaction.

BBB, they also may: (1) directly infect cerebral microvascular endothelial cells before infection of adjacent glia and neurons; (2) be carried between cerebral endothelial cells in infected leukocytes after BBB disruption; (3) initially infect glia without evidence of endothelial cell infection; (4) enter the choroid plexus epithelium; or (5) spread along olfactory nerve or peripheral nerve pathways.[53] Once a virus has invaded the CNS, it attaches within susceptible cells and induces the cellular changes and inflammatory responses that manifest as meningitis or encephalitis.

Clinical Evaluation

Bacterial and other causes of meningoencephalitis as well as other causes of encephalopathy such as trauma, hepatic failure, electrolyte abnormalities, and toxic ingestions must be ruled out before viral encephalitis is diagnosed. A careful history will yield important information such as immunization status, recent viral or other infections, history of immune diseases, travel history, tick or mosquito exposure, and the history of maternal herpes infection in the case of neonates. Physical examination should focus on evaluation of the mucous membranes and skin as well as a complete neurologic examination including the funduscopic examination. A high level of suspicion and vigilance along with serial neurologic examinations is essential because viral injury may result in the development of cerebral edema and even brainstem herniation. As in the case of meningitis, antibiotics and/or antiviral medications should not be withheld while the laboratory and imaging workup of encephalitis is pursued.

Laboratory Manifestations

Lumbar puncture with an opening pressure is essential in the evaluation of the patient with suspected meningoencephalitis. Initial evaluation of cerebrospinal fluid includes blood cell count, protein, glucose, culture, HSV PCR, enteroviral PCR, and oligoclonal bands.[54] CSF findings in viral encephalitis include pleocytosis with CSF white blood cell counts in the 100 to 1000 cells/μL range. Polymorphonuclear cells often are predominant in early infection and even up to 48 hours of infection; lymphocytes typically become more predominant later in the time course.[55] At least a mild elevation in CSF protein is usually seen, and mildly decreased levels of glucose may be present; however, the glucose level is often normal. Elevated levels of red blood cells often are seen in persons with herpesvirus meningitis. In addition to CSF, blood should be obtained for a complete blood cell count and culture, erythrocyte sedimentation rate or C-reactive protein, and electrolytes. If suggested by the history, additional samples for viral studies should be obtained. These samples often include CSF and serum arboviral titers and serum, urine, and/or nasal specimens to test for viruses such as HSV, varicella, EBV, CMV, adenovirus, influenza, and parainfluenza.

As a more rapid alternative to tissue culture, PCR techniques allow for relatively sensitive and specific diagnosis of enteroviruses, herpesviruses, and arboviruses in the clinical setting. For enteroviruses, PCR is directed at genomic RNA in the highly conserved regions of the 5' noncoding region. PCR allows for accurate diagnosis of enteroviruses in a few hours and sensitivity has been shown to be approximately 98%.[56] Specific virologic diagnosis of enteroviruses requires recovery of virus from CSF or tissue culture, with a sensitivity of 65% to 75%.[57] For HSV, CSF PCR is the test of choice, with approximately 98% sensitivity and 94% specificity.[58,59] PCR for varicella-zoster deoxyribonucleic acid (DNA) has been found to be 95% specific but only 30% sensitive. Therefore it is recommended that in cases of suspected VZV encephalitis the CSF be tested for intrathecal synthesis of VZV-specific antibody (IgM and CSF-to-serum immunoglobulin [Ig] G ratio).[60,61] PCR testing is also available for EBV and CMV from the CSF. For human herpesvirus-6 (HHV) infection, which may cause a severe encephalitis in immunocompromised patients, PCR has been shown to be somewhat sensitive; however, it may unreliably detect the virus, and viral isolation may be required.[62,63] Arboviruses in the CSF and serum are detected by IgG and IgM antibody testing. According to Centers for Disease Control and Prevention (CDC) criteria, confirmed cases of arboviral disease must demonstrate either: (1) a fourfold or greater change in virus-specific antibody titer; (2) isolation of virus from or demonstration of specific viral antigen or genomic sequences in tissue, blood, or CSF; (3) virus-specific IgM in CSF by antibody-capture enzyme immunoassay; or (4) virus-specific antibodies demonstrated in serum by antibody-capture enzyme immunoassay and confirmed by IgG antibodies in either the same or a later specimen.[64] Many states have epidemiological programs to provide surveillance of arboviral infections, and consultation with local and state health departments will help guide serologic testing.

In some rare cases, despite a thorough laboratory evaluation, a brain biopsy is required for definitive diagnosis and remains the gold standard to diagnose viral infections of the CNS.[65-67]

Neuroimaging

The initial noncontrast head CT scan may be normal in patients with meningoencephalitis. While most patients will require a CT scan in the early period of illness, MRI is most sensitive for detecting inflammation, edema, and hemorrhage in viral encephalitis. If there is concern for spinal cord involvement (e.g., transverse myelitis or enterovirus), then the MRI should also include the spine.[54] Depending on disease severity, patients with viral encephalitis may show focal or diffuse cerebral edema and even uncal or transtentorial herniation on either CT or MRI.

Specific infections often show characteristic MRI findings that may be helpful in formulating a diagnosis. The MRI appearance of viral encephalitis is generally that of diffuse scattered or confluent areas of T2-weighted hyperintensity. A variable degree of mass effect and edema is seen. Inflammation often involves meninges, and gadolinium enhancement is diffuse. The classic finding in HSV and HHV-6 encephalitis is hemorrhagic inflammation, often bilateral, of the temporal lobe, which manifests as T2-weighted hyperintensity on MRI and usually spares the deep nuclear structures (Figure 65-1).[68,69] Neonates with HSV encephalitis may demonstrate less defined areas of inflammation on MRI and may have a loss of gray-white matter distinction only.[54] Among other herpesviruses, varicella-zoster encephalitis may demonstrate multifocal ischemia and infarction as well as demyelinating lesions in the white matter and at gray-white junctions. CMV often shows characteristic enhancement in the ependyma around the lateral ventricles.[69] Togaviruses, including West Nile Virus, St. Louis encephalitis virus, Japanese encephalitis virus, and Eastern

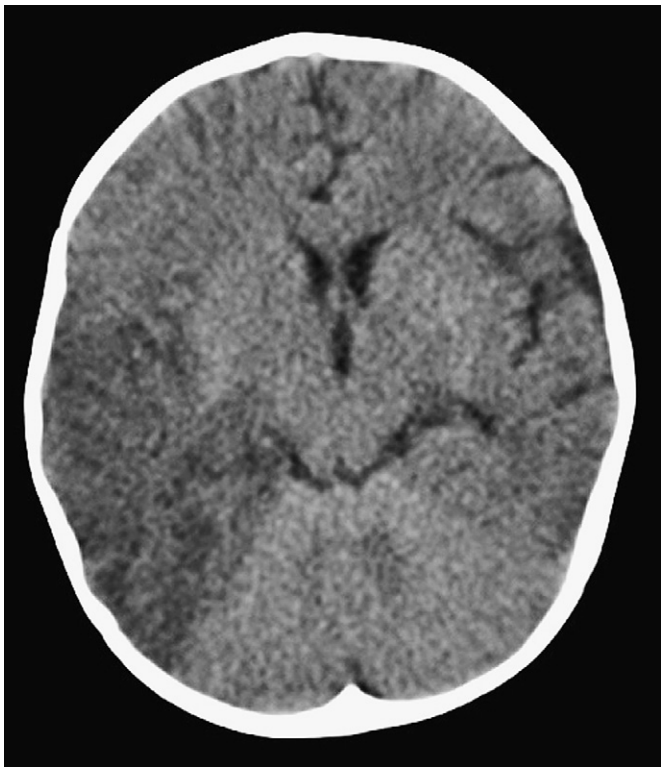

Figure 65–1. A magnetic resonance image of a pediatric patient with herpes simplex encephalitis. The image demonstrates the attenuation of the white matter of the right temporal lobe.

and Western equine encephalitis viruses, show involvement in the subcortical white matter, thalami, and substantia nigra.[69] In particular, Eastern equine encephalitis has been shown to produce focal lesions in the basal ganglia, thalami, and brainstem.[70] MRI findings in enterovirus encephalitis are less clearly defined and may be highly variable. However, patients with enterovirus 71 infection have demonstrated increased T2 and fluid-attenuated inversion recovery signal intensity in the midbrain, pons, medulla, and even the spinal cord.[71]

Clinical Presentation and Course

The clinical course of viral meningoencephalitis is highly variable, ranging from mild disease to death. Children with viral meningoencephalitis or encephalitis usually present with a prodrome of fever, headache, irritability, malaise, decreased oral intake, nausea, and possibly neck pain and/or nuchal rigidity. These signs and symptoms are essentially identical to the presentation of viral meningitis. However, a child with encephalitis also shows a decline in the level of consciousness and may demonstrate confusion, ataxia, seizures, aphasia, visual changes, and focal motor deficits or sensory deficits corresponding to the affected areas of the brain. In general, the most common focal neurologic deficits seen in encephalitis are hemiparesis, aphasia, ataxia, cranial nerve palsies, seizures, and myoclonus. Patients may also demonstrate autonomic dysregulation or hypothalamic dysfunction resulting in diabetes insipidus or syndrome of inappropriate antidiuretic hormone. Seizures are possible, especially in infants and children with herpes encephalitis. At the most extreme end of the encephalitis spectrum, focal or diffuse cerebral edema and even brainstem herniation may occur.

HSV remains the most common cause of fatal sporadic encephalitis in humans, despite specific antiviral therapy.[72] This may be either a new infection or latent reinfection.[72] HSV encephalitis is particularly severe in children with an immunocompromised status due to chemotherapeutic regimens, genetic immune defects, or HIV infection. Children and adolescents with HSV encephalitis present with nonspecific neurologic signs and often have seizures. Support for the diagnosis of HSV encephalitis may be bolstered by findings of temporal lobe involvement on MRI as well as spike and slow-wave activity on electroencephalogram (EEG).[73] Adults and children typically present with HSV-1 infection. In neonates, the majority of encephalitis cases are caused by HSV-2 due to perinatal transmission and shedding of virus in the maternal genital tract. Neonates presenting with encephalitis attributed to HSV often do not demonstrate fever. The most common presenting signs for neonates with HSV CNS disease are seizures and lethargy.[74] Skin lesion findings are variable. Infants with HSV infection also may have disseminated disease, which increases the morbidity and mortality significantly.

Enteroviral encephalitis may be highly variable in its presentation. The majority of cases are self-limited, but a large proportion of patients experience at least short-term morbidity. While HSV has predilection for the temporal lobes in many cases, the enteroviral infections in general are more global in nature. Patients with enteroviral encephalitis often present with fever, headache, nausea, vomiting, and nuchal rigidity. They also may demonstrate confusion or delirium and have seizures or focal neurologic signs.[75]

Enterovirus 71, a cause of hand-foot-mouth disease/herpangina, usually causes flu-like symptoms and a characteristic rash on hands, feet, and buttocks along with oral ulcers. It also can cause flaccid paralysis, inflammation, necrosis of the tissues of the brainstem, and death in about 16% of cases.[76] In addition, myocarditis and heart failure also have been reported with enterovirus 71 infection. Severe enterovirus 71 outbreaks were originally described in Asia. They have since been reported in other areas of the world, including the United States, Australia, Sweden, Bulgaria, and Hungary. This virus may represent an important emerging pathogen.[77] Unfortunately, the neurodevelopmental follow-up of children with severe enterovirus 71 brainstem encephalitis reveals significant long-term cognitive and motor deficits.[78]

Neuroinvasive arboviral infections include the California serogroup viruses, Eastern and Western equine encephalitis viruses, Powassan virus, St. Louis encephalitis virus, and West Nile virus. Their incidence increases when mosquito vectors are most active, usually in the summer months, and incidence varies significantly based on geographic region. This group of viruses causes encephalitis as well as myelitis. In fact, West Nile virus infection has been misdiagnosed as Guillain-Barre syndrome because of the flaccid paralysis that accompanies it. According to the 2004 CDC case definition, arboviral encephalitis is characterized by fever, headache, and altered mental status ranging from confusion to coma, with or without additional signs of brain dysfunction. Arboviral myelitis causes acute bulbar or limb paresis or a flaccid paralysis.[64]

Other zoonotic pathogens can cause encephalitis. Exposure to tick populations may suggest infection with Colorado tick fever in the western United States or nonviral etiologies such as Lyme disease or Rocky Mountain spotted fever. Nipah virus encephalitis has been seen in Malaysia, Singapore, and

Bangladesh and may be associated with exposure to bats or pigs.[65-67] Lymphocytic choriomeningitis virus is caused by a rodent-borne arenavirus and is transmitted via mice, rat, and hamster secretions. Rabies, although rare in the United States, should be suspected in patients with prodromal symptoms of encephalitis followed by hydrophobia and pharyngeal spasms as well as exposure to bats or other reservoirs. The incubation period is typically 20 to 60 days but can be in the 5-day to 6-month range.[72] In the developing world, canine rabies transmission to humans remains a significant public health problem, with an estimated (but probably severely underestimated) 55,000 deaths annually in Africa and Asia.[79]

Influenza virus infection has been associated with a number of neurologic complications such as seizures and mild encephalopathy.[80] The neuroimaging of many of these patients demonstrates a distinct pattern of bilateral, multifocal lesions of the thalami that have been described as acute necrotizing encephalopathy.[81-83] In addition, many patients with influenza-associated encephalitis and necrotizing encephalitis progress to multisystem organ failure. In a survey of more than 140 cases in Japan during the 1998-1999 influenza A (H3N2) outbreak, 31.8% of patients with influenza-associated encephalitis or encephalopathy died and another 27.7% experienced either short-term or long-term disability.[82] Brain CT revealed abnormalities in 66% of patients, with the most frequent findings being cerebral edema and hypodensities in the thalamus, brainstem, and brain parenchyma. Approximately 10% of the patients in the 1998-1999 case series showed the characteristic findings of acute necrotizing encephalopathy.[82] Only a small number of these patients have had influenza RNA isolated from CSF, and autopsies demonstrate a lack of direct viral invasion in the CNS. Many of the cases have been described in Japan and other parts of Asia, leading to speculation that some people may have a genetic susceptibility to the development of influenza-associated encephalitis/encephalopathy, but cases also have been described in Europe and North America.[82,84-86]

Treatment

With the exception of patients with herpesviruses, therapy for patients with viral encephalitis is largely supportive. Patients with severe neurologic dysfunction and/or status epilepticus may require airway, respiratory, and circulatory support. Clinicians should maintain careful attention to fluid and electrolyte status because of the risk of diabetes insipidus, syndrome of inappropriate antidiuretic hormone, and cerebral salt wasting. ICP monitoring has been used at some centers, and therapies to decrease ICP may be required.[87-90] Several small case series and case reports have discussed the use of decompressive craniotomy or craniectomy in the setting of severe encephalitis-induced intracranial hypertension in both adults and children.[91-93] However, to date no large studies have been conducted on the outcomes of children with severe viral encephalitis and increased ICP who have been treated with ICP monitoring and/or decompressive craniectomy. Seizures, both clinical and subclinical, should be treated and prevented as often as possible. Continuous EEG monitoring and induction of a barbiturate coma has been used in selected cases; however, the literature suggests that patients with refractory status epilepticus and viral encephalitis have extremely poor outcomes.[94-97]

Medical treatment of viral encephalitis is most effective in the treatment of herpes virus. In neonates with HSV encephalitis, antiviral therapy has significantly improved survival and decreased disease progression. The current recommended treatment for patients with HSV encephalitis from infancy to age 12 years is "high-dose" intravenously administered acyclovir (20 mg/kg every 8 hours) given for 21 days for both encephalitis and disseminated disease.[98] Patients older than 12 years should receive acyclovir at 30 mg/kg per day in three divided doses for 21 days.[98] Acyclovir-resistant HSV infections, while rare, have been reported and are best treated with foscarnet.[99]

Infants born to mothers who contract primary varicella infection from 5 days prior to delivery until 2 days after delivery are at increased risk for severe varicella encephalitis. Exposed newborns may be candidates for varicella-zoster specific immunoglobulin (variZIG) or intravenous immunoglobulin prophylaxis if the mother has severe skin involvement. Data are scarce, but the use of intravenous acyclovir at doses identical to treatment for HSV infection is recommended for neonates with clinical signs of varicella because of the risk of severe disease.[99] Intravenous acyclovir therapy is also recommended for other pediatric patients with encephalitis as well as immunocompromised patients with any form of varicella disease. Children with varicella should not receive salicylate agents because of the increased risk for Reye syndrome, and administration of salicylate drugs should be stopped in patients receiving chronic salicylate therapy for other conditions. Like HSV, acyclovir-resistant varicella has been treated with foscarnet.[99]

Case reports of immunocompromised patients with HHV-6 encephalitis suggest that this may be an emerging pathogen, particularly among transplant recipients.[100] Encephalitis may be caused either by a new infection or by reactivation of latent HHV-6. Isolation of HHV-6 from the blood or detection of viral DNA in serum or plasma via PCR indicates active viral infection. Serology is considered unreliable, particularly in immunocompromised patients. Foscarnet, ganciclovir, and cidofovir have been shown to have efficacy against HHV-6, and the International Herpes Management Forum recommends foscarnet and ganciclovir, either alone or in combination, for treatment of HHV-6–related CNS illness.[101]

CMV has caused encephalitis in immunocompromised patients and is particularly fatal in HIV disease. Foscarnet-ganciclovir combination therapy has been used with limited success.

Influenza encephalitis remains a challenge because often the virus is not detected in the CSF or even in autopsy brain specimens. The neuraminidase inhibitor oseltamivir as well as the ion channel blocker amantadine were both used in the largest prospective study of acute encephalitis/encephalopathy and influenza. It is currently unknown whether these agents change the outcome of this particularly clinically diverse and evolving entity.[102]

Prognosis

The prognosis of patients with meningoencephalitis is extremely variable and depends on the causative agent and the degree of CNS injury. Some patients with relatively mild disease may experience only short-term sequelae of their infection. Although antiviral therapy has significantly improved mortality for HSV encephalitis in neonates, studies suggest

that the long-term cognitive and neurodevelopmental consequences for survivors of HSV encephalitis and disseminated HSV disease include static encephalopathy, mental retardation, autism, cortical blindness, and epilepsy.[103] Focal signs on neurologic examination, multiple seizures or status epilepticus on admission, leukopenia, and focal slow waves or continuous generalized delta waves on EEG are all associated with poor neurologic outcomes.[104-105] Serial neuroimaging studies and close neurologic follow-up may aid in counseling families regarding prognosis for individual patients, but predicting neurologic functional outcomes in this group of patients remains a challenge for clinicians.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder most common in childhood and adolescence. The median age of onset is 6.5 years. The incidence of ADEM is estimated to be 0.8/100,000 patients annually.[106]

ADEM is believed to have an immune pathogenesis. This belief comes from the observation that ADEM typically develops in a post- or parainfectious time period. The diagnosis often is made in the setting of a defined viral illness or vaccination in the month preceding the onset of neurologic symptoms and signs. A recent pediatric study from the United States showed that the most common risk factor was not a vaccination or infection but rather exposure to an ill sibling in the month before the onset of symptoms.[107] Neurologic symptoms can begin as early as 1 to 2 weeks following a febrile event. Documented prodromal viral illness or vaccination occur in only 50% to 75% of patients with childhood ADEM, and half of the patients in these studies were well past the age of the standard childhood immunizations.[108] Serologic studies for viral or bacterial pathogens causing antecedent or coincident infections are documented in less than 20% of cases.[107] In countries where immunizations against measles, mumps, rubella, and varicella were not commonly given, these agents were most commonly associated with ADEM.[109] For most vaccines, incidence rates are approximately 0.1 to 0.2 per 100,000 vaccinated individuals.[106] Of note, the incidence of measles vaccination–associated ADEM is 0.1/100,000. This incidence is considerably lower than the incidence of ADEM after wild-type measles, which is associated with ADEM in approximately 100 per 100,000 cases.[110] Two specific vaccines against Japanese B encephalitis and rabies are associated with ADEM, with incidence rates as high as 1/600.[110] Interestingly, in populations that routinely receive vaccinations, nonspecific upper respiratory tract illnesses are cited as the most common cause of childhood cases of ADEM.[111]

Although the exact pathophysiologic mechanism of ADEM is uncertain, the concept of molecular mimicry is one of the most prevalent theories.[112] It is believed that certain amino-acid sequence homologies and antigenic epitopes are shared between an invading pathogen or inoculated vaccine and the host CNS protein. The pathogen is neither recognized as "foreign" in order to be eliminated nor as "self," which would result in immune tolerance. Initially the pathogenic material is processed at the site of infection or inoculation. The adaptive immune response causes T cell activation and ultimately production of antigen-specific B cells. These autoreactive T cells and B cells are capable of entering the CNS. During routine immune surveillance, they may encounter the homologous myelin protein. Following local reactivation by antigen-presenting cells, an inflammatory immune reaction against the presumed foreign antigen is elicited. Thus a physiologic immune response causes detrimental autoimmunity distant from the original site of infection or inoculation.

Another theory on the pathogenesis of ADEM concerns release of CNS autoantigens following encephalitis.[113] After a direct CNS infection with a neurotropic pathogen (such as measles), CNS tissue may be damaged and the BBB disrupted. This phenomenon may result in systemic leakage of CNS-confined autoantigens into the systemic circulation, where they are processed in systemic lymphatic organs, causing breakdown of tolerance with subsequent emergence of a self-reactive T cell response. Subsequent expression of proinflammatory cytokines may perpetuate CNS inflammation even further. However, although there appears to be an immune response component to the pathophysiology of ADEM, the CSF of these patients has significantly less interferon-γ and interleukin (IL)-10 concentrations when compared with patients with CNS enteroviral infections but similar IL-12 values.[107]

From a histological perspective, the lesions of ADEM often can be confused with those found in patients with multiple sclerosis (MS). However, both ADEM and MS lesions have unique histopathological findings. MS lesions are heterogeneous in terms of lesion age and composition of the cellular components. In contrast, ADEM lesions are almost always of similar age and consist of mostly one distinct pattern.[114] The inflammation tends to cluster around small vessels (particularly veins) in both white and gray matter. Lesions are infiltrated by lymphocytes, macrophages, and, to a lesser extent, neutrophils. In addition, perivascular edema, endothelial swelling, and vascular endothelial infiltrations are present. Demyelination may not be present in the acute lesions but tends to develop later in the lesion's evolution, often in a "sleevelike" pattern confined to the area of inflammation. Damage to the axon itself is rare.

Although most episodes of ADEM are solitary with no further clinical relapse or new radiographic findings, recurrences have been reported.[108] In other patients additional areas of demyelination develop with localizations that differ from those of the initial episode. In these patients, the diagnosis of MS is often considered once they reach adulthood. Some patients have recurrent episodes in temporal proximity to or with the same localizations as the initial presentation. These very early temporally circumscribed relapses are thought to represent part of the same acute monophasic immune process, and the terms *monophasic disseminated encephalomyelitis* or *relapsed ADEM* are used occasionally to describe these cases.[115] Monophasic disseminated encephalomyelitis is characterized by older age of patients at onset (typically >10 years), more severe and prolonged local neurologic symptoms, marked extrapyramidal signs, and distinct demyelination patterns on MRI.[116]

A combination of altered consciousness or behavior and multifocal neurologic deficits, especially in close relation to an infection, should raise the clinician's suspicion of ADEM. The initial clinical presentation is often of nonspecific complaints. Patients may experience headaches, vomiting, lethargy, and low-grade fevers. Distinct functional neurologic or cognitive defects develop gradually, with most patients demonstrating

findings at the time of admission. Clinical deterioration and development of new neurologic abnormalities are prominent features of the hospital course of many patients. The majority of patients exhibit multiple abnormalities including ataxia, inability to walk, slurred speech, or decreased speech output. Cranial neuropathies (especially of extraocular movements) and abnormal reflexes (typically hyperreflexia) are common findings. Altered mental status, including agitation, delirium, nonresponsiveness, and inability to recognize parents or siblings, is noted in up to two thirds of patients.[107]

No specific laboratory criteria exist for the diagnosis of ADEM. CSF examination is commonly performed at the time of clinical presentation in most patients with ADEM, and often it is normal. Abnormalities generally include moderate elevation in the numbers of leukocytes, typically lymphocytes or monocytes, and moderately elevated protein levels. Oligoclonal bands are rare in patients with ADEM, occurring in 3% to 29% of the samples studied.[115] Oligoclonal bands may only be present transiently, which is in sharp contrast to MS. EEGs typically show diffuse slowing, especially when the patient exhibits an altered level of consciousness. Focal epileptiform activity is noted in 2% of patients with ADEM.[108]

A CT scan usually does not detect the lesions noted in most patients with ADEM. The radiologic study of choice for diagnosing ADEM is the MRI scan. Abnormalities are most frequently identified on T2-weighted and fluid-attenuated inversion recovery sequences. ADEM-associated MRI lesions are often multiple and asymmetric. They frequently involve the subcortical and central white matter, cortical gray-white junction, and gray matter of the thalamus and basal ganglia (Figure 65-2). One third of MRI abnormalities completely resolve, while a partial resolution is noted in 35% to 50% of patients.[108,111,115] In addition, the MRI may have a role in the clinical prognosis of patients with ADEM. Delayed development of MRI lesions in deep gray matter and brainstem may herald a prolonged clinical course and lack of response to glucocorticoid therapy.[117]

Because there is no single radiologic study or serologic test to confirm ADEM, a differential diagnosis must be entertained in all suspected cases. Meningoencephalitis, HIV encephalopathy, Behçet's disease, CNS vasculitis, CNS neoplasia or metastases, and mitochondrial encephalopathies are a few diseases that can potentially present with clinical symptoms similar to those of ADEM. However, the most important and most common differential diagnosis with regard to therapeutic options and prognosis is MS. In a recent study from Germany, the authors noted that the incidence of MS was fivefold higher than ADEM in the pediatric population.[118] While the diagnosis rates of ADEM and MS were virtually identical during childhood, MS was more prevalent in adolescence. The clinical picture of MS is often indistinguishable from that of ADEM, although CSF findings are much more likely to show oligoclonal banding in persons with MS. Cerebellar and brainstem clinical signs are the most frequent initial presentation of pediatric-onset MS, occurring far more frequently than adult-aged control subjects with MS.[118]

A recent study indicated that initial MRI findings might be helpful in distinguishing MS from ADEM in children. Although the total lesion number did not differentiate ADEM from MS, periventricular lesions were more frequently found in children with MS. Further, the authors noted that the presence of two or more periventricular lesions combined with

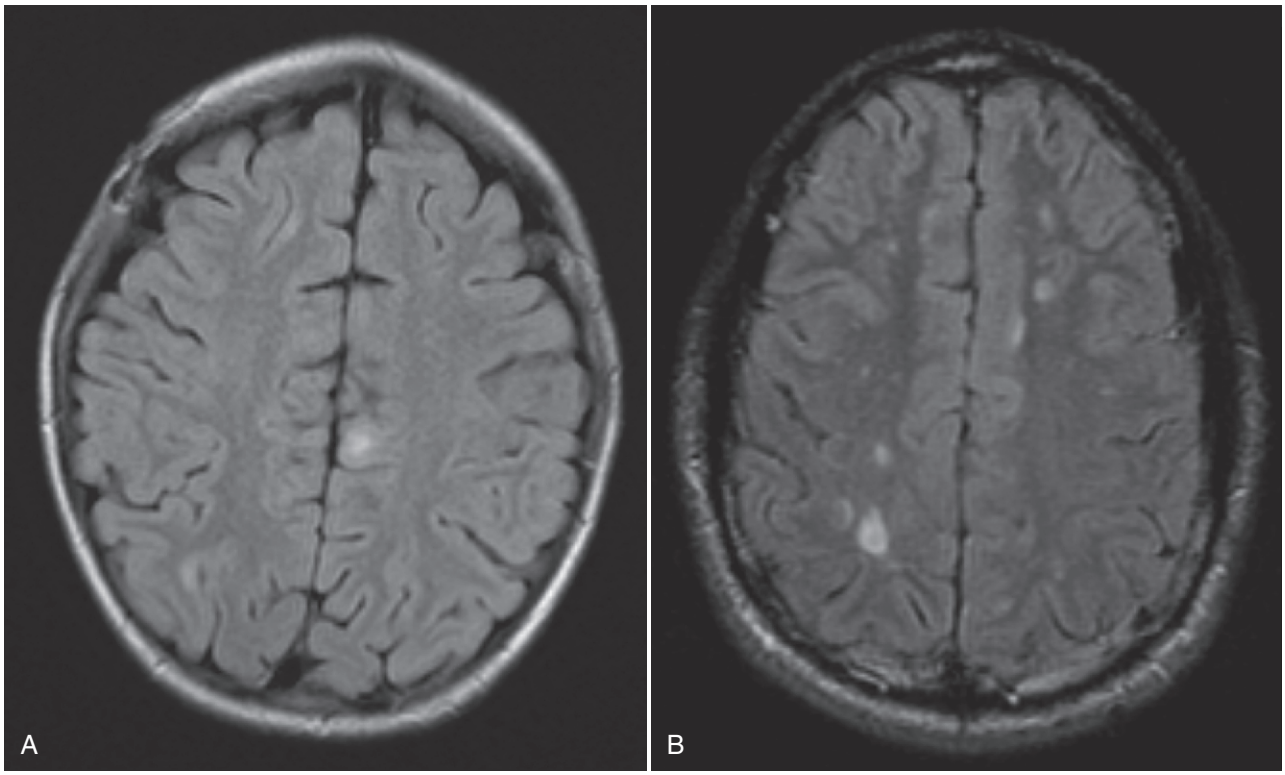

Figure 65–2. Radiographic overlap between multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM). **A,** ADEM tends to have a single area of demyelination, often involving the cortical gray-white junction. This T2 fluid-attenuated inversion recovery (FLAIR) image shows involvement of the subcortical white matter. **B,** MS tends to involve the deep white matter and corpus callosum. This T2 FLAIR image demonstrates lesions in these areas.

either the absence of a diffuse bilateral lesion pattern or the presence of nonenhancing lesions on T1-weighted images (black holes) was highly sensitive and specific for MS in children.[119]

Given the presumed autoimmune nature of ADEM, high-dose steroid therapy remains the mainstay of treatment. Therapies such as intravenous immunoglobulin or cyclophosphamide do not appear to offer clinical benefit. Methylprednisolone appears to have clinical benefit over other high-dose steroids.[111] Clinical improvement is generally noted with 24 hours of initiation of therapy. Although the duration of therapy lacks consensus, most clinicians recommend a 3- to 5-day course of methylprednisolone. Relapses are common, occurring in 25% to 35% of patients. Some authors advocate administration of intravenous immunoglobulin or use of plasmapheresis as treatment options for patients with ADEM, especially when the course is aggressive or the patient has severe disease that has not responded to use of corticosteroids.[117]

Most pediatric patients recover from ADEM. More than 70% of children with ADEM, including many with significant neurologic deterioration upon admission to the PICU, recover completely from their initial attack, generally within 6 months after the initial presentation.[120] Residual disability appears to be more common in patients with large or bithalamic lesions on MRI.

Brain Abscesses

The brain parenchyma is remarkably resistant to microbial infections. Despite the relative frequency of occult bacteremia in the pediatric age patient, cerebral abscess formation is a rare occurrence. The incidence of brain abscesses in children is 4 cases per million, with a peak age of presentation between 4 and 7 years of age.[121] Certain medical conditions, especially those that impair the immune response, predispose patients to brain abscess formation. These conditions include prolonged steroid use, diabetes mellitus, alcoholism, and primary immunodeficiencies.[122] A brain abscess is a focal intracerebral infection that begins as a localized area of cerebritis and matures into a collection of pus surrounded by a well vascularized capsule. Although it is a rare occurrence, its presence is often serious and life threatening.

Brain abscesses are usually classified according to their likely point of entry. The most common origin of CNS abscesses in children is direct or indirect extension from the middle ear or paranasal sinus or dental abscesses.[123] Brain abscesses are sequelae in 6% to 8% of untreated sinusitis cases and up to 10% of mastoiditis cases.[121] Abscesses in the temporal lobe or cerebellum typically are linked to ear or mastoid air cell points of entry. Frontal lobe abscesses often are due to sinus or dental infections. Metastatic lesions often are noted in the CNS parenchymal area, especially in the middle cerebral artery distributions, including the parietal and occipital regions (Figure 65-3). The etiology is often from distant foci in children with cardiac or pulmonary right-to-left shunts.

Extensions from cranial osteomyelitis, scalp infections, endocarditis, and meningitis are rare causes of CNS abscess formation. Historically, penetrating head trauma and neurosurgery represent a small proportion of the predisposing causes of CNS abscess, but the proportion is increasing, possibly as other predisposing factors such as middle ear infection become less important. Cyanotic congenital heart disease also has been reported to increase the risk of brain abscess.[121,124] Of pediatric patients diagnosed with brain abscesses, one third have an underlying cardiac defect. This increased predisposition may be due to the presence of areas of brain ischemia caused by decreased arterial oxygen saturation and increased hemoglobin that may act as a focus for infection to develop. Right-to-left shunting also may predispose a person to a brain abscess, as the removal of organisms from the systemic circulation by the lungs is bypassed. In roughly one quarter of brain abscess cases, no identifiable route or predisposing factors are identified.[123]

In the first few days of a developing abscess, cerebritis with a focal area of acute inflammation, vascular dilation, microthrombus formation, and rupture of small vessels are all noted. After 4 to 9 days, the center of the lesion undergoes liquefaction necrosis. By 10 to 14 days, a well-vascularized collagenous capsule with peripheral gliosis or fibrosis is typically present.

The clinical presentation varies, depending on the size, multiplicity, and location of the lesion. Most patients are symptomatic within a week of the onset of abscess formation. Symptoms in adults are nonspecific and include headache (70%), fever (60%), vomiting (50%), focal neurologic deficits (45%), and seizures (40%).[125] However, in pediatric patients the classic triad of fever, headache, and focal deficits occurs in less than 30% and meningeal signs in less than 25% of cases.[126] More than half of the cases will feature papilledema. The sudden worsening of a preexisting headache can indicate rupture of the brain abscess into the ventricular space or impending herniation from the lesion's mass effect. A significant alteration in mental status is an ominous clinical finding. Children with abscesses located within their brainstem typically present with fever, headaches, hemiparesis, and often have palsies of cranial nerves III, VI, and VII.

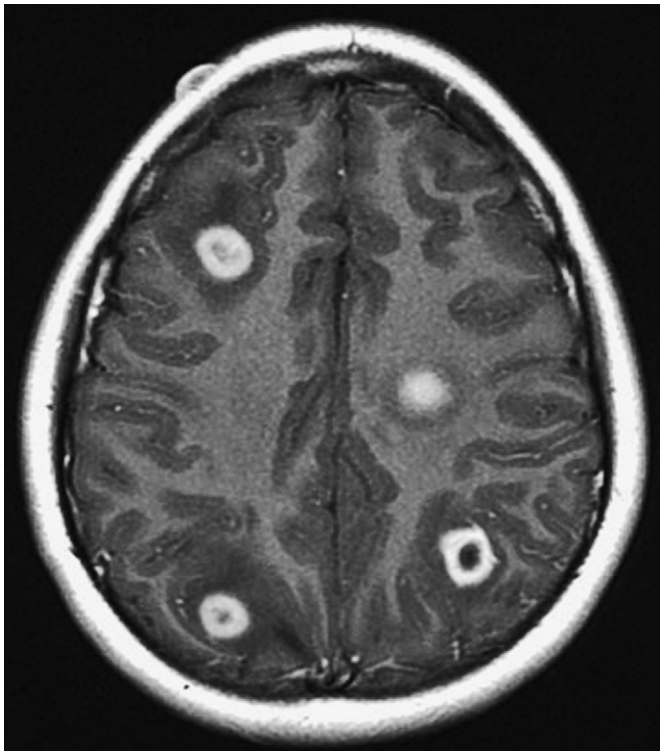

Figure 65–3. This magnetic resonance image demonstrates multiple brain abscesses in a pediatric patient with chronic granulomatous disease. A culture of the abscess material grew aspergillus.

The most important microbiological investigation in the management of patients with brain abscess is culture of the abscess fluid. CT-guided stereotactic aspiration of brain abscesses, a minimally invasive procedure with low morbidity and mortality, is often indicated. This procedure allows both rapid and effective drainage of the brain abscess and obtains material for culture. A lumbar puncture to obtain CSF may be contraindicated in a patient with a brain abscess. Raised ICP may lead to brainstem herniation in these patients. Additionally, CSF culture does not contribute significantly to the identification of the organism. Blood cultures can be helpful in a small percentage of patients, especially in those in whom the abscess is thought to be the result of hematogenous spread.

The microorganisms cultured from the brain abscess are variable and often depend on the original source. *S. aureus*, multiple species of aerobic, anaerobic, and α-hemolytic *Streptococcus*, and Gram-negative anaerobic bacilli tend to predominate. *Citrobacter* and *Cronobacter* spp. are frequently associated with brain abscesses in neonates. In children with impaired host defenses, fungi and uncommon pathogens such as *Toxoplasma, Nocardia*, and *Mycobacterium* organisms can be identified. Mixed aerobic and anaerobic flora are isolated in up to one third of patients, especially in children with chronic otitis and sinusitis.[127] One quarter of samples may demonstrate no bacterial growth.

The clinical presentation of brain abscess is often nonspecific. As such, the diagnosis often is made through radiographic means. Without imaging, it may be difficult to differentiate between a brain abscess and other intracerebral pathologic processes. The advent of CT, and more recently MRI, has altered the prognosis of brain abscess by improving diagnosis. In addition, both CT and MRI are able to locate the position of the abscess accurately, thus enabling a more focused surgical intervention. MRI may have a diagnostic advantage over CT by better differentiation of edema from liquefaction necrosis, greater sensitivity for early satellite lesions, and more sensitivity in the detection of early cerebritis.[128] Serial CT scanning may provide additional information about response to treatment.

Stereotactic CT-guided drainage of the abscess is the treatment of choice in most patients, followed by antibiotic therapy. Even in the critically ill ICU patient, a stereotactic procedure is minimally invasive and the risk-benefit profile will often support its use. Aspiration of the abscess allows both removal of infected nidus and likely identification of the causative organism. Endoscopic drainage may be useful in lesions located in a periventricular distribution. Few indications exist for the nonoperative management of brain abscesses. Typically, abscesses >2.5 cm require surgical drainage.[129] Occasionally the abscess is inaccessible or there are multiple abscesses. In specific cases where there is a small lesion and the infecting organism is known, medical treatment alone may be considered appropriate. Craniotomy and direct surgical drainage is required in some cases of fungal, helminthic, or multiloculated abscesses or after failed stereotactic drainage. Also, brain abscesses resulting from traumatic head injury should be considered strongly for surgical excision because of the possibility of retained foreign bodies or bone fragments. Lastly, primary excision should be chosen over stereotactic aspiration for lesions located in the cerebellum because this approach demonstrates a lower mortality, lower incidence of the development of obstructive hydrocephalus, and an overall shorter hospital stay.[130]

A combination of a third-generation cephalosporin and metronidazole is a reasonable combination for initial antibiotic therapy in persons with brain abscesses. Vancomycin can be added if *S. aureus* is identified or suspected as the causative organism. Vancomycin also is a reasonable choice if the abscess is believed to have occurred as a consequence of a neurosurgical procedure, because in these circumstances, *Staphylococcus* is frequently a pathogen. No prospective studies in children are available to guide antibiotic therapy. Duration of treatment is best based on clinical response. Duration of treatment can be as short as 1 to 2 weeks of intravenous antibiotic therapy followed by 2 to 4 weeks of an oral antibiotic after surgical drainage. Some clinicians recommend that intravenous therapy be continued as long as 4 to 6 weeks.[128] If antibiotics alone are utilized, the duration of intravenous therapy is typically longer, with some clinicians recommending a treatment period of up to 6 to 8 weeks.[129]

Mortality attributed to brain abscess was 60% prior to 1970. Since the advent of newer radiologic procedures such has high-resolution head CT or MRI, detection of brain abscesses is more efficient. With earlier detection, mortality has dropped and currently is about 10% to 15%.[125-126] Long-term neurologic morbidity attributed to the abscess and therapy ranges from 10% to 30% depending on both the size and location of the lesion as well as the response to therapy. The patient's neurologic status at presentation is a significant predictor of outcome, with an increased mortality rate in those who present to the PICU with an altered mental status or rapid neurologic deterioration.[131] Brain abscesses resulting from a contiguous focus of infection and those developing after a traumatic injury tend to have a good prognosis. Those resulting from neurosurgery for neoplasia or where there is a medical or cardiac predisposing factor are more likely to have a poorer outcome.

Primary and Granulomatous Amoebic Central Nervous System Infections

Primary amebic meningoencephalitis (PAM) is a rare, often fatal disease caused by infection with *Naegleria fowleri*, a thermophilic, free-living amoeba found in freshwater environments. In 2007, six cases of PAM in the United States were reported to the CDC, five of which involved pediatric patients. All of the patients reported to the CDC died.[132]

Naegleria fowleri is the causal agent of most PAM infections, but other species of *Naegleria* with pathogenic potential have been described (e.g., *Naegleria australiensis* and *Naegleria italica*). Currently, more than a dozen species of *Naegleria* have been recognized based on small subunit ribosomal DNA.[133] The habitat for *N. fowleri* is natural or man-made fresh water lakes or an inadequately chlorinated swimming pool where the amoebas can feed upon bacteria and proliferate. In the United States, *N. fowleri* is commonly found in warm freshwater environments in 15 southern-tier states (Arizona, Arkansas, California, Florida, Georgia, Louisiana, Mississippi, Missouri, Nevada, New Mexico, North Carolina, Oklahoma, South Carolina, Texas, and Virginia).

In 2007, the CDC and the Council of State and Territorial Epidemiologists formed the *Naegleria* Workgroup. They used multiple resources to conduct a review of all PAM cases reported in the United States from 1937 to 2007. Preliminary

results indicate that a total of 121 cases (range: 0 to 8 cases per year) occurred in the United States from 1937 to 2007. The six cases of PAM reported to the CDC in 2007 were among the highest during the study period. From 1937 to 2007, the median age of the patients was 12 years (range: 8 months to 66 years). Among the 119 cases for which the sex of the patient was known, male patients accounted for 93 (78%) of the cases. Only one survivor was reported. Among the 112 cases for which the month of exposure was known, 95 (85%) occurred during July to September.[132]

Naegleria species typically cause PAM in children and healthy adults who have been swimming in infested water. *N. fowleri* enter through the olfactory neuroepithelium at the level of the cribriform plate and invade the submucosal nervous plexus. Symptoms begin after a 3- to 7-day incubation period. PAM presents in a manner very similar to acute bacterial meningitis, but physicians often miss the diagnosis initially. History is vital for making the diagnosis. Residence in or travel to a southern-tier state in the United States must be verified. Recent exposure to diving, swimming, or splashing in warm fresh water should suggest the possibility of amoebic meningoencephalitis, and the CSF should be promptly examined for *N. fowleri*. The onset of PAM is abrupt, with sore throat, headache, nausea, vomiting, malaise, and fever. Early findings also may include irritability, hallucinations, meningismus, cerebellar ataxia, and cranial nerve palsies, although focal neurologic defects are usually absent. Alterations in taste and smell may occur, likely due to involvement of the olfactory nerve.[134]

Differential diagnosis includes acute bacterial meningitis, HSV-1 encephalitis, and viral or fungal meningitis. With immunosuppressed patients, amoebic meningitis might be confused with toxoplasmosis, CMV infection, and other opportunistic pathogens. The diagnosis is made by examination of CSF wet mounts for motile trophozoites; however, failure to visualize these amoebae does not exclude PAM. The diagnosis is often missed when *Naegleria* organisms are mistaken for atypical monocytes or lymphocytes.

Currently, the most effective therapy is amphotericin B, given both intravenously and intrathecally. Miconazole, rifampin, and doxycycline are often used in conjunction with amphotericin B.[134] Given the difficulty in making a diagnosis, early infectious diseases consultation should be considered for any patient with a history of stagnant warm water exposure, clinical signs of early meningoencephalitis, CSF findings consistent with meningitis, and a CSF Gram stain showing no bacterial organisms.

PAM infections tend to be fulminant, with seizures progressing to coma and death within 4 to 6 days. Autopsy findings typically demonstrate acute hemorrhagic necrotizing meningoencephalitis with purulent exudates in the brain, brainstem, and cerebellum.

The extremely low incidence of PAM makes epidemiologic study difficult. It is unknown why certain individuals become infected with the amoebae when many others who are exposed to the same freshwater sources do not become infected. Attempts are under way to determine what concentration of *N. fowleri* in the environment poses an unacceptable risk, how a standard might be set to protect human health, and how regulators might measure and enforce such a standard.

Another amoebic organism, *Acanthamoeba* spp., causes a subacute CNS infection known as granulomatous amoebic encephalitis. More so than the *Naegleria* organism, *Acanthamoeba* is ubiquitous in the environment, with amoebas widely disseminated in soil and water. Unlike the healthy individuals acquiring *Naegleria* infections, *Acanthamoeba* infections of the CNS are typically in found in compromised hosts who have concurrent diseases such as acquired immunodeficiency disorder or IgA deficiency or those undergoing suppressive therapy for organ transplantation. The portal of entry of this species of ameba can vary. It may be intranasal, allowing amoebas to migrate directly to the CNS, via a break in the skin or through the respiratory tract, with subsequent spread of amoebas to the CNS by a hematogenous route. The disease assumes a chronic status, leading to slow deterioration. Gadolinium-enhanced T1-weighted MRI of the brain show multiple punctate focal areas of enhancement bilaterally throughout the cerebellar hemispheres, with some scattered foci supratentorially.[135] These lesions may represent focal cerebritis or microabscesses. Diagnosis is most often made by postmortem examination of brain tissue showing patchy, chronic granulomatous encephalitis with trophozoites and cysts in the lesions.

Conclusions

Acute infections of the CNS are common in childhood and can be associated with significant morbidity and mortality. The field of pediatric CNS infections is ever changing with the advent of new conjugate vaccinations for bacterial meningitis and the emergence of new pathogens. Further, pressure in the community to prescribe antibiotics has led to the development of drug-resistant organisms, thereby causing infections that are increasingly difficult to control. The best approach for management of CNS infections in the PICU continues to rely on successful integration of treatment strategies designed to correct the systemic and intracranial pathophysiologic issues. A thorough knowledge of the pathophysiology, screening laboratory tests and radiographic studies, and best treatment options is mandatory in the training of all pediatric intensivists. Insight into the etiologies and nuances of CNS infections remains a crucial component for therapeutic success.

References are available online at http://www.expertconsult.com.

Renal Structure and Function

Maury N. Pinsk and Victoria F. Norwood

PEARLS

- The efferent blood supply from a single glomerulus will contribute to the capillary vascular supply of tubules from different nephrons. This arrangement of the vascular supply explains the patchy distribution of tubular damage after ischemic injury.
- Combinations of angiotensin-converting enzyme inhibitors and nonsteroidal antiinflammatory drugs result in inhibition of afferent arteriolar vasodilation and inhibition of efferent arteriolar vasoconstriction. In low flow states, these agents can cause precipitous loss of glomerular filtration pressure and kidney function
- Tubular dysfunction in the setting of acute tubular necrosis results in the inability to transport sodium into the medulla to establish concentration gradients, impairing the concentration of urine and resulting in diuresis. Furosemide and other loop diuretics, which also impair sodium transport into the medulla, are often ineffective at increasing urine output in this setting.

Renal Development

The human kidneys begin development in the third week of gestation, at which time they are primitive organs called pronephroi. These early kidneys are functional but regress as development unfolds. As gestation continues in the fourth week, the secondary kidney elements, the mesonephroi, form from parallel strips of mesoderm along the paravertebral axis. The mesonephroi begin functioning between the sixth and tenth week of gestation before involution in a cranial-caudal direction beginning at 10 weeks' gestation. The definitive kidney, or metanephros, begins development at the fifth week of gestation and begins functioning between the tenth and fourteenth week. This kidney develops in the pelvis as the branching ureteric bud and undifferentiated metanephric mesenchyme interact in a complex series of reciprocal inductions.[1-3] These interactions lead to the formation of glomeruli, whereas vessels and tubules form from mesenchymal precursors, and distal tubules and collecting ducts derive from ureteric bud epithelium. This process occurs in a centrifugal fashion so that deeper corticomedullary nephrons form earliest in organogenesis, whereas the more peripheral cortical nephrons form later. As the metanephros develops, the maturing kidney ascends into the retroperitoneal space to its final location with the upper poles at the T12 vertebra. During the ascent, the systemic blood supply is derived from more cranial aspects of the aorta and from the lumbar renal arteries at the final position of the kidney. The ureters elongate and canalize during the ascent to maintain drainage to the bladder. By the time human nephrogenesis is complete at 34 to 36 weeks of gestation, repeated cycles of mesenchymal induction, ureteric branching, and morphogenesis result in approximately 1 million nephrons per kidney.

Renal Anatomy

Normal human kidneys reside in the retroperitoneal space at the level of the T12 vertebra. The liver is superior to the right kidney and thus displaces it lower than the kidney on the left side. The spleen and stomach overlie the superior aspect of the left kidney. Kidneys, however, can be found in a variety of other locations and have altered morphologies as a result of alterations of the normal developmental program (reviewed by Schedl[4]). For example, failure of the kidney to ascend normally results in a pelvic kidney that has abnormal vascular supplies from the aorta and iliac vessels. Mesenchymal regions of the two kidneys coming in contact during early development likely cause fused kidneys, most commonly the horseshoe kidney. Partial or complete renal duplications comprise a variety of abnormalities that may arise from aberrant branching of the ureteric bud into the developing mesenchyme. Unilateral agenesis likely results from failure of ureteric bud development or abnormal mesenchymal induction, leading to regression of the metanephric mesenchyme and failed renal development.

Renal Vasculature

Vascular Development

Markers of early vascular development are expressed in undifferentiated metanephric mesenchyme, which suggests that the blood supply to the nephron develops at least partially from precursors inherent to the maturing kidney.[5] Migration of committed endothelial cells into the developing glomerulus occurs in response to secreted factors such as vascular endothelial growth factor, which is secreted under the transcriptional regulation of the oxygen-sensitive hypoxic inducible factor.[6] Control of the corresponding branching of extraglomerular vessels is an area of active study and may involve branching from existing vessels, de novo vessel formation, or both processes. These actions appear to be regulated in part by the renin-angiotensin system.[7]

Vascular Anatomy

The arterial supply of the kidney branches from the main renal artery and enters the kidney in a series of rays called interlobar arteries. The interlobar vessels branch at the corticomedullary junction to run parallel to the surface of the kidney as arcuate arteries. Arcuate arteries penetrate the cortex as interlobular arteries, which ascend into the cortex in a radial pattern. It is from the interlobular arteries that afferent arterioles of the glomeruli arise. After filtration across the glomerular tuft, blood exits the glomerulus by efferent arterioles, which travel to the surface of the cortex and eventually feed the peritubular capillary vascular beds, the vasa rectae. The efferent arteriole of a single nephron can supply blood to multiple vasa rectae. The postglomerular vasculature of the cortex is supplied by efferent arterioles from midcortical and superficial cortical nephrons, whereas the blood supply to the medulla is entirely derived from juxtamedullary efferent arterioles. The vasa rectae of the medulla branch as they descend toward the papilla of the kidney and form the complex meshwork of the medullary capillary vascular beds. Only a few vessels of the vasa rectae eventually reach the papillary tip.

Venous drainage of the vasa rectae is divided into two types: the vessels of the deep medulla ascend to join the arcuate veins at the corticomedullary junction, and those of the superficial medulla ascend into the cortex to join the cortical capillary network and ultimately the interlobular and arcuate veins (Figure 66-1). The arcuate veins join with the interlobar veins via the interlobular veins and finally drain into the main renal vein to join the main circulation.

Vascular Function

The kidneys are extraordinarily vascular organs; they receive 15% to 18% of cardiac output in the neonate and up to 20% of cardiac output in the adult.[8] Blood flow to the kidney is tightly regulated to ensure continued renal function over a range of blood pressures. Sympathetic α_1-receptors, myogenic contraction, and vasoactive mediators control vascular resistance and provide autoregulation of renal blood flow. Maintenance of glomerular filtration rate at the level of the glomerulus occurs by vasoconstriction of efferent arterioles in response to pressors such as angiotensin II, whereas afferent arterioles relax in response to vasodilators such as prostacyclin. Circulating angiotensin II is elevated in the neonate,[9] as are corresponding vasodilators.[10,11] Therefore infants have a decreased capacity to regulate renal blood flow, which explains their increased susceptibility to renal ischemia in hypotensive states.

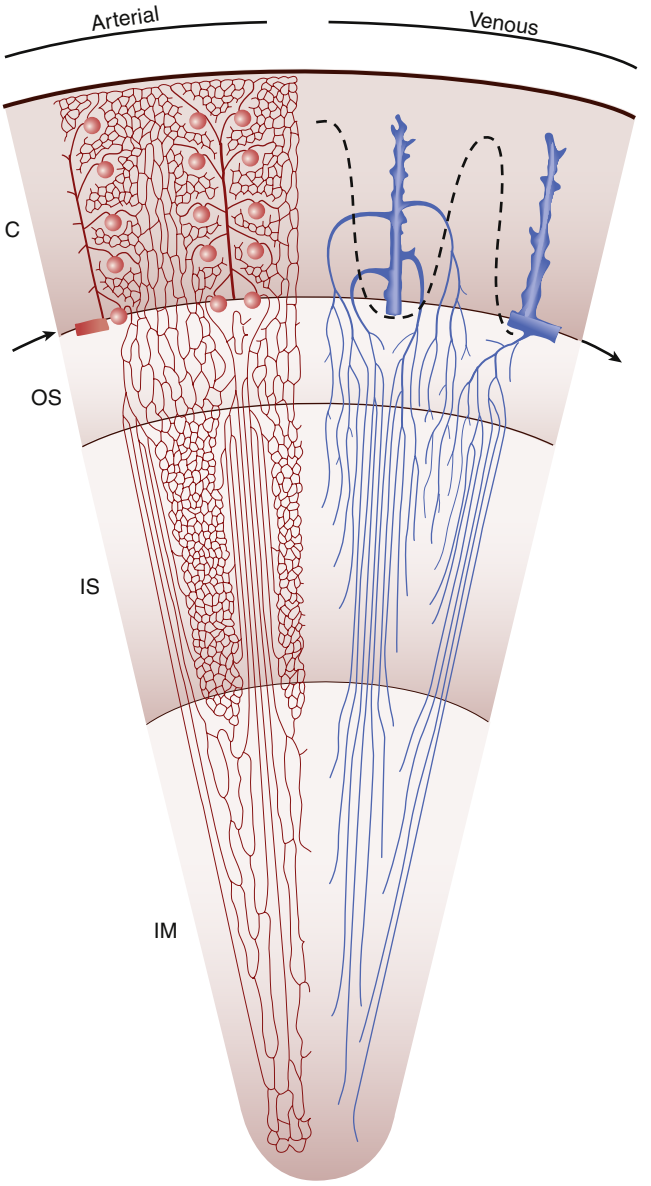

Figure 66–1. The microvasculature of the mammalian kidney. Arterial supply (*left*): The arcuate artery (*arrow*) travels parallel to the surface of the kidney, branching into interlobular arteries that travel toward the kidney surface, and further branches into afferent arterioles supplying each glomerulus. The efferent arterioles travel to the medulla forming the vasa rectae. Venous drainage (*right*): Interlobular veins receive blood from the vasa rectae of the medulla and superficial cortex. Interlobular veins drain into arcuate veins and ultimately rejoin the systemic circulation via the renal vein. *C,* Cortex; *IM,* inner medulla; *IS,* inner stripe; *OS,* outer stripe. *(Modified from Kriz W, Lever AF: Renal countercurrent mechanisms: structure and function,* Am Heart J *78:101-118, 1969; and Rollhäuser H, Kriz W, Heinke W: Das Gefässsystem der Rattenniere,* Z Zellforsch *64:381-403, 1964.)*

The Nephron Unit

The nephron unit consists of a glomerular tuft, proximal tubule, loop of Henle, distal tubule, and collecting duct (Figure 66-2). The proximal tubule is an extension of the urinary space of the glomerulus and courses into the loop of Henle. Two types of nephrons are characterized on the basis of the location of the glomerulus and the path of the loop of Henle: the juxtamedullary nephrons and the cortical nephrons. Most nephrons are cortical in location, have short loops of Henle that extend into the superficial medulla, and have a relatively low capacity to reabsorb solute and water. Juxtamedullary nephrons are fewer in number but have longer loops of Henle that extend deep into the medulla. Consequently, these nephrons absorb larger amounts of salt and water, generate steep osmotic gradients, and produce highly concentrated urine. Regardless of the location of the nephron, the loop of Henle returns to the cortex to become a distal tubule. The distal tubule then continues on to form the collecting duct, the final common pathway for several nephrons draining into the renal papilla.

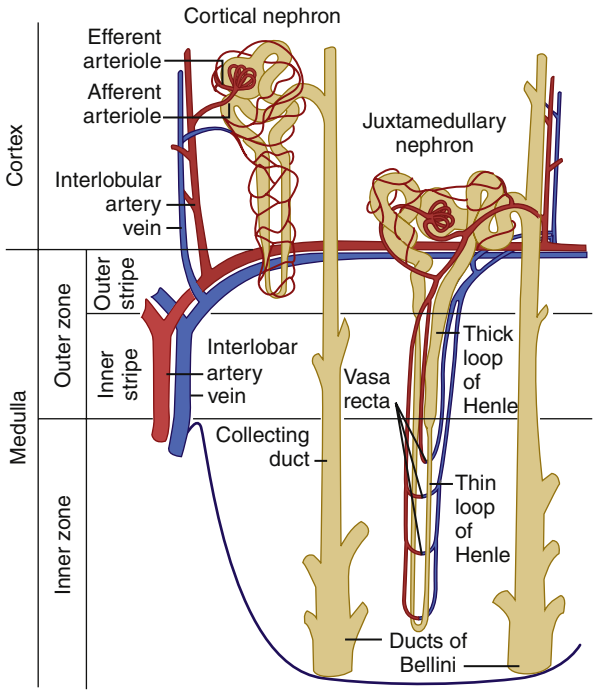

Figure 66–2. The nephron structure. *(From Guyton A: Formation of urine by the kidney: I. Renal blood flow, glomerular filtration, and their control. In Wonsiewicz M, editor:* Textbook of medical physiology, *ed 8, Philadelphia, 1991, WB Saunders.)*

Nephron Development

Nephron development occurs through a complex, interactive series of processes that remains to be completely understood.[1-3] Nephron development begins with the outpouching of the ureteric epithelium, the ureteric bud. This precursor to the collecting duct encroaches on undifferentiated mesenchyme in the caudal retroperitoneal space and induces the development of an epithelial cell condensate, the precursor to the future glomerulus and tubule (Figure 66-3). Simultaneously, factors within the metanephric mesenchyme induce the ureteric bud to continue branching. The epithelial condensate forms a vesicle that convolutes progressively into a comma-shaped body and then an S-shaped body, signifying the development of the urinary space and early tubule segments. The terminal portion of the tubule is contributed by the ureteric bud derivatives and forms the collecting duct. The mechanisms by which the ureteric bud epithelial derivatives link to the corresponding mesenchymal derivatives in the distal nephron remain unknown. The glomerular capillary loops appear to form through the angiogenic processes of committed endothelial cells,[5] and supporting mesangial cells develop from committed metanephric mesenchyme with myoblastic characteristics.[12] Nephrogenesis in the human is essentially complete by the thirty-fourth week of gestation, but functional maturation continues into the second year of life.[1-3]

Glomerular Anatomy

The glomerular tuft consists of endothelial cells, specialized epithelial cells (podocytes), and supporting mesangial cells. Epithelial cells form the urinary compartment into which ultrafiltrate passes (Bowman's space). Endothelial cells and podocytes sit on opposite sides of the glomerular basement membrane, the entirety of which forms the filtration apparatus. The epithelial side is characterized by fingerlike extensions of the podocyte cell membrane that interdigitate to form a mesh on the glomerular basement membrane. Glomerular endothelial cells on the blood side of the filtration barrier are highly fenestrated, thereby enhancing solute and fluid transfer. Mesangial cells form the supporting network of the glomerular structure, provide some phagocytic function, and participate in control of glomerular filtration.

Glomerular Function

Filtration is the primary function of the glomerulus. For filtration to occur, there must be a gradient across the glomerular basement membrane favoring the movement of filtrate to a low-pressure area. There are generally four factors that determine the quantity of filtrate obtained across the glomerular basement membrane (Figure 66-4). First, hydrostatic pressure in the glomerular capillary drives filtration of fluid across the glomerular basement membrane. If the blood flow to the glomerulus decreases, the hydrostatic pressure also drops, which necessitates an increase in efferent vascular resistance to maintain glomerular perfusion pressure. Hormones, predominantly angiotensin II and prostaglandins, and renal sympathetic activity control afferent and efferent vascular tone to carefully regulate glomerular vascular resistance.

The second factor controlling filtration is the oncotic pressure of the blood entering the glomerulus. As blood is filtered and water leaves the vascular compartment to enter the urinary space, the oncotic pressure in the blood compartment rises, retarding the further passage of fluid across the glomerular basement membrane. In situations of low oncotic pressure, such as nephrotic syndrome, the initial rate of ultrafiltrate formation is increased because of low oncotic pressure. Low oncotic pressure, however, also causes a concomitant redistribution of intravascular volume into peripheral tissue spaces, resulting in decreased vascular hydrostatic pressure, thus causing ultrafiltrate production to finally drop. Lower hydrostatic pressure therefore balances the low oncotic pressure.

The third factor determining the efficiency of ultrafiltrate formation is tubular hydrostatic pressure, or the resistance within the urinary space. Tubular hydrostatic pressure is an important factor limiting ultrafiltrate generation in the setting of urinary obstruction because it can rise above the hydrostatic pressure of the blood compartment and arrest ultrafiltrate generation.

The last important factor in the determination of ultrafiltrate formation relates to the intrinsic properties of the glomerular basement membrane. Both the area of available membrane surface and the efficiency of the membrane to filter affect the generation of ultrafiltrate. Physiologically, the "size" of the glomerular basement membrane can be determined at the whole kidney level or at the glomerular level. At the whole kidney level, the number of nephrons receiving adequate blood supply determines glomerular basement membrane area available for filtration. For example, shunting of blood from the cortex into the medulla, as seen in persons with hepatorenal syndrome, effectively decreases the available glomerular basement membrane area by reducing the number of actively filtering nephrons. At the glomerular level, glomerular basement membrane area can be altered

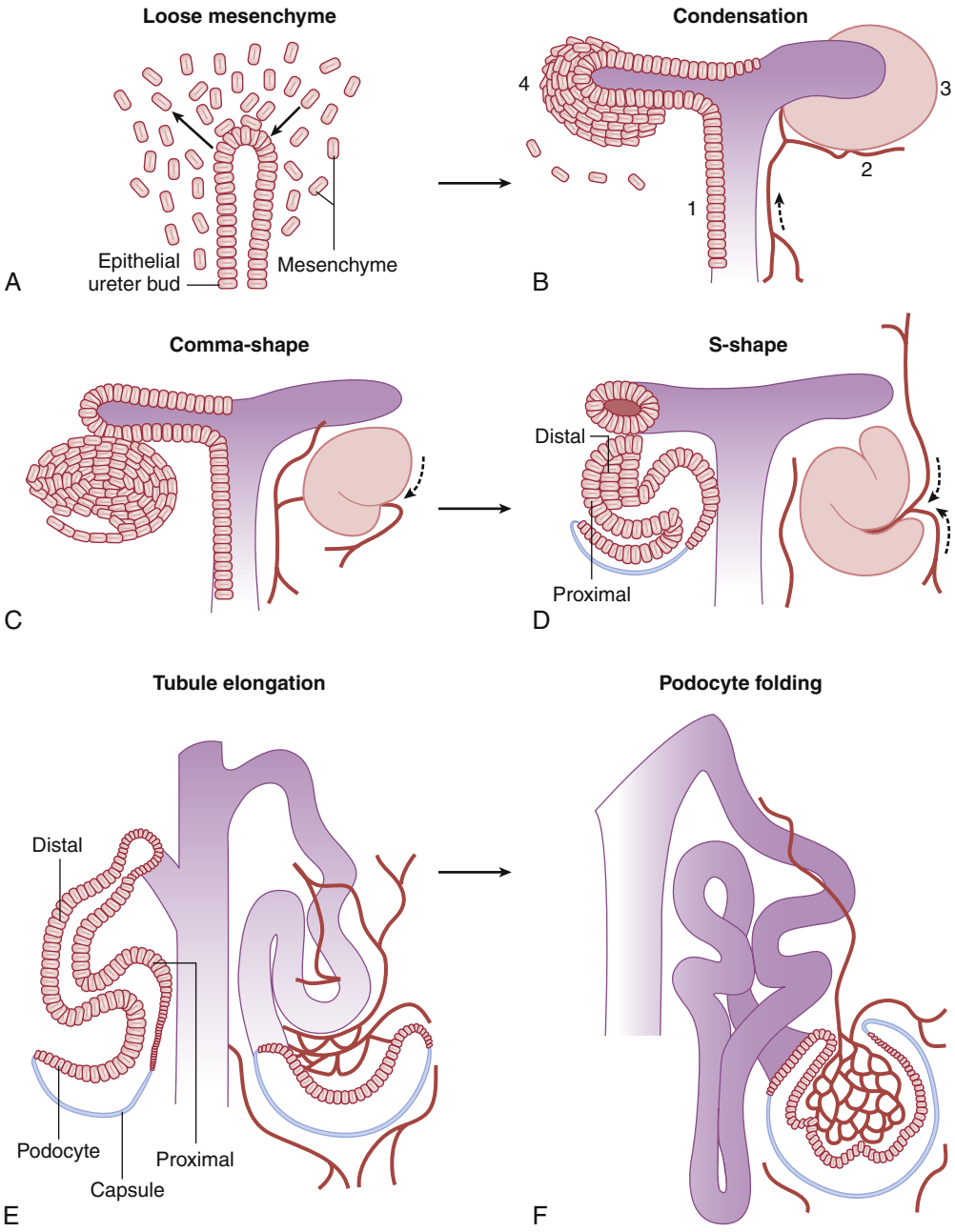

Figure 66–3. Branching morphogenesis of the developing kidney. **A** and **B,** The ureteric epithelium interacts with the metanephric mesenchyme, inducing condensation of the mesenchyme (*1* = ureteric epithelium, *2* = vasculature, *3* = undifferentiated mesenchyme, *4* = condensed mesenchyme [precursor to epithelium]). **C** and **D,** Infolding of the glomerular epithelium forms a comma-shaped body, followed by development of an S-shaped body. **E** and **F,** Infolding of the glomerular epithelium and vascular structures and elongation of the tubular elements form the completed nephron. The mature glomerular capillary network is likely initiated during **C** and **D. G**, Fluorescent microscopy of branching morphogenesis in organ culture. (**A** to **F,** *From Gomez RA, Norwood VF: Recent advances in renal development,* Curr Opin Pediatr *11:136, 1999.* **G,** *Courtesy John Bertram, Kidney Development and Research Group.)*

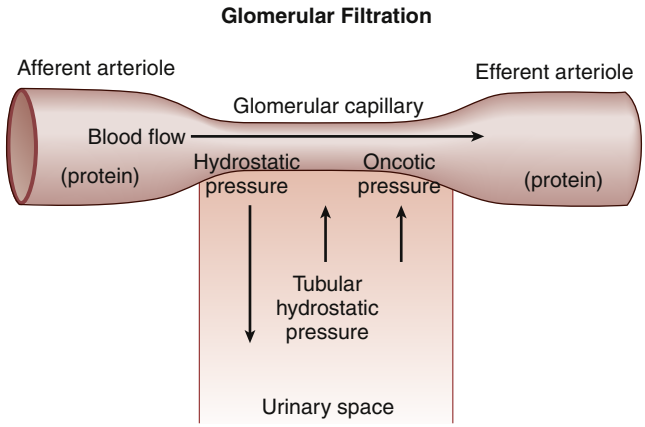

Figure 66–4. Forces affecting ultrafiltrate formation in the isolated nephron.

by mesangial cell function. In hypovolemic states, mesangial cell contraction is thought to decrease glomerular basement membrane area in response to hormonal mediators, resulting in decreased filtration and preservation of intravascular volume.[13] The efficiency of basement membrane filtration also can be affected by disease states including immune complex deposition, fibrosis, or complement activation, which disrupt the integrity and efficiency of the membrane.

Finally, selectivity of the filtration barrier is determined by the ability of the basement membrane to permit some materials to pass into the urine while restricting others to stay in the blood compartment. Selectivity appears to be the result of both size discrimination of the glomerular basement membrane and the orientation of podocyte foot processes on the glomerular basement membrane. Disruption of the normal podocyte physiology results in nephrotic range proteinuria.[14,15]

Tubular Anatomy

Proximal Tubule

The proximal tubule consists of polarized epithelia with a distinctive apical brush border not seen in other parts of the tubule (Figure 66-5). The brush border functions to increase the surface area of the luminal side of the cell so that maximal contact of the cell with the ultrafiltrate is made. Increased surface area facilitates reabsorption of solute and water, which occurs through an abundant variety of sodium-coupled transport proteins. Also on the brush border membrane are ion channels and ion exchange proteins that maintain electrochemical gradients across the apical membrane. On the basolateral aspect of the proximal tubular cells are located sodium-potassium adenosine triphosphatase (Na/K-ATPase) proteins and a high density of mitochondria. It is through the Na/K-ATPase that favorable sodium and electrochemical gradients are generated to facilitate transcellular and paracellular transport of solutes and water. The lateral membranes of the proximal tubule cells are characterized by the presence of cell-cell adhesion complexes called tight junctions. Tight junctions maintain the polarity of the proximal tubule cells by separating transport proteins on the apical side from the gradient-generating basolateral membrane proteins.

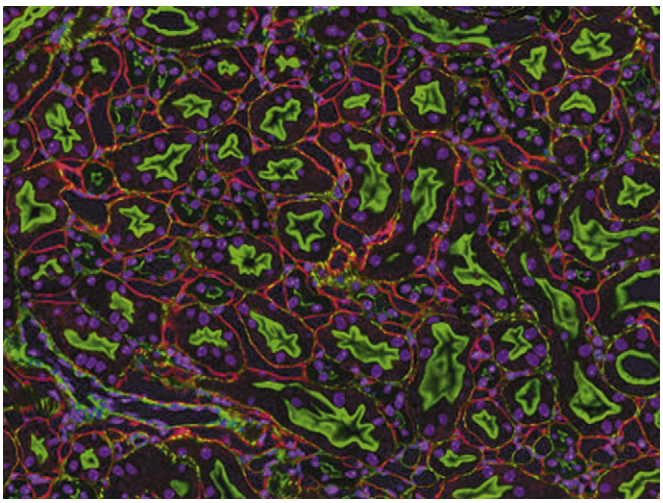

Figure 66–5. Proximal and distal tubules. *(Courtesy Thomas J. Deerinck, National Center for Microscopy & Imaging Research.)*

Loop of Henle

The cortical and juxtamedullary nephrons are defined by their position within the cortex but also by the length of the loop of Henle. The juxtamedullary nephrons have loops of Henle that extend deep into the hyperosmolar medulla, whereas most nephrons are cortical and have loops that reach only the mildly hyperosmolar outer medulla. The properties of the epithelial cells change throughout the length of the loop of Henle. The proximal portions have cells with prominent microvilli and permeable cell junctions that permit passage of fluid via aquaporin type 1 channels.[16] The distal sections of the loop of Henle consist of flat epithelia lacking microvilli and are devoid of aquaporin-1 channels. Thus the thin ascending limb of the loop of Henle is impermeable to water and urea but transports other solutes, particularly chloride, and is important in assisting with the establishment of medullary gradients.[17]

An abrupt transition occurs at the beginning of the thick ascending limb of the loop of Henle (TALH). The TALH is impermeable to water but transports solute in an active, adenosine triphosphate (ATP)-dependent manner. These cells do not have prominent microvilli but do have dense tight junctions. These tight junctions allow solute, but not water, to move among cells into the basolateral space. TALH cells are characterized by the dense localization of mitochondria and Na/K-ATPase at the basolateral membrane that generate gradients for solute transport across the luminal surface. Compared with the proximal tubule, the TALH basolateral surface is larger than the luminal surface, accommodates a larger number of Na/K-ATPase pumps, and is more metabolically active than the proximal tubular epithelium.[18] At the distal end of the TALH, the tubule courses back toward its originating glomerulus. Here a small plaque of tall, narrow cells, the macula densa, contacts the vascular pole and extraglomerular mesangial cells (Figure 66-6). The primary function of the macula densa cells appears to be the detection of tubular chloride content and the regulation of glomerular filtration.

Distal Nephron

The distal nephron segment from the TALH to the beginning of the collecting duct is marked by the presence of three distinct morphological regions. The first region is the distal

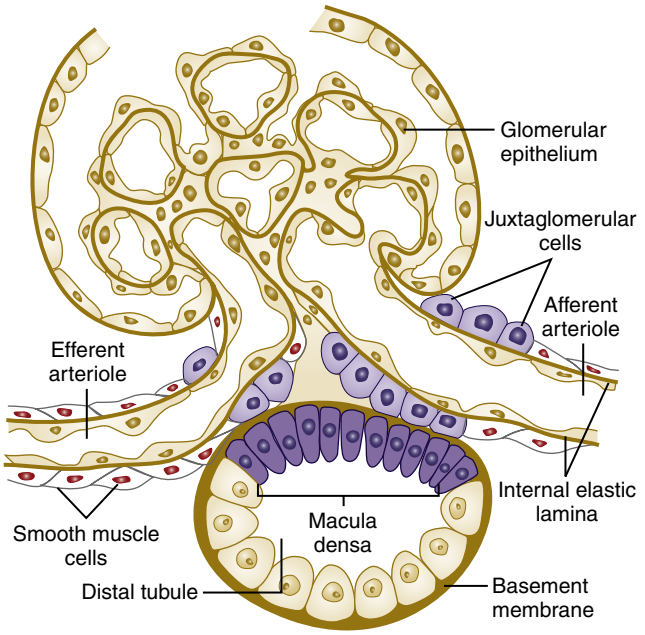

Figure 66–6. Structure of the juxtaglomerular apparatus. *(From Guyton A: Formation of urine by the kidney: I. Renal blood flow, glomerular filtration, and their control. In Wonsiewicz M, editor:* Textbook of medical physiology, *ed 8, Philadelphia, 1991, WB Saunders.)*

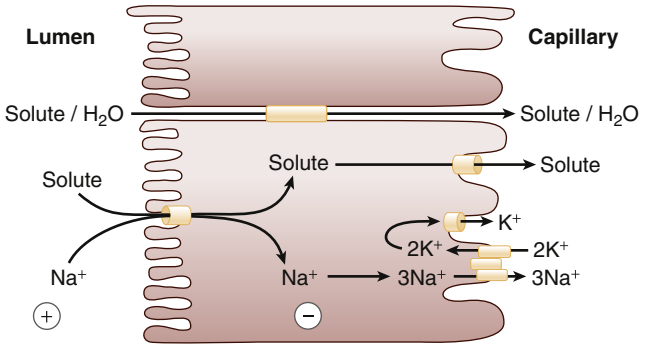

Figure 66–7. Proximal tubule transport of solute and water. Apical solute reabsorption (glucose, amino acids, phosphate, and organic acids) is sodium coupled and follows an electrochemical gradient generated by basolateral sodium-potassium adenosine triphosphatase (Na/K-ATPase) activity.

convoluted tubule, the cells of which contain the luminal sodium chloride transporter (NCC2, or thiazide-sensitive transporter) and the highest density of mitochondria in the nephron. The basolateral membrane of this segment is composed of interdigitating membranes from adjacent cells, giving the appearance of membranous convolutions. This composition maximizes the basolateral surface area to accommodate the high density of mitochondria and allow for high levels of Na/K-ATPase function. Moving distally, the tubule contains transitional cells that have a smaller basolateral surface area and fewer mitochondria at the basolateral membrane. Transitional cells express both the NCC2 channel and the luminal epithelial sodium channel (ENaC), with the quantities of ENaC increasing and NCC2 decreasing with distal progression along the segment.

The next segment is the connecting tubule, where cells show even fewer mitochondria and smaller basolateral membranes. These cells are distinguished by a more flattened appearance, an expression of ENaC, and a luminal potassium channel (ROMK), but not NCC2. The basolateral membrane is expanded to some degree by infoldings of the basal membrane, but there is no interdigitation from neighboring cells. Because of the presence of magnesium transporters (TRPM6) and calcium transporters (TRPV6), there is also a role for divalent cation regulation.[19,20]

The last segment in the distal nephron is the collecting duct. The primary cells of this segment, the principal cells, are characterized by apical vacuoles, some of which store aquaporin-2 channels. They also contain mineralocorticoid receptors and apical sodium channels that function in sodium and potassium balance. The basolateral membrane is infolded but to a lesser degree than other cells in the region. These infolds diminish in cells of the medullary collecting duct compared with those in the cortical collecting duct. In the medullary portions of the collecting duct, urea transporters again appear.

Two forms of intercalated cells, "type A" and "non–type A," exist as single cells interspersed throughout the distal nephron. These cells have prominent microfolds in the apical membrane, have high densities of mitochondria, and express several important membrane proteins such as the luminal H^+-ATPase and H^+/K^+-ATPase, as well as cytoplasmic carbonic anhydrase, serving an integral role in acid-base balance. The essential difference between type A and non–type A intercalated cells is that cell polarity is opposite in the two cell types. In "type A" intercalated cells, the apical membrane contains an H^+/K^+-ATPase, whereas the basolateral membrane contains AE1, a bicarbonate/chloride exchanger that provides a mechanism for proton secretion. The non–type A intercalated cell has vacuolar H+-ATPase on the basolateral and apical surfaces and a chloride bicarbonate exchanger, pendrin, on the apical surface, allowing for both bicarbonate secretion and proton reabsorption.[21] Generally, the number of type A and non–type A intercalated cells can vary to accommodate the acid base status in the blood.[22]

Tubular Function

While the function of the glomerulus is filtration, the function of the tubule is to modify the ultrafiltrate to maintain metabolic balance. This task is accomplished through the mechanisms outlined in the following section but includes the reabsorption of water and solutes and excretion of waste products generated from daily metabolism.

Proximal Tubule

Solute and water are transported in the proximal tubule via both paracellular and transcellular routes (Figure 66-7). Paracellular transport is a high-flux means of moving water and solute between cells along chemical or electrical gradients generated by the basolateral Na/K-ATPase. The mechanism for high flux movement of sodium out of the lumen is explained by a net luminal positive charge generated by the basolateral Na/K-ATPase and net anion reabsorption. The bulk of the sodium therefore follows an electrochemical gradient through paracellular pathways into the blood space. The same principle applies to other cations, such as calcium, which are passively reabsorbed down electrochemical gradients in the proximal tubule. Neutrally charged solutes, such as glucose, move between cells following concentration gradients, the transport

becoming less effective more distally as the gradient dissipates. Water movement generally follows sodium movement and is facilitated by the high oncotic pressure of the peritubular capillary network. This favorable osmotic gradient allows for reabsorption of approximately 70% of the filtered water in the adult proximal tubule.

Transcellular movement of solute is a high-resistance method of sodium-coupled transport that results from electrochemical and concentration gradients established by the basolateral Na/K-ATPase (see Figure 66-7). The Na/K-ATPase pumps three sodium molecules into the basolateral extracellular milieu against a concentration gradient and imports two potassium molecules into the cell against a concentration gradient. The process, which is ATP dependent, establishes a low intracellular sodium concentration and permits luminal sodium entry along a concentration gradient coupled with solutes such as phosphate, glucose, amino acids, and organic acids. In a similar fashion, protons are exported from the luminal membrane by an Na/H+ exchanger that exploits the intracellular movement of sodium to facilitate the export of protons. Bicarbonate is indirectly absorbed through the activity of luminal carbonic anhydrase and the Na/H+ exchanger. The high oncotic pressure of the blood in the arterioles and early vasa recta drives transcellular water reabsorption in the proximal tubular cells via constitutively expressed aquaporin-1 channels that permit water to flow from lumen to vasculature.[23] Some proximal solute reabsorption is modifiable by hormone activity. Parathyroid hormone binding to the proximal tubule receptors activates several second messenger systems that ultimately result in decreased sodium-phosphate transporter activity and phosphate excretion.[24] The proximal tubule is also a site of hormone production, with 1α-hydroxylase activity converting 25-hydroxyvitamin D to the active 1,25-dihydroxy form. This conversion permits vitamin D to act in calcium and phosphate metabolism.[24]

Maturational development of the proximal tubule imparts functional differences in neonatal proximal tubules compared with those in adult kidneys. The relatively low outer cortical nephron blood flow in infancy results in a generalized decrease in proximal tubule resorptive capacity because fewer nephrons participate in active solute and water reabsorption. In the neonate, the proximal tubule also expresses specific neonatal isoforms of the Na/H+ exchanger, has decreased chloride permeability, and expresses different permeability proteins (claudins) in the transcellular space. As a result, neonatal reabsorptive capacity is reduced compared with adults.[25] In addition, hormone receptors are expressed in fewer numbers or may have higher thresholds for activation in the neonate. For example, isoforms of sodium-phosphate transporters of the premature neonate exhibit a relatively low sensitivity to parathyroid hormone but a high transport capacity for phosphate, resulting in lower urinary excretion of phosphate and higher serum phosphate levels than those seen in adults.[26]

Loop of Henle

The loop of Henle plays an important role in establishing the osmotic gradients facilitating water reabsorption in the kidney. In the descending limb of the loop of Henle, the tubular epithelium is impermeable to solute but not water. Therefore as ultrafiltrate passes down the descending loop of Henle, ultrafiltrate becomes increasingly hyperosmolar as water

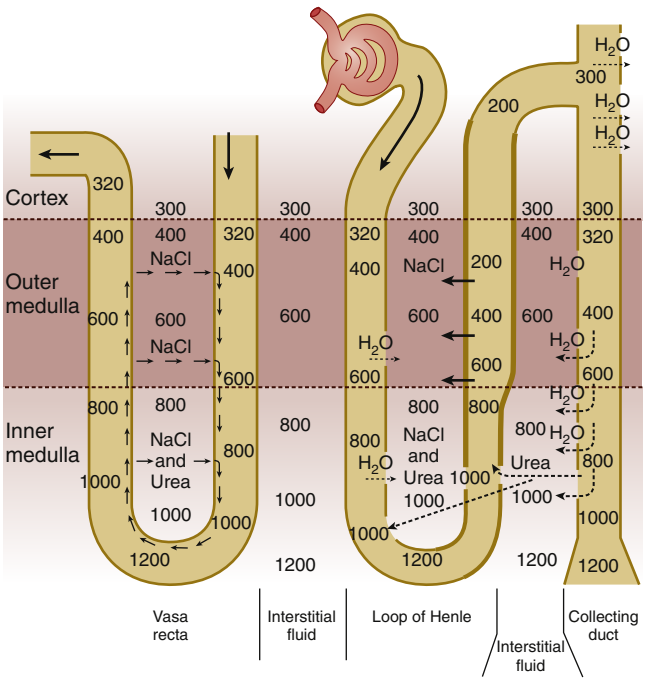

Figure 66–8. The countercurrent amplification mechanism permitting urinary concentration. *(From Guyton A: Renal and associated mechanisms for controlling extracellular fluid osmolality and sodium. In Wonsiewicz M, editor:* Textbook of medical physiology, *ed 8, Philadelphia, 1991, WB Saunders.)*

leaves the luminal space. Water permeability decreases, however, in the ascending loop, and solute transporters become more prevalent, allowing the filtrate to become hypoosmolar by the time it reaches the outer cortex.

The thick ascending loop of Henle is responsible for roughly 25% of the total sodium reclamation in the kidney, primarily by the NKCC2 channel, that allows one sodium, one potassium, and two chloride ions to move from the tubular lumen into the cell.[27] Potassium subsequently leaks back into the lumen via the ROMK potassium channel, causing the lumen to become positively charged. This electrochemical gradient permits paracellular reabsorption of cations such as calcium and magnesium as they are propelled out of the tubular lumen.

The reabsorption of sodium in the TALH also helps establish osmotic gradients in the renal interstitium by the countercurrent amplification mechanism (Figure 66-8). Although sodium, potassium, and chloride are absorbed into the interstitium, back leak of ions occurs into the descending limb of the loop of Henle, thereby increasing the concentration of solute in the descending limb tubular fluid. As this fluid passes into the ascending loop of Henle, the higher sodium content is also reabsorbed into the interstitium, augmenting the osmotic gradient in the medulla. Under normal conditions, ultrafiltrate leaving the ascending loop of Henle is more dilute than that entering the descending loop because of the proficient solute reabsorption in the late ascending limb. Loop diuretics such as bumetanide or furosemide block the NKCC2 channel function and impair the ability both to establish osmotic gradients and to reabsorb solute. The result is the production of large volumes of urine that is isotonic to plasma.

In the immature kidney, the loop of Henle is relatively short and impedes the ability to set up steep osmotic gradients. In the setting of stable vasopressin levels, neonatal

urinary concentrating ability is relatively weak compared with that of the mature adult kidney.[28] The thick ascending loop of Henle returns to its glomerulus of origin where the tubular epithelium is attached to the triangle between the efferent and afferent arteriole. The tubular epithelium in contact with the glomerulus contains about 15 to 20 cells in the form of a plaque, called the macula densa (see Figure 66-6). The macula densa actively reabsorbs sodium, potassium, and chloride through the NKCC2 channel and, in doing so, acts as a sensor of tubular chloride concentration.[29] This sensing mechanism is integral to the functioning of the juxtaglomerular apparatus, which consists of the macula densa, the afferent arteriole containing renin-producing granular cells, the efferent arteriole, and the extraglomerular mesangium. In response to low tubular chloride, such as in hypovolemia, the macula densa secretes chemical mediators (prostaglandins, nitric oxide, adenosine, and ATP) that trigger renin release from the granular cells in the afferent arteriole.[30] Similar effects can be induced by sympathetic nervous system stimulation and arteriolar baroreceptor activation.[31]

Renin activity ultimately leads to the production of the potent vasoconstrictor angiotensin II, vascular smooth muscle contraction in the efferent arteriole, increased efferent arteriolar vascular resistance, and a rise in glomerular perfusion pressure.[31] The macula densa also signals the mesangial cells and neighboring smooth muscle cells to contract through a process that involves gap junction signaling and calcium flux. This contraction results in increased vascular tone and decreased effective filtration area of the glomerular basement membrane.[32,33]

Distal Tubule

The distal convoluted tubule is also a site of active sodium reabsorption and functions to help fine-tune the urinary filtrate. When tubular fluid enters the distal convoluted tubule, it is relatively dilute because of active solute reabsorption in the TALH. Thus reabsorption of sodium and chloride in this segment occurs against a concentration gradient. Sodium and chloride are actively reabsorbed through the luminal thiazide-sensitive cotransporter (NCCT) following electrochemical gradients generated by the basolateral Na/K-ATPase. However, regulation of the NCCT, and hence sodium flux, is modifiable through a series of modulator kinases (WNK-1 and WNK-4).[34] Approximately 10% of filtered calcium is also reabsorbed from the luminal space in the distal convoluted tubule through parathyroid hormone activation of ATP-dependent TRPV5 calcium channels.[35] Once inside the cell, calcium is sequestered by calbindin-D28k, a protein that facilitates the transport of calcium to the basolateral membrane. Calcium exits the cell through either a basolateral Na-Ca exchanger, NCX1, or the plasma membrane Ca efflux ATPase.[35]

Collecting Duct

The collecting duct also functions to fine-tune the final composition of the renal ultrafiltrate adjusting sodium, potassium, and water content and acid-base balance. Approximately 5% of the filtered sodium is reabsorbed at this location and occurs through active transport. Sodium enters the cell through apical epithelial sodium channels (ENaC) and generates a luminal electronegative gradient.[36] Consequently, the excretion of cations such as potassium (principal cell) or protons (a-type intercalated cell) is favored (Figure 66-9). Because relatively little potassium is in the tubular fluid when it reaches this segment, potassium excretion down a concentration gradient is facilitated. As potassium is excreted, urine flow keeps the concentration in the tubular fluid low, and the favorable gradient is maintained. In states of low urine flow the tubular potassium concentration rises, the gradient is reduced, and potassium excretion decreases.

Potassium excretion and sodium reabsorption are also enhanced by the presence of aldosterone. Binding of aldosterone to its receptor and subsequent translocation to the cell nucleus induces transcription of the luminal sodium channel and basolateral Na/K-ATPase.[37] Increased efficiency and numbers of ENaCs on the luminal membrane tend to increase cell permeability to sodium, and this increase allows the tubular fluid to become more negatively charged after the influx of sodium. This process is facilitated by the increased activity and number of Na/K-ATPase pumps at the basolateral membrane, which creates larger electrical gradients. The net result is an increased capacity to excrete potassium or, in the hypokalemic state, an increased capacity to excrete protons.

The electrical gradient in the collecting duct also favors proton secretion into the tubular lumen, but the chemical gradient does not; the pH in the lumen can be as low as 5, whereas that of the intracellular space is 7.3. Excretion of protons occurs through an apical H-ATPase in the a-type intercalated cells and is also increased by aldosterone action in principal cells, as previously described. Protons secreted into the lumen are bound by ammonia to form NH_4 or are bound by other titratable acids such as phosphate or sulfate. This sequestration lowers the concentration of free protons in the ultrafiltrate, prevents diffusion of protons back into the intracellular space, and ultimately promotes acid secretion.

The collecting duct is also responsible for establishing the final concentration of the urine by controlling water reabsorption. At the beginning of the medullary collecting duct, the ultrafiltrate remains relatively dilute and the cells are relatively impermeable to water and solute (see Figure 66-8). In the setting of hypovolemia or hyperosmolarity, however, arginine vasopressin binds to V2 vasopressin receptors on the basolateral membrane of the medullary collecting duct cell. V2 receptor signaling results in aquaporin-2 channel migration from intracellular vesicles to the apical surface, and this migration increases tubular permeability to water. Because of the high interstitial osmolality, water is reabsorbed through the aquaporin channels along an osmotic gradient into the blood space; thus the urine is concentrated.[38]

Although largely established by active sodium reabsorption in the TALH, the medullary osmotic gradient is also maintained by the presence of urea gradients generated in the collecting tubule (see Figure 66-8). As tubular fluid moves down the collecting duct, the water entering the interstitium allows the urine to become more concentrated and the urea concentration to rise. The interstitium, however, becomes less hyperosmolar with the influx of water. As the distal tubular permeability to urea increases distally, urea moves from an area of high concentration (the lumen) into an area of lower urea concentration (the interstitium) via the UT-1 urea transporters.[39] The interstitium becomes more hypertonic with the influx of urea, and the concentrating mechanism of the interstitium is partially restored.

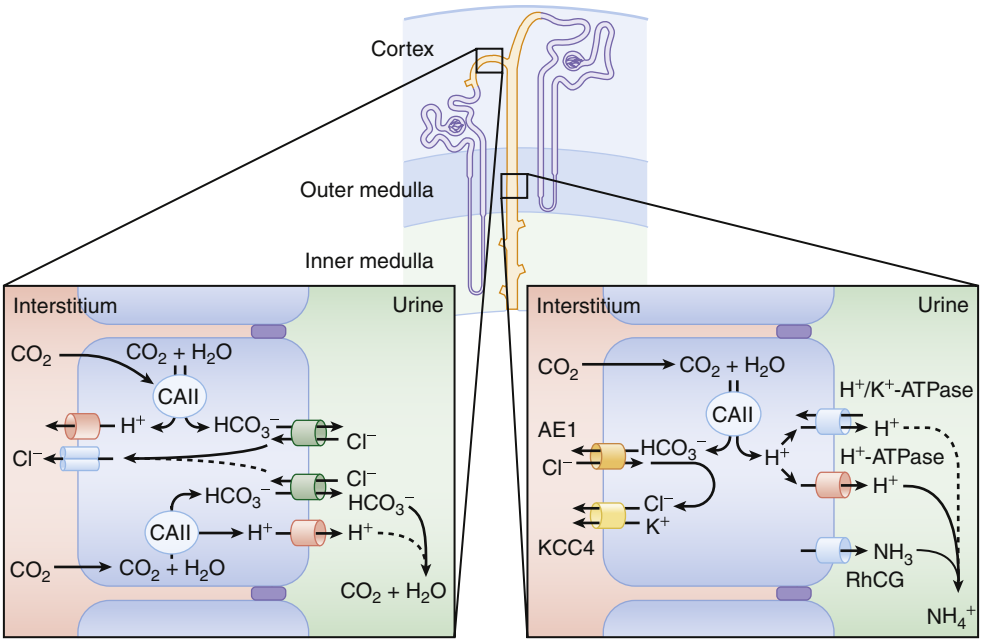

Figure 66–9. Two types of intercalated cells. Intercalated cells are expressed from the late distal convoluted tubule to the initial third of the inner medullary collecting duct *(shaded red). Left,* Cell model of non–type A intercalated cell. These cells express on the luminal membrane the chloride/bicarbonate exchanger pendrin mediating bicarbonate excretion and chloride absorption. Bicarbonate is produced from CO_2 and H_2O catalyzed by carbonic anhydrase II (CAII). Non–type A intercalated cells express also V-type H^+-adenosine triphosphatases (ATPases), which can be found on the basolateral and/or luminal membrane and may drive pendrin transport activity. Chloride is released across the basolateral membrane through chloride channels that consist of ClC-kb and Barttin subunits. *Right,* Cell model of type a intercalated cell. Bicarbonate and proton generation is catalyzed by CAII, providing protons for luminal V-type H^+-ATPases and bicarbonate for basolateral chloride/bicarbonate exchangers, including AE1. Type A intercalated cells also express basolateral KCC4 KCl-cotransporters, which may function in maintaining in low intracellular chloride. Type A intercalated cells also express on their luminal membrane H^+/K^+-ATPases that are not further discussed in this review and serve mostly for preservation of potassium during potassium deficiency. Moreover, both type A and non–type A intercalated cells participate in ammonium excretion. *(Adapted from Wagner CA, Devuyst O, Bourgeois S et al: Regulated acid-base transport in the collecting duct,* Pflugers Arch *458[1]:137-156, 2009.)*

The Interstitium

Development

The tubular interstitium remains a poorly understood region of the kidney, both from developmental and functional standpoints. From a developmental perspective, the interstitium arises from cells that surround the ureteric bud and condensing mesenchyme and are possibly of mesenchymal origin. As the metanephros develops, the primordial insterstitium differentiates to form the larger inner and outer medullary interstitium and the smaller cortical interstitium. In the inner medulla, the interstitium is involved in growth and branching of the collecting duct. In the outer medulla, the interstitium is involved in the elongation of the Loops of Henle of the corticomedullary nephrons. Although the mechanisms for both processes remain unclear, the role of the interstitium appears to be in the promotion of growth/branching and attachment, respectively occuring through the secretion of growth factors and matrix proteins.[40]

Structure and Function

The interstitium is a composite of cells, fluid, matrix proteins, and fibrils that form a network supporting the function of tubules. In the cortex, the interstitium contains two dominant components: fibroblasts and dendritic cells. Cortical interstitial fibroblasts provide both structural support of the kidney and a synthetic role in the synthesis of erythropoietin.[41] The dendritic cells appear to originate from bone marrow and function largely in an immune capacity, presenting antigen in MHC class II molecules to surveying cells of the immune system.[40,41] In the medulla, the interstitium is the site where the steep osmotic gradients are maintained. Additionally, some evidence supports a role for medullary intersitium in the secretion of vasodepressors. The role of these depressors, on either a local or systemic effect, requires further study.[40]

The interstitium is also a target of disease, with the result often being interstitial fibrosis. The development of interstitial fibrosis in response to injury is modulated by dendritic cell activity and subsequent cytokine release, as well as the synthesis of matrix by fibroblasts, most notably transforming growth factor β. A number of chronic inflammatory processes may induce chronic renal insufficiency through development of interstitial fibrosis, a phenomenon that remains an area of active study.[41]

Summary

Structural development of the human kidney support the observation that renal physiological processes change with maturation. Perfusion, tubular function, and hormonal responses are unique in young patients and affect the renal response in health and disease. Understanding the functions of the pediatric kidney at various stages of development is important in predicting therapeutic responsiveness in the critically ill child and in monitoring recovery from illness.

References are available online at http://www.expertconsult.com.

V

Chapter 67

Fluid and Electrolyte Issues in Pediatric Critical Illness

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PEARLS

- Distinguishing the syndrome of inappropriate antidiuretic hormone secretion from cerebral salt wasting may be intellectually challenging, particularly when one is faced with a severely hyponatremic, obtunded, or seizing patient. Save the patient now and save the argument for later. The immediate need is the same: raise the serum osmolality 5 to 10 mOsm/L with 3% saline solution, repair any marked intravascular volume deficit, and then analyze the etiology while continuing to stabilize the patient.
- In several case reports, patients diagnosed with prolonged cerebral salt wasting resistant to resolution have stabilized when treated with fludrocortisone, a potent synthetic mineralocorticoid. The evidence is not strong, but some cases are very reminiscent of mineralocorticoid deficiency.
- Calcium infusion for hyperkalemia is indicated when electrocardiographic changes are present. In the absence of electrocardiographic changes, other choices such as glucose/insulin and inhaled β-agonist have a better risk/benefit ratio. If digoxin toxicity is a possible cause of the hyperkalemia, calcium infusion is inappropriate as initial therapy because the arrhythmogenic potential of the digoxin will be enhanced by intravenously administered calcium.
- New antitumor treatments are producing tumor lysis syndrome somewhat unexpectedly, because monoclonal antibodies, enzyme inhibitors, and tumor embolization or catheter-delivered chemotherapy can produce dramatic, sometimes disturbing results.
- Seizures in a recent recipient of a solid organ transplant should provoke a search for hypomagnesemia. Calcineurin inhibitors are everywhere and are associated with this scenario.
- Acute changes in Ca^{++} binding equilibrium or chelation are the most frequent causes of hypocalcemia in the intensive care setting.
- Acidic pH decreases calcium binding and increases ionized calcium (Ca^{++}), whereas alkalosis increases binding and reduces Ca^{++}.

Fluid and electrolyte management is a basic tool used for every critically ill patient. A grasp of the physiology and its serious disturbances is valuable both for crisis management and for recognition of the underlying processes resulting in the fluid and electrolyte abnormality. The body of fluid and electrolyte knowledge pertinent to pediatric critical care continues to evolve. Sodium homeostasis has been reconsidered in light of the influence of postoperative hypotonic intravenous fluids and mild hyponatremia. Cerebral salt wasting, perhaps more appropriately labeled cerebral-renal salt wasting (CRSW), continues to have conceptual challenges. Arginine vasopressin receptor antagonism is now available in the pharmacy, and use of 3% saline solution is increasing. Human albumin may be safe, but is it effective? What is the role for extravascular lung water measurement in pediatrics? New approaches to tumor management occasionally provoke unexpected episodes of life-threatening tumor lysis syndrome. The challenges of our patients demand our continuing attention to the changes in science and expert opinion pertinent to their care.

Fluids Update

Fluid management in the intensive care unit (ICU) is conceptually simple. One provides maintenance fluid plus any extra losses and minus any unexpected retention. Complexities arise, however, in patients with abnormal critical organ function, disturbed fluid distribution among internal spaces, and gross abnormalities of humoral function or metabolic and caloric needs. Many of these issues are addressed in basic texts or in organ-specific sources in this text or others. Here, we provide a few comments on current issues.

Albumin

Several specific concerns about the safety of the use of human albumin in critical care resulted in a large, prospective, randomized, stratified, and very convincing[1] study that demonstrated no difference in mortality or in the number of days spent in the ICU in the hospital undergoing ventilation, or undergoing dialysis between those receiving 4% albumin for volume replacement versus those receiving normal saline solution. While this study provides strong evidence for the safety of albumin administration, its use in some specific patient populations will require further studies of adequate power and design. Evidence of efficacy in patients with certain clinical problems needs to be strengthened and must be weighed against its large cost disadvantage. Developing guidelines in individual ICUs may be useful.[2] Recombinant[3] and pegylated[4] albumin preparations are under study.

Starch

Synthetic colloid solutions are less expensive than human albumin and continue to be of interest. Hydroxyethyl starch 6%, 130/0.4 appears to have an improved safety profile compared with earlier products,[5] has Food and Drug Administration approval, and may be safe in limited doses and circumstances. Significant questions about safety remain, however.[6]

Fluid Balance

In pediatric ICU (PICU) patients with significant cardiopulmonary disease, fluid administration requires judgments about volume as well as content. The evolving area of extravascular fluid volume measurement appears to have value in adults[7] and has been extended to the pediatric population.[8] Its efficacy in pediatrics remains to be determined.

Diabetic Ketoacidosis/Cerebral Edema

Various regimens for limiting hydration fluids during the first 24 hours of diabetic ketoacidosis (DKA) treatment have been utilized and seem to have had some effect in decreasing the incidence of cerebral edema. Knowledgeable observers are aware that cerebral edema has developed in some patients receiving less than the fluid limit and has not developed in many patients who exceeded the limit. Evidence now suggests that cerebral edema occurs when a significant increase in the permeability of the blood-brain barrier allows excessive transudation of intravascular fluid.[9] This degree of this change may be associated with the severity of acidosis, and the overall risk of edema would be multifactorial, consistent with clinical observations. Although not primary or universally sufficient, continuing limitation of initial hydration fluids given adequate hemodynamics is certainly a rational aspect of a DKA protocol (also see Chapter 78).[10]

Sodium

Sodium distribution is 90% extracellular. With its associated anions, it largely determines the osmotic condition of the extracellular fluid (ECF). Disturbance of ECF osmolality affects cell volume with particularly dramatic clinical significance in the central nervous system (CNS). Mild disturbance of sodium concentration has limited clinical danger but may serve as a warning of an ongoing process of greater significance. More severe hyponatremia or hypernatremia or simply a rapid change in sodium concentration may be life threatening. These disturbances may result from the gain or loss of either sodium or water. Pathological sodium retention may occur in disorders such as congestive heart failure (CHF), cirrhosis, and nephrosis without causing a significant change in ECF concentration, but the induced expansion of the ECF volume may be damaging.

Hyponatremia

Sudden, severe hyponatremia is life threatening and its management demands prompt, measured action and ongoing monitoring and therapeutic adjustment. The syndromes of inappropriate antidiuretic hormone (ADH) secretion (SIADH) and CRSW are the most common causes for severe hyponatremia, although a gross feeding or iatrogenic misadventure also should be considered. Severe hyponatremia is uncommon and usually associated with known risk factors such as pulmonary or central system disease or injury or the use of certain drugs.

Mild hyponatremia is common in patients with some renal, hepatic, or cardiac issues and occurs predictably in postoperative patients, particularly those with prolonged general anesthesia. The use of isotonic intravenous fluids postoperatively may decrease the frequency of mild hyponatremia,[11,12] but severe SIADH or CRSW may lead to profound hyponatremia despite the use of isotonic intravenous (IV) fluid.[13-15] Appropriate monitoring of electrolytes in patients at risk will allow an early and specific response to evolving hyponatremia, whether related to water retention or sodium excretion. Even knowing the underlying diagnosis in severe, acute hyponatremia may not be as important as prompt, careful osmolality management with a continuing cycle of monitoring and therapeutic adjustment.[16]

Pathophysiology and Etiology

Hyponatremia may occur in the presence of decreased, increased, or normal amounts of total body sodium.

Decreased Total Body Sodium. Loss of total body sodium results in hyponatremia if total body water is retained in relative excess of the sodium loss. Hypovolemic stimulation of ADH release may overwhelm osmotic ADH control, maintaining water retention despite hyponatremia and hypoosmolality. Sodium deficit may occur through extrarenal or renal losses. In children, extrarenal losses most often occur from vomiting and diarrhea. In critically ill patients, large extrarenal losses may result from fluid sequestration occurring with septicemia, peritonitis, pancreatitis, ileus, rhabdomyolysis, and burns. Various skin conditions including burns may cause large transcutaneous losses. Renal losses include diuretic use, osmotic diuresis, various salt-losing renal diseases, CRSW, and adrenal insufficiency.[17] If renal function is preserved, these conditions, especially with concurrent thiazide or loop diuretics, may result in hyponatremia with hypovolemia and generally are associated with hypokalemic metabolic alkalosis.[18] Concentrated urine is produced by the equilibration of fluid in the collecting tubules with the hyperosmotic medullary interstitium, which in turn is generated by sodium chloride (NaCl) reabsorption without water in the ascending limb of the loop of Henle. Thiazides act in the cortical distal tubule and do not impair the ability of ADH to increase water reabsorption in the collecting tubules and collecting duct,[18] resulting in thiazide-associated hyponatremia. Osmotic sodium and water losses occur in a child with uncontrolled hyperglycemia with glucosuria, with mannitol use, and during urea diuresis following relief of urinary tract obstruction. Sodium wasting is greater in the presence of massive ketonuria because the keto acids are anions obligating cation losses. Hyperglycemia and mannitol, in addition to inducing urinary sodium and water losses, produce osmotic water movement from the intracellular fluid (ICF) to the extracellular fluid (ECF), further lowering serum sodium. Sodium levels drop about 1.5 mEq/L for every 100 mg/dL rise in blood glucose level. Significant salt wasting may occur with several intrinsic renal diseases and may result in hyponatremia when associated with decreased access to water and sodium (Box 67-1).

In the absence of these causes, adrenal insufficiency must be considered. Generally it is associated with hyperkalemia

Box 67–1 Causes of Hyponatremia

Decreased Total Body Sodium Level

Extrarenal

Vomiting/diarrhea
Fluid sequestration
Septicemia, peritonitis, pancreatitis, ileus, burns, rhabdomyolysis
Cutaneous losses
Burns, cystic fibrosis
Ventriculostomy drainage

Renal

Cerebral-renal salt wasting
Diuretics
- Thiazides > loop agents
- Mannitol, glucose, urea

Tubulointerstitial diseases
Medullary cystic disease, obstructive uropathy, tubulointerstitial nephritis, chronic pyelonephritis, renal tubular acidosis, Kearns-Sayre syndrome
Adrenal insufficiency
Congenital adrenal hyperplasia, Addison disease

Increased Total Body Sodium Level

Congestive heart failure
Cirrhosis
Nephrotic syndrome
Advanced renal failure

Normal Total Body Sodium Level

Syndrome of inappropriate antidiuretic hormone secretion
Glucocorticoid deficiency
Hypothyroidism
Infantile water intoxication
Abusive water intoxication

and decreased urinary potassium excretion. In each of the renal salt wasting states, urinary sodium excretion is generally greater than 20 mEq/L (fractional excretion of sodium more than 1%). Cerebral salt wasting was reported in 1950, was attributed to SIADH in the 1960s and 1970s, and then was rediscovered. Despite lingering skepticism, its clinical identity continues to be supported (Table 67-1).[19-21]

Patients typically have neurologic injury with hemorrhage, infection, or a mass and often undergo surgical procedures. The development of hyponatremia may be attributed to SIADH but appears distinct in that large urine volumes contain very high sodium concentrations that lead to rapid depletion of both sodium and ECF volume. A distinct and otherwise unexplained intravascular contraction is expected for diagnosis, may cause a secondary boost in ADH release, and appears to occur in a variety of CNS disorders. Renal sodium loss is central to this diagnosis. Both atrial natriuretic peptide and brain natriuretic peptide are attractive as mediators, but niether has a proved etiological role.[22,23] Both cerebral and renal components are key, but the connecting link is unknown, thus some favor cerebral-renal (CRSW) terminology.[24] Distinguishing CRSW from complex SIADH may be difficult; however, in severe hyponatremia cases, it may be temporarily unnecessary because the initail therapy is similar.[16] Administration of enough concentrated sodium to result in a small increase in osmolality is appropriate, and support of intravascular volume is required, which may entail administering 5 to 6 mL/kg of 3% NaCl followed by isotonic or hypertonic crystalloid as necessary. The absolutely essential part of therapy is the frequent measurement and evaluation of the results of therapy with treatment adjustments as indicated.

Table 67–1 Cerebral-Renal Salt Wasting Syndrome

Trigger	Subarachnoid hemorrhage or other acute intracranial injury or illness
Onset	Usually a few days after the injury
Signs	Falling serum Na^+, high urine output, high urine Na^+
Course	Without treatment, it proceeds to intravascular volume depletion, hypoperfusion, and hypotension
Treatment	Replace salt and water loss; restoring serum Na^+ may require 3% NaCl, furosemide, rarely fludrocortisone
Resolution	Days to weeks
Differential diagnosis of SIADH, adrenal insufficiency, osmotic diuresis	

Increased Total Body Sodium. Hyponatremia occurs when the increase in total body water exceeds the sodium retention. Four clinical situations are commonly seen: congestive heart failure, cirrhosis, nephrotic syndrome, and advanced renal failure. In all four conditions, hyponatremia tends to be mild, asymptomatic, and nonprogressive. These patients come to ICUs primarily for care of the other aspects of their chronic conditions.

Congestive Heart Failure

Hyponatremia in heart failure is associated with a worse prognosis.[25,26] In a low cardiac output animal model, renal sodium excretion is decreased primarily from the associated decrease in "effective" blood volume.[27] Stimulation of aortic and carotid vasoreceptors and right and left heart volume receptors may result in sodium retention through increased sympathetic activity and stimulation of the renin-angiotensin-aldosterone axis, producing increased renal vascular resistance, decreased glomerular filtration rate (GFR), and resultant decreased urinary sodium excretion. In addition, decreased aldosterone degradation and altered levels of other vasoactive and nonvasoactive substances result in the primary increased tubular sodium reabsorption. Impaired water excretion occurs from both nonosmotic ADH release and decreased distal renal tubular delivery of fluid.[11]

Cirrhosis

Early in cirrhosis, increased intrahepatic pressure may initiate renal sodium retention before ascites formation. Later, peripheral vasodilation mediated with nitric oxide, multiple arteriovenous fistulae, and a decrease in the effective blood volume occur. These decompensated patients have higher levels of renin, aldosterone, vasopressin, and norepinephrine than do compensated patients with cirrhosis.[28]

Nephrotic Syndrome

Humoral factors involved in patients with decreased central volume appear to be similar to decompensated patients with cirrhosis. The cause of hyponatremia in patients reported to have normal central volume status is unclear.

Renal Failure

As a diseased kidney loses nephrons, the remaining nephrons exhibit a dramatically elevated fractional sodium excretion in efforts to maintain sodium balance. Edema develops when larger quantities of sodium are ingested than can be excreted. The ability to excrete water is also impaired, primarily because of the progressive decrease in GFR. Hyponatremia occurs when water intake exceeds insensible losses plus the maximum volume that can be excreted.

Normal Total Body Sodium

Hyponatremia with no evidence of hypovolemia or edema in the pediatric population is almost exclusively associated with SIADH. Renal concentrating and diluting ability ultimately depends on the presence or absence of ADH to modulate water permeability in the collecting duct. Osmoreceptors for ADH reside in the anterior hypothalamus, responding to changes of as little as 1% in plasma osmolality. The nonosmotic stimuli that induce release are generally associated with changes in autonomic neural tone such as those that occur with physical pain, emotional stress, hypoxia, cardiac failure, adrenal insufficiency, and volume depletion. When stimuli for ADH release are competitive, the volume-sensitive pathway appears to rule. Vasopressin synthesized in the hypothalamus is transported in neurosecretory granules to the axonal bulbs in the median eminence and posterior pituitary gland and is released by exocytosis. After release, binding to V2 receptors occurs at the basolateral membrane of the collecting duct, increasing cyclic adenosine 3′, 5′-monophosphate formation, facilitating phosphorylation of aquaporin-2. Incorporation of aquaporin-2–containing vesicles into the apical (luminal) membrane increases cell permeability to reabsorptive water movement.[29]

Several categories of clinical diseases have been associated with SIADH, including CNS and pulmonary disorders, malignancies, glucocorticoid deficiency, hypothyroidism, and adverse effects of numerous drugs (Box 67-2).[30]

Postoperative pediatric ICU patients frequently have increased ADH release and are at risk of (usually mild) hyponatremia.[31,32] The appropriate use of isotonic intravenous fluid in these patients will decrease the incidence of mild hyponatremia. For patients with severe SIADH or CRSW, the use of isotonic fluids alone may not be adequate to prevent life-threatening complications. Monitoring sodium and avoiding large amounts of hypotonic fluid is mandatory. SIADH should be considered when hyponatremia occurs in the absence of hypovolemia, edema, endocrine dysfunction, renal failure, or suspect drugs. Urine osmolality is inappropriately high compared with plasma osmolality. A urine osmolality of 200 to 250 mOsm does not rule out the diagnosis because a decrease of 4 to 5 mEq/L below normal in serum sodium should maximally inhibit ADH secretion with a resultant urine osmolality of less than 100 mOsm. The urinary sodium level is generally more than 20 mEq/L; however, it can be much less than 20 mEq/L in patients who are provided a low sodium intake or in whom some degree of volume depletion occurs concurrently.[33] Urinary sodium may be generous, but the overall amount of sodium excretion should not grossly exceed intake without provoking consideration of a salt-wasting syndrome.

Box 67–2 Conditions Associated with SIADH

Central Nervous System
Meningitis
Encephalitis
Head trauma
Brain tumors
Brain abscess
Guillain-Barré syndrome
Hypoxia (neonatal)
Hydrocephalus
Rocky Mountain spotted fever
Vincristine
Salicylates
Cerebral thrombosis or hemorrhage
Subarachnoid or subdural hemorrhage
Acute psychosis
Peripheral neuropathy
Multiple sclerosis
Hypopituitarism

Pulmonary
Pneumonia
Positive-pressure ventilation
Asthma
Pneumothorax

Tumors
Lymphoma, thymoma
Ewing sarcoma, mesothelioma
Carcinoma (bronchogenic, duodenum pancreas, ureter, bladder, prostate)

Drugs
Antidiuretic hormone analogs
Chlorpropamide
Vincristine
Cyclophosphamide
Carbamazepine
Barbiturates
Colchicine
Haloperidol
Fluphenazine
Tricyclics, selective serotonin reuptake inhibitors
Clofibrate
Salicylates
Indomethacin, nonsteroidal antiinflammatory drugs
Interferon
Ecstasy (MDMA)

Miscellaneous
Infants (0–6 mo) receiving diluted feeding
Marathon runner
Postoperative, postprocedural patients

Signs and Symptoms

The severity of signs and symptoms depends on the rapidity of development. Acute decreases in sodium are associated with lethargy, apathy, and disorientation often accompanied by nausea, vomiting, and muscle cramps. No predictable correlation exists between the degree of hyponatremia and its resulting symptoms. In general, however, most patients exhibit seizures and coma with acute decreases in sodium to less than 120 mEq/L. Other signs include decreased deep tendon reflexes, pathologic reflexes, pseudobulbar palsy, and Cheyne-Stokes respiratory pattern. Signs and symptoms are related

to cellular swelling and resultant cerebral edema, which may be severe enough to result in herniation.[34] Patients in whom hyponatremia develops over several days to weeks may be symptom free or may have nonspecific symptoms of nausea, vomiting, and lethargy.

Treatment

Severe hyponatremia is associated with significant morbidity and mortality. A decrease in the serum sodium concentration would be expected to cause a shift of water from the ECF to the ICF compartment, resulting in generalized cellular edema. When this swelling occurs in the brain, which is limited by the presence of meninges and the cranium, neurologic symptoms are expected. Cerebral edema and transtentorial herniation may result. Hyponatremia developing over a more prolonged period is unlikely to cause herniation. Brain cells prevent massive swelling when gradual hyponatremia is produced by the extrusion of electrolytes and other osmolytes. Total brain amino acid content, particularly taurine, is strikingly decreased in hyponatremic rats with prolonged deficits. Brain water content is also lower in these animals. These data suggest that brain edema develops when the plasma/brain osmotic gradient reaches a critical level before these adaptive processes have been fully developed. Hyponatremia that has been present less than 4 hours can be corrected promptly. However, when adaptation of brain cells has already occurred, a rapid rise in serum sodium concentration may induce a shift of water from the ICF to the ECF compartment, resulting in brain dehydration, brain injury, and the osmotic demyelination syndrome.[35] Originally noted in the pons, both pontine and extrapontine myelinolysis has been reported in children.[36-38] Extrapontine sites have included the cerebellum, thalamus, lateral geniculate body, and hippocampus. Osmotic demyelination can occur without hyponatremia as a starting point.[38,39] Large bolus doses of hypertonic saline solution may place the patient at risk regardless of starting sodium concentration. Electrolyte fluctuations around the time of liver transplantation may account for the risk of myelinolysis noted in these patients.[40] Even rapid correction of hypernatremia is a possible cause of myelinolysis and suggests that pressure effects may be capable of causing damage to myelinated structures. Symptoms of osmotic demyelination may include obtundation, quadriplegia, pseudobulbar palsy, tremor, amnesia, seizures, and coma.[41,42] Approaches to patients with hyponatremia may vary depending on whether the hyponatremia has developed suddenly, that is, in fewer than 4 hours, in which case rapid reversal may be safe. If asymptomatic hyponatremia has developed over many hours, or has developed over a longer period (i.e., chronic hyponatremia), gradual, conservative reversal is likely to be uncomplicated. In planning treatment it is critical to determine the presence or absence of CNS symptoms or imaging suggestive of cerebral edema. Development of CNS cellular swelling and symptoms is more likely with acute hyponatremia or with severe chronic hyponatremia.[43,44] In these patients, an initial small but rapid correction of serum sodium, about 5 mEq/L, should stabilize or begin to reverse cerebral swelling and avoid impending herniation. Subsequently, further correction of the hyponatremia should occur more slowly.

A dose of 3% saline solution at 5 to 6 mL/kg would be expected to initially raise the serum sodium approximately 5 mEq/L. The subsequent correction rate for patients with acute hyponatremia with CNS symptoms or for any patient with chronic hyponatremia should raise the serum sodium no more than 0.5 mEq/L/h. For patients with acute hyponatremia but no CNS symptoms, rates of 0.7 to 1 mEq/L/h have been reported without patient morbidity or mortality. In many patients, a regimen of hypertonic 3% saline solution at 1 to 2 mL/kg/h plus periodic administration of a loop diuretic results in an appropriate correction for those patients for whom "rapid" correction is safe. Further correction may require isotonic fluids or a mixture of isotonic and hypertonic fluids, particularly in patients with CRSW. In resistant, severe CRSW, mineralocorticoid treatment has been helpful in several reports.[45,46] Other protocol approaches are available.[47] CNS symptoms that develop during correction suggest osmotic demyelination and have occurred most frequently in patients or experimental animals that are euvolemic rather than hypovolemic. At least three patients have been reported who had symptoms of osmotic demyelination and whose course was subsequently reversed; their serum sodium level was decreased to its nadir followed by a slower rate of correction resulting in recovery without neurologic sequelae.[48-50] Conivaptan, an ADH V1 and V2 receptor antagonist, is in use as an IV agent in adults for treatment of hyponatremia, particularly in fluid-retaining states.[51,52] This receptor blocker group[53] increases urine volume and reduces urine osmolality. Pediatric usage has been reported,[54] but further study of kinetics, safety, and efficacy will be needed to clarify the clinical role in pediatrics. In the patient in whom less severe hyponatremia occurs (i.e., serum sodium 125 to 130 mEq/L), slow correction through water restriction, occasionally with the use of oral sodium supplements, is all that is required for normalization to occur. In the patient with hypovolemia, volume status clearly must be corrected in addition to the hyponatremia.

Hypernatremia

As with hyponatremia, hypernatremia can develop with low, normal, or high levels of total body sodium. History and weights are particularly important in evaluating the hydration state of patients with hypernatremia because a shift in the ICF to the ECF tends to obscure the physical findings of dehydration. Accurate assessment of total body sodium and water aids considerably in planning management, although the most important management principle is the frequent monitoring of the patient's progress with treatment adjustments as needed.

Low Total Body Sodium Level

Patients with a low total body sodium level have a loss of water in relative excess of sodium losses. Because the ECF space is hyperosmolar, water movement from the ICF occurs with resulting ICF dehydration. Therefore the ECF space is somewhat preserved until extreme degree of hypovolemia has occurred. Losses of sodium and water may be extrarenal or renal (Box 67-3).

In the pediatric patient, extrarenal causes are commonly seen from vomiting and diarrhea, although hospital-acquired hypernatremia from insufficient free water administration is a major concern.[55,56] Excessive sweating with inadequate replacement also may occur. Renal causes of hypernatremia include osmotic diuresis from mannitol, hyperglycemia, or increased urea excretion. Urine is either hypotonic or isotonic,

Box 67–3 Causes of Hypernatremia

Low Total Body Sodium

Extrarenal Losses
Vomiting/diarrhea
Sweating
70% sorbitol

Renal Losses
Osmotic diuresis
- Mannitol, glucose, urea

Inadequate Intake
Insufficient lactation

Normal Total Body Sodium

Extrarenal Losses
Respiratory insensible losses
Dermal insensible losses
- Fever
- Burns
- Radiant warmers
- Phototherapy

Renal
Diabetes insipidus
- Central
- Nephrogenic
- Hypodipsia (reset osmostat)

Increased Total Body Sodium

Administration/ingestion of sodium
Improperly diluted formula
Near drowning (sea water)

Box 67–4 Causes of Diabetes Insipidus

Central

Congenital
Inherited
Idiopathic

Acquired
Head trauma
Orbital trauma
Tumors, suprasellar and intrasellar
Infections
- Encephalitis
- Meningitis
- Guillain-Barré syndrome
- Hypoxia (infant)

Postneurosurgical procedures
Miscellaneous
- Vascular
- Cerebral aneurysms, thrombosis, hemorrhage
- Histiocytosis
- Granulomas
- Nontraumatic brain death

Nephrogenic

Congenital
VR_2 mutation, X linked
AQP-2 mutation

Acquired
Chronic renal failure
Renal tubulointerstitial diseases
Hypercalcemia
K^+ depletion
Drugs
- Alcohol, lithium, diuretics, amphotericin B, methoxyflurane, demeclocycline

Sickle cell disease
Dietary abnormalities
- Primary polydipsia, decreased sodium chloride intake, severe protein restriction or depletion

and urine sodium is more than 20 mEq/L. Infants are particularly susceptible to hypernatremic dehydration because their surface area/weight ratio is high and their relative renal immaturity results in greater water losses for excretion of a solute load compared with older children and adults.[57] Insufficient maternal lactation places small infants at risk of hypernatremic dehydration. Infants with prolonged hospitalization because of bronchopulmonary dysplasia seem particularly susceptible to hypernatremic dehydration with intercurrent gastrointestinal illnesses.

Normal Total Body Sodium Level

Loss of water occurs without excessive sodium losses in some conditions. Extrarenal causes include increased respiratory losses as may occur with tachypnea, hyperventilation, or mechanical ventilation with inadequate humidification and increased skin losses associated with fever, burns, extreme prematurity, or use of phototherapy or radiant warmers in the neonate without adequate water replacement. Renal losses result from acquired or congenital diabetes insipidus (DI), either central or nephrogenic. Acquired forms of DI are more commonly seen by the intensivist. Major insults resulting in central DI include head trauma, tumors, infections, hypoxic injury, neurosurgical procedures, and nontraumatic brain death. Often, in experimental animals and in humans, three stages occur: (1) an initial polyuric phase (hours to several days); (2) a period of antidiuresis probably due to ADH release from injured axons (hours to days); and (3) a second period of DI that may or may not resolve.[58,59] Sudden onset of polyuria is characteristic, as is polydipsia (in the conscious patient). In the critically ill patient, lack of access to increased water may result in life-threatening hypernatremia.[60] Patients with the rare congenital nephrogenic DI may have repeated bouts of hypernatremic dehydration, resulting from x-linked alteration of the vasopressin receptor V2 or the autosomal recessive changes in the aquaporin II water channel physiologically regulated by ADH.[61] Acquired forms are much more common, and manifestations are less severe. Causes of DI are shown in Box 67-4.

Increased Total Body Sodium Level

Hypernatremia with an increased total body sodium level is most often an iatrogenic problem. In the critical care unit, administration of hypertonic solutions of sodium bicarbonate during resuscitation efforts or as therapy for intractable metabolic acidosis is often responsible for this condition. Particularly at risk is the patient after cardiac arrest, when renal failure from hypoxic injury may ensue as well. Other causes include excessive hypertonic NaCl administration for treatment of hyponatremia, near drowning in salt water, ingestion by infants of improperly diluted formula, inadvertent intravascular infusion of hypertonic saline solution during a therapeutic abortion, and dialysis against a high sodium concentration. Normonatremic patients with massive edema who undergo a forced diuresis frequently become mildly

hypernatremic because the induced urine may be hypotonic and water loss exceeds sodium loss.

Hypernatremia is purposely induced in patients with head trauma as a form of osmotherapy for control of intracranial hypertension (also see Chapter 59).[62,63] Such patients have tolerated a serum sodium of 175 mEq/L when carefully managed. When the ECF osmolality of these patients is manipulated, the risks involved with rapid changes in either direction must be kept in mind.

Signs and Symptoms

Clinical manifestations of hypernatremia relate predominantly to the CNS. Marked irritability, a high-pitched cry, a decrease in sensorium varying from lethargy to coma, normal or increased muscle tone, and frank seizure activity may occur in children with development of severe hypernatremia over 48 hours or more. Hyperglycemia and hypocalcemia also may occur. In infants with acute hypernatremia, vomiting, fever, respiratory distress, spasticity, tonic-clonic seizure activity, and coma are common.[64] Death from respiratory failure occurred in experimental animals when serum osmolality reached about 430 mOsm/kg.[64] Mortality in children has ranged from 10% to about 45% with chronic and acute hypernatremia, respectively. Morbidity in survivors also may be high.

Anatomic changes seen with the hyperosmolar state include loss of volume of brain cells with resultant tearing of cerebral vessels, capillary and venous congestion, subcortical or subarachnoid bleeding, and venous sinus thrombosis. During the first 4 hours of experimental acute hypernatremia, brain water significantly decreases while the concentration of solutes (electrolytes and glucose) increases. A small portion of increased osmolality is not accounted for by the increase in electrolytes and glucose, termed idiogenic osmoles. By 48 hours, however, brain water has returned to normal with idiogenic osmoles (amino acids, polyhydric alcohols, and urea and trimethylamines) accounting for about 60% of the increased osmoles.[65] The central demyelination syndrome has been seen in patients with hypernatremia. It remains unclear as to whether it results from a rapid rise in serum osmolality or from some other aspect of the clinical course.

Treatment

Whenever possible, therapy of hypernatremia should address correction of the underlying disease process as a primary goal. Correction of dehydration with slow hypernatremia correction is the target. When sodium exceeds 165 mEq/L, isotonic fluid and colloid may be used for correction of shock or circulatory collapse and initial reversal of hypernatremia. Some data are available regarding the ideal rate of correction. Numerous fatal cases of cerebral edema have occurred with correction over a 24-hour period, leading to recommendations for correction over no less than a 48-hour period[66,67] and general agreement that plasma osmolality should not be decreased more rapidly than 2 mOsm/hr (1 mEq/h sodium). Patients with serum sodium levels greater than 165 mEq/L for more than 48 hours deserve particular care, and a correction rate of no more than 1 mOsm/h may be appropriate. Thus corrections from extreme hypernatremia may take several days. This slower rate of correction appears to allow time for dissipation of idiogenic osmoles without development of cerebral edema. Estimated deficits, ongoing maintenance requirements, and additional excessive losses must be accounted for in calculations of amount of fluid replacement. Although it is not frequently required, calculation of tonicity balance may give an accurate analysis of the disturbance.

Central DI is a likely cause of hypernatremia in an ICU patient with high urine volume and low urine osmolality, particularly in patients who have head trauma, cerebral edema, or have undergone a recent intracranial operation. In these patients, a trial of vasopressin is in order. Either aqueous vasopressin given subcutaneously or intravenously (0.5 to 10 mU/kg/h) or 1-deamino-8-D-arginine vasopressin (DDAVP) may be used. An increase in urine osmolality to values exceeding that in serum suggests the diagnosis of central DI. Careful adjustments must be made in fluid administration to avoid iatrogenic hyponatremia. DDAVP is generally begun in a dosage ranging from 0.05 to 0.1 mL by nasal spray once or twice daily.

In patients with an increased total body sodium level (and often hypervolemia), the goal is sodium removal. In patients with intact renal function, sodium removal may be accomplished with diuretics and a decrease in sodium administration. If renal failure is present, dialysis may be required.

Potassium

Hypokalemia is common among ICU patients receiving diuretics and β-agonists. Hypokalemic arrhythmias can be dangerous but are infrequently fatal. Severe hyperkalemia is much less frequent but extremely life threatening. Ninety-eight percent of the potassium total body stores (about 50 mEq/kg) are intracellular. The distribution of potassium between intracellular and extracellular compartments is critical and is maintained by hormonal and nonhormonal factors.

The transcellular distribution of potassium establishes the resting membrane potential of cells, including the myocardium. Factors involved in total body distribution include acid-base status, insulin, catecholamines, magnesium, and aldosterone.[68,69] Acidemia tends to increase the serum potassium, and alkalemia lowers it. The type of acid-base disturbance (metabolic or respiratory), the duration of the disturbance, and the nature of the anion accompanying the hydrogen ion in metabolic acidosis, however, are important in determining what effect a particular acid-base disorder may have on potassium concentration.[70] The greatest effect occurs with mineral acids, where cellular permeability to accompanying anions is low so that hydrogen ions enter cells alone. In this case, potassium must move out of the cells to maintain electrical neutrality. In metabolic acidosis caused by organic acids such as lactate and β-hydroxybutyrate, however, hydrogen ions presumably enter cells with their accompanying anions so that cation exchange with potassium is not required.

Hyperkalemia associated with DKA may reflect the effects of hyperosmolality and decreased circulating insulin rather than the acidemia itself.[71,72] Epinephrine initially causes serum potassium to rise, reflecting release from the liver, and then fall, as potassium moves into cells.[73] This effect is abolished by β-adrenergic blocking drugs. In rats with experimentally induced insulin deficiency, both epinephrine and the peripheral sympathetic nervous system have been shown to regulate cell potassium uptake.[74] Change in intracellular magnesium may affect the sodium-potassium adenosine triphosphatase (ATPase) pump and alter the transcellular distribution. All

of these mechanisms, however, are generally representative of fine-tuning in potassium homeostasis. Ultimately, potassium balance is regulated through excretion by the kidney and to a lesser extent the gastrointestinal (GI) tract. Conditions associated with massive cell lysis require management of the sudden shift of intracellular potassium into the ECF, which occurs frequently in the presence of compromised renal function.

Most of the filtered potassium is absorbed before the distal nephron in normal kidneys.[75] The potassium excreted in the urine then is mainly due to secretion in the distal convoluted tubule and cortical collecting duct. As with sodium, the kidney's capacity to vary potassium excretion is profound, ranging from a low of approximately 5 mEq/L to amounts exceeding 100 mEq/L of urine. Factors influencing renal potassium excretion include mineralocorticoid and glucocorticoid hormones, acid-base balance, anion effects, tubular fluid flow rate, sodium intake, potassium intake, ICF and plasma potassium concentrations, and diuretics.[75] Aldosterone is a major kaliuretic hormone. Metabolic acidosis decreases and metabolic alkalosis increases intracellular potassium activity in cells of the distal tubule, causing enhanced potassium secretion during alkalosis and reabsorption during acidosis. Fluid delivery to the distal tubule probably enhances potassium secretion by two mechanisms: (1) the faster fluid moves past the secretory site, and a greater amount of potassium can be secreted; and (2) because tubular fluid potassium concentration decreases as flow rate increases, a favorable gradient for potassium movement is maintained at high flow rates.[76]

Hypokalemia

Causes of Hypokalemia

Hypokalemia Without Potassium Deficit. The detection of a low serum potassium level may reflect a true deficit in total body stores or an apparent deficit from the shift of this ion from the ECF to the ICF pool. A shift to the ICF pool may occur in patients with alkalemia, exogenous administration and likely endogenous release of β-adrenergic agonists, familial hypokalemic periodic paralysis,[77] barium poisoning,[78] and excess insulin. In the case of alkalemia, potassium moves into the cell in exchange for H^+ in an attempt to maintain extracellular pH. The pediatric patient with alkalemia also may have a true potassium deficit because of decreased potassium intake or increased losses. Numerous studies have confirmed an acute decrease in serum potassium after administration of β_2 agonists, including epinephrine and albuterol, presumably from cellular influx of potassium into skeletal muscle cells. Endogenous levels of epinephrine equal to or greater than levels obtained by exogenous administration have been reported in adults with acute myocardial infarction and in children after near drowning.[79]

Periodic paralysis is a rare autosomal dominant disorder presenting with intermittent episodes of profound muscle weakness associated with a sudden fall in serum potassium concentration precipitated by a high-carbohydrate/low-potassium diet, exercise, infection, stress, or alcohol ingestion.[77,80] Barium poisoning can produce hypokalemic paralysis and weakness probably by competitive blockade of inward rectifying potassium channels. Insulin produces potassium shifts into the liver in association with glycogen formation and into muscle cells.

Hypokalemia with Potassium Deficit. A deficit in total body potassium may occur from decreased intake, from renal losses, or from GI losses. Poor intake coupled with increased GI or renal losses is common. Any history of geophagia in the toddler should be sought because ingested clay binds potassium in the GI tract.[81]

Renal Losses. Major categories that may be seen in the ICU setting include diuretic use, osmotic diuresis, use of various other drugs, renal tubular acidosis, hyperaldosteronism, magnesium deficiency, and recovery from acute renal failure (ARF). Osmotic diuresis from glucosuria is the primary cause of renal potassium wasting in patients with prolonged DKA that can present with ventricular arrhythmia. Primary aldosteronism, congenital adrenal hyperplasia, adrenal adenoma, and familial idiopathic hyperaldosteronism are rare in children and even rarer in the pediatric ICU setting. Secondary hyperaldosteronism is common, however, either from volume depletion or from CHF, cirrhosis, or nephrotic syndrome. Patients with the latter conditions, however, rarely have severe hypokalemia unless they are additionally treated with diuretics. The infant with Bartter's syndrome may initially come to the ICU because of multiple metabolic derangements including hypokalemia, metabolic alkalosis, and often hypomagnesemia and hyperuricemia. Other findings include weakness, polyuria, and failure to thrive, with elevated renin and aldosterone levels in the absence of hypertension.[82] Other conditions associated with elevated renin secretion, secondary hyperaldosteronism, and hypokalemia include renal artery stenosis, malignant hypertension, renin-producing tumor, or Wilms' tumor. Additional mechanisms include secondary hyperaldosteronism and increased distal tubular fluid delivery. The severity of hypokalemia is often masked by the shift of potassium from the ICF to ECF space related to insulin deficiency, metabolic acidosis, and hypertonicity.

If a brisk diuresis is induced by loop, thiazide, or osmotic diuretics, kaliuresis may result, and this may lead to acute hypokalemia. Use of combinations of these diuretics, in particular loop diuretics and metolazone, may accentuate potassium losses. Each agent leads to increased distal delivery of tubular fluid. Other drugs that induce excessive renal losses include amphotericin B (kaliuresis with reduced renal function and tubular injury); aminoglycosides, particularly gentamicin; and high-dose penicillin and carbenicillin, which produce an osmotic load in addition to acting as nonreabsorbable anions.[83] Renal tubular acidosis or hypomagnesemia may cause renal potassium wasting.[84]

Gastrointestinal Losses. Upper GI losses from vomiting or from nasogastric (NG) suction are frequently associated with hypokalemia, although they are rarely responsible for the total depletion seen. The gastric concentration of potassium ranges from 5 to 10 mEq/L.[85] However, concomitant volume depletion and metabolic alkalosis associated with NaCl and hydrogen ion losses often result in secondary aldosteronism and an increased filtered load of bicarbonate with resultant renal potassium losses. Diarrhea, regardless of cause, may result in large potassium losses, the amount lost being related to the volume of fluid lost. Other GI causes are listed in Box 67-5.

Signs and Symptoms

For the intensivist, cardiovascular and neuromuscular effects of potassium deficiency are of particular concern, although metabolic, hormonal, and renal effects also may occur.[68]

Box 67–5 Causes of Hypokalemia

Hypokalemia Without Potassium Deficit

Alkalosis
β-Agonist, exogenous or endogenous
Familial periodic paralysis
Thyrotoxic periodic paralysis
Barium poisoning
Excessive insulin

Hypokalemia with Potassium Deficit

Decrease intake
Renal losses
- Hyperaldosteronism
  - Primary or secondary
  - Barter syndrome
  - Liddle syndrome
  - Laxative and/or diuretic abuse
  - Licorice ingestion
- Osmotic agents
- Drugs
  - Caffeine
  - Diuretics
  - Amphotericin B
  - Aminoglycosides
  - High-dose penicillin, carbenicillin
- Miscellaneous
  - Hypomagnesemia
  - Renal tubular acidosis
  - Toluene toxicity

Extrarenal loses
- Gastrointestinal
  - Vomiting, nasogastric suction
  - Diarrhea
  - Laxative abuse
  - Ureteral sigmoidostomy
  - Obstructed or long ileal loop

Electrocardiographic (ECG) changes include T-wave flattening or inversion, ST depression, and the appearance of a U wave. Atrial and ventricular arrhythmias and conduction disturbances may occur. Resting membrane potential is increased, as are both the duration of the action potential and the refractory period. The decreased conductivity predisposes a patient to arrhythmias. Finally, threshold potential and automaticity are increased, and this increase makes automatic arrhythmias possible.[86]

Hypokalemia diminishes skeletal muscular excitability, which can present as a dynamic ileus or a skeletal muscle weakness resembling Guillain-Barré syndrome. Eventually it can affect the trunk and upper extremities, becoming severe enough to result in quadriplegia and respiratory failure.[81,87-89] Rhabdomyolysis also has been reported from decreased muscle blood flow, decreased glycogen stores, and altered sodium/potassium (Na/K)-ATPase and membrane potential.[90,91] Autonomic insufficiency may also occur, generally manifested as orthostatic hypotension. In patients with severe liver disease, hypokalemia may precipitate or exacerbate encephalopathy. Glucose intolerance in the presence of primary hyperaldosteronism and in certain patients receiving thiazide diuretics has been corrected with potassium repletion. Renal effects of hypokalemia include polyuria and polydipsia, renal structural changes with cellular vacuolization in the proximal tubule, and occasional interstitial fibrosis.

Treatment

Because of the wide spectrum of abnormalities resulting from marked potassium depletion, judicious correction is generally in order. Most PICU patients with cardiovascular disease are given NG or IV potassium supplements at serum levels of 3.0 to 3.5 mEq/L. In the patient without life-threatening complications, the oral route is generally preferred for treatment, if possible, because this route is rarely associated with "overshoot" hyperkalemia if normal renal function exists. Oral dosage is frequently 1 mEq/kg up to a maximum of 20 mEq per dose, repeated if necessary. If, however, depletion is associated with digoxin use or with life-threatening complications, including cardiac arrhythmias, rhabdomyolysis, extreme weakness with quadriplegia, or respiratory distress, then urgent IV therapy is generally needed. Recommendations for IV dosage in the pediatric patient have ranged from infusions of 0.25 mEq/kg/h to those as high as 1 to 2 mEq/kg/h in the face of severe hypokalemia associated with DKA, arrhythmias, or quadriparesis and respiratory insufficiency. Ventricular tachycardia clearly associated with hypokalemia may initially require more rapid administration. Continuous ECG monitoring is essential, along with frequent physical examination and determination of serum potassium levels to avoid hyperkalemic complications. Highly concentrated potassium IV solutions should only be administered centrally. Preoperative potassium repletion of patients with cardiac disease who are treated with diuretics may be beneficial,[86] although some persons would argue against routine screening.[92] Patients who receive albuterol continuously are frequently mildly hypokalemic, but they rarely warrant potassium chloride replacement.

The potential for catastrophic drug error in replacing potassium is real. In most PICUs, patients with cardiovascular disease are given NG or IV supplements at serum levels of 3.0 to 3.5 mEq/L. Steps to decrease the chance of error include satellite pharmacy dosing, use of a mandatory drug request form,[93] NG replacement when possible, use of a single solution concentration for all doses, and small aliquot solution containers. Continuing education regarding this risk for the pediatric ICU staff is essential.[94]

Hyperkalemia

Causes of Hyperkalemia

Hyperkalemia may result from artifactual elevation; from redistribution of potassium from the ICF to the ECF space; or from increased intake, decreased losses, or both. Causes of hyperkalemia are listed in Box 67-6.

Artifactual. Tight, prolonged tourniquet use produces spurious potassium elevation due to potassium release from ischemic muscle.[95] Even more common is hemolysis of red cells with potassium release associated with capillary sampling or aspiration or delivery under pressure through a small needle. Hemolysis may be noted by the laboratory, but artifactual normality or actual elevation should always be considered. Less commonly, in vitro release of potassium occurs from white blood cells (>100,000/μL) or platelets (>1,000,000/μL) and may result in increased levels.[96,97]

Box 67–6 Causes of Hyperkalemia

Artifactual

Ischemic potassium loss from tourniquet use
In vivo red cell injury
In vitro hemolysis, profound leukocytosis, thrombocytosis

Redistribution

Change in pH
Hypertonicity
Drugs
- Digoxin toxicity, β-blockers (β_2-inhibitory activity), succinylcholine, arginine, or lysine hydrochloride, chemotherapeutic agents, sodium fluoride, epsilon-amino caproic acid

True Potassium Excess

Increased Load

Exogenous
- IV infusion, PO supplements, potassium-containing salt substitutes, potassium penicillin, blood transfusion

Endogenous
- Tissue necrosis
  - Burns, trauma, rhabdomyolysis, intravascular coagulation
- Gastrointestinal bleeding
- Tumor cell lysis
- Reabsorption of hematoma

Decreased Excretion

Acute renal failure
Chronic renal failure
Mineralocorticoid deficiency
Addison disease
Adrenal biosynthetic defects
- 21-Hydroxylase deficiency
- Desmolase deficiency
- 3- -OH-dehydrogenase deficiency

Aldosterone deficiency
Diabetes mellitus
Renal tubulointerstitial disease
Drugs
- Indomethacin, converting enzyme inhibitors, heparin, cyclosporine, tacrolimus, trimethoprim, pentamidine, amphotericin B

Renal tubular secretory deficit
- Pseudohypoaldosteronism

Sickle cell disease
Systemic lupus erythematosus
Renal allograft
Urinary tract obstruction
Very low birth weight infants

Inhibition of Tubular Secretion

Drugs
- Spironolactone, triamterene, amiloride

Redistribution. In general, when extracellular pH falls, potassium exits from cells; the result is an increase in serum potassium levels. As mentioned earlier, metabolic acidosis from mineral acids has a more pronounced effect than that of organic acids. Plasma potassium does not change in parallel with the pH change; rather, it gradually rises even as extracellular pH returns to normal after acute acid loading. Respiratory acidosis does not usually cause a marked change in potassium concentration.[98]

Hypertonicity per se produces a shift of potassium from ICF to ECF. Studies of anephric animals show potassium increasing by 0.1 to 0.6 mEq/L for each increment of 10 mOsm/kg H_2O in tonicity. Hypertonicity causes cellular dehydration and therefore an increase in ICF potassium that favors increased passive diffusion out of cells. A very small percentage shift of intracellular potassium delivers a significant potassium load to the ECF. In the hyperkalemic patient in the ICU who has acute oliguria, mannitol should not be used for diuresis because further potassium elevation may result. In the patient with hyperglycemia, hypertonicity is likely only one of several mechanisms resulting in elevated serum levels.

Several commonly used drugs result in net movement of potassium from ICF to ECF. Digoxin inhibits the net uptake of potassium by cells by inhibiting Na/K-ATPase, with hyperkalemia commonly occurring in severe digitalis poisoning.[99] Other drugs include β_2 antagonists and the muscle relaxant succinylcholine. This drug induces a prolonged dose-related increase in the ionic permeability of muscle, with subsequent efflux of potassium from muscle cells. Normal serum potassium concentration rises about 0.5 mEq/L. Succinylcholine should be avoided in patients with burns, muscle trauma, spinal injuries, certain neuromuscular diseases, near drowning, and closed head trauma, because upregulated and new forms of acetylcholine receptors may respond with life-threatening hyperkalemia.[100] New examples of patients at risk will continue to be reported.[101,102] Hyperkalemia may result in nonsuspect patients via rhabdomyolysis or malignant hyperthermia following administration of succinylcholine.[103] Familial hyperkalemic periodic paralysis appears to be related to potassium redistribution related to changes in ion channel function.[77,104] Rebound hyperkalemia may be life threatening after coma-inducing barbiturate is stopped[105] or surgical insulinoma removal.[106]

Increased Potassium Load. Hyperkalemia due to an increased potassium load is unusual as long as renal function is normal. Transient elevations may be seen with inappropriate IV infusion, delivery of large volumes of cold-stored blood,[107] oral potassium supplements, salt substitutes containing potassium, or large doses of potassium penicillin.[108] Strict measures to guard against accidental potassium overdoses are mandatory. Large endogenous loads of potassium are more likely in the patient who is in the ICU. The release of cellular potassium associated with tissue necrosis from burns, trauma, rhabdomyolysis including that from spider bites[109] or the propofol syndrome,[110] massive intravascular coagulopathy, massive hemolysis, or GI bleeding may lead to hyperkalemia.

Tumor lysis syndrome (TLS) is classically associated with drug or radiation treatment of sensitive lymphoid malignancies and results in hyperkalemia often accompanied by hypocalcemia, hyperphosphatemia, acidosis, and compromised renal function (also see Chapter 81). Many fatalities have been reported. The list of TLS-producing events or therapies has been increasing and now must include transcatheter chemical and embolic tumor necrosis,[111,112] monoclonal antibody treatment with rituximab,[113] and newer enzyme-inhibiting agents bortezomib,[114] imatinib,[115,116] and sorafenib.[117] It also seems possible that endogenous corticoids associated with surgical stress[118] or dexamethasone given for potential airway edema could cause severe TLS.

Decreased Excretion. Hyperkalemia in patients with ARF results from a profound reduction in the GFR, decreased distal water and solute delivery limiting Na/K exchange,

and an insufficient time for renal and extrarenal adaptive mechanisms to develop. These conditions often are associated with increased catabolism and metabolic acidosis. Nondiabetic chronic renal failure is rarely associated with hyperkalemia until the GFR falls below 5% to 10% of normal. Progressive, gradual impairment induces excretion of more potassium per the remaining nephron.[119] Other adaptations include increased stool loss and more rapid redistribution of potassium into cells.[120] Decreased mineralocorticoid activity regardless of origin causes hyperkalemia. Addison's disease, although rare in the PICU, may present in crisis with life-threatening hyperkalemia, as may adrenogenital syndromes. Hyporeninemic hypoaldosteronism is commonly seen in adults but may become more common in children; the classic example is the patient with diabetes mellitus and mild to moderate renal insufficiency.[121] Aldosterone production may be suppressed and potassium elevated by heparin, angiotensin-converting enzyme inhibitors, prostaglandin inhibitors, tacrolimus, or cyclosporin.[108]

Renal tubular secretory defects occur in patients with pseudohypoaldosteronism presenting in children with failure to thrive, metabolic acidosis, hyperkalemia, and elevated aldosterone levels, as well as in rare patients with sickle cell disease, systemic lupus erythematosus, urinary tract obstruction, and renal allografts. Premature infants without renal failure, especially those weighing less than 1000 g, may demonstrate life-threatening hyperkalemia and increased sodium excretion in association with decreased potassium excretion.[122] Tubular immaturity with unresponsiveness to aldosterone has been postulated.[123] Finally, potassium-sparing diuretics, trimethoprim, and pentamidine may produce hyperkalemia, particularly when used in combination with other drugs that decrease potassium excretion or in patients with renal insufficiency.[108]

Manifestations of Hyperkalemia

Life-threatening complications are most likely to result from the cardiac changes caused by hyperkalemia. ECG signs include tall, peaked T waves in the precordial leads, followed by a decrease in amplitude of the R wave, bradycardia, widened QRS complexes, prolonged PR intervals, and decreased amplitude and disappearance of the P wave. Finally, the classic sine wave of hyperkalemia from the blending of the QRS complex with the P wave may appear. Recognizing that ventricular arrhythmias or cardiac arrest may occur at any point in this progression and that progression may occur over a matter of minutes is extremely important.

Treatment

Treatment of hyperkalemia depends on the level of plasma potassium and the state of neuromuscular irritability.[124] If the potassium is less than 6.5 mEq/L without ECG changes, discontinuation of exogenous potassium and drugs that decrease its excretion with close follow-up of potassium levels may be all that is necessary. In the patient with renal compromise, extra potassium may be eliminated with use of the potassium-binding agent sodium polystyrene sulfonate (Kayexalate, resonium) (oral, NG, or rectal doses of 1 to 2 g/kg in a sorbitol or dextrose solution). When administered rectally, sorbitol may not be necessary, and it certainly should not be given rectally in a concentration greater than 20%. Highly concentrated sorbitol may cause severe proctitis and colonic injury. Increasing reports of colonic injury, particularly in hemodynamically compromised or premature patients, suggests that caution be exercised in using this preparation. However, when it is needed, having the pharmacy stock a premixed 10% to 20% suspension of sodium polystyrene sulfonate and sorbitol allows either oral or rectal administration on short notice. If the potassium concentration is more than 6.5 mEq/L with associated ECG changes, additional measures are indicated. In the absence of digitalis toxicity, hyperkalemia with ECG changes should be treated with a secure and rapid IV infusion of calcium chloride or calcium gluconate. Hand injection with ECG monitoring is reasonable beginning with the administration of 10 mg/kg of calcium chloride (or gluconate equivalent) over 1 to 5 minutes. Infusion may be stopped if the ECG has normalized or if deterioration of the ECG seems to be precipitated by the calcium, suggesting a clinical scenario more complex than simple hyperkalemia. If the ECG improves but is not normalized by this calcium dose, additional calcium chloride may be given at a lower rate. It should be anticipated that ECG changes will recur in 15 to 30 minutes unless additional measures are taken immediately to treat the hyperkalemia. The effective calcium dose may be repeated as necessary to preserve cardiac function while additional treatments are in progress. Additional, rapidly effective treatments include nebulized albuterol (rapid nebulization or continuous nebulization of 0.3 to 0.5 mg/kg) or salbutamol (IV dose of 4 to 5 μg/kg over 20 minutes and repeated after 2 hours).[125,126]

Insulin and glucose are also rapidly helpful in redistributing potassium to the ICF. Glucose (1 g/kg) and insulin (0.2 units/g glucose) may be given over 15 to 30 minutes and then infused continuously with a similar amount per hour. Blood glucose monitoring is essential because the relative glucose and insulin dosing may need adjustment.

Sodium bicarbonate (1 to 2 mEq/kg IV) has been a part of the classic treatment of hyperkalemia. Its benefit, however, is more difficult to predict and slower in onset than that of the measures mentioned earlier.

Sodium polystyrene sulfonate binds potassium and may be administered while dialysis arrangements are made. Sodium polystyrene sulfonate administered rectally must be retained for 15 to 30 minutes to be effective. If the oral route is available, it is generally more efficient.

In the patient with severely compromised renal function, these measures generally allow stabilization of potassium long enough to institute dialysis. Although hemodialysis is much more efficient for potassium removal than peritoneal dialysis, the latter may be more quickly instituted in many centers, particularly in the small infant in whom vascular access to support reasonable blood flow may be difficult to accomplish. In the absence of renal failure, loop diuretics or thiazide diuretics or both are useful for the increase of renal excretion. If mineralocorticoid activity is deficient, the administration of fludrocortisone may be indicated. In patients with severe hyperglycemia and moderate hyperkalemia, early steps to improve glucose control should decrease ECF potassium shifts from hyperosmolality and decreased insulin.

Magnesium

Magnesium deficiency that leads to overt clinical symptoms and signs is a recognized problem in the ICU setting.[127,128,129] Less than 1% of magnesium is distributed within the ECF

space, with the remainder distributed in the ICF space. More than 50% of ICF magnesium is located in bone; 20% in skeletal muscle; and the remainder in other soft tissues. ECF forms include free ion (Mg^{++}) (55% to 65%), magnesium complexed with anions (phosphate, oxalate, and citrate) (20% to 30%), and protein bound (5% to 20%).[130] Magnesium plays a key role in numerous metabolic processes, including cellular energy production, storage, and utilization involving adenosine triphosphate (ATP); the metabolism of protein, fat, and nucleic acids; and the maintenance of normal cell membrane function. It also is involved in neuromuscular transmission, cardiac excitability, and cardiovascular tone.[131]

Magnesium balance is maintained through intestinal absorption and renal excretion; 25% to 65% of ingested magnesium is absorbed in the ileum. Absorption varies inversely with intake and is also affected by paracellular water reabsorption. Increased bowel water that is due to any cause results in decreased magnesium reabsorption. Regulation of renal excretion occurs by glomerular filtration and reabsorption. The bulk (50% to 70%) of filtered magnesium is reabsorbed in the ascending limb of the loop of Henle[132] resulting from active NaCl reabsorption and is susceptible to loop diuretic inhibition. The threshold value for magnesium excretion varies between 1.5 and 2 mg/dL in different species. Thus if serum magnesium levels fall even slightly, renal excretion dramatically decreases under normal circumstances. Primary factors that increase renal magnesium excretion include ECF volume expansion; hypermagnesemia; hypercalcemia; metabolic acidosis; phosphate depletion; and various drugs, including loop and osmotic diuretics, cisplatin, aminoglycosides, cyclosporin, and digoxin. Decreased excretion occurs with ECF volume depletion, hypomagnesemia, hypocalcemia, hypothyroidism, and metabolic alkalosis, to a lesser extent. Parathyroid hormone (PTH) may decrease magnesium excretion, but that effect may be offset by the opposite effect of causing hypercalcemia.[133]

Hypomagnesemia

Clinically significant magnesium depletion may be present despite normal serum magnesium levels. Serum total magnesium correlates fairly well with bone concentration but may be normal in the presence of low tissue or muscle levels. Free, ionized magnesium is physiologically the most important form, but determination of total magnesium is still generally used. Critically ill children, however, frequently are reported to have low ionized magnesium levels despite having normal total magnesium levels.[129] Evidence supporting obligatory ionized magnesium measurement remains elusive more than a decade after it became feasible.

Magnesium depletion may result in hypocalcemia; the mechanism includes the suppression of parathormone secretion.[134-136] Hypokalemia also occurs in patients with hypomagnesemia. Magnesium deficiency impairs the Na/K pump, allowing potassium loss from the ICF, which in turn is excreted in the urine. Magnesium repletion is important for the resolution of these secondary disturbances.

Causes of Hypomagnesemia

Intensivists deal with hypomagnesemia most often in patients receiving loop diuretics or transplant immunosuppressives. Other causes must be considered.

Magnesium deficiency may be caused by decreased intake or increased losses. Although slight falls in serum magnesium levels may occur after 1 week of a deficient diet, a more sustained period of deprivation is generally necessary for significant hypomagnesemia to occur.[128,137] In children, magnesium deficiency has been particularly common in patients with protein-energy malnutrition and anorexia nervosa. Intestinal malabsorption is a major cause of magnesium deficiency. Isolated familial primary hypomagnesemia occurs from selective malabsorption of magnesium; patients generally have symptoms in infancy. These symptoms often include tetany and convulsions as a result of severe hypomagnesemia with consequent hypocalcemia, and patients respond well to supplemental magnesium. Other causes associated with magnesium malabsorption include regional enteritis, ulcerative colitis, massive small bowel resection, generalized malabsorption syndromes, pancreatic insufficiency, and cystic fibrosis. In some of these cases, the formation of insoluble soaps due to the complexing of magnesium with unabsorbed fat is the postulated mechanism for hypomagnesemia.

Intrinsic renal tubular disorders associated with hypomagnesemia are rare in the ICU setting. Various causes of hypomagnesemia are displayed in Box 67-7.

Drugs that induce renal magnesium wasting are more common causes and include aminoglycosides,[138] cisplatin,[139] amphotericin B,[140] diuretics,[141] cyclosporin A,[142] and

Box 67–7 Causes of Hypomagnesemia

Decreased Intake

Low Mg^{++} TPN, IVF

Increased Losses

Gastrointestinal

Malabsorption

- Familial primary hypomagnesemia
- Small bowel disease
- Regional arteritis, ulcerative colitis, massive bowel resection
- Pancreatic insufficiency, pancreatitis
- Cystic fibrosis

Renal

Congenital renal magnesium wasting
Diffuse tubular disorders
Hypophosphatemia
Postrenal transplantation
Drugs: aminoglycosides, cisplatin, amphotericin B, diuretics, cyclosporine, tacrolimus, pentamidine, foscarnet, GM-CSF
Hypercalciuria
Diabetic ketoacidosis
Barter syndrome
Hyperaldosteronism
Inappropriate ADH secretion

Miscellaneous

Epinephrine, β-agonists
Thyrotoxicosis
Citrated blood transfusion (massive)
Burns
Alcoholism

ADH, Antidiuretic hormone; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *IVF,* intravascular fluid; *TPN,* total parenteral nutrition.

tacrolimus.[142] Furosemide produces greater losses of magnesium than of sodium and calcium.[143] Hypomagnesemia requiring supplementation is common in transplant recipients who receive cyclosporine or tacrolimus. Fractional excretion of magnesium and total excretion are elevated. Patients with DKA also may have marked renal magnesium wasting during the acidotic period, as well as in early treatment. An increased urine calcium level, from whatever cause, is often associated with magnesium wasting from competitive inhibition of renal tubular reabsorption of magnesium in the ascending limb.

Signs and Symptoms

In addition to biochemical derangements associated with hypomagnesemia, a wide spectrum of other clinical disorders have been attributed to its depletion, including cardiac arrhythmias, increased sensitivity to digoxin, coronary spasm, hypertension, seizures, and neuromuscular derangements.

Hypomagnesemic arrhythmias include ventricular premature beats, ventricular tachycardia, torsades de pointes, and ventricular fibrillation.[144,145] Supraventricular arrhythmias are less common. Improvement in resistant ventricular arrhythmias following magnesium infusion has been reported, although other metabolic derangements often coexist in such patients. Magnesium deficiency enhances myocardial cell uptake of digoxin and toxicity. Both inhibit Na/K-ATPase with resultant ICF potassium depletion.

Depletion is thought to contribute to the development or worsening of hypertension by increasing vascular smooth muscle tone and reactivity. Increased cellular influx of calcium and decreased reuptake by sarcoplasmic reticula occur; the result is increased cytosolic calcium for activation of actin-myosin contractile proteins. Similar effects in coronary and cerebral vessels also have been observed.

Seizures may be the first symptom of hypomagnesemia noted in a ICU setting. Other neuromuscular changes may include tremors, fasciculations, spontaneous carpopedal spasm, muscle cramps, paresthesias, seizures, and coma. Personality changes, including apathetic behavior and depression, also have been associated with hypomagnesemia.[146,147]

Treatment

Patients undergoing or at immediate risk of hypomagnesemic malignant ventricular arrhythmias (such as torsades de pointes) or seizures can be given magnesium sulfate intravenously with careful monitoring. An IV infusion of 25 to 50 mg/kg of magnesium sulfate per dose diluted to 10 mg/mL can be administered over 15 to 60 minutes. The rate of infusion should not exceed 150 mg/min. Doses may be repeated as needed depending on patient response. Complications of parenteral magnesium therapy include neuromuscular and respiratory depression, rare arrhythmias, flushing, hypotension, and prolonged bleeding times.[148] Other routes of therapy include intramuscular magnesium sulfate, injections of which are painful, and oral therapy with magnesium oxide or citrate. In situations known to be associated with the development of hypomagnesemia, it seems particularly important to attempt to avoid deficiency through adequate magnesium intake before life-threatening symptoms develop. The use of supplemental magnesium infusions in perinatal asphyxia is intriguing[149] but remains to be fully tested or extended to other hypoxic-ischemic encephalopathies.

Hypermagnesemia

Hypermagnesemia is seen much less commonly than is hypomagnesemia. Magnesium infusions in patients with status asthmaticus have become common, however, and may be associated with hypermagnesemia. Although elevated, the levels achieved are unlikely to cause toxicity.

Causes of Hypermagnesemia

Hypermagnesemia occurs in patients with renal failure and is generally associated with iatrogenic administration of magnesium as antacids, cathartics, or enemas or through total parenteral nutrition (TPN) containing magnesium. In the absence of renal failure, the administration of large quantities of magnesium cathartics in the management of constipation[150] or overdoses[151] and antacid use with increased peritoneal absorption of magnesium in the presence of a perforated viscus[152] are causes of hypermagnesemia. Magnesium levels as high as 10 to 12 mEq/L have been reported. Megadose vitamin-mineral supplementation, including magnesium oxide, has been fatal.[153]

Signs and Symptoms

Acute elevations of magnesium depress the CNS and the peripheral neuromuscular junction. Pseudocoma with fixed, dilated pupils has been reported. Deep tendon reflexes are depressed at levels greater than 4 mEq/L with total disappearance along with flaccid quadriplegia at levels greater than 8 to 10 mEq/L. Hypotension, hypoventilation, and cardiac arrhythmias also may occur.[154-157] Moderate hyperkalemia has resulted from prolonged magnesium infusions in occasional patients.

Treatment

Calcium acts as a direct antagonist to magnesium. In life-threatening situations associated with severe magnesium intoxication, intravenous calcium should be used as the initial therapy. Adults have been treated with 5 to 10 mEq of calcium in either the chloride or gluconate forms over 5 to 10 minutes, with doses repeated if necessary. An initial dose of calcium chloride at 10 mg/kg or an equivalent amount of calcium gluconate has been suggested for infants and children. Medications that contain magnesium obviously should be discontinued. If renal function is normal, IV furosemide may be administered to increase magnesium excretion while urine output is replaced with half-normal saline solution. In patients with renal failure or severe toxicity, dialysis may be necessary for removal of magnesium.

Phosphorus

Virtually all of plasma phosphorus is in the inorganic form, with a small organic component composed entirely of phospholipids bound to protein. Serum levels vary with age; approximate normal values (specific to the analytical instrument) are 4.8 to 8.2 mg/dL for neonates, 3.8 to 6.5 mg/dL for children aged 1 week to 3 years, 3.7 to 5.5 mg/dL for children aged 3 years to 12 years, and 2.9 to 5 mg/dL for adolescents aged 12 to 19 years.[158] Differences are thought to be related to more rapid rates of skeletal growth in the pediatric population. Most total body phosphorus resides in bone. More than 50% to 65% of ingested phosphorus is absorbed, primarily in

the jejunum. Its absorption may be decreased by a high calcium intake or by ingestion of antacids, which binds phosphorus in the bowel. Urinary excretion depends primarily on oral intake. About 80% of the inorganic phosphorus is filtered, with reabsorption occurring predominantly in the proximal tubule by an active mechanism coupled to sodium transfer. Renal phosphorus reabsorption is decreased by parathormone and by calcitonin with resultant phosphaturia. Glucose competitively inhibits phosphorus reabsorption. Glucocorticoids produce phosphaturia by a decrease in sodium-dependent transport in the proximal tubule. Vitamin D may increase or decrease reabsorption, depending on conditions.

Phosphorus plays an important role in cellular structure and function, bone mineralization, and urinary acid excretion. The development of severe phosphorus depletion affects the availability of intracellular ATP for every production; depletes the erythrocyte of 2,3-diphosphoglycerate (2,3-DPG), with resultant tissue hypoxia; and impairs urinary acid excretion. The major acute effect of hyperphosphatemia is hypocalcemia; the long-term consequence is soft tissue calcification.[159]

Hypophosphatemia

Hypophosphatemia as measured by serum or plasma levels may or may not indicate true phosphorus deficiency. Severely depressed levels of serum-measurable phosphorus may occur in the absence of true deficiency after transcellular shifts from the ECF to the ICF, whereas a moderate phosphorus deficiency may be indicated only by slightly decreased serum levels.[160] Moderate hypophosphatemia has been defined as levels between 1.5 and 2.5 mg/dL and severe hypophosphatemia as levels less than 1.5 mg/dL on serum determination. In general, only with severe deficiency of phosphorus do multiple symptoms occur, as well as overt cell dysfunction or necrosis. Risk is greatest when superimposed additional cellular injury exists.

Cause of Severe Hypophosphatemia

Although numerous abnormalities may result in moderate decreases in phosphorus levels, severe hypophosphatemia has been associated with only a handful of clinical syndromes. These syndromes include significant respiratory alkalosis, prolonged use of phosphate-deficient TPN, the nutritional refeeding syndrome, thermal burns, DKA, pharmacologic binding of phosphorus in the gut, and alcohol withdrawal.[160,161] Association with continuous renal replacement therapy and bone recovery after renal transplant also have been reported.[162,163] The increase in the ICF pH associated with acute respiratory alkalosis stimulates the enzymes of glycolysis, with subsequent depletion of ICF phosphorus, which is replaced by an influx from the ECF space. Although carbon dioxide diffuses across membranes much more readily than bicarbonate does, metabolic alkalosis rarely produces a decrease in phosphorus levels, whereas very low levels may be seen with respiratory alkalosis.[164] An absolute deficiency from malnutrition and transcellular shifts from the ECF to the ICF with an anabolic response to increasing caloric intake are the causes associated with TPN use.[165] In the pediatric population, the preterm infant is particularly susceptible. Nearly 80% of calcium-phosphorus assimilation in the fetus occurs in the last trimester of pregnancy. The preterm infant is therefore born deficient in total body phosphorus. When reasonable nutrition has been absent for even short periods or when phosphorus has not been provided in TPN, severe hypophosphatemia has occurred, associated in several cases with the development of hypercalcemia.[166] A similar situation may occur with the refeeding of patients who have significant protein calorie malnutrition.[167] As previously noted, an absolute phosphorus deficiency and transcellular shifts from the ECF to the ICF in the face of an anabolic response are responsible.

Significant hypophosphatemia in burn patients during their recovery phase has been associated with the presence of respiratory alkalosis, diuresis of initially retained sodium and water, and acceleration of glycolysis.[160] As previously described, ECF phosphorus shifts to the ICF compartment when intracellular-free phosphorus has been used in phosphorylation of organic compounds such as occurs during glycolysis, oxidative phosphorylation, glycogenolysis, and synthesis of glycogen, protein, and phosphocreatine. Acidosis decomposes organic compounds within the cell with subsequent movement of inorganic phosphorus from ICF to ECF and excretion in the urine. Osmotic diuresis augments these losses. Decreased intake also commonly occurs. During treatment of DKA, renal phosphorus clearance generally increases with fluid administration. In addition, insulin therapy results in stimulation of glycolysis and anabolism with a shift of phosphorus back to the ICF. If the acidosis has been present for only a few days, then rarely is there a severe phosphorus deficiency. Although levels may decrease, they generally return to normal without extra phosphorus therapy. In the patient whose symptoms have been present for a number of days to weeks, however, severe deficiency may exist at the time of admission. These patients may have life-threatening complications of hypophosphatemia if they are not treated. In general, this subset of patients has low phosphorus levels on admission, whereas phosphorus levels are normal or increased at admission in less severely affected patients.

Signs and Symptoms

Multiple organ systems may be affected by severe hypophosphatemia, including CNS, cardiac, respiratory, musculoskeletal, hematological, renal, and hepatic abnormalities.[168-171] Decreased diaphragmatic contractility in patients with hypophosphatemia with acute respiratory failure significantly improved as measured by transdiaphragmatic pressures during phrenic stimulation with treatment of hypophosphatemia.[172] Respiratory muscle weakness in patients with hypophosphatemia but without respiratory failure also has been documented and shown to normalize with phosphorus repletion.[173]

Neurologic symptoms may initially include irritability and apprehension followed by weakness, peripheral neuropathy with numbness, and paresthesias. Dysarthria, confusion, obtundation, seizures, and coma may occur in more profound cases.[170,174] Reports in the literature include Guillain-Barré–like syndrome,[175] diffuse slowing on electroencephalogram, and congestive cardiomyopathy[176] that significantly improved with correction of phosphorus depletion. In dogs, decreased cardiac output, decreased ventricular ejection velocity, and increased left ventricular end diastolic

pressure reversed with phosphorus repletion. In humans, rhabdomyolysis has been predominantly seen in alcoholic patients, in whom subtle myopathy was likely present, and rarely in patients with DKA or after TPN therapy. Decreased levels of 2,3-DPG in red blood cells (RBCs) may depress P-50 (oxygen half-saturation pressure) values so that the release of molecular oxygen to peripheral tissues is decreased, with resultant tissue hypoxia.[168] Structural defects of RBCs associated with hypophosphatemia have included rigidity and rarely hemolysis and have generally occurred when additional metabolic stresses such as metabolic acidosis or infection were placed on the RBC. Decreased levels of ATP in neutrophils may result in decreased chemotaxis, phagocytosis, and bacterial killing.[177] The mechanisms underlying the development of metabolic acidosis include decreased phosphorus excretion that thereby limits titratable acid excretion and decreased ammonia levels.

Treatment

As with other minerals and electrolytes, when oral therapy is potentially possible, it is the preferable route for administration. In patients with severe hypophosphatemia, IV therapy is often indicated.[178,179] Few data exist in the pediatric literature regarding dosage. Therefore most data are extrapolated from adult literature.[180-182] Reasonable recommendations in children with severe phosphorus depletion are to use 0.15 to 0.33 mmol/kg per dose, given as a continuous infusion over 4 to 6 hours. Subsequent doses are generally calculated on the basis of response to this initial dosage. Either potassium or sodium phosphate may be administered with the attendant potential complications of hypernatremia or hyperkalemia. Other potential complications of therapy include hyperphosphatemia, metastatic deposition of calcium phosphate, hypocalcemia, potential nephrocalcinosis with renal failure, and hypotension. Both sodium and potassium phosphate contain 3 mmol of phosphate per mL and 4 or 4.5 mEq of sodium or potassium, respectively. For oral administration, a combination product of sodium with potassium phosphate (Neutra-Phos) has been used commonly in children. One capsule supplies 8 mmol of phosphorus along with 7.1 mEq of sodium and potassium. Capsules can be reconstituted in water as well. Hypophosphatemia associated with continuous renal replacement therapy provides a special case. IV replacement is required in many such patients.[162]

Hyperphosphatemia

Causes of Hyperphosphatemia

Acute and chronic renal failure with decreased phosphorus excretion are the most common causes of hyperphosphatemia, with elevation in serum phosphorus occurring when the GFR is less than 30 mL/min/1.73 m^2. Extreme hyperphosphatemia associated with several deaths has been reported from the use of sodium phosphate enemas in infants and children.[183-185] Abnormalities of intestinal anatomy or motility predisposing to retention of enemas or renal insufficiency represent risk factors, but no risk factors are identified in 30% of reported patients The administration of IV boluses of sodium or potassium phosphate rather than slow infusion may result in symptomatic hyperphosphatemia. An error in parenteral nutrition resulted in hyperphosphatemia in multiple infants,[186] and severe hyperphosphatemia has been reported related to use of liposomal amphotericin B.[187]

TLS represents an additional cause of hyperphosphatemia along with hyperkalemia, acidosis, hypocalcemia, and renal failure. It results from drug-induced lysis of tumor cells and is always a concern in a child with a lymphoid malignancy and substantial cellular mass, but it can occur in a variety of settings.[111,113,115] Initial chemotherapy or radiation of B-cell lymphoma is particularly likely to produce cell lysis and hyperphosphatemia along with hyperuricemia, acute renal failure (ARF), hyperkalemia, metabolic acidosis, and hypocalcemia. Aggressive hydration and careful initiation of chemotherapy usually will result in a manageable degree of electrolyte abnormality. Urinary alkalinization to increase urate solubility is usually recommended but is being reexamined. Rasburicase is replacing allopurinol in the control of urate levels. Hemodialysis is an essential resource to have available if managing such a patient (Table 67-2).

Table 67–2 Tumor Lysis Syndrome

At risk	Lymphoid malignancies
High risk	Large tumor mass, B-cell lymphoma
	Renal compromise
Initiating event	Cytolytic chemotherapy
	Radiation therapy
	Embolic tumor infarction
Prophylaxis	Hydration, urinary alkalinization, allopurinol
	Gradual chemotherapy initiation, rasburicase
Serious disturbances	Hyperkalemia, hypocalcemia, acidosis, renal failure, hyperuricemia, hyperphosphatemia
Management	Obsessive electrolyte monitoring
	Hemodialysis available stat CVVHD helpful, may not be adequate

CVVHD, Continuous venovenous hemodialysis; *stat,* immediately.

Signs and Symptoms

The major clinical consequence of severe hyperphosphatemia is its associated hypocalcemia, as well as soft tissue deposition of calcium phosphate salts. Seizures, coma, and cardiac arrest have been reported, generally in the presence of both hypocalcemia and hyperphosphatemia. In one case report, however, seizures, malignant ventricular arrhythmias, and cardiac arrest with acute hyperphosphatemia alone were described.[188] Hyperphosphatemia may be a proximate cause of ARF via precipitation in renal tissue.[189,190]

Treatment

In patients with life-threatening complications or multiple additional electrolyte disturbances or in the presence of renal failure, dialysis may be required. Intravenous fluid loading to increase renal phosphorus losses and intravenous calcium may increase excretion. Mannitol diuresis will inhibit proximal phosphorus reabsorption and theoretically should expedite phosphaturia. If oral administration is possible, Sevelamer has been used in patients with TLS to bind

phosphorus and perhaps decrease the need for more invasive therapy.[191]

Disorders of Calcium Homeostasis

The extracellular ionized calcium (Ca^{++}) concentration must be maintained within narrow limits for its vital and ubiquitous role in normal metabolism. Entry of Ca^{++} into cardiac and skeletal muscle cells, facilitated by membrane depolarization and β-adrenergic stimulation, mediates conversion of electrochemical into mechanical energy with resultant muscle contraction. Additionally, several enzyme systems (e.g., adenylate cyclase, phosphodiesterase, and protein kinases) are to be regulated by the interaction of Ca^{++} with calmodulin. A similar interaction stimulates myosin kinase in vascular smooth muscle so that Ca^2 influx (enhanced by α-adrenergic and inhibited by β-adrenergic stimuli) causes vasoconstriction. Ca^{++} also plays a critical role in the clotting system and various membrane transport systems. Alterations in calcium homeostasis occur frequently among critically ill patients.

Extracellular Ca^{++} is monitored by Ca^{++}-sensing receptors.[192] These receptors are plentiful on the surface of the chief cells of the parathyroid glands, on numerous kidney sites (e.g., the juxtaglomerular apparatus, luminal surface of the proximal convoluted tubule, basolateral surface of the cortical thick ascending limb of the loop of Henle, and apical and luminal membrane of the inner medullary collecting duct in the kidneys), in the intestine, parts of the brain, thyroid C cells, breast, and adrenal glands. In classic hormonal negative feedback fashion, binding of Ca^{++} to this receptor activates phospholipase C and accumulation of inositol triphosphate, which secondarily leads to inhibition of the secretion and synthesis of PTH and activation of its proteolysis.

Regulation of Extracellular Calcium

Derangements in calcium homeostasis result from (1) changes in protein binding and chelation (with phosphate [PO_4] or other anions) and (2) excessive or deficient hormonal action. The former scenario is more common in the ICU. A majority of total serum calcium is bound to proteins, and this binding is pH dependent. Acidic pH decreases calcium binding and increases ionized calcium (Ca^{++}), whereas alkalosis increases binding and reduces Ca^{++}. Fortunately, direct measurement of Ca^{++} is now readily available in PICUs.

Hormonal Regulation of Calcium

Hormonal control of calcium homeostasis involves PTH, vitamin D, and calcitonin. Secretion of PTH by the parathyroid chief cell varies inversely with the serum Ca^{++} and is inhibited by hypomagnesemia and $1,25(OH)_2$-vitamin D. Rapid proteolytic degradation of PTH yields a physiologically inactive C-terminal fragment and an active NH_2-terminal fragment. PTH binds to cell surface receptors in bone osteoblasts and kidney and exerts its effects through binding of a subunit of a membrane-associated heterotrimeric protein, which mediates increased formation of cyclic adenosine 3′,5′-monophosphate.

In the kidney, PTH inhibits proximal tubular PO_4 reabsorption and promotes phosphaturia. This loss of PO_4 inhibits bone mineralization and tends to shift the flow of calcium from bone to the ECF. Distal tubular reabsorption of filtered calcium is also increased by PTH. PTH stimulates 1a-hydroxylation of 25(OH)–vitamin D, resulting in production of metabolically active 1,25(OH)2–vitamin D that stimulates intestinal absorption of calcium and PO_4. The overall effect of PTH is to raise serum calcium levels and lower serum PO_4 levels. This characteristic reciprocal relationship is helpful in distinguishing PTH disorders from those involving vitamin D alone.[193]

Hyperphosphatemia lowers Ca^{++} by shifting the equilibrium in calcium flux from ECF toward bone and by inhibiting 1a-hydroxylation activity. Calcitonin is a 32-amino-acid, calcium-lowering hormone elaborated by C cells of the thyroid in response to rising Ca^{++} levels. Although it rapidly reduces the bone resorptive function of osteoclasts and promotes calciuria and phosphaturia, its excess or absence causes no discernible disorder.

Hypocalcemia

Clinical and Laboratory Diagnosis

Hypocalcemia is frequently associated with critical illness in children. In some cases, hypocalcemia is associated with PTH deficiency, whereas in others hypercalcitoninemia or hypermagnesemia is cited. In children with severe burns, hypocalcemia, magnesium depletion, hypoparathyroidism, and renal resistance to PTH may develop. Here a reduced set point for Ca^{++} suppression of PTH secretion, rather than magnesium depletion, appears be the primary cause of low PTH production.[194]

Reduced Ca^{++} inhibits acetylcholine release and impairs effective muscular contraction in both sensory and motor nerves. Accordingly, a variety of peripheral and CNS effects (tetany, convulsions [grand mal, petit mal, or focal], carpopedal spasms, muscle cramps and twitching, paresthesias, laryngeal stridor, and apnea in the newborn) are characteristic features of hypocalcemia. Latent tetany is manifested by Chvostek (provoked facial muscle twitching) and Trousseau (provoked carpopedal spasm) signs. Cardiovascular manifestations of hypocalcemia include hypotension, myocardial depression, CHF, and dysrhythmias. Somatic changes accompanying prolonged hypocalcemia include dry, coarse skin, eczematous dermatitis, brittle hair with areas of alopecia, brittle nails with smooth transverse grooves, and dental enamel hypoplasia.

Determination of the free ionized Ca^{++} level is diagnostic, although the rate of decline also contributes to the development of symptoms. Estimations of Ca^{++} correcting for protein binding (i.e., for every 1 g/dL reduction of serum albumin, the protein-bound calcium fraction is reduced by 0.8 mg/dL) and pH must be interpreted cautiously. Prolongation of the QT interval may be helpful in confirming reduced ionized calcium levels, although the correlation is not strong.

The causes of hypocalcemia are best recalled by reviewing the mediators of normal calcium homeostasis as summarized in Box 67-8.

Reduced PTH effect can result from parathyroid gland failure (e.g., autoimmune or postsurgical hypoparathyroidism), insensitivity to PTH (e.g., pseudohypoparathyroidism), or suppression of PTH release (e.g., hypomagnesemia, maternal hypercalcemia, and burns). Hyperphosphatemia is frequently present, and accompanying clinical features (e.g.,

Box 67–8 Causes of Hypocalcemia

Reduced PTH Effect

Parathyroid Gland Failure

Hypoparathyroidism—idiopathic or autoimmune
Trauma
Postsurgery
Post–^{131}I therapy
Infarction
Infiltration (e.g., sarcoid hemosiderosis)

Insensitivity to PTH

Pseudohypoparathyroidism
Hypomagnesemia

Suppression of PTH Release

Hypomagnesemia
Neonatal, resulting from maternal hypercalcemia
Burns
Sepsis
Drugs
- Aminoglycosides
- Cimetidine
- Cisplatin
- β-Adrenergic blockers

Reduced Vitamin D Effect

Vitamin D Deficiency

Dietary insufficiency
Increased losses related to:
Malabsorption
Nephrotic syndrome
Phenytoin, phenobarbital

Impaired Activation of Vitamin D

Renal disease
Hypoparathyroidism
Liver failure
Rhabdomyolysis

Changes In Ca^{++} Binding or Chelation

Alkalosis

Respiratory alkalosis
Bicarbonate infusion

Hyperphosphatemia

Renal failure
Phosphate administration (e.g., high-phosphate formulas, enemas)
Chemotherapy
Rhabdomyolysis
Malignancy
Pancreatitis
Fat embolism
Transfusion with citrate-preserved blood

Drug/Toxins

Glucagon
Mithramycin
Calcitonin
EDTA
Protamine
Sodium fluoride
Colchicine
Theophylline
Ethylene glycol

EDTA, Ethylenediamine tetraacetic acid.
Modified from Chernow B, Zaloga GP: SCCM, ions for society members. In Shoemaker WC, editor: *Critical care: state of the art, vol 5,* Fullerton, CA, 1984, Society of Critical Care Medicine.

short stature, mental retardation, and shortened metacarpals in pseudohypoparathyroidism and moniliasis of the nails in hypoparathyroidism)are seen. Measurement of immunoreactive PTH (iPTH) levels distinguishes hormonal deficiency from resistance to hormone action. Reduced vitamin D effect results from vitamin D deficiency (e.g., malabsorption, best detected by low 25(OH) –vitamin D levels), impaired activation of vitamin D (e.g., renal disease, best detected by low 1,25(OH)2–vitamin D levels), or exaggerated losses or metabolism (e.g., phenytoin). Acute changes in Ca^{++} binding equilibrium or chelation are perhaps the most frequent causes of hypocalcemia in the intensive care setting. Respiratory alkalosis or hyperphosphatemia may dramatically reduce total and ionized calcium levels. Infusion of large amounts of citrate-preserved blood and acute phosphorus overload or retention (e.g., in patients with acute renal failure) rapidly deplete ECF calcium levels. Various drugs also contribute to development of hypocalcemia.

Treatment

Correction of hypocalcemia should be preceded by consideration of readily treated factors (such as acute respiratory alkalosis) or confounding factors. Rapid development of hyperphosphatemia suggests acute renal failure, cell lysis, or excessive supply (also see Chapter 81). As appropriate, efforts should be made to reduce serum phosphate levels, because intravenous calcium therapy may cause metastatic deposition of calcium-phosphate salts. Hypomagnesemia impairs PTH release, response to PTH, and, consequently, correction of hypocalcemia. Hypomagnesemia may develop in critically ill patients by several mechanisms as previously discussed.

Urgency of therapy is determined by the child's clinical status. Asymptomatic hypocalcemia is appropriately treated with oral calcium salts. For the seriously ill patient with overt or evolving hypocalcemia, replacement therapy is accomplished with IV calcium chloride, 5 to 20 mg/kg, or an equivalent calcium gluconate infusion. Potential bradycardia and asystole with infusion of calcium should be anticipated, with cardiac monitoring and atropine readily available. Care is required to prevent tissue damage by extravasation, precipitation with concomitantly administered bicarbonate, and untoward cardiac rhythm disturbances in patients receiving digitalis.

Oral administration of calcium salts is efficient for control of persistent hypocalcemia and is preferable to prolonged infusion. Liberal amounts can be administered orally (e.g., calcium 50 mg/kg/day in four to five divided doses), with attention paid to the differing Ca content of various oral preparations. For patients with fat malabsorption, supplementation of calcium therapy with magnesium or vitamin D will be needed for maintenance of normocalcemia. In the setting of hypoparathyroidism secondary to magnesium depletion, magnesium replenishment will need to occur.

Hypercalcemia

Clinical and Laboratory Diagnosis

In contrast to dramatic neuromuscular manifestations of hypocalcemia, the physical effects of hypercalcemia may be subtle and nonspecific. However, a serum total calcium greater than 15 mg/dL represents a medical emergency. Renal,

cardiovascular, and CNS disturbances predominate and reflect both the degree and duration of calcium elevation. Increased filtered load of calcium creates hypercalciuria and accompanying polyuria, reduced urine-concentrating ability, dehydration, and eventual renal lithiasis. Hypertension is common, possibly mediated through increased renin production or direct effects on peripheral vasoconstriction and inotropy. Alterations in the cardiac conduction system include a shortened QT interval and a tendency to dysrhythmias. Impaired nerve conduction resulting from excess calcium creates hypotonia, hyporeflexia, and paresis in severe cases. Alterations in CNS function, including lethargy, confusion, and even coma, can occur. Constipation, anorexia, and abdominal pain resulting from reduced intestinal motility are frequent symptoms of hypercalcemia. Promotion of gastrin release by calcium may account for an increased incidence of peptic ulcer disease. Soft tissue deposition of calcium, usually facilitated by associated hyperphosphatemia, can impair function of the lungs, kidneys, blood vessels, and joints.

In the absence of hyperproteinemia, determination of elevated serum total calcium levels reliably indicates increased Ca^{++} concentrations. Because common causes of hypercalcemia in adults (hyperparathyroidism and malignancies) are less common in children, hypercalcemia is encountered less frequently than is hypocalcemia by the pediatric intensivist. Diagnostic possibilities are best approached by considering the predominant underlying mechanism of hypercalcemia as outlined in Table 67-3.

Increased bone resorption reflects excess PTH effect (e.g., hyperparathyroidism and ectopic PTH), immobilization, or bone lysis by metastatic malignancy (e.g., neuroblastoma). PTH-mediated hypercalcemia is distinguished by a depressed serum phosphate concentration, decreased renal tubular reabsorption of phosphate ($TmPO_4$/GFR), and an iPTH level inappropriately elevated for the simultaneous serum Ca^{++}. In the child with hyperparathyroidism, evaluation for multiple endocrine neoplasia is warranted. Heightened vitamin D effect is manifested by increased intestinal calcium absorption and can be related to vitamin D intoxication, increased sensitivity to vitamin D, or ectopically produced 1,25(OH)2–vitamin D, as seen in sarcoidosis. Serum PO_4 levels and $TmPO_4$/GFR) ratios are normal or increased, and iPTH levels are suppressed in these disorders. Detection of an elevated 25(OH) –vitamin D level (nutritional excess) or 1,25(OH)2–vitamin D level (sarcoidosis, hyperparathyroidism) may be helpful. Decreased excretion of calcium occurs with dehydration or treatment with thiazide diuretics and frequently aggravates the severity of hypercalcemia in patients with unrecognized hyperparathyroidism. Familial hypocalciuric hypercalcemia, an autosomal dominant disorder resulting from partially deactivating mutations in Ca^{++}-sensing receptor, is characterized by normal to slightly elevated iPTH levels and decreased urinary calcium excretion.[195] Thus determination of (a logical combination of) serum Ca^{++}+, PO_4, iPTH, vitamin D metabolites, and urinary calcium and PO_4 excretion allows differentiation of most hypercalcemic disorders.

Treatment

A serum calcium level greater than 15 mg/dL may be life threatening and requires direct Ca-lowering therapy in addition to attention to the underlying disorder. Hydration with isotonic saline solution (200 to 250 mL/kg/day) and furosemide diuresis (1 mg/kg administered every 6 hours) results in calciuresis and amelioration of hypercalcemia in the majority of cases. Excessive losses of sodium, potassium, magnesium, and PO_4 may occur. Thiazide diuretics should not be used because of their hypercalcemic effects.

Adjunct therapy is directed at the specific cause of hypercalcemia. Drugs that inhibit excessive bone resorption include calcitonin (10 U/kg IV every 4 to 6 hours), mithramycin (25 mg/kg IV over 4 hours), and indomethacin (1 mg/kg/day). Calcitonin, now available in human recombinant form, blocks PTH-induced bone resorption, facilitates calciuria, is relatively nontoxic, and has a prompt (but transient) peak effect by 1 hour. Mithramycin is a toxic antibiotic that inhibits osteoclastic activity

Table 67–3 Differential Diagnosis and Biochemical Findings in Childhood Hypercalcemia

		SERUM					URINE	
Predominant Mechanism of Hypercalcemia	**Disorder**	**Ca**	**PO4**	**25(OH)–Vitamin D**	**1,25(OH)2–Vitamin D**	**iPTH**	**Ca**	**$TmPO_4$/GFR**
Increased bone reabsorption	1. Hyperparathyroidism	H	L	N	H	H	H	L
	2. Malignancy-ectopic PTH	H	L	N	N or L	L	H	L
	3. Immobilization, thyrotoxicosis, or bone lysis	H	N or H	N	L	L	H	H
Increased intestinal calcium absorption	1. Vitamin D intoxication	H	N or H	H	N or H	L	H	H
	2. Sarcoidosis	H	N or H	N	H	L	H	H
	3. Idiopathic infantile hypercalcemia or Williams syndrome	H	N	N	L, N, or H	L	H	N or H
	4. Abrupt glucocorticoid withdrawal or deficiency	H	N or H	N	N	L	H	N or H
Decreased renal excretion of calcium	1. Familial hypocalciuric hypercalcemia	H	N or L	N	N or H	N or H	L	L

H, High; *L,* low; *N,* normal.

within 24 hours but has potential adverse effects, including thrombocytopenia and hepatic and renal toxicity. Indomethacin (or aspirin) is useful when excessive prostaglandin E2 production is suspected (e.g., some tumor-related hypercalcemic syndromes). More recently, bisphosphonates (e.g., pamidronate and etidronate) have been used successfully for treatment of persistent hypercalcemia.[196] Intestinal calcium absorption is reduced by corticosteroids (hydrocortisone 1 mg/kg administered every 6 hours or equivalent). Consequently, corticosteroids are especially useful for treatment of vitamin D–related hypercalcemia. Delayed onset of corticosteroids action, however, limits their use in the acute setting. Phosphates are not recommended because of the likelihood of soft tissue deposition of calcium-phosphate salts.

References are available online at http://www.expertconsult.com.

Acid-Base Balance and Disorders

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PEARLS

- The classical acid-base approach states that acidosis is produced by the gain of acids (endogenous or exogenous) that directly release H^+, and/or the loss of bicarbonate. For alkalosis, the opposite must occur. PCO_2, pH, standard base excess (SBE), HCO_3^-, and anion gap are the assessment tools used in this physiological view. However, with the exception of PCO_2, all these variables have a *correlation* with pH but have *no causal* relationship with it.
- According to the physical-chemical approach, water is a virtually inexhaustible source of hydrogen ion, and thus it is water itself that actually provides hydrogen ions through its dissociation or recomposition: $H_2O \leftrightarrow H^+ + OH^-$.
- Blood plasma contains numerous ions. Some of them are fully dissociated, chemically nonreacting in aqueous solutions, and are called "strong ions," such as Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^-. Certain organic acids, such as lactate and keto acids, are also considered strong ions.
- The determinants of $[H^+]$ and pH are the determinants of water dissociation, and the quantification of the water dissociation is made through the measurement of the hydrogen ion concentration, i.e., the pH.
- The model of acid-base balance was redefined as a consistent system in an aqueous solution with only three "independent variables" that are *causally* related to the H^+:
  - Partial pressure of carbon dioxide (PCO_2).
  - The strong ion difference (SID). In blood plasma, strong cations outnumber strong anions. The difference between the sum of all strong cations and all the strong anions is called SID; it has a powerful electrochemical effect on water dissociation, and hence on H^+. Sodium and chloride are the two most important plasma strong ions.
  - The most important nonvolatile weak acid—partially dissociated acid—is albumin, with a minor effect from phosphate.
- Normal acid-base status occurs when the independent variables have normal values. Abnormality of one or more of the independent variables underlies all acid-base disturbances. Adjustment of the independent variables is the essence of all therapeutic interventions because none of the dependent variables (e.g., pH, SBE, or HCO_3^-) can be changed primarily or individually; the dependent variables change, all of them simultaneously, if, and only if, one or more of the independent variables changes.
- Since PCO_2 is regulated by ventilation, its changes result in respiratory acid-base disorders. Metabolic acid-base disorders stem from changes in either SID or in total concentration of nonvolatile weak acids.
- Acid-base disorders must be considered more important for what they tell the clinician about the patient than for any harm that is directly provoked by the acid-base imbalance. Mortality is more closely related to the nature of an acid-base disorder, than to the magnitude of the derangement of the pH, whether acidotic or alkalotic.
- The main type of acid-base derangement in the critical care setting is metabolic acidosis. When the origin is lactic acidosis, the correlation with mortality is greatest. It has become evident, however, that iatrogenic hyperchloremic acidosis, related to resuscitation fluids, is much more frequent than previously thought, a fact that should be corrected through a better supervision of the fluids given to the patient and their impact in Cl^- and on SID.
- The clinical approximation to an acid-base disorder should include all the tools of the classical approach, but with some merging concepts from the physical-chemical approach: the anion gap must always be "corrected" for albumin levels, and sodium, chloride, and lactate levels must be checked. If a high volume of resuscitation fluids is given to the patient, or if the presence of unmeasured anions is expected, or if a complex or mixed pattern of acid-base metabolic derangement is suspected, then SID, strong ion gap (SIG), and probably "partitioned" SBE should be calculated.
- For easy bedside calculation of extensive formulas, there is an online free software solution, offering free decision support in complex acid-base scenarios at AcidBase.org [analysis module].

Physics, chemistry, and the physiology of acid-base balance are among the first subjects that are taught at medical school, and are one of the best examples of the close correlation between basic and clinical sciences. However, physicians seem to display only a superficial knowledge of this field. When queried, 70% of medical doctors at a university hospital stated that they needed no help in correctly interpreting arterial blood gases. However, they succeeded in only 40% of the cases presented to them.[1] Similar experiences have been reported more recently, involving both physicians and nurses.[2,3] As a paradox, it is likely that the easily available software for computers and hand-held devices, along with internet-available "primers" for

the interpretation of blood gases and acid-base status, are all contributors to this situation, as they provide physicians, residents and nurses with a fast-track mechanical interpretation of the arterial blood gases and acid-base status, even when all the complexities are not fully understood.[3] Because intensivists spend much of their time managing problems related to fluids, electrolytes, and acid-base balance, every hour making important clinical decisions after interpreting the available acid-base parameters, a thorough but practical understanding of the physiology and pathophysiology of acid-base disorders is a central aspect of the expertise of the critical care practitioner.

Understanding Acid-Base Physiology: Traditional and Newer Approaches

Most of the concepts of acid-base physiology were developed in the early twentieth century,[4,5] and are based mainly on the accepted definition of acid.[5-7] As early as 1887, Arrhenius had defined acid as a substance that, when dissolved in water, produces an increased concentration of hydrogen ions; in other words, it is not mandatory for this given substance to have hydrogen atoms in its molecule, as the water itself can be the source of the hydrogen ions.[5] Accordingly, by 1900, Naunyn and others proposed that the acid-base status was, at least partially, determined by the concentration of some electrolytes, mainly sodium and chloride, that had been formerly described by Faraday as "base-forming cation" and "acid-forming anion," respectively.[5] In the 1920s, Brönsted and Lowry stated that an "acid" is any molecule that contains hydrogen atoms and that is able to release them in a soluble manner; that is, an acid is a "proton-donor substance."[6,7] Thus an acid (HA) may dissociate and donate a proton (H^+) to the solution, forming the conjugate base (or anion) A^- in a reversible manner:

$$[HA] \overset{K_a}{\longleftrightarrow} [H^+] + [A^-] \qquad (1)$$

where K_a is the equilibrium or dissociation constant, particular to every different substance and influenced by the characteristics of the particular solution in which the reaction is taken place. Therefore a base is a molecule with the ability to accept or "trap" free hydrogen ions (proton-acceptor substance).[7] Examples include bicarbonate, hemoglobin, many other proteins, and phosphates.

Whatever definition of acid is used, its validity depends on the situation that one is trying to understand or the event one is attempting to explain. In biologic solutions such as plasma, the situation is a water-based solution with tightly controlled solute concentrations. It is remarkable that, in this scenario, all the former acid definitions are valid[5] because water can supply both hydrogen and hydroxyl ions:

$$H_2O \leftrightarrow H^+ + OH^- \qquad (2)$$

Therefore water must be seen as the major natural reservoir of hydrogen (and hydroxyl) ions; thus the acid-base balance relies on the chemical properties of water, that is, acid-base unbalance can be seen as an alteration of water dissociation. In physiologic conditions, there is little dissociation of water molecules into its components. Electrical charge and temperature represent the main determinants for its eventual dissociation. Electrical neutrality is always held constant; that is, the number of positive charges must equal the number of negative charges. Both extracellular and intracellular fluids are an ionic mix of electrolytes, proteins, and other substances, whose charges tend to modify the electrical balance and then can have an influence on the dissociation of water. In order to keep the electroneutrality, more (or fewer) water molecules will have to dissociate. In other words, the determinants of H^+ are the determinants of water dissociation, and the quantification of the water dissociation is made through the measurement of the hydrogen ion concentration H^+.

Normal concentration of hydrogen ions in the extracellular fluid is extremely low, in the nanoequivalent (nEq) or nanomole (nmol) range (i.e., the order of magnitude of the H^+ is in the millionth of a milliequivalent range [1 nanoequivalent = 10^9 equivalent = 10^6 milliequivalent]). The usual arterial blood H^+ is about 40 nEq/L (or nmol/L) (i.e., 0.000040 mEq/L, with a normal range of 35 to 45 nEq/L [0.000035 to 0.000045 mEq/L or mmol/L]).[4] In other words, serum H^+ is about 3 million times less than the serum sodium concentration.[9] Because hydrogen ion concentration in body fluids and tissues has a strong influence on the function of almost all enzymatic systems of the organism, a tight regulation of its concentration is mandatory for the body. For convenience, the H^+ value is usually expressed as pH units, that are derived as the negative $\log_{10}$ of the hydrogen ion concentration in nanoequivalents per liter.This concept was developed by Sörenson and adapted by Karl Hasselbalch to clinical medicine in 1909. A normal pH of 7.4 corresponds to a blood hydrogen ion concentration of 40 nEq/L, at 37° C. The relationship between pH and serum H^+ is nonlinear, but it is almost linear over the narrow normal range of 7.35 to 7.45 (corresponding to 45 to 35 nEq/L of H^+).[9]

Acids, Bases, Buffers: The Traditional Understanding

An acid is *strong* when it dissociates its hydrogen ion easily because the corresponding base has a low affinity for it (high Ka–dissociation constant value). *Weak* acids only partially dissociate because their corresponding base has high affinity for hydrogen ions (low K_a value). When the latter is the case, both the hydrogen ion and the base form of the parental molecule are present in the resulting solution in equimolar proportions. As a consequence, this solution has the ability to resist changes in acidity (or pH) after the addition of a strong acid or base. This solution, constituted by an acid-base pair, is known as a buffer. The dissociation constant K_a, as in the case of pH, can be expressed as $\log_{10}K_a$, is termed pK_a, and represents a measure of the tendency of the acid-base pair to ionize. Strong acids have a low pK_a (high K_a) and weak acids have high pK_a (low K_a). A weak acid-base pair is more effective as a buffer in living systems when the pK_a is close to physiologic pH.[6,7,10]

Physiologic buffering systems may be classified into two general categories: the bicarbonate/carbonic acid (HCO_3^-/H_2CO_3) buffering system, that acts in both the extracellular space and inside the cells, and the nonbicarbonate buffers, which include hemoglobin and oxyhemoglobin, organic phosphates, inorganic phosphates, and plasma proteins. Extracellular buffers (HCO_3^-, plasma proteins) represent the body's first and immediate line of defense against any alteration of pH of the body fluids. After extracellular buffering occurs, a second intracellular phase takes place, as long as intracellular buffers (intracellular proteins, dibasic phosphates, hemoglobin-oxyhemoglobin, and carbonate in bones) reach

buffering capacity over the next several hours.[10] The buffering systems cannot truly eliminate hydrogen ions from the body, but they tamper sudden changes in $[H^+]$ (or pH) and "buy time" until a new balance can be achieved. Altogether, extracellular and intracellular buffers provide a volume of distribution close to that of the total body water to any exogenous acid load (or deficit). This represents a formidable capacity for resisting changes in pH.

Acid Production in the Body

Acid production in the body occurs in two major ways. The first one involves CO_2 production during oxidative metabolism of carbohydrates, fat, and amino acids. The CO_2 is then hydrated by the cytoplasmic enzyme carbonic anhydrase to produce carbonic acid (H_2CO_3), a weak acid that dissociates in hydrogen ion and bicarbonate.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (3)$$

The second pathway involves nonvolatile metabolic acids that are produced by the normal daily catabolic load (oxidation of sulfur-containing amino acids, hydrolysis of pyrophosphate and orthophosphate esters) or during situations with incomplete catabolism of fat and carbohydrates, such as lactic acidosis or diabetic ketoacidosis (DKA). The free hydrogen ions are neutralized by extracellular and intracellular buffers, but because these acids are not in equilibrium in the normal plasma, they must be metabolized, mainly in the liver, and then excreted by the kidneys.[10]

The major acid-base buffering system in the blood is the bicarbonate/carbonic acid system, which has the tremendous advantage of interconversion of CO_2 with H_2CO_3. Any increase in $[H^+]$ (or drop in pH) will shift the former reaction (Equation 3) to the left through an increase in both alveolar ventilation and elimination rate of CO_2. This respiratory response begins within minutes, but may not reach a steady state for 12 to 24 hours. This method of achieving a rapid decrease of the actual acid component is a unique characteristic of the bicarbonate/carbonic acid buffering system. For the other buffers, the addition or removal of hydrogen ions has the corresponding opposite effect on the buffer components, limiting the maximum buffering capacity. On the contrary, the capacity of the bicarbonate-CO_2 system is greatly increased because the lungs can eliminate a vast amount of CO_2 per day. Similarly, the kidneys can eliminate or regenerate bicarbonate as needed, although this response is slower than that of the lungs.

The Classic Paradigm: H^+ Depends on CO_2, H_2CO_3, and HCO_3^-

The quantitative importance of the bicarbonate/carbonic acid buffering system was clearly noticed by Henderson when he developed his famous equation, which was modified by Hasselbalch shortly after. The Henderson-Hasselbalch equation[4,5] expresses the relationship of the bicarbonate/carbonic acid buffering system to pH:

$$pH = pK_a + \log([HCO_3^-]/[H_2CO_3]) \quad (4)$$

The pH is equal to a constant (pK_a, the $\log_{10}$ of K_a, the first dissociation constant for H_2CO_3, which has a value of 6.1 for human plasma in physiological conditions) plus the log of the ratio of HCO_3^- (proton acceptor) to H_2CO_3 (proton donor). The modified Henderson-Hasselbalch equation takes into consideration that H_2CO_3 is in equilibrium with dissolved CO_2 and is rewritten as[9]:

$$pH = pKa + \log([HCO_3^-]/0.03 \times PCO_2) \quad (5)$$

where *0.03* is the solubility coefficient for carbon dioxide in blood at 37° C.

What the Henderson-Hasselbalch equation tells us is how pH is affected by the change in the ratio of the concentration of nondissociated acid HA (in this case carbonic acid or PCO_2) to the concentration of the conjugated base or anion A^- (in this case HCO3$^-$). When pH is altered as the result of changes in the volatile component (increases or decreases of PCO_2), clinically speaking, the change is referred to as *respiratory*.[9] When pH is modified by changes in nonvolatile acids (e.g., lactic acid, keto acids), or by changes in serum cations and/or anions (e.g., hyperchloremia/hypochloremia), it is referred to as *metabolic in origin*.[5,8,9] The term *acidosis* is used to describe the process that tends to produce an increase in H^+, whether or not there is a change in pH. *Alkalosis* is the opposite; that is, the process that tends to produce a decrease in H^+, with or without changes in pH. *Acidemia* and *alkalemia* are the corresponding terms for those situations in which blood pH actually changes.[9] Thus this equation allows disorders to be classified according to the primary type of acid being increased or decreased. For example, if a patient's pH is low (acidemia), then the patient may have either an increased PCO_2 or a PCO_2 within normal or decreased values. If the PCO_2 is increased (alveolar hypoventilation), the condition is classified as *respiratory acidosis*. If it is not increased, there cannot be a respiratory acidosis. Therefore some nonvolatile acid or anion must be the cause of the acidemia, and this is then referred to as *metabolic acidosis*. If these examples are reversed, then alkalemia can also be classified as resulting from either respiratory or metabolic alkaloses.[9]

The Henderson-Hasselbalch equation is useful but has intrinsic limitations.[5,8] The first one is that it does not quantify the severity of the metabolic derangement as it does for the respiratory component. In a respiratory acidosis, the increase in the PCO_2 quantifies the derangement even when there are mixed disorders. The metabolic component can only be approximated, however, by the change in HCO_3^-. Although the relationship between PCO_2 and HCO_3^- provides a useful clinical guide for uncovering a metabolic origin of a given derangement, this is dampened because PCO_2, H_2CO_3, and HCO_3^- are all interlinked (Equations 3 and 5), so the bicarbonate will also increase if PCO_2 increases.[6,8] The second important characteristic of the Henderson-Hasselbalch equation is that it does not provide information about any acids other than carbonic acid.

Using the Brönsted-Lowry definition of acid as a "proton donor,"[4,6,7,11] many physiologists dismissed defining chloride as an acid and sodium as a base, arguing that there was an insufficient link between these and other electrolytes and the subsequent changes in hydrogen ions. Thus, by accepting only Brönsted-Lowry acids while looking for factors controlling the nonrespiratory component of acid-base balance, many physiologists focused on the plasma bicarbonate concentration and the Henderson-Hasselbalch equation.[5] This was the beginning of the still-dominant concept that plasma bicarbonate is not only the best indicator of acid-base status, but also a main determinant of it. Unfortunately, this way of thinking

overlooked the fact that *all* weak acids in a given aqueous solution such as plasma can be inserted into a Henderson-Hasselbalch type of equation to calculate pH, as Lawrence Henderson himself demonstrated in 1908.[4] The reason is easy to understand: for a single solution containing several weak acids (as human plasma), all the weak acids are equilibrated with a single pool of hydrogen ions. This is called the isohydric principle.[5] Consider two buffer systems: bicarbonate/carbonic acid and phosphate/phosphoric acid:

$$H_2CO_3 \leftrightarrow HCO_3^- + H^+ + HPO_4^{2-} \leftrightarrow H_2PO_4^- \qquad (6)$$

Note that the H^+ that will eventually form both carbonic acid and phosphoric acid actually comes from the single plasmatic pool. Expressing the same concept in the Henderson-Hasselbalch way:

$$pK_{a1} + \log([HCO_3^-]/[H_2CO_3]) = pH = pK_{a2} + \log([HPO_4^{2-}/[H_2PO_4^-]) \qquad (7)$$

Thus according to the isohydric principle, the ratio of *any pair* of conjugate base or anion and its nondissociated acid will be able to describe the H^+ or pH.[5,12] This means that although the ratio of PCO_2 to bicarbonate can describe what the pH and acid-base status is, the system bicarbonate/carbonic acid is not necessarily the primary or underlying mechanism for explaining changes in pH.

Correlation and causation are not the same.[5,8] Immersed in the bicarbonate-centered approach, investigators yielded basically three solutions for analyzing the "metabolic side" of the equation: the base excess method, the six bicarbonate "rules of thumb," and the use of anion gap (AG).[4,5,9,13-15]

Base Excess and Standard Base Excess

The change in pH of a given buffered solution is dependent on both the amount of strong acid (or strong base) that is added, and on the buffering capacity of the system. As acid is added, for every H^+ that is buffered, one molecule of conjugate base of the buffer is consumed. Therefore, quantifying the changes in the concentration of the conjugate base of the buffer is more useful than the degree of change in the pH in estimating the amount of nonvolatile acids present.

Siggaard-Andersen, from Copenhagen, developed the "base excess" method in the late 1950s.[4,14,15] Base excess (BE) is defined as the amount of strong acid (or strong base), in moles per liter (mol/L), that must be added to a whole blood sample to return the pH of the sample to 7.40, while the PCO_2 is maintained at 40 mm Hg.[5,15,16] Therefore if the blood sample is normal (i.e., its pH is 7.4 and its PCO_2 is about 40 mm Hg), the BE will be 0 mmol/L. Positive values mean literally an excess of metabolic bases; negative values mean an excess of metabolic acids.[9,15,16] To apply the BE to the clinical setting, a nomogram was developed that was later mathematically transcribed to allow BE calculation by blood gas analyzers.[17,18] However, several flaws appeared.[19-21] For clinical accuracy, other assumptions had to be incorporated (correction factors, adjusted formulas, nomogram modifications),[5,18,22] and, remarkably, an empiric estimate of hemoglobin concentration throughout the entire extracellular fluid space (whole blood plus interstitial fluid) had to be established, in order to consider the net effect of the intracellular buffers, hemoglobin the main one.[5] A hemoglobin concentration of 50 g/L (5 g/dL)[5,22] was chosen to calculate standard base excess (SBE), a parameter reported nowadays by modern gas analyzers and used in the classical approach to acid-base balance (Table 68-1). Although SBE has good correlation with bicarbonate levels and quantifies the change in metabolic acid-base status in vivo, its accuracy depends on the 5 g/dL of hemoglobin assumption, and it still does not provide information about the origin or mechanisms of the metabolic acid-base derangement because SBE is not a substance that can be regulated, absorbed, or excreted by the body.[8] Perhaps the main pitfall is that the SBE value represents the net effect of all metabolic acid-base abnormalities. Therefore the effects of coexisting metabolic acidoses and alkaloses may cancel each other, and the normal figure of the SBE will mistakenly suggest that no acid-base derangement exists. Actually, 15% to 18% of critically ill adults with acid-base disorders have a normal SBE.[13,23]

Bicarbonate Rules

In a "great transatlantic debate,"[18,21] strong criticism of the SBE from Schwartz and Relman from Boston yielded the six bicarbonate "rules of thumb" (Table 68-2).[18] The Henderson-Hasselbalch equation easily disclosed derangements into "respiratory" and "metabolic," the so-called *simple derangements*.[9] Because the body always seeks to tightly control H^+, however, several physiologic responses become active over time, and then the relationship between PCO_2 and HCO_3^- is modified so pH changes can be minimized. This minimization gives origin to more complex or "mixed" conditions.[9,10,24] Despite this, through careful examination of the changes that occur in PCO_2 and HCO_3^- in relation to each other, it was possible to find patterns and to derive rules (the so-called *six rules of thumb*) for uncovering mixed disorders and to differentiate acute from chronic respiratory unbalances. These rules describe the physiological compensation to acid-base changes to optimize acid-base homeostasis. With the expected physiologic compensation allowed for, residual changes in CO_2 or bicarbonate are then seen as the mechanisms for changes in acid-base status (Tables 68-2 and 68-3). This approach is still the most practical acid-base balance diagnostic tool for the busy clinician.[9]

Anion Gap and Corrected Anion Gap

The AG was introduced as a complementary diagnostic tool for either SBE or bicarbonate rules-of-thumb approaches to metabolic disturbances.[25] It is based on the principle of electroneutrality, which states that there is no electrical charge in plasma. Accordingly, serum positive-charged cations must equal serum negative-charged anions[9] (see Table 68-1):

$$[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] + [H^+] = [Cl^-] + [HCO_3^-] + [\text{proteins}^-] + [PO_4^{3-}] + [SO_4^{2-}] + [OH^-] + [CO_3^{2-}] + [XA^-]) \qquad (8)$$

where *[XA⁻]* is the unmeasured acid anions. Sometimes they are abbreviated as UMAs.

The plasma concentrations of SO_4^{2-}, OH^-, CO_3^{2-}, and H^+ are quite small and can be neglected. Concentrations of Na^+, K^+, Cl^-, and HCO_3^- (in the form of total CO_2) are reported in a standard chemistry panel. The sum of the remaining anion

Table 68–1 Classical Acid-Base Parameters

pH	$\log_{10} H^+$. Measured directly by electrode. Normal = 7.35–7.45.
PCO_2	Partial pressure of gaseous CO_2. Measured directly by electrode. Usually expressed in mm Hg. Normal value: 35–45 mm Hg (sea level, arterial blood).
HCO_3^-	Bicarbonate concentration. A calculated parameter, derived from pH and PCO_2 values using a nomogram or the Henderson-Hasselbalch equation, or equal to the difference between serum total CO_2 (CO_{2TOT}) and the dissolved CO_2. ($PCO_2 \times 0.03$). Normal value: 22–28 mEq/L.
Base excess (BE or BE/D)	Also known as base excess/deficit. Defined as the amount of strong base (negative base excess, or "base deficit") or strong acid (positive base excess) in mmol/L that would be needed to restore a pH of 7.4 to a liter of whole blood equilibrated at PCO_2 = 40 mm Hg. It is calculated by a nomogram or equation that was derived from an experimental series of in vitro titrations of strong acid and base in whole blood samples at various PCO_2 levels. It excludes the effect of acute changes in PCO_2, so it loses accuracy if PCO_2 is abnormal. It should not be used in critically ill patients.
Standard base excess (SBE)	An improvement of base excess to allow equilibration across the entire extracellular fluid space (whole blood interstitial fluid) and thus preserve accuracy at variable PCO_2 values. The new equation assumes an "average" concentration of hemoglobin through that space of 5 g/dL. Despite being a somewhat arbitrary figure, it indeed works in vivo.
CO_{2TOT} or CO_2	Total CO_2 or CO_2 concentration. A serum chemistry measured value. Its components include HCO_3^-, dissolved gaseous CO_2, carbonic acid (H_2CO_3), carbamino CO_2, and carbonate (CO_3^{2-}). About 95% exists as HCO_3^-, and 4% to 5% as dissolved gaseous CO_2. Remaining species are negligible. Because the difference between CO_{2TOT} and HCO_3^- is about 1 mEq/L at physiological pH, for clinical purposes they are taken almost as equivalents.
Anion gap (AG)	A calculated value that, taking advantage of the electroneutrality principle that rules plasmatic ions (total amount of cations should be the same as the total amount of anions), indicates the presence of "unmeasured" anions (mostly organic acids). $AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$. Normal values are 16 mEq/L (if K^+ is included) or 12 mEq/L (without K^+, with variations of ± 2 to 4 mEq/L. These values may be influenced by the way the values of some of the parameters are measured, so it is always better to consult each institution's own expected normal AG.
Corrected anion gap (AG_{CORR})	An improvement in the calculation of AG, that acknowledges that an increase in AG from organic acids may be masked by a decrease in AG from low protein (albumin) levels. AG is corrected for the patient's own albumin concentration as follows: $AG_{CORRECTED} = AG_{OBSERVED} \times 2.5$[normal albumin (g/dL)] – [observed albumin (g/dL)], considering normal albumin from 3.2 to 4.5 g/dL. In order to avoid [lactate$^-$] influence on AG_{CORR} that could mask the detection of other unmeasured anions, it has been suggested that AG should be corrected not only for albumin, but also for lactate. This is simply made by subtracting the serum lactate concentration (in mmol/L) from the already albumin-corrected AG: $AG_{CORRLACT}$ = Albumin-corrected AG – [lactate$^-$ (mmol/L)].
Urinary anion gap (uGap)	The same principle of the anion gap applied to urinary ions, that is, uGap estimates unmeasured urinary ions. It has also been designated by some as urine strong ion difference (uSID), a functionally correct name, as all the involved ions are strong ions: $uGap = uSID = [uNa^+ + uK^+] - [uCl^-]$. The most important unmeasured urinary strong anion (Ur^-) is SO_4^{2-} (derived from the metabolism of sulfur amino acids), whereas the most important unmeasured cation (Ur^+)is ammonium (NH_4^+). In physiologically normal conditions, uSID must equal the plasmatic SID_{APP}, or 38–42 mEq/L.

Table 68–2 Classical Acid-Base Approach: Observational Acid-Base Patterns

Primary Disorder	Expected Changes $[HCO_3^-]$ (mEq/L or mmol/L)	Expected Changes PCO_2 (mm Hg)	Expected Changes SBE (mmol/L)
Metabolic acidosis	<22	$= (1.5 \times HCO_3^-) + (8 \pm 2)$ $= 40 + SBE$	<–5
Metabolic alkalosis	>26	$= (0.7 \times HCO_3^-) + (21 \pm 2)$ $= 40 + (0.6 \times SBE)$	>+5
Acute respiratory acidosis	$= [(PCO_2 - 40)/10] + 24$	>45 or $\Delta pH = 0.008 \times (PCO_2 - 40)$	= 0
Chronic respiratory acidosis	$= [(PCO_2 - 40)/3] + 24$	>45 or $\Delta pH = 0.003 \times (PCO_2 - 40)$	$= 0.4 \times (PCO_2 - 40)$
Acute respiratory alkalosis	$= [(40 - PCO_2)/5] + 24$	<35 or $\Delta pH = 0.008 \times (40 - PCO_2)$	= 0
Chronic respiratory alkalosis	$= [(40 - PCO_2)/10] + 24$	<35 or $\Delta pH = 0.017 \times (40 - PCO_2)$	$= 0.4 \times (PCO_2 - 40)$

Modified from Kellum JA: Determinants of plasma acid-base balance, *Crit Care Clin* 21:329-346, 2005; and Kraut JA, Madias NE: Approach to patients with acid-base disorders, *Respir Care* 46(4):392-403, 2001.

Table 68–3 Classical Acid-Base Approach: Additional Clues

1. A metabolic acid-base derangement exists if:
   a. pH is abnormal.
   b. pH and PCO_2 have changed in the same direction (both increased or both decreased).
   c. Respiratory compensation is intact if P_aCO_2 resembles last two digits of pH (e.g. pH 7.23 and P_aCO_2 ≤23 mm Hg).
2. A respiratory acid-base derangement is overlapped if any of the following occurs:
   a. pH is abnormal but PCO_2 is reported within normal limits.
   b. PCO_2 reported is higher than expected PCO_2 (respiratory acidosis overlapped).
   c. PCO_2 reported is lower than expected PCO_2 (respiratory alkalosis overlapped).
3. A respiratory acid-base derangement exists if:
   a. P_aCO_2 is abnormal.
   b. PCO_2 and pH have changed in opposite directions (i.e., raised PCO_2 and decreased pH or vice versa).
4. If the change of pH is … (see formulas in Table 68-2)
   a. 0.008 × change in PCO_2, there is no compensation; then the derangement is acute.
   b. >0.003 but <0.008 × change in PCO_2, there is a partial compensation.
   c. 0.003 × change in PCO_2, there is full compensation; then the derangement is chronic.
   d. >0.008 × change in PCO_2, there is an overlapping metabolic derangement.
5. There is a mixed derangement (acidosis and alkalosis) if any of the following occurs:
   a. P_aCO_2 is abnormal and pH has not changed as expected or is within normal values.
   b. pH is abnormal and P_aCO_2 has not changed as expected or is within normal values.

Modified from Marino PL: Acid-base interpretations. In: *The little ICU book of facts and figures,* Philadelphia, 2009, Lippincott Williams & Wilkins, pp 349-362.

species, proteins$^-$, PO_4^{3-}, and XA^-, is defined as the unmeasured anions (UA), whereas the sum of the remaining cation species, Ca^{2+} and Mg^{2+}, is defined as the unmeasured cations (UC). Thus AG is commonly defined as[9]:

$$AG = UA - UC = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) \quad (9A)$$

Sometimes [K+] and its effect are disregarded[26]:

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-]) \quad (9B)$$

Typically, normal values are 16 mEq/L (if K^+ is included) or 12 mEq/L (without K^+), with variations of ±2 to 4 mEq/L. These values may be influenced by the way the values of some of the parameters—particularly chloride levels—are measured, so it is always better to consult each institution's own expected "normal AG."[26,27]

It must be realized that calculated AG is affected by any change in the concentrations of either the UA or UC. Plasma proteins and phosphate levels can be significantly decreased in the critical care setting. Reduced protein and phosphate levels result in a decreased UA and hence in a decreased AG. Therefore, an increase in AG from organic acids may be masked by a decrease in AG from low protein and phosphate levels and thus it is wise to make the proper corrections.[28] This is particularly true in the pediatric critical care setting, where hypoalbuminemia is nearly ubiquitous.[26,29,30] Phosphate influence is rather small, and so is the effect of globulins, since their pK_a is much greater than plasma pH (they do not easily dissociate) and hence they do not have a significant H^+ contribution.

Figge et al. showed that in most patients, the AG could be corrected (AG_{CORR}) as follows[26]:

$$AG_{CORR} = AG_{OBSERVED} + 0.25 \times [\text{Normal albumin (g/L)}] - [\text{Observed albumin (g/L)}] \quad (10)$$

considering normal albumin from 3.2 to 4.5 g/dL.

The albumin-corrected AG (AG_{CORR}) can unmask an organic acidosis previously undetected in the setting of hypoalbuminemia, and adds sensitivity for detecting unmeasured anions, including lactate, although the specificity for hyperlactatemia is poor.[28,31-33] Thus lactate must be directly determined.

Despite the fact that it is not useful for quantifying the metabolic derangement, AG is a powerful tool for the clinician in the categorization of metabolic acidoses, as not all metabolic acidoses result in an elevated AG.[34] As an hypothetical example, the reader might consider that acid in the form of HCl is added to the circulation. Upon dissociation, Cl^- remains as the conjugate base, while the plasmatic bicarbonate buffer is "consumed" by the hydrogen ion. The result is that an increase in Cl^- is balanced by a decrease in HCO_3^-, that is, there is metabolic acidosis without a change in the AG. Thus through the AG_{CORR} it is possible to differentiate hyperchloremic acidosis (normal AG) from "gap acidoses" (increased AG).[26,34] The last category includes all conditions of metabolic simple acidosis caused by increased concentrations of nonvolatile anions other than chloride, usually unmeasured (or unmeasurable), such as lactate, keto acids, phosphate, sulfates (and other anions in renal failure setting), salicylate, some β-lactam antibiotics, organic acids from congenital errors of metabolism, and acetate from parenteral nutrition (Table 68-4).[31,34] Non-AG hyperchloremic acidoses include excessive infusion of chloride salts (saline or parenteral nutrition) and increased renal or gastrointestinal bicarbonate losses. On the contrary, metabolic alkalosis may stem from hypochloremia from chloride loss or bicarbonate gain, and from hypoalbuminemia.[31] AG performance is not so good in mixed acid-base physiology, despite several attempts to improve it. This represents an important limitation to its use in critical care patients, in whom single metabolic acid-base disorders are more the exception than the rule. In spite of several attempts, the "corrections" and adaptations for the AG that have been proposed in order to detect mixed disorders have not fulfilled the expectations.[24,31]

Water as the Main Source of Hydrogen Ions: The Stewart Approach

It is remarkable that not one of the classic acid-base approaches examined the role of water as a virtually inexhaustible source of hydrogen ion, as Peter Stewart later did.[5,8,35] Although pure water dissociates only slightly into H^+ and OH^- in plasma, the presence of electrolytes, CO_2, and other weak acids produces powerful electrochemical forces influencing water dissociation.[8] In the late 1970s and early 1980s, Peter Stewart proposed that Arrhenius' more general definition of an acid, along with Naunyn's ideas from 1900, was more useful to acid-base physiology than the Brönsted-Lowry definition.[36,37] Applying several basic principles of physical chemistry, particularly

Table 68–4 Causes of Metabolic Acidosis in Critically Ill Patients

I. Accumulation of unmeasured anions: the anion gap acidoses
  A. Endogenous source of acids
    1. Type A hyperlactatemia (decreased tissue O_2 delivery)
    2. Type B hyperlactatemia (not associated with tissue hypoxia)
    3. Ketoacidosis (diabetic, alcoholic, starvation)
    4. Renal failure: accumulation of phosphates, sulfates, and organic ions
    5. Unidentified anions in sepsis other than lactate
    6. Certain organic acids from inborn errors of metabolism
    7. Late metabolic acidosis of prematurity
  B. Exogenous source of acids
    1. Ingested toxins and drugs that directly provoke acidosis
      a. Methanol, formic acid, keto acids, lactate
      b. Ethylene glycol, glycolic acid, oxalic acid, paraldehyde
      c. Ethanol
      d. Salicylate, salicylic acid, acetic acid
      e. Illegal drugs
    2. Total parenteral nutrition*
II. Hyperchloremic acidoses: the non–anion gap acidoses
  A. Exogenous chloride load
    1. Normal saline or hypertonic saline resuscitation
    2. HCl, NH_4Cl, arginine HCl administration
    3. Total parenteral nutrition*
  B. Loss of cations from the lower gastrointestinal tract (postpyloric gastrointestinal fluid losses)†
    1. Infectious secretory diarrhea and dehydration
    2. Short bowel syndrome
    3. Drainage from ostomies, tubes, fistulas (small bowel, pancreatic, or biliary drainage)
    4. Sulfamylon, cholestyramine
  C. Renal causes‡
    1. Chronic renal insufficiency (impaired ammonium [NH_4^+] generation)
    2. Renal tubular acidoses
    3. Hypoaldosteronism
    4. Recovery phase of diabetic ketoacidosis
    5. Urinary tract obstruction
    6. Drug-mediated loss of cations and tubulopathies
      a. Acetazolamide
      b. Amphotericin B
      c. K^+-sparing diuretics
  D. Urinary reconstruction using bowel segments

*Total parenteral nutrition may cause both anion gap and non-anion gap acidosis. In the first case, an excessive amount of exogenous acids is the cause, mainly if liver or renal functions are impaired; in the latter, an unbalanced, excessive chloride content in the formulation provokes the derangement, which is easily produced in the setting of renal failure.
†This class corresponds to the gastrointestinal loss of bicarbonate type of acidosis, according to the classical approach.
‡This class corresponds to the renal loss of bicarbonate type of acidosis, according to the classical approach.

electroneutrality, conservation of mass, and dissociation equilibrium of partially dissociated substances (electrolytes and others),[5,8,13,38] Stewart developed a mathematical model of acid-base balance. He defined the system as an aqueous solution that contains strong ions that are completely dissociated at physiologic pH, weak acids that are partially dissociated at physiologic pH, and carbon dioxide that is in equilibrium with an external partial pressure of carbon dioxide. The main concepts of this approach are summarized in Table 68-5, and a classification of primary acid-base disturbances based in this system is presented in Table 68-6. Thus according to Stewart, there are only three independent controlling variables of H+ concentration[5,8,38-40]:

1. Partial pressure of carbon dioxide (PCO_2).
2. The strong ion difference (SID). Blood plasma contains numerous ions, which may be classified not only in regard to their electrical charge (cations are positive, anions are negative), but also according to their tendency to dissociate. Some ions are fully dissociated and chemically nonreacting in aqueous solutions, and are called "strong ions," such as Na^+, K^+, Ca^{2-}, Mg^{2+}, and Cl^-. Others, such as albumin, phosphate and HCO_3^-, can exist both as charged (i.e., dissociated) and uncharged forms, and are called "weak ions." Certain organic acids, such as lactate and others, are nearly completely dissociated under physiologic conditions, and so are considered strong ions. In blood plasma, strong cations outnumber strong anions. The difference between the sum of all strong cations and all the strong anions is called SID. Sodium and chloride are the two most important plasmatic strong ions.[23,41]
3. The total concentration of nonvolatile weak acids (A_{TOT}), that is, for each of them, the sum of its dissociated and undissociated forms ($A_{TOT} = A^- + HA$).[13,36,38-40] The most important weak acid—partially dissociated acid—is albumin, with a minor effect from phosphate.

"Independent variables" mean that PCO_2, SID, and A_{TOT} are causally related to the hydrogen ion, rather than being merely correlated.[38,39] Normal acid-base status occurs when the independent variables have normal values. Abnormality of one or more of the independent variables underlies all acid-base disturbances. Adjustment of the independent variables is the essence of all therapeutic interventions, because none of the dependent variables (e.g., pH, BE, HCO_3^-) can be changed primarily or individually; the dependent variables change all of them simultaneously if, and only if, one or more of the independent variables changes.[8,13,39] Since PCO_2 is regulated by respiration, its changes result in respiratory acid-base disorders. Metabolic acid-base disorders stem both from changes in either SID or A_{TOT}.

CO_2 and Bicarbonate in Stewart's Approach

In Stewart's approach, CO_2 represents a primary independent determinant of pH, just as in the bicarbonate-BE-centered approaches, that is, there are no changes in the understanding of the respiratory acid-base derangements. However, the role of bicarbonate is reduced from being causative to a mere indicator, as hydrogen ion and bicarbonate concentrations are totally dependent on the three independent controlling variables. Hence, according to Stewart, the major use for the bicarbonate rules of thumb and SBE are to determine the extent of the clinical acid-base disorder, rather than the mechanism.[5,8,39]

The rise of the PCO_2, according to the Henderson-Hasselbalch equation (Equation 5), will increase both H^+ and HCO_3^- concentrations. Therefore the change in HCO_3^- concentration is mediated by chemical equilibrium (Equation 3) and not by any systemic adaptive response.[8] The total CO_2 concentration (and hence the $[HCO_3^-]$) is determined by the PCO_2, which is in turn determined by the balance between alveolar ventilation and CO_2 production at tissue level. Therefore HCO_3^- cannot

Table 68–5 Concepts and Parameters Used in the Quantitative Physical-Chemical Approach to Acid-Base Balance: A Summary

Variable	Comment
Strong ions	Blood plasma contains numerous ions, which may be classified not only in regard to their electrical charge (cations are positive, anions are negative), but also according to their tendency to dissociate. Some ions (such as Na^+, K^+ Ca^{2+}, Mg^{2+}, and Cl^-), are fully dissociated, chemically nonreacting in aqueous solutions, and are called "strong ions." Certain organic acids, such as lactate and other nonvolatile organic acids, are nearly completely dissociated under physiologic conditions, and so they are considered weak ions.
Weak ions	Ions that can exist both as charged (i.e., dissociated) and uncharged forms, such as albumin, phosphate, and HCO_3^-.
Strong ion difference (SID)	In blood plasma, strong cations outnumber strong anions. The difference between the sum of all strong cations and all the strong anions is called SID. Sodium and chloride are the two most important plasmatic strong ions.
Apparent strong ion difference (SID_{APP})	When SID is calculated from direct measurement of serum strong ions, it is termed apparent SID (SID_{APP}): $SID_{APP} = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-])$. Ionized concentrations of Mg and Ca are used. If available, lactate should be included: $SID_{APP} = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate^-])$. In healthy volunteers, the usual SID_{APP} is 38–42 mEq/L. In stable critical care patients, SID_{APP} is around 33 ± 5.6 mEq/L. If this patient then has metabolic acidosis, SID_{APP} will decrease further. The lower the baseline of the SID_{APP}, the greater the susceptibility to a subsequent acid load.
Effective strong ion difference (SID_{EFF})	According to the principle of electroneutrality, blood plasma cannot be charged, so there should be remaining negative charges balancing the "excess" of plasma strong cations in relation to the strong anions; this is the origin of SID_{APP}. These balancing negative charges come from total CO_2 (~$[HCO_3^-]$) and from albumin and inorganic phosphate. Thus SID can be derived, accounting for electrical neutralitiy, as the sum of $[HCO_3^-]$ plus the negative electric charges contributed by albumin ($[Alb^-]$) and by inorganic phosphate ($[Pi^-]$). This calculation of SID is known as effective SID (SID_{EFF}): $SID_{EFF} = [HCO_3^-] + [Alb^-]$ (g/L) + $[Phosphate^-]$ (mmol/L). The negative electrical charges contributed by serum albumin and phosphate are as follows: [Alb] = [Alb] × (0.123 × pH × –0.631) and [Phosphate] = [Phosphate] × (0.309 × pH × [–0.469]). Taking in account the complexity of the albumin molecule, its charge should be expressed as a linear function of the pH. Thus, a more accurate calculation of SID_{EFF} is: $SID_{EFF} = 2.46 \times 10^{-8} \times PCO_2/10 - pH +$ [albumin (g/dL)] × (0.123 × pH –0.631) + [Phosphate (mg/dL)] × (0.309 × pH – 0.469). For its clinical application, this equation needs access to an Internet-based engine designed for calculating the SID_{EFF} and other physicochemical acid base parameters (consult http://www.acidbase.org).
Strong ion gap (SIG)	In the healthy individual, SID_{APP} and SID_{EFF} are nearly identical. In disease states, this may not be true, as plenty of unmeasured ions not included in equations may be present in plasma (e.g., ketones, sulfates, organic acids from inborn errors of metabolism, certain medications), along with abnormal weak ions (such as proteins). Clearly, this will make both SID_{APP} and SID_{EFF} inaccurate. So, the simplest way to approximate $[XA^-]$ is through the SIG. This term is far from ideal, since the unmeasured anions creating the 'gap' can be either strong or weak. It is calculated as follows: $SIG = SID_{APP} - SID_{EFF}$ with the result expressed in mEq/L. By convention, SIG is positive when unmeasured anions exceed unmeasured cations (acidosis) and negative when unmeasured cations exceed unmeasured anions (alkalosis).
Nonvolatile weak acids (A_{TOT})	These are acids that cannot be eliminated by respiration (unlike H_2CO_3 through its conversion to CO_2), and that have a pKa almost equal to the physiological pH of 7.4. Therefore weak acids, as opposed to strong ions, can exist at physiologic pH as dissociated (A^-) or associate with a proton (AH). Weak acids are often referred to as buffers. The concentration of each one of these weak acids, is the sum of its dissociated and undissociated forms: $A_{TOT} = AH + A^-$ The two nonvolatile weak acids with great enough concentrations in plasma to have an influence on acid-base status are albumin and inorganic phosphate, the latter having a minor effect. They provide the remaining charges to satisfy electroneutrality.
Independent variables	PCO_2, SID, and A_{TOT} are the independent variables that control acid-base status, which means that they are causally related to the hydrogen ion, rather than being merely correlated. Normal acid-base status occurs when the independent variables have normal values. Abnormality of one or more of the independent variables underlies all acid-base disturbances.
Unexplained, or unmeasured, or unidentified acid anions (abbreviated as XA^- or UMA)	Includes organic acids not routinely measured, such as lactate (if not measured), and keto acids. They are the main self-unmeasured acids. Additionally, sulfates and other acids may be high in the chronic renal failure setting, and less common organic acids may appear in other scenarios, as in inborn errors of metabolism. Exogenous UMAs may include salicylate, formate, and other drug or toxic-derived acids that can be responsible for acidosis in some patients. All these (XA^- or UMAs) are strong acids.

Table 68–5 Concepts and Parameters Used in the Quantitative Physical-Chemical Approach to Acid-Base Balance: A Summary—Cont'd

Variable	Comment
Partitioned standard base excess (SBE) or BE gap	It is an attempt to combine the approaches of Siggaard-Andersen and Stewart in a kind of physicochemical adjusted standard base excess (SBE), which seeks to quantify the effect of each individual metabolic component of standard base excess, i.e., each component has its own "adjusted" or "partitioned" SBE. The lab-reported SBE, or total SBE (SBE_{TOTAL}) should equal the sum of the BE for each one of the components. More specifically, $SBE_{TOTAL} = BE_{fw} + BE_{Cl} + BE_{alb} + BE_{XA}$, where the effects of free water (fw), chloride (Cl), albumin (alb), and unexplained or unmeasured anions (XA^- or UMAs) were taken in account. The level of XA^- is, of course, unknown. Hence, the SBE for the unmeasured anions is determined from the others. This is termed by some as the "BE gap": BE_{XA} (also abbreviated as BE_{UMA}) = $SBE_{TOTAL} - BE_{fw} - BE_{Cl} - BE_{alb}$. BE_{fw} and BE_{Cl} (sodium and chloride effects), both being strong ions, were later combined in a single BE due to SID (BE_{SID}): BE_{XA} or $BE_{UMA} = SBE_{TOTAL} - BE_{alb} - BE_{SID}$ in which $BE_{ALB} = (42 - [albumin]) \times 0.25$, and $BE_{SID} = [Na^+] - [Cl^-] - 32$. These values are used to solve the equation: BE_{XA} or $BE_{UMA} = SBE_{TOTAL}$ (blood gas analyzer-derived) – $\{(42 - [albumin]) \times 0.25\} - \{[Na^+] - [Cl^-] - 32\}$.

Table 68–6 Classification of Primary Acid-Base Disturbances: Independent Variables-Oriented Approach

RESPIRATORY		**METABOLIC***					
ALTERATION IN P_aCO_2		**IMBALANCE OF STRONG IONS**				**ABNORMAL NONVOLATILE WEAK ACIDS†**	
ACIDOSIS	**ALKALOSIS**	**ACIDOSIS**		**ALKALOSIS**		**ACIDOSIS**	**ALKALOSIS**
Hypoventilation	**Hyperventilation**	**Excess XA^-†**	**↑ Cl^- and/or ↓ Na^+‡**	**↓ Cl^-‡**	**↑ Na+§**	**↑ Alb, ↑ Pi‖**	**↓ Alb, ↓ Pi¶**
↑ P_aCO_2	**↓ P_aCO_2**	**↓ SID, ↑ SIG^-**	**↓ SID, ↓SIG**	**↑ SID**	**↑ SID**	**↑ A_{TOT}**	**↓ A_{TOT}**
Central nervous system depression: brain edema from head trauma, from sedation, etc. Neuromuscular function impairment, damage to efferent nerves or to the muscles of respiration Lungs (airway and alveoli)	Inappropriately set mechanical ventilation parameters, central nervous system disorders, and some psychiatric diseases	**Endogenous**: Lactic acid, ketoacids, inborn errors of metabolism, sulfates, late metabolic acidosis of prematurity, etc. **Exogenous**: salicylate, methanol, ethylene glycol, diethylene glycol, propylene glycol, etc.	**Exogenous Cl load**: Sodium chloride resuscitation, TPN, etc. **Loss of cations from postpyloric losses** without proportional losses of chloride: secretory diarrhea, drainage tubes, ostomies, fistulas. **RTA and drug mediated tubulopathies**: amphotericin B, topiramate, acetazolamide, etc. **Urinary reconstruction using bowel segments**	**Cl responsive**: Gastrointestinal losses of Cl^-: Vomiting, gastric drainage, chloride-wasting acute diarrhea Renal losses of Cl^- and K^+: diuretics, posthypercapnea, certain antibiotics **Cl nonresponsive**: Mineralcorticoid excess: Genetic renal tubular defects of electrolyte transport Drug-induced hypokalemic alkalosis Miscellaneous	Na^+ load (as acetate, citrate, lactate) Ringer solution, TPN, blood transfusion, or Na^+ relative excess (water deficit)	Exogenous administration of phosphates	Nephrotic syndrome, hepatic cirrhosis

The most important weak acid—partially dissociated acid—is albumin, with a minor effect from phosphate.

*Metabolic acidoses arise from conditions that cause either a reduction in the plasma SID or increase in A_{TOT}. Conversely, metabolic alkaloses stem from conditions that produce either a primary increase in the plasma SID or a decrease in A_{TOT}. However, whereas there appears to be complex regulation of SID for acid-base purposes, no such mechanisms are known to control A_{TOT} for this purpose. For this reason, there is no agreement as to whether changes in A_{TOT} should be accepted as acid-base disorders or not, despite their influence on pH.

†Excess of acid anions corresponds to the anion gap acidoses. Includes several organic acids, endogenous and exogenous (e.g., lactate, keto acids, salicylate); also sulfate and other anions in chronic renal failure and unknown anions in conditions such as sepsis. Unlike in anion gap, Pi is not included because it is not a strong ion.

‡Hyperchloremic (non-anion gap) acidosis and hypochloremic alkalosis. The hyperchloremic acidosis occurs either as a result of an increase in chloride concentration relative to strong cations (especially sodium) or because of the absolute or relative loss of cations (water excess) with retention of chloride.

§Excess of cations (Na^+)

‖Not a single cause of acidosis, but is a component of metabolic acidosis in severe extracellular volume loss, such as in cholera.

¶This source of alkalosis is clinically insignificant; the normal value of Pi (~1 mmol/L) cannot decrease enough to have an appreciable acid-base effect.

be regulated independently of PCO_2. Plasma bicarbonate concentration will always increase if PCO_2 increases, but this is not an alkalosis. Therefore the increased bicarbonate concentration is not "buffering" the rise of $[H^+]$, and there will be no change in the SBE. As CO_2 easily diffuses through membranes, when PCO_2 increases there is always tissue acidosis. If PCO_2 remains high, the body will attempt to compensate by altering another independent determinant of pH. The kidneys are the main organs involved in this compensation.[8,39]

The Strong Ion Difference

Strong ion difference (SID) is defined as the charge difference between the sum of all strong cations and the sum of all strong anions. When SID is calculated from direct measurement of serum strong ions, it is termed *apparent* SID (SID_{APP}),[8,31,42,43] with the understanding that more unmeasured (or unmeasurable) ions might also be present (see Table 68-5):

$$SID_{APP} = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - [Cl^-] \quad (11A)$$

In the critical care setting, it is wise to include lactate levels if they are available, because the sicker the patient, the higher the chance that lactate or other strong anions are increased:

$$SID_{APP} = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate^-]) \quad (11B)$$

From actual measurements in healthy volunteers, the normal range of SID_{APP} has been estimated from 38 to 42 mEq/L.[5,8,13,42,44] In critical illnesses, SID_{APP} may be substantially reduced, even when there is no evidence (by the traditional approach) of a metabolic acid-base derangement.[42,45] Gunnerson et al.[42] found in stable critical care patients a SID_{APP} value of 33 ± 5.6 mEq/L, but others have found different values. Thus, in spite of the lack of consensus about what value of SID_{APP} one should expect in an ICU population, it is clear that their SID_{APP} values are different from healthy volunteers' figures.[23,44,45] The tendency of critical care patients to have a lower SID_{APP} is not surprising, given the fact that the positive charge of the SID_{APP} is balanced by the negative charges of the weak acids, $[A^-]$ (albumin and phosphate), and total CO_2. Because P_{CO_2} is usually modified by the body for other reasons (e.g., hyperventilation in a patient that tends to be hypoxemic) and because hypoalbuminemia is the rule rather than the exception in this setting, $[A^-]$ tends to be reduced, and this decrease leads to a reduction in SID_{APP} to keep the normal pH. Thus a typical critical care patient might have a SID_{APP} around 30 to 35 mEq/L, rather than the "usual" range of 38 to 42 mEq/L. If this patient then has metabolic acidosis, the SID_{APP} will decrease further. The lower the baseline of the SID_{APP}, the greater the susceptibility to a subsequent acid load.[42,44,45]

Additional strong anions may become significative (e.g., hyperlactatemia, sulfate, keto acids, anions from Krebs cycle) or appear de novo in disease states (several organic acids from inborn errors of metabolism), or enter the body as medications or toxic substantes (salicylates, certain β-lactam antibiotics, etc.). They may eventually have an influence on the value of SID_{APP}.[44-47] Because it is usually not possible to have a direct measure of $[XA^-]$ at bedside (with the exception of lactate), it is not always convenient to rely only on SID_{APP} to determine the strong ion status. The more ill the patient, the more accurate is this statement. Then, in critically ill patients, it is better to calculate SID to account for electrical neutrality. According to the principle of electroneutrality (Equation 8), blood plasma cannot be charged, so there should be remaining negative charges balancing the "excess" of plasma strong cations in relation to the strong anions, which is the origin of SID_{APP}. These balancing negative charges come from total CO_2 ($\sim[HCO_3^-]$) and from two substances that act as nonvolatile weak acids, that have concentrations in plasma large enough so that changes in them can produce significant acid disturbances: the weak acids (A^-) albumin and inorganic phosphate. Thus SID can be derived, accounting for electrical neutrality, as the sum of HCO_3^- plus the negative electric charges contributed by albumin (Alb^-) and by inorganic phosphate (Pi^-).[13] This calculation of SID is known as *effective* SID (SID_{EFF})[13,48]:

$$SID_{EFF} = [HCO_3^-] + [Alb^-](g/L) + [P_i^-](mmol/L) \quad (12A)$$

where the negative electrical charges contributed by serum albumin and phosphate are as follows:

$$[Alb^-] = [Alb] \times (0.123 \times pH \times -0.631) \text{ and}$$
$$[P_i^-] = [P_i] \times (0.309 \times pH \times [-0.469]).$$

A less-accurate, simplified version of this formula, which assumes a stable pH of 7.4, appears in some publications[31]:

$$SID_{EFF} = [HCO_3^-] + 0.28 \times [Alb^-](g/L) + 1.8 \times [P_i^-](mmol/L) \quad (12B)$$

where *factors 0.28* and *1.8* are, respectively, the negative electric charges displayed by 1 g albumin and 1 mmol of [Phosphate] in plasma at pH 7.4 (0.6 instead of 1.8 if [Phosphate] is in mg/dL).[48]

Human serum albumin must be treated as a polyproteic macromolecule, exhibiting multiple apparent equilibrium dissociation constants corresponding to different classes of amino acids side chains. Accordingly human albumin charge should be expressed as a linear function of the pH. Thus Eqation 12A from Figge et al.[48] is more useful in sicker patients. Actually, SID was derived from a mathematical model with much more complex nonlinear equations, which might be encountered by the clinician while reviewing certain books and articles.[49-51] Constable and coworkers[42,52] have now developed some adaptations for clinical application, which are claimed to be more accurate:

$$SID_{EFF} = 2.46 \times 10^{-8} \times PCO_2 / 10^{-pH} + [albumin(g/dL)] \times (0.123 \times pH - 0.631) + [P_i(mg/dL)] \times (0.309 \times pH - 0.469) \quad (12C)$$

However, this equation is not very easy for the busy clinician to solve, and therefore its clinical application requires access to an Internet-based engine especially designed for calculating the SID_{EFF} (see the section on Strong Ion Gap in this chapter).

SID has a powerful electrochemical effect on water dissociation, and hence on H^+. Both H^+ and OH^- behave as a weak cation and anion, respectively. Because practically all the cations in plasma are strong ions, except for H^+, only H^+ concentration can vary in response to changes in anions. On the other hand, there are several anions that are weak ions,

and thus there are several "options" for anion molecules that can change their charges if cations change.[8,53] As the SID_{APP} increases (strong cations in excess over strong anions) plasma becomes positively charged. Hence H^+, a weak cation, decreases, and pH increases, to maintain electrical neutrality, and alkalosis is produced. On the other hand, if the SID_{APP} decreases (strong anions in relative excess over strong cations), plasma becomes negatively charged, more water is dissociated producing more H^+ for maintaining electroneutrality, and acidosis is produced.[8,40,51]

Changes in SID result from either a relative or an absolute change in strong ion concentrations. A change in free water content produces an alteration in the relative concentration of the strong ions, and hence a change on SID. If, as a result, Na^+, K^+, and Cl^- decrease, the absolute value for SID will decrease proportionately. Thus an excess of free water lowers SID and results in a tendency towards metabolic acidosis. In a similar manner, a free water deficit causes a metabolic alkalosis by increasing the SID through a relative increase in concentration of all strong ions. Relative and absolute changes in sodium concentration primarily result from osmoregulation, and thus they are reflective of changes in free water. The remaining strong cations, potassium, magnesium, and calcium, as they are tightly regulated by the body for other functions (coagulation, membrane excitability, neuromuscular plates, muscle contraction, etc.) do not vary significantly enough to directly cause alterations in acid-base balance.[13] On the other hand, changes in strong anion concentrations are significant to acid-base status. Traditionally, hypochloremia (from gastrointestinal or renal losses) is associated with metabolic alkalosis, and hyperchloremia (e.g., from resuscitation with saline infusion) is associated with metabolic acidosis. Because chloride concentration can be affected by free water content just as is sodium concentration, according to some authors,[31] it is important to take in account alterations in free water content that might exist, and thus Cl^- would need to be corrected based on the sodium concentration:

$$Cl^-_{CORR} = (140 / [Na^+) \times Cl^- \qquad (13)$$

However, the need for this "correction" is not universally accepted (see the section on Merging Traditional and Newer Approaches).

As the SID requires an actual change in the relative concentrations of strong cations or anions, the kidneys are the primary organs regulating SID. As the kidneys can excrete only small amounts of strong ion into the urine each minute, several minutes to hours are required to achieve a significant change in the SID. The control of the kidney is important and precise because every chloride ion that is filtered and not reabsorbed increases the SID. Acid handling of the kidney has traditionally focused on H^+ excretion and the role of ammonia (NH_3) and ammonium (NH_4^+) as hydrogen ion carriers.[9,10,54] Because water provides an essentially infinite source of H^+, its excretion, *per se,* is possibly not as relevant as formerly taught. In fact, the net H^+ excretion by the kidney as water molecules is larger than the excretion as NH_4^+. Therefore the purpose of renal NH_4^+ production is to allow the excretion of Cl^- without the excretion of Na^+ or K^+. Thus NH_4^+ is important to systemic acid-base balance, not for its role as an H^+ carrier or for its direct action in the plasma (normal $[NH_4^+]$ is ~0.01 mmol/L), but because it allows a "safe" excretion of Cl^-.[8,55]

A urinary anion gap (uGap) was described some time ago.[9] This urinary gap has also been designated by some authors[8] as "urine strong ion difference" (uSID):

$$uGap = uSID = [uNa^+ + uK^+] - [uCL^-] \qquad (14)$$

Certainly, sodium, potassium, and chloride are all strong ions, so the name is, at least, functionally correct. What is the value in measuring the uSID? As its serum analogue, the uSID estimates the unmeasured urinary ions. In terms of its amount, the most important unmeasured urinary strong anion (Ur^-) is SO_4^{2-} (derived from the metabolism of sulfur-containing amino acids), whereas the most important unmeasured cation (Ur^+) is ammonium (NH_4^+). In physiologically "normal" conditions, uSID must equal the plasmatic SID_{APP}, that is, 38 to 42 mEq/L. When a strong ion enters the plasma (e.g., lactate, or a chloride load), plasmatic SID will obviously decrease. Normal kidneys will react by increasing their excretion of chloride, thereby decreasing the plasma chloride concentration, while Na^+ and K^+ must be maintained within normal ranges. This is accomplished by increasing the excretion rate of NH_4^+, which is the more efficient way to increase chloride elimination without losing sodium or potassium. The increased excretion of chloride will decrease the uSID.[55]

In addition to the kidney, both the liver and the gastrointestinal tract may have an influence on SID. In the stomach, Cl^- is pumped out of the plasma and into the lumen, reducing the SID (and pH) of the gastric fluids, but increasing the SID (and pH) in the plasma side (alkaline tide), because of the exit of Cl^- to the stomach. However, only a slight change in plasma pH becomes evident, because Cl^- is reabsorbed in the duodenum just as fast as it was pumped out. However, if gastric secretions are removed, either by vomiting or suction catheter, the SID will progressively increase, as will the pH, as a result of Cl^- loss. Although H^+ is excreted as HCl, it is also lost with every water molecule that exits the body. When the body loses Cl^-, a strong ion, without also losing a strong cation, SID is increased; therefore H^+ is decreased and alkalosis ensues. When H^+ is excreted as H_2O rather than as HCl, there is no change in SID, and consequently there is no change in H^+. At present it is not known whether the gastrointestinal tract, the liver, and the pancreas are capable of compensatory actions to regulate strong ion uptake.[9,39]

Strong Ion Gap

In the healthy individual, SID_{APP} and SID_{EFF} are nearly identical, and therefore are adequate estimates of the "true" SID and of the acid-base status.[8,26,28] However, in disease states, this might not be true, as many unmeasured ions (mainly anions) may be present in plasma. Actually, unexplained anions, and in some case unexplained cations, have been found in the circulation of patients with various diseases and in animal models.[46,47,55-58] Blood samples from certain patients often encountered in the critical care setting may contain unmeasured strong ions (e.g., ketones, sulfates, organic acids from inborn errors of metabolism, certain medications, etc.), making the SID_{APP} an inaccurate estimate of the "true" SID or SID_{EFF}. Similarly, patients of this type may have abnormal weak ions (such as proteins) that can make the SID_{EFF} inaccurate as well. In order to address this situation, Jones[59] and Figge[48] independently proposed a similar scanning tool. Kellum and coworkers coined the term "strong ion gap" (SIG) to

name this new tool[60,61]; however, the term is not ideal, since the unmeasured anions creating the 'gap' can be either strong or weak (see Table 68-5).[46,47,62] Nowadays, a modern clinical lab can easily measure all the components of the SID_{APP} and SID_{EFF} equations, including lactate. As a result, XA^- is easily approximated through SIG, which is calculated as follows:

$$SIG = SID_{APP} - SID_{EFF} \quad (15)$$

By convention, SIG is positive when unmeasured anions exceed unmeasured cations (acidosis) and negative when unmeasured cations exceed unmeasured anions (alkalosis). In ideal theoretical conditions, it would be possible for the sum of strong cations and weak anions to cancel each other out, with a SIG equal to zero. In the real world, most SIGs are positive (anions < cations). The use of SIG is advocated in situations in which SID_{APP} and SID_{EFF} are not equal.[28,60,61] SIG different from zero may also be explained, at least in part, by the difference between *ionic molar concentration* (the basis for SID_{APP}) and *ionic activity* itself (the basis for SID_{EFF}). Ionic molar concentration is a measure of the actual number of ions in solution. In contrast, ionic activity is a measure of the effective concentration of electrolytes that results from the charge interaction on dissociated species. The difference between ionic concentration and ionic activity is important because the molar concentration of any electrolyte will not affect the molar concentration of any other electrolyte, but ionic activities are mutually interactive. The principle of electrical neutrality only refers to the latter.[44] Both SID_{EFF} and SIG have been evaluated as prognostic markers in both children and adults. Both indexes have shown good predictive capability in most publications, but there is no universal agreement regarding their clinical usefulness.[13,30,63-70] If one would like to increase the precision of SIG, one should include as many factors as possible in the calculation of SID_{EFF}. However, a theoretical downside is that each additional analyte may increase imprecision,[62] and the calculations become rather cumbersome in the clinical arena. On the other hand, innovative software solutions have been developed. One is the so-called *strong ion calculator*[71,72] and several similar tools available at http://www.acidbase.org.[73] They can be consulted online through computers and handheld devices. This should be the proper solution for the present time albeit not for the future. The SIG has demonstrated good stability in the setting of severe pH stress (<6.85, >7.55), a clear advantage when compared to AG, which has the tendency to increase steadily as PCO_2 falls and when pH rises. The well-known AG increase parallel with pH has been related to altered albumin and phosphate dissociation in extremes of pH.[60]

Nonvolatile Weak Acids (Albumin and Phosphate)

As already explained, there are normally only two substances that act as nonvolatile weak acids with large enough concentrations to influence H^+: proteins (albumin being the most important by far) and phosphates. They provide the remaining charges to satisfy electroneutrality: $SID - (CO_{2TOT} + [A^-] = 0$ (from Equation 12A): CO_{2TOT} is exchangeable with bicarbonate; A^- is the negative charge of anions, mainly albumin and phosphate). It should be noted that A^- is not an independent variable because it changes with alterations of SID and P_{CO_2}. Rather, $A_{TOT} = ([AH] + [A^-])$ is the independent variable, because its value is not determined by any other. However, mathematical and chemical independence does not necessarily means physiologic independence. Although the loss of weak acid (A_{TOT}) from the plasma space is an alkalinizing process, there is no evidence that the body regulates A_{TOT} directly to maintain acid-base balance, as there is no evidence that clinicians should treat hypoalbuminemia as an acid-base derangement.[8] It is not uncommon that critically ill children develop hypoalbuminemia, and hence their A_{TOT} decreases. However, these patients are not always alkalemic. They usually maintain pH, SBE, and HCO_3^- within normal limits, despite the fact that their SID is also reduced. Because changes in A_{TOT} tend to occur rather slowly, the development of alkalemia would require the kidney to continue with its Cl^- excretion despite an evolving alkalosis; as such, this scenario would probably be considered hypochloremic metabolic alkalosis, and SID would increase as a result of the increased loss of anion (and thus from a net increase in strong cations). However, what is observed in hypoalbuminemic patients is the opposite, that is, the SID tends to be decreased in relation to healthy individuals. This means that the kidney has already compensated the alkalinizing effect of hypoalbuminemia by increasing the reabsorption of Cl^-, then increasing plasma strong anion, then reducing the SID. Thus a hypothetical patient with an albumin around 2 g/dL would have an already "compensated" pH through a SID_{APP} around 30 to 32 mEq/L.[8] It is possible to see that changes in these three independently variable quantities, Alb, Pi, and SID, may have additive or offsetting effects on the metabolic acid-base balance. Such offsetting effects may result in normal values of the dependent variables pH, HCO_3^- and SBE, whereas some independent variables are abnormal. In such a case, the condition could not be considered a normal acid-base status, despite the absence of acidemia or alkalemia.

Merging Traditional and Newer Approaches: Is an Integrated Approach Ready for the Bedside?

Despite the apparent differences between the traditional bicarbonate-centered and the physicochemical approaches to acid base physiology, they are complementary. Through PCO_2 analysis and the Henderson-Hasselbalch equation, it is possible to describe and quantify the respiratory side of the acid-base balance, and to describe the metabolic side, which requires a more complex analysis. The traditional tools for approaching the metabolic side, AG and SBE, now have been supplemented by Stewart's physical-chemical concepts, and their performance has been improved.[29-31,67,74-77] In spite of the apparent differences among these three methods, they all share a common theoretical foundation based on the principle of electroneutrality and the role of plasma weak acids. Prompt identification of unmeasured anions is essential in any acid-base analysis in the critical care setting. This was demonstrated recently in a retrospective study, in which the main finding was that mortality associated with strong ion acidosis, either lactic or nonlactic, was significantly higher than that associated with hyperchloremic acidosis (56%, 39%, and 29%, respectively).[31,42,70] Hence, the presence of an elevated amount of unmeasured anions is a predictor of mortality, and the best diagnostic tool for the early detection of the unmeasured anions XA^- should be preferred. A better correlation

of indicators of unmeasured anions has been found between AG_{CORR} (not AG), SIG, and physicochemical adjusted SBE (also known as *partitioned SBE* or *BE gap*). This has been confirmed in several clinical studies.[31,42,75] Pediatric studies have been made using both SIG and partitioned BE.

Corrected Anion Gap

The correction factor required for the AG to account for hypoalbuminemia improves its performance (see the sections on Anion Gap and Anion Gap Corrected), yet some caveats must be understood by clinicians.[34] For its performance to improve, AG_{CORR} needs additional corrections. For example, the classical AG method does not consider the correction of chloride concentration in the setting of altered free water. Thus, hyperchloremic acidosis may go undetected with the AG_{CORR} method, in the setting of a dilutional alkalosis.[31] Hence a corrected value of chloride would theoretically be needed (see Equation 13). However, the very concept of "corrected chloride" is under criticism by some authors, as no other element of the AG equation (nor of SID or SIGs) is corrected for water excess or deficit,[62,78] and because the sodium correction of the chloride assumes a fixed sodium-chloride relationship that does not occur in vivo, as large transcellular shifts of chloride can occur in exchange for bicarbonate (and thus independently of sodium) in different acid-base states.[67,77,79,80] Hence there is no uniform acceptance of the need to use corrected Cl^- values in calculating AG. It is of much greater importance to be aware of the reference values for chloride that are in use in a given setting. On the other hand, in order to avoid [lactate$^-$] influence on AG_{CORR} that could mask the detection of other unmeasured anions, it has been suggested that AG should be corrected not only for albumin, but also for lactate. This is simply derived by subtracting the serum lactate concentration (in mmol/L) from the already albumin-corrected AG (see Equation 10A):

$$AG_{CORRLACT} = \text{Albumin-corrected AG} - [\text{Lactate(mmol/L)}] \quad (16)$$

This albumin- and lactate-corrected AG ($AG_{CORRLACT}$) seems to correlate well with the SIG, as was found by Moviat et al. in a small but precise study ($r^2 = 0.934$, $P < .001$).[57,64,67] In which case, $AG_{CORRLACT}$ may be an easy bedside measurement that could approximate the SIG in critically ill patients, although more clinical experience is needed. Therefore, using the single, uncorrected value derived for AG in critically ill patients may not represent good practice, given the high prevalence of hypoalbuminemia. If AG needs to be determined, albumin and lactate levels should be taken in account, so the proper correction can be made (AG_{CORR} or $AG_{CORRLACT}$).[28-34,42,74,75]

Partitioned SBE, or BE gap, is an attempt to combine the approaches of Siggaard-Andersen and Stewart in a kind of physicochemical adjusted SBE that seeks to quantify the metabolic component of acid-base disorders. Based on an analysis of Stewart's model, Gilfix[81] proposed that only four conditions may create nonrespiratory acid-base disturbances: (1) free water deficit or excess (BE_{fw}), as determined by changes in sodium concentration; (2) changes in chloride concentration (first corrected for the free water effect) (BE_{Cl}); (3) changes in protein charges, mainly albumin (BE_{alb}); and (4) the presence of organic unmeasured anions (BE_{XA}). Therefore to be precise, SBE needs to be "partitioned" (using abridged Stewart equations)[64,82-84] into four "physicochemical" segments, that is, each one of the four conditions requires its own adjusted or partitioned SBE. Gilfix[81] showed that the lab-reported SBE, or total SBE (SBE_{TOTAL}) should equal the sum of the BE for each one of the four conditions:

$$SBE_{TOTAL} = BE_{fw} + BE_{Cl} + BE_{alb} + BE_{XA} \quad (17A)$$

The concentration of unmeasured anions is, of course, unknown. Hence, the SBE for the unmeasured anions is determined from the others. This is termed by some as the BE gap:

$$BE_{XA}(\text{also abbreviated as } BE_{UMA}) = SBE_{TOTAL} - BE_{fw} - BE_{Cl} - BE_{alb} \quad (17B)$$

BE_{fw} and BE_{Cl} (sodium and chloride effects), both being strong ions, were later combined in a single BE due to SID (BE_{SID}) [77]:

$$BE_{XA}(\text{also abbreviated as } BE_{UMA}) = SBE_{TOTAL} - BE_{alb} - BE_{SID} \quad (17C)$$

This approach has received some criticism for small but potentially important inaccuracies derived from the partition of BE, a whole-blood–derived parameter, into plasma compartments, which may generate discrepancies that magnify as PCO_2 deviates from normal, from the exclusion of phosphate as a part of [A_{TOT}]) and from the lack of uniformity in reference values.[62] In spite of these physiologic and conceptual caveats, this approach was first tested in children in a pediatric intensive care unit in 1999, with apparent success.[64] Reported successful applications in mortality prediction and classification of acidosis in several settings, including sepsis and septic shock, cardiac surgery, diabetic ketoacidosis, and others, soon followed.[70,84,85] Unfortunately, lack of standardization in regard to the formulae used for BE partitioning has been a serious inconvenience for the comparison of these studies.[64,77,81-87] In a recent review,[77] an analysis of the four published methods of partitioning SBE showed large and clinically important discrepancies between them. Of all the documented methods for BE partitioning, the one from Taylor et al., [84] in which $BE_{ALB} = (42 - [\text{Albumin}]) \times 0.25$, and $BE_{SID} = [Na^+] - [Cl^-] - 32$ seems to be the most accurate.[31,64,77] These values must be used to solve Equation 17.

In spite of enthusiastic publications, until a consensus is reached, caution must be applied if the clinician chooses to employ the SBE partitioning approach. Nowadays, certainly an "integrated approach" to the metabolic acid-base disorders is the best advice. This should include the PCO_2/bicarbonate approach for respiratory acid-base disturbances and for the initial appraisal of the metabolic problems (bicarbonate and SBE). For these, AG_{CORR} ($AG_{CORRLACT}$ (if [lactate$^-$] is available) and SIG are the best available tools. SBE partitioning (Taylor's method) could also be employed. The advantage of this approach is that it allows the clinician to detect complex mixed acid-base derangements in the critical care setting, which may result in the identification of more patients with major acid-base disturbances. The physicochemical approach yielded the additional diagnosis of metabolic disorders in 33.7% of patients in one single-center adult study.[88] However, it remains unclear if the identification of these additional acid-base disorders translates to new and otherwise unanticipated therapeutic interventions in these patients. It is important to understand the limitations of all the acid-base assessment tools, to identify when perturbations in AG, SBE, or SIG are significant, and when they are not.[31,75,89]

New Insights for Old Problems

The classical acid-base approach yielded some common sense explanations for some acid-base disturbances often seen in the clinical arena. For example, it is said that the metabolic alkalosis seen with severe emesis or nasogastric tube losses is due to a *loss of* H^+; that the metabolic acidosis seen in persistent postpyloric fluid losses is due to a *loss of bicarbonate*; that an acidosis caused by large volume fluid administration is caused by *dilution of bicarbonate*; and that sodium bicarbonate ($NaHCO_3$) therapy corrects metabolic acidosis by contributing bicarbonate ion (HCO_3^-) to the body. These time-honored explanations have been challenged by the new view of acid-base balance, in which water dissociation represents a core principle.[8,35] According to the water-dissociation principle, pH has no direct relationship with any total body direct loss or gain of H^+ or HCO_3^-, but rather reflects the change of SID_{EFF} and A_{TOT} and their effect on water dissociation, the true antecedent of the resultant pH change and concentrations of H^+ or HCO_3^-, that are then merely effects rather than the cause of the acid-base derangements. For example, it is well-recognized that the acute expansion of extracellular volume with normal saline solution (sodium chloride [NaCl] 0.9%) or with any unbalanced synthetic colloid solution (6% hydroxyethyl starch solution or 4% gelatin) may result in hyperchloremic acidosis.[68,82,87,90-97] The understanding of this condition has improved through the physicochemical comprehension of the acid-base equilibrium: saline causes acidosis not through "dilution" of bicarbonate, but rather by its Cl^- content, which decreases the SID and produces an increase in water dissociation and in H^+.[87,90-94] This occurs despite equal amounts of Na^+ and Cl^- in saline solution, because sodium and chloride concentrations are different in plasma. Therefore when large amounts of NaCl in solution are infused, they will have a proportionally greater effect on total body chloride than on total body sodium. The elevated gastric fluid losses seen with severe emesis or nasogastric drainage are the opposite example: loss of high amounts of chloride lead to an increase in SID and to alkalosis.[98] Sodium bicarbonate, by contributing the strong ion sodium (Na^+), increases the SID and hence pH increases; thus it is the sodium, not the bicarbonate, that actually corrects an acidemia (see Strong Ion Difference in this chapter).[99]

In addition to these examples, the water-dissociation–centered model from Stewart may provide new insight into the molecular biology and transport physiology of the renal tubule. For example, renal tubular acidosis (RTA) and Bartter syndrome may be redefined as "chloride channelopathies," rather than disorders of net acid excretion.[49,100] In spite of the theoretical and mathematical certainties and the experimental and clinical evidence regarding the pertinence of the physicochemical approach, there is still no universal agreement about the clinical validity of these explanations, neither about their clinical relevance.[101-103]

The Clinical Problem: Does Abnormal pH Harm?

The clinician has been taught to fear abnormal pH, in particular acidemia. The rationale for such a fear is that every protein in the body contains areas of both positive and negative charge, and hence it is a fact that they are electrochemically sensitive and thus sensitive to the H^+ concentration of their environment. Therefore a decrease or increase in arterial pH might be expected to have important detrimental effects on a host of bodily functions. In the critical care unit, acid-base disorders are often considered more important for what they tell the clinician about the patient than for any harm that is directly provoked by the acid-base imbalance. Several studies[8,104] have reinforced this concept by showing that mortality was more closely related to the nature of acid-base disorders than to the magnitude of metabolic acidosis (estimated by partitioned SBE). Hyperlactatemia, more than the elevation of unmeasured anions (AG_{CORR}, SID, SIG) or SBE, is predictive of a poor outcome. Despite this reliable data from children with shock, it is generally accepted that acid-base derangement itself may cause harm in certain circumstances.[10,14,105] The obvious examples are the extreme conditions of pH (<7.0 or >7.7). It is also important, however, to consider how fast the acid-base derangement is evolving, along with the specific expected consequences of the alteration in specific patients. For example, in a patient who depends on vasopressors, vasodilation due to alkalosis, either respiratory or iatrogenic in origin (overzealous hand bagging of the patient), or metabolic as a consequence of gastric fluid losses caused by a mechanically obstructed jejunum, can be catastrophic. Another typical example is the spontaneously breathing patient with metabolic acidosis, who tries to compensate by increasing minute ventilation; if the patient gets tired, there is the possibility that hypoxemia will develop along with a respiratory acidosis. In such cases, the underlying disorder must be treated, but one must also provide immediate treatment for the acid-base derangement itself.

The main expected physiologic effects of acidemia and alkalemia are as follows. Acidemia initially causes sympathetic and adrenal stimulation, an effect that is counterbalanced, as the drop in pH becomes more and more severe, by a depressed responsiveness of adrenergic receptors to circulating catecholamines.[14,106,107] In isolated animal heart preparations and in isolated human ventricle muscle, there is no doubt that acidosis reduces contractile function.[108-110] The net influence of acidosis in the whole animal and in real patients, however, is more complicated to discern, and depending on the experimental or clinical model, it has been found that acidosis caused myocardial contractility to remain constant, decrease marginally, or transiently rise and then fall.[111] Hence, the whole-body response to acidosis is much less clearly detrimental in real individuals. In many preclinical and clinical studies of patients undergoing permissive hypercapnia, a pH less than 7.2 was well tolerated,[112,113] as it is in children with diabetic ketoacidosis,[114] children and adults with hypercarbia,[115] and those with grand mal seizures.[116] Thus it is now clear that the effect of acidosis may differ according to type, magnitude, and time of onset.[70,115] Three types of extracellular acidosis—inorganic, respiratory, and lactic—may have disparate effects on left ventricular function, as shown in a model of isolated rabbit hearts.[107,117]

Lactic acidosis caused a significant increase in the time to peak left ventricular pressure, while retarding ventricular relaxation. This reinforced the concept that lactate ions have an independent and deleterious effect on myocardial function.[110,117] These findings make sense (with some reserve) when they are extrapolated to clinical grounds. Despite the frequent coincidence of clinical shock and metabolic acidosis, the striking discordance between the clinical course and

outcome of patients with lactic acidosis compared with those who have ketoacidosis or ventilatory failure, suggests that the low pH itself is important but not crucial for the presentation of the hemodynamic collapse of these patients.[42,107,111] Therefore the net effect on ventricular performance, heart rhythm, and vascular tone depends on the relative effects of many, sometimes competing, influences. In general terms, severe acidemia (pH <7.10 according to most, pH <7.20 according to others)[9,10,14,42,107] is associated with decreased cardiac performance that provokes a drop in cardiac output, along with decreased vascular reactivity that manifests itself as arterial vasodilatation and venous constriction. An important effect in the critical care setting is the marked increase in cerebral blood flow associated with acute respiratory acidemia, and its abrupt decrease with respiratory alkalosis.[118,119] When PCO_2 acutely raises in excess of 70 mm Hg, loss of consciousness and seizures can be seen, probably due to the abrupt lowering of intracellular pH. Cultured lung epithelial cells exposed to cyclic stretch similar to that seen with mechanical ventilation produced a lactic acidosis that markedly enhanced the growth of *Escherichia coli*.[120] In contrast, alkalinizing the pH abolished this effect. The demonstration that clinically relevant levels of metabolic acidosis enhance bacterial growth is of concern. However, in patients with acute respiratory distress syndrome (ARDS) under mechanical ventilation and treated with "permissive hypercapnia," the gradual rise of the PCO_2 and the consequent drop in the pH are well-tolerated in general terms, with no significant negative effects on systemic cardiac output, oxygen delivery, or vascular resistances, both pulmonary and systemic.[112,113] Actually, the hypercapnic acidosis has been shown to provide beneficial effects on pulmonary function by interacting with reactive oxygen species, the immune system, and the alveolar-capillary barrier.[119,120] However, recent evidence showed, through a multivariate analysis, that changes in arterial pH, but not in positive end-expiratory pressure (PEEP) levels, were significantly correlated with impaired right ventricular function, whereas the left ventricle was spared.[121] Thus the net effect of respiratory acidemia to the patient, beneficial or detrimental, may be complex to elucidate and must be carefully assessed in each case. Other potential effects of acidemia include endogenous catecholamine, aldosterone, and parathyroid hormone stimulation; insulin resistance; increased free radical formation; increased protein degradation; gut barrier dysfunction; further respiratory depression; decreased sensorium; hyperkalemia; hypercalcemia; and hyperuricemia.[8,14] In regard to the effect of extracellular acidemia on inflammatory response and immune function, recent research has indicated that different acids produce different effects, despite similar extracellular pH.[105]

When associated with severe alkalemia (pH >7.60), both metabolic and respiratory alkalosis lower blood pressure and cardiac output. The potential deleterious effects of this drop in systemic and regional blood flow may be aggravated by the increased oxygen affinity of hemoglobin (shift to the left of the oxyhemoglobin dissociation curve), particularly in acute alkalosis. In chronic alkalemia this effect is counterbalanced by an increase in the 2,3-diphosphoglyceric acid concentration in red cells.[10] Cerebral circulation responds dramatically to alkalemia with marked vasoconstriction. Cerebral blood flow may drop in response to an acute hyperventilation to about 50% of the basal flow, at a PCO_2 of 20 mm Hg. This effect has been used as an emergency management of an impending rise in intracranial pressure but has the risk of producing an excessive drop of blood flow to the most affected areas of the brain, increasing the possibility of ischemia and subsequent cerebral infarction.[119] Because both metabolic and respiratory alkalemia may provoke abrupt transcellular membrane shifts of several electrolytes, mainly potassium and calcium, the net effect is an increase in neuromuscular irritability and excitability. The occurrence of seizures and severe cardiac arrhythmias has been reported if pH is approaches 7.7.[10,98]

The answer to the question "Does abnormal pH harm?" is therefore quite complex; potential harm always exists, but the occurrence of real damage depends on many factors: clinical setting of the patient; type of derangement (metabolic vs. respiratory); timing of presentation (gradual vs. sudden); renal, lung and liver functional status; type of metabolic acidosis; and magnitude (mild, moderate, or severe), for example. On the basis of available evidence, one more question must be asked: does acid pH confer some advantage? The answer here is also quite complex, but should be a cautious "maybe" for mild-to-moderate acidosis in at least two settings: permissive hypercapnia and cardiopulmonary resuscitation.

Blood Gases: Arterial, Central Venous, or Capillary Samples?

Arterial blood gases (ABG) are the usual gold standard for assessing the acid-base status of a patient. However, once the diversity of microcirculations and tissue metabolism throughout the body is taken into account, clinicians must be aware that the value of a single arterial blood pH as a physiological marker is rather limited, even more so if it is recognized that most functional proteins are intracellular.[107,111] There is significant correlation in pH, PCO_2, partial pressure of oxygen (PO_2), SBE, and HCO_3^- between arterial, central venous (VBG), and capillary blood gases (CBG) in healthy volunteers and in stable patients. However, in the presence of hypotension or shock, there is a very poor or no correlation at all with PO_2 with most acid-base parameters.[122] Thus, capillary and central venous blood gas measurements may be useful alternatives to arterial samples when an arterial line is not in place, in particular for acid-base evaluation, as this good correlation extends also to lactate.[123] However, in the setting of severe circulatory failure, such as in decompensated, catecholamine-resistant septic shock and cardiac arrest, significant widening of the arteriovenous differences in pH, PCO_2, and lactate may occur.[8,10,14] Thus, in the presence of severe hypoperfusion, hypercapnia and acidemia at the level of the tissues are better detected in central venous blood than in arterial blood samples because they directly reflect the average acid-base status of the venous blood returning from the tissues, without the influence of pulmonary function. If this is the case, an apparent improvement in the ABG could be observed as a patient slowly recovers from a cardiac arrest, but a simultaneously obtained VBG may reflect a more severe acidosis for a longer time.[124] On the other hand, in the setting of ARDS, the lungs may become important lactate producers, leading to significant higher levels of lactate in ABGs than in the VBGs (also discussed in *Lactic Acidosis* in this chapter). Therefore both arterial and central venous blood samples are needed to assess acid-base status in patients with severe hemodynamic compromise.

Metabolic Acidosis

The classical approach to metabolic acidosis is to classify the disorders as those with either *elevated AG* or *normal AG*, which continues to be a very practical, although not a pathophysiologically-based, classification (see Table 68-4). Using the more physiological independent variables-oriented approach, metabolic acidosis can be classified as due to an *imbalance of strong ions* (decreased SID) or due to the presence of *abnormal nonvolatile weak acids* (increased A_{TOT}).[42] In turn, decreased SID acidosis can be classified in two categories: excess of unmeasured anions (excess XA^-) (which grossly corresponds to the elevated AG acidosis), and as due to an excess of chloride and/or relative or absolute deficit of sodium-water excess (which corresponds to the non-AG acidosis) (see Table 68-6). There appears to be a complex regulation of SID for acid-base purposes, but no such mechanisms are known to control $[A_{TOT}]$ for this purpose. For this reason, there is no agreement about whether changes in $[A_{TOT}]$ should be accepted as acid-base disorders or not, despite their influence on pH.

The classic approach will be used as the main frame for approaching the metabolic acidoses, with additional information, mainly about pathophysiology, from the physicochemical approach.

Elevated Anion Gap Acidoses

These are a group of disorders in which there is the accumulation of an acidic anion. There are three clinically more relevant examples: lactic acidosis, ketoacidosis, and acidosis secondary to the ingestion or administration of some toxin or drug. In children, most of the "toxins" are actually drugs, and most of them provoke lactic acidosis, and will be mentioned under that subheading. Some interesting miscellaneous disorders will be also mentioned.

Lactic Acidosis

The popular classification of hyperlactatemia as type A (*associated with or caused by* inadequate tissue oxygen delivery) or type B (adequate tissue oxygen delivery) is sustained because of its simplicity, despite the fact that it is not necessarily a reflection of the pathophysiologic mechanism underlying this alteration, as considerable overlap exists between types A and B[125] (Table 68-7). Type B was originally further subdivided into types B1, B2, and B3, with type B1 lactic acidoses being associated with an underlying disease (e.g., diabetes mellitus, asthma, malignancies). B2 includes the lactic acidoses due to drugs or toxins (e.g., cyanide, metformin, epinephrine, etc.), and B3 those due to inborn errors of metabolism. Type A seems to be the most frequent cause of lactic acidosis encountered in critical care patients.[10,14,125,126]

Among all metabolic acidoses, lactic acidosis in the ICU unit signals trouble, regardless of patient age.[10,14,126-131] Depending on the source, hyperlactatemia is defined as a lactate level between 2 and 5 mmol/L, whereas lactic acidosis is said to be present when lactate level exceeds 5 mmol/L and the arterial pH is less than 7.35. Yet these definitions are arbitrary. Blood lactate concentration, both in terms of the magnitude and duration, has been shown to correlate with mortality in pediatric and adult patients in many settings, including septic and hemorrhagic shock, neonates receiving ventilation, and during necrotizing enterocolitis, [70,104,126-131] and has been used for the titration of inotropes and blood cell transfusions during early goal-directed therapy for severe sepsis and septic shock,[132] with a performance not inferior to that of the mixed venous saturation. Hyperlactatemia may also be present in children following cardiac surgery.[133] Therefore lactate measurement has become a common attribute in "point of care" blood gas analyzers used at bedside in modern ICUs.[134]

Lactate represents the end product of anaerobic metabolism (i.e., it is a product of pyruvate reduction via the enzyme lactate dehydrogenase and the reduced nicotinamide hypoxanthine dinucleotide/nicotinamide hypoxanthine dinucleotide

Table 68–7 Causes of Lactic Acidosis

I. Type A: inadequate tissue oxygen delivery*
   A. Hypodynamic shock or inadequate resuscitation
   B. Ischemic tissue (bowel or traumatized tissue)
   C. Severe hypoxemia
   D. Severe anemia
   E. Carbon monoxide poisoning
II. Type B: not associated with tissue hypoxia*
   A. Alterations in cellular metabolism
      1. Hypermetabolism
         a. Increased aerobic glycolysis
         b. Increased protein catabolism
         c. Systemic inflammatory response syndrome, sepsis, and severe sepsis
         d. Huge "tumoral" burden
      2. Postcardiopulmonary bypass
      3. Burn injury
      4. Hematological malignancy
      5. End-organ failure (liver, lungs [ARDS])
      6. Diabetes mellitus
      7. Thiamine deficiency
      8. Mitochondrial myopathies
      9. Severe alkalosis/hyperventilation
   B. Increased oxygen consumption
      1. Strenuous exercise
      2. Grand mal seizure, status epilepticus
      3. Malignant hyperthermia
      4. Neurological malignant syndrome
      5. Severe asthma
      6. Pheochromocytoma
   C. Toxins and drugs or their metabolic byproducts
      1. Epinephrine
      2. Propofol
      3. Terbutaline and other β-agonists
      4. Salicylate
      5. Acetaminophen
      6. Cocaine
      7. Ethanol
      8. Methanol
      9. Cyanide (nitroprusside)
      10. Stavudine and other antiretroviral agents
      11. Biguanides (metformin)
      12. Ethylene glycol, glycolic acid, oxalic acid
      13. Others
   D. Congenital
      1. Glucose-6-phosphate deficiency
      2. Fructuose-1,6-diphosphate deficiency
      3. Pyruvate carboxylase deficiency
      4. Pyruvate dehydrogenase deficiency
      5. Oxidative phosphorylation defects
   E. Decreased lactate clearance
      1. Fulminant hepatic failure
   F. D-Lactate
      1. Short gut syndrome
      2. Antibiotic-induced

*Despite the fact that they are grouped under specific categories, significant overlap exists and one single cause may fit under several categories.

[NADH/NAD] cofactor system (see Chapter 74).[126] It derives primarily from skeletal muscle, gut, brain, and circulating erythrocytes, with a production of about 1 mmol/kg/hr. The healthy liver takes up most lactate and recycles it through three primary options: conversion back to glucose (Cori cycle); oxidation back to pyruvate, which subsequently can be oxidized to CO_2 via the Krebs cycle; or transamination into alanine.[126,135] A decrease in oxygen availability at tissue and cellular levels results in an impairment in oxidative phosphorylation, which results in an increase of the intracellular levels of NADH, the cofactor in the conversion of pyruvate to lactate.[126,135] Because of its close relationship with anaerobic metabolism, increased lactate has been largely considered a dead-end waste product of glycolysis due to hypoxia. This mechanism is clear and easily understandable by the busy clinician seeking prompt explanations for what he or she is facing in the critical care unit. However, using blood lactate concentration as evidence of tissue hypoperfusion, hypoxia, and hyperactive anaerobic glycolysis is, at best, an oversimplification.[124] Strong and compelling evidence from living tissue, animal models of hemorrhagic and septic shock, humans during incremental exercise, and humans in septic shock has demonstrated that stimulation of aerobic glycolysis, that is, glycolysis not attributable to oxygen deficiency, occurs not only in resting, well-oxygenated skeletal muscles, but also in experimental and clinical shock. In this setting, skeletal muscle appears to be a leading source of lactate formation as a result of exaggerated aerobic glycolysis through Na^+K^+ATPase stimulation by circulating epinephrine, both endogenous and exogenous.[136-139] Thus it now appears that increased lactate as a result of hypoxia or dysoxia is more the exception than the rule, at least in the hyperdynamic hypermetabolic phase of sepsis, severe sepsis, and septic shock. As there is evidence that lactate is an important intermediate in the process of wound healing and tissue regeneration, it should no longer be considered just an indicator of damage due to hypoxia/hypoperfusion, but as an important intermediary in numerous metabolic processes, a highly mobile fuel for aerobic metabolism through cell-to-cell "shuttles," allowing the coordination of intermediary metabolism in different tissues, and between cells within those tissues. Therefore, in septic shock patients, a high lactate concentration should be interpreted as a marker of the severity of the disease, but it should not be taken as an irrefutable proof of oxygen debt, requiring increases in systemic or regional perfusion or oxygenation to supranormal values.[136,137]

During systemic hypoperfusion, several tissues are a clear source of lactic acid. For example, underperfused intestine can release lactate but will not do so if mesenteric perfusion is maintained.[56] Causes of hyperlactatemia and lactic acidosis are numerous in the critical care setting[10,14,125,126,129,140] (see Table 68-7). Lactate levels may fluctuate in response to exogenous catecholamines, particularly epinephrine,[135-141] which clearly increases lactate levels through stimulation of glycogenolysis and glycolytic flux with a resultant increase in pyruvate production. This effect does not occur with norepinephrine or dobutamine infusions and is not related to decreased tissue perfusion.[135,141,142] Several studies have shown that the lung is a major source of lactate in severe sepsis/septic shock,[142,143] and that decreased lactate clearance by the liver is also an important component of sepsis-associated hyperlactatemia and lactic acidosis.[142,144] Therefore, instead of being caused by cellular oxygen debt, the persistent lactate elevations often seen in patients with sepsis (and in patients after trauma resuscitation) may be a consequence of a much more complex physiological, inflammatory, and metabolic response, the so-called cytopathic or mitochondriopathic dysoxia (see Chapter 74).[135-144] Thus it is not surprising that lactate levels correlate so well with outcome and survival in several subtypes of shock.

Correlation of lactate levels in terms of rate of increase, magnitude of the increase, and persistence represent well-known prognostic markers in both children and adults,[10,14,70,104,126-131] and are used clinically in gauging the response to treatment.[70,126,128,132] Lactic acidosis, more than just the lactate level, correlates with the severity of sepsis and septic shock.[130] Given the complex and incompletely understood metabolism of lactate in sepsis, however, the belief that lactate levels can be accurately used as a stand-alone marker of outcome and mortality is probably naive.[135,136,138] Although the source and pathophysiological interpretation of lactic acidosis are matters of discussion, no question exists about the ability of lactate accumulation to produce acidemia.

Given its pKa of 3.9, which indicates that more than 3000 molecules are dissociated for every one that is not within clinically encountered pH, lactic acid behaves as a strong ion. Therefore the accumulation of lactate (a strong anion), without the addition of an important strong cation such as sodium, will be expected to lower the SID, increase H^+, and decrease the pH. Lactic acidosis would also be expected to be associated with increased adenosine triphosphate (ATP) hydrolysis, another source of hydrogen ions. Because the body can produce and clear lactate rapidly, it functions as one of the most dynamic components of the SID.[135]

Type B lactic acidoses are probably operative in many clinical circumstances where the so-called type A lactic acidoses have traditionally been invoked. Particularly in the patient with sepsis, lactic acidosis may be associated with a variety of coexisting mechanisms.[135-140,142-145] In addition, there likely exists significant overlap between many of these mechanisms, and hence their categorization is a real challenge. A potentially useful method for distinguishing anaerobically produced lactate from other sources is to measure the whole blood pyruvate concentration. The normal lactate to pyruvate ratio is 10:1. Because pyruvate is reduced to lactate during anaerobic metabolism, the ratio of lactate to pyruvate increases. Therefore if this ratio is higher than 25:1, it is considered evidence of anaerobic metabolism.[141] Unfortunately, pyruvate is unstable in solution, and an accurate measurement in the clinical setting is therefore difficult to obtain. Thus the clinical usefulness of this approach is reduced.[126] In many settings, including septic shock and liver failure, the magnitude of the accumulation of lactate does not always account for the whole of the acid-balance derangement observed.[30,70,104,141,145] In fact, the increase in the AG, SID, and SIG observed in severe sepsis is often substantially greater than the actual lactate concentration. This finding has led to the active search for the so-called unexplained or unmeasured anions (abbreviated XA^- or UMA).[8,56,64,70]

Donnan equilibrium alterations due to sepsis-mediated endothelial damage and a switch from a hepatic anion-uptake state to an anion-release state during endotoxemia have been the main proposals for explaining the fact that as much as 15% to 50% of the increased AG, SID, and SIG is not related to the increased lactate.[8,34,56,142-144] Accumulation

of molecules such as succinate, citrate, and formate has also been implicated.[46,47,57,62]

In addition to epinephrine, numerous drugs and toxins encountered in critical care medicine may cause or contribute to increased lactate, with or without acidemia. Likewise, drugs associated with the release of endogenous catecholamines, such as cocaine, can stimulate lactate production.[146] A similar mechanism is advocated in patients with pheochromocytoma.[147] Sodium nitroprusside remains a key vasodilator drug. Because it is metabolized to cyanide, this toxin may accumulate if excessive drug is administered or impaired cyanide clearance occurs, as in the setting of renal failure. In such cases, mitochondrial respiratory chain activity may be inhibited and lactate production increased.[140] Thus, nitroprusside toxicity is usually heralded by the rise in lactate levels, with or without a drop in the pH.[135,140,144] Similarly, propofol toxicity resulting in lactic acidosis, rhabdomyolysis (including the cardiac muscle), and myocardial, renal, and hepatic failure, seems to involve mitochondrial toxicity, which occurs more often with continuous, high-dose, and prolonged infusion. Hence, its designation as *propofol infusion syndrome*.[148,149] Lactacidemia has also been observed with short-term propofol infusions for general anesthesia. It is a highly lethal complication of propofol use.

There are some other conditions in which lactic acidosis or hyperlactatemia may occur. As noted previously, in acute lung injury (ALI) and ARDS, lactate levels may be high even in the absence of shock or sepsis.[143] In ALI/ARDS the lung is an important source of lactate.[143,150] This was first evidenced by higher lactate levels in arterial blood than in the mixed blood obtained from patients with ALI/ARDS, a phenomenon not seen in patients with other serious lung diseases. It has also been shown that the lung is a source of lactate production in patients receiving mechanical ventilation after cardiopulmonary bypass.[151,152] Potential mechanisms of lactate production by the injured lung may include not only the onset of anaerobic metabolism in hypoxic zones, but also direct cytokine effects on pulmonary cells and a stress-induced enhancement of glycolysis and lactate synthesis by both the parenchymal and nonparenchymal cells (e.g., endothelial cells and inflammatory cells infiltrating lung tissue such as macrophages and neutrophils).[143,150-152]

A similar mechanism is operative in wound tissue, the intestine, and the liver in patients with trauma.[144] Hyperlactatemia, lactic acidosis, or both occur in about 80% of cases of acute liver failure.[153,154] Both decreased hepatic clearance of systemically produced lactic acid and increased hepatic production of lactate are involved.[144,153,154] Hypermetabolism associated with lactate accumulation has been observed in organs rich in mononuclear phagocytes, especially the liver and spleen. Murphy et al.[153] found that, in patients with severe hepatic failure, both the liver and intestine behave as net producers of lactate. After transplantation, the grafted liver became a net consumer of lactate as evidenced by a negative lactate gradient between hepatic and portal venous blood. The intestinal bed, however, continued to produce lactate after transplantation, but arterial blood levels dropped back to normal values. Thus, before transplant, hyperlactatemia and lactic acidosis were due both to defective clearance of lactate by the sick liver and to an increased lactate production resulting from hepatic inflammation, in addition to lactate released from the intestine, the lung, and other organs participating in this multisystem problem.[153,154] Cessation of hepatic lactate release after transplantation was the result not only of improved lactate clearance, but also of the removal of a large body of activated, lactate-producing inflammatory cells.

However, this concept of lactate being produced and not cleared by some "damaged" cells has been challenged. So, the bad reputation of lactate as a waste product of a "defective," inefficient, anaerobic physiology, is about to shift. The key concept is to acknowledge that lactate can be considered a waste product when released from one cell, but it becomes a very useful substrate when taken up by another cell, just as in Murphy's findings. In fact, the rate of lactate turnover in vivo in humans is quite similar in order of magnitude to that of glucose, alanine, or glutamine, indicating that lactate has one of the highest recycling rates in the intermediary metabolism. So, increased lactate levels can be viewed as an organic, adaptive response, by which some lactate-producing cells are providing other group of cells with a highly energetic substrate, the so-called lactate "shuttle."[137-139,155]

In status asthmaticus, 1% of patients admitted to a pediatric ICU demonstrated lactic acidosis.[156] This incidence is lower than that reported in adults with acute severe asthma, which is around 25% to 30%.[157] Pathogenesis of lactic acidosis in this setting seems to be multifactorial and includes contributions from lactate production by overwhelmed respiratory muscles, tissue hypoxia, a hyperadrenergic state, and the metabolic effect of pharmacological β_2 agonists.[158-160] Muscle participation does not seem to be so important, however, because lactic acidosis has been described even in patients with asthma under muscle relaxation.[161] Of interest, nonlactic, non-AG acidosis has been found in adults presenting with status asthmaticus. The hypothetical mechanism is hyperchloremia associated with exacerbated chronic hypocapnia, which would decrease SID in hyperventilating asthmatic patients.[162] In head trauma, it is possible to find lactic acidosis in arterial blood samples, both as an effect of polytrauma and hemorrhagic shock and as a manifestation of severe traumatic brain injury. At the regional level, brain tissue acidosis is associated with increased tissue PCO_2 and lactate concentration. These pathobiochemical changes are more severe in patients who died and in those who remain in a persistent vegetative state.[163]

Salicylate intoxication is a special situation in which lactic acidosis may play an important role (see also Chapter 106) Although salicylate toxicity occurs less frequently now than in the past because of the increased use of alternative antipyretics in young children, it must still be considered in therapeutic situations (e.g., rheumatic diseases), as well as in cases of overdose. Salicylates directly or indirectly affect most organ systems in the body by uncoupling oxidative phosphorylation, inhibiting Krebs cycle enzymes, and inhibiting amino acid synthesis. These derangements can result in variable acid-base patterns: respiratory alkalosis, mixed respiratory alkalosis plus metabolic acidosis, or (less commonly) simple metabolic acidosis. Respiratory alkalosis is caused by direct stimulation of the respiratory center by salicylates, leading to hyperventilation and a compensatory alkaluria, with both potassium and bicarbonate being excreted in the urine.[164,165] This first phase may last for several hours after ingestion in adolescents but may be overlooked in young infants. During the next 12 to 24 hours (or less in younger patients), hypokalemia develops and urinary excretion of hydrogen ion starts. This "paradoxic

aciduria" occurs despite continued respiratory alkalosis and aggravates the clinical manifestations because a higher percentage of salicylate in acidic urine remains in the nonionized form, and is reabsorbed from the glomerular filtrate. Soon after the onset of hypokalemia, dehydration and progressive metabolic acidosis develop. The metabolic acidosis is mainly due to lactic acid, but keto acids and other metabolic acids also participate. As metabolic acidosis ensues, more acidic urine is produced, and the plasma salicylate level may be even higher than in early phases because of the inability to excrete the drug in urine. Chronic salicylate poisoning has been described, in which the patient usually has metabolic acidosis and a "pseudosepsis" syndrome similar to some inborn errors of metabolism, with a high rate of permanent organ dysfunctions and mortality.[166]

Elevation of blood lactate, up to the 5 mmol/L level, may be seen in about 25% of human immunodeficiency virus (HIV)-positive patients who receive nucleoside reverse transcriptase inhibitors (mainly stavudine). Most patients remain asymptomatic, but a small proportion of them may present with dyspnea and abdominal pain, as manifestations of lactic acidosis, 3 to 4 months after starting the treatment. If the drug is discontinued and fluids are replaced, the process is reversible. The mechanism appears to involve uncoupled oxidative phosphorylation due to inhibition of DNA polymerase-γ.[167] As a result of the worldwide problem of overweight and obesity, more school-age children and adolescents must receive some treatment for peripheral resistance to insulin. Thus, metformin, the use of which was formerly limited to adult patients, is now being used with increasing frequency in pediatric patients. The incidence of metformin-associated lactic acidosis is low, but it has a high mortality rate when it presents. There is limited experience in pediatrics, but obese children and adolescents who receive metformin in the setting of intercurrent illnesses that may predispose to accumulation of the drug, such as renal function impairment, are at risk of developing metformin-associated lactic acidosis.[135,168] It also may occur as a consequence of accidental ingestion or suicide attempt. Survival depends on the nadir pH and the peak levels of lactate and drug serum concentration. The mechanism involves uncoupling of oxidative-phosphorylation, with acceleration of the glycolytic flux that increases lactate production.

A curious form of lactic acidosis is the so-called D-lactic acidosis. The lactic acid produced by mammals is a levoisomer; some bowel bacteria produce a dextroisomer.[169] D-lactate derived from bacterial fermentation in the bowel lumina may reach systemic circulation and lead to metabolic acidemia, especially if liver function (and thus lactate clearance) is suboptimal. D-lactic acidosis must be considered in patients with a history of intestinal disease who have neurological findings such as confusion and ataxia along with high-AG metabolic acidosis with normal L-lactate levels. Symptoms worsen after high-carbohydrate meals or tube hyperalimentation. In patients with short bowel syndrome, there is not only an overgrowth of bacteria but also accumulation of carbohydrates in the colon. Therefore the development of the syndrome requires some of the following: (1) carbohydrate malabsorption with increased delivery of these compounds to the colon; (2) colonic bacteria flora producing D-lactic acid; (3) ingestion of large amounts of carbohydrate; (4) diminished colon motility, allowing time for bacterial fermentation; and (5) impaired D-lactate metabolism.[169] Treatment focuses on decreasing gut bacteria overgrowth with antibiotics and the avoidance of high-carbohydrate or lactose feeding. Some studies have advocated the use of probiotics for treating and preventing this problem,[170] but the reports are conflicting, as some cases of encephalopathy associated with D-lactic acidosis have been probably related to their use in patients with short bowel syndrome.[171]

Ketoacidosis

This is another common cause of increased AG acidosis. Ketones are formed by beta oxidation of fatty acids, a process that increases substantially in insulin-deficient states. In the pediatric intensive care setting, this is most often seen in patients with diabetes mellitus with overproduction and underutilization of acetone, β-hydroxybutyric (β-OH-B) and acetoacetic acids (ketone bodies), that accumulate in plasma (see also Chapter 78). This problem is exacerbated because of the glucosuria-mediated diuresis and intravascular volume contraction. Ketoacidosis is also seen in various inborn errors of amino acid and organic acid metabolism, and a mixed ketoacidosis and lactic acidosis is seen with glycogen storage disease type I (glucose-6-phosphate deficiency) (see also Chapter 76). The urinary dipstick for ketones uses a nitroprusside reagent; hence it detects acetoacetate but not β-OH-B. If a patient with DKA develops shock, β-OH-B:acetone may be produced in ratios up to 3:1. Hence, the urine will mistakenly appear to have few ketones, and ketone concentration may paradoxically rise as perfusion improves and the patients gets better.[172-173] The capillary blood determination of β-OH-B is a better alternative for treatment guidance.[173,174] As the renal threshold for the ketone bodies is low, ketones are readily filtered, with no reabsortion mechanism; accordingly the kidneys can eliminate a significant amount of ketones. This loss can shift the AG, which may appear less than expected because of the anions eliminated though the urine, with renal retention of chloride and bicarbonate. The picture can be even more complicated if hypocapnia from hyperventilation is present. Therefore AG (even corrected AG) may not be very useful in severe cases. SIG may provide more information in these more complicated situations.[60] Another form of ketoacidosis, the so-called *alcoholic ketoacidosis,* an uncommon syndrome in acute ethanol drinkers, may be a scenario with which pediatric and adolescent patients occasionally present in the PICU. This presentation is more frequent among patients with chronic ethanol intake and liver disease, and usually occurs after a period of heavy drinking, in association with reduced food intake. Alcoholic ketoacidosis is quickly responsive to fluid administration, with faster resolution when dextrose and saline are infused together.[175]

Toxic Compounds that Directly Provoke Acidosis

Alcohol-related intoxications, including methanol, ethylene glycol, diethylene glycol, and propylene glycol, may present with a high anion gap metabolic acidosis, with a decrease in serum bicarbonate and a rise in the osmolality, with an increased serum osmolar gap (i.e., difference between calculated and measured osmolality) (see also Chapter 106).

The acidosis and cellular dysfunction are direct effects of the metabolites of these substances, while the parent compounds are associated with an increase in serum osmolality. These are rather infrequent problems in the pediatric age group, but adolescents who ingest alcohol or illicit drugs (including inhalants), or who attempt suicide, are potential victims.[175] Younger ages are occasionally affected. Clustering of such cases usually uncovers locally prepared antipyretic (paracetamol elixir) contaminated with diethylene glycol. Similar cases have been reported for propylene glycol. The clinical presentation depends on the total dose of the adulterated medication received, and hence ranges from mild subclinical poisoning to unexpected and rather sudden onset of high anion gap acidosis, renal failure, and encephalopathy, with elevated mortality and a high probability of neurologic sequelae.[176] The intoxication is best treated with supportive critical care including proper alkalinization and early continuous hemofiltration or hemodiafiltration. In some areas a competitive inhibitor of alcohol dehydrogenase (4-methylpyrazole [or fomepizole]) is available for use in ethylene glycol and methanol poisoning, but extracorporeal removal should also be utilized. Fomepizole is possibly useful also in diethylene glycol and propylene glycol intoxications. For methanol and ethylene glycol, ethanol infusion is an alternative competitive inhibitor of the alcohol-dehydrogenase enzyme.[175,177]

Other Forms of Metabolic Acidosis Associated with an Increased Anion Gap

The pediatric critical care physician should be aware of a condition often called *late metabolic acidosis of prematurity*.[178] Although its incidence is greater in the premature infant when compared with that in the term infant (20% compared with 5%), the lesser capacity of not fully developed renal tubules to excrete H^+ and Cl^- and to concentrate urine is a fairly common situation during the first month of life. This level of renal tubular development is adequate for the breastfed infant, but if the protein intake or solute load is excessive, the renal capacity may be exceeded and a metabolic acidosis may develop. This is particularly true during periods of stress. In the setting of renal disease, the clinician must anticipate the occurrence of metabolic derangements. When chronic renal insufficiency develops, hyperchloremic metabolic acidosis—a non–anion gap acidosis—may initially occur because of impaired ammonium (NH_4^+) generation. When the glomerular filtration rate falls below 20 mL/min, the kidneys are incapable of excreting fixed acids. The resulting accumulation of sulfates among other acids may increase the AG. These acidoses are usually mild, producing an excess AG of approximately 10 mEq/L. A mixed metabolic acidosis (high-normal AG mechanism) is not uncommon in this setting.[10,172] If the patient has sepsis or another condition associated with hypermetabolism, however, the rate of acid generation increases and the acidosis may become rather severe. The SID decreases and, because of the lack of renal compensation, some intervention must be taken. Patients who do not yet require dialysis and those who are between their dialytic processes are often administered $NaHCO_3$ (provided there is no hypernatremia) or sodium potassium citrate.[179] In cases where bicarbonate is contraindicated, a dialytic process is in order.

Hyperchloremic Acidoses: The Non–Anion Gap Metabolic Acidoses

In the classical view, hyperchloremia was considered an epiphenomenon of the drop in bicarbonate concentration, due to its *abnormal loss* through urine or stools (see Table 68-4). The rise in chloride concentration is responsible for maintaining a "normal" anion gap, in spite of the drop in bicarbonate levels, i.e., a "non–anion gap" acidosis is produced. When bicarbonate is consumed to buffer an "acid load," hyperchloremia is not produced, because there are other anions emanating from the acid load that will preserve electroneutrality as bicarbonate falls. In this case, the anion gap increases, because of the presence of these "new" (and unmeasured) anions.[9,10,54] As new biological evidence accumulates, this physiological interpretation is increasingly being challenged, and a more central role for chloride is being emphasized.[55,64] Accordingly, the physiological shift is moving from kidneys that directly sense and regulate H^+ to kidneys that react to Cl^- balance, and therefore directly control the independent variable SID in acid-base regulation. This is supported by new insight in the physiology of several ion-transporters of the renal tubules.[51,54,55,100,180-183]

Thus, hyperchloremic acidoses occur either as a result of an increase in chloride concentration relative to strong cations (especially sodium) or because of the loss of cations with retention of chloride (see Table 68-6). When the pH drops, the normal response by the kidney is to increase chloride excretion as ammonium chloride (NH_4Cl), in order to increase the SID and raise back the pH. Thus, the role of the formation of ammonium (NH_4^+) and its eventual tubular excretion, is not for the elimination of H^+, but to allow Cl^- excretion without losing sodium or potassium. Failure to do so identifies the kidney as the problem,[10,49,172] as in renal tubular acidosis.

There are four main causes of non–anion gap acidoses: (1) exogenous chloride loads, such as saline boluses, parenteral nutrition; (2) loss of cations from the lower gastrointestinal tract without proportional losses of chloride, as in secretory diarrhea, also seen in conditions in which loss of alkaline small bowel, biliary, or pancreatic secretions is present (such as drainage from ostomies, tubes, fistulas); (3) renal tubular acidoses and drug-mediated tubulopathies; and (4) urinary reconstruction using bowel segments.

Exogenous Chloride Load

In the critical care unit, mandatory therapeutic interventions are frequently associated with hyperchloremic metabolic acidosis. The more common of such interventions are rapid infusion of isotonic saline (0.9% NaCl) and the infusion of parenteral nutrition. As stated before, the classical explanation for acidosis following saline administration was the so-called *bicarbonate dilution*. This mechanism probably plays a role in certain conditions.[80,101] Healthy, metabolically stable individuals, such as scheduled surgical patients, exhibit plasma SID around 40 mEq/L, while in critically ill patients SID is typically ~30 mEq/L (see Strong Ion Difference in this chapter). On the other hand, the SID of normal saline is 0 mEq/L, because sodium and chloride are both strong ions. Therefore, intravenous administration of 0.9% NaCl will necessarily decrease plasma SID, creating a strong ion acidosis, as long as such an infusion does not cause a change in PCO_2 or albumin or phosphate concentrations. The magnitude of the decrease in plasma SID when 0.9% NaCl is administered

is dependent upon the relative volumes of the extracellular space and the infused normal saline, and the speed of the infusion. Therefore, hyperchloremic acidosis should be expected whenever large volumes of normal saline are rapidly administered, such as in fluid boluses for treating shock, or during surgical procedures under anesthesia.[82,87,93,96] Even the acid-base status of disorders in which one or more unmeasured anions is clearly participating, such as septic shock (lactate) and DKA (ketones), has been shown to be influenced by the chloride supplied through resuscitation fluids,[84,87,92,94] and one recent report warned about hyperchloremic acidosis from saline resuscitation slowing the recovery of children with DKA.[184] This concern is one example of the usefulness of the "partition" of the SBE (see Merging Traditional and Newer Approaches in this chapter).[77,84]

In one study of 81 children with meningococcal sepsis, metabolic acidosis was common and prolonged (persisted for 48 hours), but the pathophysiology changed from one of unmeasured anions at admission to predominantly hyperchloremia-associated by 8 to 12 hours. Thus most of the time the acidosis was iatrogenic.[87] Development of hyperchloremic acidosis was related to the amount of chloride received during intravenous fluid resuscitation. From this and other similar studies, there is little doubt, if any, about the relationship between normal saline resuscitation and the development of hyperchloremia and acidosis (not necessarily acidemia), whatever the underlying mechanism.[87,101,183,185] However, it is not clear whether this hyperchloremic acidosis is really detrimental, implying that hyperchloremic acidosis due to exogenous administration of normal saline might be not an important issue.[65,69,94-97,185] Actually, in a group of 97 children (mean age, 57 months) evaluated in their postoperative period following open cardiac surgery, the occurrence of hyperchloremia was associated with reduced requirement for epinephrine therapy; thus the authors suggested that hyperchloremic metabolic acidosis is a benign finding that should not lead to the escalation of the hemodynamic support, hence the importance of its recognition.[82]

Interestingly, hypoalbuminemia (an alkalinizing force) was associated with prolonged length of stay in the critical care unit. In a recent review of laboratory, animal, human volunteer, and patient investigations focused on the physiological effects of hyperchloremia and acidosis,[95] it was concluded that there is a trend in scientific evidence indicating that both hyperchloremia and hyperchloremic acidosis have subtle, but potentially significant physiological and clinical undesirable effects. Although the acidosis is often quoted as the cause, it is unclear whether this is true or whether the high chloride levels should be of concern. Most of the clinical studies have revealed trends but not statistical significance toward a worse outcome in patients with hyperchloremic acidosis.

Hence, the conclusion so far is that the effects of hyperchloremia, hyperchloremic acidosis, or both are unlikely to influence outcome for most patients. However, given that hyperchloremic acidosis is often iatrogenic and is associated with some proven morbidity (increased length of stay in intensive care, delayed recovery of DKA, higher incidence of nausea/emesis in postoperative period, etc.,[42,184] it should be avoided whenever possible.[42,95,186] How can this task be achieved? Several groups have suggested and assessed the use of the so-called *balanced* fluids, that is, fluids with SID nearer to the SID of human plasma.[42,93,180,186,187] However, the results are still inconclusive. Besides, at least one prospective study in adults has suggested that the amount of fluids administered, rather than the types of fluids, had the stronger effect on the changes in base excess.[188] Meanwhile, the best approach is to keep in mind the potential hazard of hyperchloremic metabolic acidosis, especially in patients with previously known renal or liver dysfunction, with shock, and in surgical patients needing a large amount of intraoperative saline for resuscitation.[189] Intraoperative monitoring of serial chloride determinations has been suggested in order to unmask or exclude hyperchloremia as a cause of acidosis, undetectable through SBE alone.[96] Use of SBE-partitioning formulas to disclosure the effects of chloride on the acid-base status (see Equations 17A to 17C and Merging Traditional and Newer Approaches in this chapter) may be useful.

With regard to parenteral nutrition formulas, they contain weak anions such as acetate, in addition to chloride, and thus they are buffered. However, if an insufficient amount of weak anions is provided, plasma Cl^- will increase, SID decreases, and acidosis may result.[97]

Postpyloric Gastrointestinal Fluid Losses

The gastrointestinal (GI) tract, liver, and pancreas can be envisioned as a giant ion exchanger organ. Through all the sequential segments of the GI tract, distinct groups of ion transporters and channels interact with one another to determine the electrolyte content, pH, and volume of the fluid in the gut lumen. The main transport system is driven primarily by Na^+/K^+-ATPase across the basolateral membrane of the epithelial cells, with the participation of several key apical membrane electrolyte transporters, including Cl^-/HCO_3^- and Na^+/H^+ ion exchangers and the so-called cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel.[190] Large masses of cations and anions traverse the specialized epithelia of the gut every day. This transport is adjusted for achieving an efficient absorption of dietary components rather than for acid-base homeostasis.

Under normal conditions, only a small amount of alkali (30 to 40 mmol/day) is lost in the stool, so kidney and lung compensation is generally not problematic. However, disruption of the normal gut function can provoke disorders that vary from severe acidosis (mostly postpyloric losses) to severe alkalosis (prepyloric losses, congenital chloridorrhea), depending on the segment of the GI tract affected and the nature of the losses that ensue.[190] For acid-base and electrolyte abnormalities to occur in diarrheal diseases, the volume of fluid lost must be large enough to overcome the kidney's ability to adjust excretion to maintain acid-base balance. With large losses, any form of diarrhea may lead to a significant fall in extracellular fluid volume, reducing the glomerular filtration rate (GFR) and limiting the ability of the kidneys to compensate for the problem. Secretory diarrheas (cholera, enteropathic *E. coli*, rotavirus, and other infectious diarrheas) most commonly produce this picture, with the typical presentation of hypovolemia, hypotension, acute renal failure, hyperchloremic metabolic acidosis (lost stools are usually rich in sodium, potassium, and bicarbonate, so SID decreases), and hypokalemia. If the hypovolemia and hypotension are not corrected, lactic acidosis superimposes, as a result of tissue hypoperfusion. Then, the AG_{CORR} is initially normal; it may increase gradually, but more frequently will remain normal in spite of lactacidemia. Hence it is always wise to monitor lactate levels.

The mechanism of the acidosis is well defined for cholera diarrhea, but is less defined for other pathogens. *Vibrio cholerae* produces a toxin that increases cAMP levels in intestinal crypt cells, producing a sustained activation of the apical membrane CFTR Cl^- channel leading to excessive Cl^- secretion into the ileum and colon. This increased chloride secretion in turn stimulates the apical Cl^-/HCO_3^- exchanger, increasing bicarbonate concentration in stools and increasing paracellular Na^+ and water entry, resulting in high-volume losses that contain a large amount of HCO_3^- as well as Na^+, Cl^-, and K^+. Replacement of the lost fluid and electrolytes can be achieved with oral solutions (100 mL/kg body weight of a solution containing 60 to 90 mEq/L of sodium).[191] In case of excessive losses or emesis, vigorous intravenous volume repletion must be implemented. Diarrhea due to laxative abuse can be seen in bulimic or anorexic adolescents, and usually does not associate with acid-base derangements. Of course, if excessive diarrheal losses occur, then metabolic acidosis can occur, as with any severe diarrhea.[190]

Both biliary and pancreatic secretions have an alkaline pH. When pancreatic or biliary drainage is required after surgery, the volume is usually low, so despite the loss of a $NaHCO_3$-rich fluid, significant metabolic acidosis does not occur. On the rare occasions in which these drainages are excessive (volume usually around 30 mL/kg/day or greater), metabolic acidosis will develop and be perpetuated by concomitant volume depletion. Repletion with saline solutions is enough for the replenishment of cations, mainly sodium, which restores SID value. Bicarbonate administration is equally effective.[190] Patients with well-functioning ileostomies usually adapt to the obligatory extra fluid loss through subtle changes in salt and water intake, as well as changes in urine volume and electrolyte and acid excretion. If the ileostomy drainage abruptly increases, the resultant salt and water losses can easily lead to clinically significant volume depletion. In this setting, the development of metabolic acidosis is the rule, because HCO_3^- in ileostomy fluid is usually higher than in plasma, causing disproportionate sodium and alkali loss. Hyperkalemia is usually present with this metabolic acidosis, reflecting the fact that K^+ is not secreted in the ileum and therefore the losses contain little K^+. In addition, renal K^+ excretion is impaired by the volume depletion. A similar problem can be seen in patients who have shortened small intestine connected to the colon for any reason, with the additional possibility of D-lactic acidosis (see section on D-Lactic Acidosis in this chapter).

Renal Tubular Acidoses and Drug-Mediated Tubulopathies

RTA comprises a group of disorders characterized by a low capacity for net acid excretion (NAE) and persistent hyperchloremic metabolic acidosis, with normal anion gap and normal or minimally affected filtration rate (GFR). On the basis of functional studies, RTA has traditionally been separated in three main categories: (1) proximal RTA, or type 2; (2) distal RTA, or type 1; and (3) hyperkalemic RTA, or type 4. Sometimes a fourth kind is recognized: combined proximal and distal RTA (mixed RTA), or type 3.[192] Type 4 RTA is of special interest in the critical care setting, as the hyperkalemia may be triggered by some drugs used in intensive care units, such as angiotensin-converting enzyme inhibitors, heparin, trimethoprim, α-adrenergic agonists, β-adrenergic antagonists, digoxin, and others. The classical acid-base approach states that metabolic acidosis arises from a lack of urine excretion of protons (hydrogen ions) or an excessive loss of bicarbonate due to a variety of tubular disorders.[100,192] Molecular studies have identified genetic or acquired defects in transporters of protons and bicarbonate in most varieties of RTA.[192,193] This classical physiological view has been challenged by the physicochemical acid-base interpretation, and is supported by the fact that these transporters are also involved in Cl^- and Na^+ transport through membranes, and that at least certain cases of RTA are clearly associated with primary defects in electrolyte transporters alone.

In a recent study, 12 children with alkali-treated distal RTA were compared to healthy controls. Both groups received a load with hypotonic saline (0.45%), but only the RTA patients developed hyperchloremia and metabolic acidosis, which was shown to be associated with high total and high distal fractional absorption of chloride. Urinary excretion of bicarbonate did not correlate with changes in either blood pH or plasma bicarbonate concentration. Thus, renal tubular avidity for chloride was indeed increased in RTA.[100,182,194] Therefore, tubular transport mechanisms determine the excretion of strong ions, Na^+, K^+, and Cl^-. This determines the balance of the concentration of SID, both in the extracellular compartment, dominated by Na^+ and Cl^-, and in the intracellular compartment, dominated by K^+. SID determines pH, and by way of partly characterized sensor and effector mechanisms, must feed back to the tubular ion transport complexes. Thus, acid-base homeostasis is directly regulated by electrolyte transport in renal tubules, and hence hydrogen and bicarbonate movements reflect ion balance requirements imposed by physical chemistry.[49,100,182,194] This supports the notion that NH_4^+ is more related to the elimination of Cl^- without loss of Na^+ or K^+, rather than in titrating urinary H^+.[49,182,194] According to the physicochemical approach, the underlying defect in all types of RTAs is an inability to excrete chloride in proportion to sodium, although the transporter involved depends on the specific type of RTA.[100,182,194] In the critical care setting, the presence of RTA may complicate resuscitation fluid management and acid-base balance. Previously unknown RTA must be suspected whenever the clinical condition of a given patient does not improve as expected with the proper therapeutic interventions. Treatment largely depends on whether there are losses of sodium that can be replaced with $NaHCO_3$ or whether the kidney will require mineralocorticoid replacement. A more detailed discussion of RTA is beyond the scope of this chapter. It is worth mentioning, however, that urinary AG (uGAP) = $[uNa^+ + uK^+] - [uCl^-]$,[195] more recently known as "urine strong ion difference" (see Equation 14 and Strong Ion Difference in this chapter),[9,55] is useful as a part of the diagnostic workup of a patient with hyperchloremic acidosis. If it is negative ($uCl^- > uNa^+ + uK^+$), it suggests either GI bicarbonate loss, acute infusion of a high volume of saline isotonic fluid (NaCl 0.9%), or a proximal RTA, which will require additional functional tests for diagnostic confirmation once the patient is discharged from intensive care. On the other hand, if the uGAP is positive ($uCl^- < uNa^+ + uK^+$), it suggests the presence of a distal renal defect. Additional functional tests will allow one to identify distal RTA, hyperkalemic distal RTA, or type 4 RTA.

Also of importance to the intensivist is iatrogenic RTA caused by the nephrotoxicity of amphotericin B aminoglycosides and other drugs. Kidney alterations due to amphotericin

B include decreased glomerular filtration rate, distal tubulopathy with urinary loss of potassium and magnesium, RTA, loss of urine concentration ability, and sometimes Fanconi syndrome. Nephrotoxicity is related to treatment duration, schedule, cumulative dosage, and combination with diuretics and other nephrotoxic drugs (aminoglycosides, cyclosporine, tacrolimus, cisplatin, ifosfamide). Each dose increment of 0.10 mg/kg/day has been found to be associated with a 1.8-fold increase in the risk of nephrotoxicity, while infusion rate and concentrations are not related.[196] The mechanisms involved in nephrotoxicity include the deoxycholate vehicle for amphotericin B, reduction in renal blood flow and GFR, increased salt concentration at the macula densa, interaction of amphotericin B with ergosterol in the cell membrane, and apoptosis in proximal tubular cells and medullary interstitial cells. Salt loading, with daily sodium intake higher than 4 mEq/kg/day, is the only measure proven by a controlled prospective study to ameliorate amphotericin B nephrotoxicity in humans, including extremely low-birth-weight infants.[197] Proper hydration must be assured with 10 to 15 mL/kg of normal saline prior to administration of the drug. Lipid formulations of amphotericin B (liposomal, lipid complex, colloidal dispersion) are indicated in all children receiving other nephrotoxic drug, with already reduced GFR, or with previously known adverse effects to regular amphotericin B. Total dose of 35 mg or more, chronic renal disease, concomitant use of cyclosporine or amikacin, and male sex have been identified in adults as risk factors. Patients with more than two risk factors demonstrated an incidence of moderate-to-severe nephrotoxicity of 29%.[198]

Trimethoprim-sulfamethoxazole is another antimicrobial that has been related to RTA and hyperchloremic metabolic acidosis.[199] Topiramate, one of the "new" antinconvulsant drugs, has been reported to cause hyperchloremic metabolic acidosis in pediatric and adult patients. Topiramate inhibits the enzyme carbonic anhydrase, and thus a type 3 or mixed RTA is produced, as it impairs both the normal reabsorption of filtered bicarbonate by the proximal renal tubule and the excretion of hydrogen ions by the distal renal tubule. This topiramate-induced RTA can present acutely with requirement for emergency or critical care, or chronically, producing growth retardation, nephrolithiasis, and osteoporosis.[200] Acute presentation includes drowsiness/lethargy, dizziness/vertigo, agitation, confusion, and nausea/vomiting. These manifestations, in a patient receiving topiramate, should prompt the clinician to evaluate acid-base and electrolyte balance. A significant decrease in HCO_3^- has been documented in roughly 50% of patients receiving topiramate, although the number of affected individuals increases with escalating doses. To date, however, the relationship between bicarbonate concentration and topiramate dosage has not been adequately defined. Depression of bicarbonate levels is usually mild, with serum HCO_3^- typically between 20 and 10 mEq/L. Severe, acute HCO_3^- decrements to values less than 10 mEq/L have rarely been documented. In this setting, AG is normal and is associated with alkaline urine, positive uAG, low urinary citrate excretion, and β_2-microglobulinuria. If the acidosis requires acute correction, or the RTA is persistent, topiramate should be discontinued.

Another rare cause of normal AG metabolic acidosis that may be seen in the ICU is acetazolamide, a carbonic anhydrase inhibitor used occasionally to decrease cerebral spinal fluid production and, more frequently, to stimulate renal bicarbonate wasting.[201] This drug impairs hydrolysis of H_2CO_3 to CO_2 and H_2O, resulting in a decrease of renal HCO_3^- reabsorption. It has recently been described that, both in humans and in an animal model, acetazolamide can produce severe lactic acidosis with an increased lactate-to-pyruvate ratio, ketosis with a low β-hydroxybutyrate-to-acetoacetate ratio, and a urinary organic acid profile typical of pyruvate carboxylase deficiency.[202] This "acquired enzymatic injury" stems from the inhibition of mitochondrial carbonic anhydrase type V, which provides bicarbonate to pyruvate carboxylase and can produce Krebs cycle inhibition. Some of these patients improved dramatically after packed red blood transfusion; the improvement was likely related to the citrate anticoagulant.

Urinary Reconstruction Using Bowel Segments

Children with irreversible lower urinary tract dysfunction due to developmental abnormalities involving the genitourinary (GU) system, neurogenic or myogenic bladder, etc., may require urological surgical procedures for their management, including continuous urinary diversion and enterocystoplasty. Various techniques and bowel segments can be used depending on the clinical situation. The GI tract is a relatively poor substitute for urothelium, and its semipermeability allows nonphysiologic fluid and electrolyte absorption leading to metabolic abnormalities.[203] The significance of these problems is related to the portion of the GI tract used and to the length of time the urine is exposed to the bowel surface. If, in addition, the loss of some portions of the GI tract results in complications such as chronic diarrhea, there may be further metabolic consequences. Jejunal substitution is associated with uniform and profound metabolic instability resulting in hyponatremic/hypochloremic/hyperkalemic acidosis, clinically manifested by nausea, vomiting, anorexia, and muscular weakness. When ileum or colon is used for the GU reconstruction, hyperchloremic/hypokalemic metabolic acidosis may present. Clinically, this may produce weakness, anorexia, vomiting, and Kussmaul breathing, and may progress to coma. In the less severe cases, a chronic metabolic acidosis may go undetected, resulting in growth retardation. In a recent series report, 41% of 44 children required constant prophylactic alkaline replacement,[204] although older reports documented hyperchloremic metabolic acidosis in 68% of ileal conduits, and acidosis being a major problem in 18% of patients with enterocystoplasties.[203] Thus, although acute decompensations may require intravenous correction of the acidosis with bicabornate and/or fluid loads in the emergency department or PICU, most cases will maintain electrolyte balance with lifelong alkalinization with oral bicarbonate, sodium citrate, or citric acid solutions.

Treating Metabolic Acidosis

How is metabolic acidosis treated? Should metabolic acidosis be treated? This topic remains controversial, except in regards to basic approach: treat the underlying cause. Certain acidoses have specific therapies, such as insulin and fluids for the patient with diabetic ketoacidosis, $NaHCO_3$ and citrate for patients with the classic distal RTA, and fomepizole for methanol intoxication. These specific cases are beyond the scope of

this chapter. The following discussion focuses on lactic acidosis, unless otherwise mentioned.

Sodium Bicarbonate

$NaHCO_3$ administration has long been the standard therapy for metabolic acidosis, including lactic acidosis.[107,172] There is consensus regarding the advantages of alkali and sodium bicarbonate therapy in normal anion gap acidosis. However, in the presence of high anion gap acidosis, especially lactic acidosis (in shock and cardiopulmonary resuscitation) but also in diabetic acidosis, there exists negative evidence regarding the safety and efficacy of sodium bicarbonate use . Justification for the persistent use of bicarbonate comes from a variety of sources, many based more on philosophy than on science.[9,107,111,172,205,206]

It seems self-evident that adding bicarbonate to acidic blood will raise the pH. However, the reality is significantly more complex. Consistent with Equations 11A and 11B, administration of $NaHCO_3$ increases the SID (which tends to raise the pH) because sodium is a strong cation and bicarbonate is a weak anion; however, in agreement with Equation 3, it is an anion that rapidly converts to carbonic acid and then to CO_2, which tends to lower the pH.[111,207,208] Therefore $NaHCO_3$ may increase arterial pH if, and only if, alveolar ventilation is not limited.[107,111,205-212] Although the risk of paradoxic intracellular acidosis after bicarbonate administration is not negligible, this neither necessarily occurs nor it is always detrimental to the cell.[107,111,208,209] The final effect of $NaHCO_3$ on intracellular pH depends on changes in PCO_2 in the medium bathing the cells, which are influenced by the extracellular nonbicarbonate buffering capacity.[208] These cells are usually depressed in the critically ill patient in whom $NaHCO_3$ is administered.

In addition, bicarbonate administration may promote metabolic reactions that may themselves alter not only PCO_2, but also the total concentration of weak acids and the SID. In fact, it has been documented that bicarbonate can increase the production of lactic acid in both animals and humans.[111] Mechanisms to explain this remain speculative but include a shift in the oxyhemoglobin-saturation relationship, enhanced anaerobic glycolysis probably mediated by the pH-sensitive enzyme phosphofructokinase, and changes in hepatic blood flow or lactate uptake.[111,142] Altogether, however, animal and human studies and time-honored clinical experience have shown that arterial pH can be raised and even normalized with $NaHCO_3$,[9,107,11,172] yet multiple compartments separated by membranes of differing permeabilities exist. Thus even when $NaHCO_3$ added to the central veins reliably elevates the arterial pH, its effect can be erratic at tissue and cellular levels.

For example, in the cerebrospinal fluid and intracellular spaces the pH may drop further, without concordance with an already alkalemic arterial blood sample. This could happen because CO_2 raised by the bicarbonate infusion may readily diffuse across cell membranes and the blood-brain barrier, whereas bicarbonate cannot. Therefore, despite its ability to increase blood pH when given intravenously, bicarbonate fails to reliably augment the intracellular pH.[208,209] In a classic report, Adrogué et al. demonstrated that bicarbonate administration in the setting of cardiopulmonary compromise actually worsened the pH and PCO_2 in central venous blood samples, indicating persistent acidosis at the tissue level.[124] Results of human studies that examined the impact of bicarbonate administration during cardiopulmonary resuscitation have uniformly shown no benefit in terms of survival and hemodynamic recovery. Several studies have demonstrated a deleterious effect in this setting, and many others have shown no discernable effects.[107,111,124,207] This is why the American Heart Association no longer recommends routine administration of bicarbonate during cardiopulmonary resuscitation. Its use is considered only after effective ventilation, chest compressions, and epinephrine are established in the prolonged arrest scenario and for cases in which bicarbonate is a "specific" therapeutic intervention (e.g., hyperkalemia, hypermagnesemia, tricyclic antidepressant poisoning, and sodium channel blocker poisoning).[213] There is also no evidence of benefit with sodium bicarbonate infusion during resuscitation of infants at birth.[214]

The argued rationale for bicarbonate use in the shock setting is to mitigate the adverse hemodynamic consequences of acidemia. However, adult studies have indicated that bicarbonate is no more effective than saline in improving heart rate, central venous pressure, pulmonary artery pressure, mixed venous hemoglobin oxygen saturation, systemic oxygen delivery, oxygen consumption, arterial blood pressure, pulmonary artery occlusion pressure, and cardiac output.[107] These findings suggested that the commonly observed hemodynamic response to bicarbonate administration in patients treated with inotropic/vasoactive drug infusions may simply be due to preload augmentation rather than enhanced catecholamine responsiveness.[111] These findings persisted in the most severely acidemic subset of patients (pH 6.9 to 7.2), a result that does not support the practice of withholding bicarbonate in patients with "mild" acidemia and allowing its administration in those with "severe" acidemia. On the contrary, it could be expected that this sicker subset of patients would develop a more profound paradoxical intracellular acidosis after bicarbonate administration. It is likely that all these data derived from adult patients can be extrapolated to most pediatric ages, excluding infants and neonates, for whom there is insufficient evidence to determine whether infusion of base or fluid bolus reduces morbidity and mortality from metabolic acidosis.[215] The most recent (2008) Surviving Sepsis Guidelines, based on a thorough evaluation of ancillary therapies in adult sepsis and septic shock, did not recommend the use of bicarbonate for hemodynamic resuscitation or reduction in vasopressors in the setting of lactic acidosis with pH greater than 7.15, while deferring judgment for more severe acidemia. A recent review further recommended a lower target pH of 7.00 or less,[107,211] a position supported by other authoritative reviews,[212] as no reliable argument exists to prove that such acidosis is harmful under these conditions in humans. Experimental data even show that hypoxic cells are able to survive only if the medium is kept acidic. However, the 2007 update of the Clinical Practice Parameters for hemodynamic support of pediatric and neonatal septic shock from the American College of Critical Care Medicine,[216] states that sepsis-induced acidosis and hypoxia can increase pulmonary vascular resistance and thus maintain patency of the ductus arteriosus, resulting in persistent pulmonary hypertension of the newborn (PPHN). Inhaled nitric oxide is the treatment of choice; however, the committee agreed that metabolic alkalinization remains an important initial resuscitative strategy during shock, as PPHN in the setting of septic shock can reverse when acidosis is corrected.

In a recent single-center, prospective, observational study that enrolled 60 adults with either severe sepsis or septic

shock, a quantitative acid-base analysis approach was applied in order to clarify the components of the metabolic acidosis.[217] It was found that at the time of admission to ICU, these patients presented with a complex pattern in their metabolic acidosis, caused predominantly by hyperchloremic acidosis (more pronounced in nonsurvivors), and partially offset by hypoalbuminemia. Acidosis resolution in survivors was attributable to a decrease in strong ion gap and lactate levels. This study is rather small and has some other limitations, but it may imply that a subset of sepsis/septic shock patients (those with hyperchloremic acidosis identified by SIG, AG_{CORR} and partitioned SBE), may indeed benefit from sodium bicarbonate administration.

The clinician must be aware that $NaHCO_3$ is not free of negative side effects, the main being related to fluid and sodium load that can cause hypervolemia, hyperosmolarity, and hypernatremia.[205] $NaHCO_3$ given as a rapid intravenous (IV) bolus can cause a transient decrease in arterial blood pressure and a transient rise in intracranial pressure, probably related to its hypertonicity.[111] This effect is ameliorated when bicarbonate is administered as a slow IV infusion. Regardless of the infusion rate, IV administration of bicarbonate can cause sudden shifts of several cations through cell membrane-mediated mechanisms. This is advantageous in treating hyperkalemia,[213] but it also can be dangerous because bicarbonate lowers ionized calcium. "Overshoot" alkalosis, in which an abrupt and poorly tolerated transition from severe acidemia to alkalemia develops, can result from overly aggressive bicarbonate "correction."[210-212] Therefore the decision whether to use bicarbonate in lactic acidosis may become a difficult one because it is a choice between loyalty to a longstanding but unproven therapy, and congruent scientific behavior that must surrender to the evidence of potential deleterious effects of bicarbonate administration in a variety of acidemic conditions.[107,111,140,142,210-212]

Nevertheless, the urge to give bicarbonate to a patient with severe acidemia may become irresistible for most clinicians. It will always be prudent to adjust the clinical decision to the specific characteristics of each patient, keeping pros and cons in mind. If bicarbonate is used, consideration must be given to employ a slow infusion and a plan for clearing the CO_2 that is produced. Additionally, ionized calcium must be measured and corrected if needed, as the resultant drop may compromise cardiac and vascular contractility and responsiveness to cathecholamines. The amount of bicarbonate to be given should be calculated to raise the pH up to 7.2.[212] Thus the decision to provide "bicarbonate correction" must be based on the best clinical judgment mixed with a knowledge of the available evidence. This science-and-art approach to the individual patient can be summarized in the clinician's answer to the following questions, modified from Forsythe and Schmidt[111]:

1. Is the level of low pH a clear and present hazard to this patient?
2. Is there a reasonable expectation that increasing the blood pH with $NaHCO_3$ will have some beneficial effect?
3. Is there a particular and specific risk to this patient from the known potentially negative effects of $NaHCO_3$?
4. Is the mechanism of the acidosis suitable for treatment with $NaHCO_3$, or might the acidosis be exacerbated?

There are no recipes for answering these questions.

Salicylate intoxication represents a special setting. Because the risk of death and the severity of neurological manifestations depend on the concentration of salicylates in the central nervous system, therapy is directed at limiting further drug absorption by administering activated charcoal in the emergency department and promoting the exit of the drug from the cerebral tissue by increasing the alkalinity of the blood, which also will raise urine pH and therefore inhibit salicylate reabsorption by ion trapping. Thus this represents a special case of lactic acidosis in which $NaHCO_3$ is clearly indicated for two reasons: (1) to establish a high urinary flow rate along with other fluids and (2) to promote salicylate excretion. The target pH of the urine is 7.0 to 7.5. Hemodialysis is reserved for severe cases, especially those involving renal dysfunction.

If the science-and-art decision is to administer $NaHCO_3$, some time-honored clinical clues are valuable. $NaHCO_3$ dose is best estimated with either the SBE or the bicarbonate level derived from PCO_2 measured by the blood gas analyzer:

$$\text{Total body base deficit} = \text{SBE} \times \text{Body weight(kg)} \times 0.3 \quad (18A)$$

$$HCO_3^- \text{ deficit} = 0.3 \times \text{Body weight (kg)} \times [HCO_3^- \text{ expected} / HCO_3^- \text{ observed}] \quad (18B)$$

The distribution volume of bicarbonate is 0.3, or 30% of the lean body weight. The theoretical distribution volume of $NaHCO_3$ equals the extracellular fluid volume, that grossly represents 60% of the body weight (70% in young infants), and therefore it can be argued that the correct arithmetic factor should be 0.6 (or 0.7) rather than 0.3. Time-honored experience has shown, however, that as the starting point, bicarbonate or SBE correction with 0.3 ("half correction") will suffice in most cases and will avoid unnecessary risks from excessive load of solutes and fluid as well as the overshoot alkalemia. It should be taken into account that the usual $NaHCO_3$ preparation available worldwide has a concentration of 0.88 mEq/mL, with pH 8 and 1461 mOsm/kg. Therefore bicarbonate is ideally administered through a central venous line and diluted 1:1 with distilled water. If it has to be infused through a peripheral vein, the dilution must be increased.

Carbicarb

Concern about the CO_2-producing effect of bicarbonate led to the development of Carbicarb, which consists of equimolar concentrations of $NaHCO_3$ and sodium carbonate (Na_2CO_3).[107,140,218-219] Carbicarb raises the SID and thus increases the pH far more than bicarbonate, with much less rise in PCO_2, thereby limiting but not eliminating the generation of CO_2. The risks of hypervolemia and hypertonicity are similar to those of bicarbonate. Animal studies have shown stabilization of serum lactate levels and improved acid-balance profile both in blood and at the intracellular level. Carbicarb administration also resulted in a significant increase in cardiac index when compared with normal saline and $NaHCO_3$, although neither Carbicarb nor $NaHCO_3$ prevented the progressive reduction in myocardial cell pH in an animal model of ventricular fibrillation. Although Carbicarb more consistently increases intracellular pH, studies of its effects on hemodynamics have yielded conflicting results.[140] Carbicarb is not currently available for clinical use, but there is no doubt that after all the years elapsed since its appearance, it deserves further clinical research.

Tris(hydroxymethyl)aminomethane

THAM, also known as tromethamine and tris buffer, is an amino alcohol that behaves as a weak base (pKa 7.8). It exists in neutral form at physiological pH. Protonated THAM is excreted by the kidneys.[220] It crosses lipid membranes and penetrates cells easily. Therefore it has the potential to raise both intracellular and central nervous system pH. In addition, THAM's buffering action occurs without producing CO_2, and thus is not dependent on pulmonary function.[221] Despite THAM being commercially available for several decades, there are few studies establishing its clinical efficacy. In animal models, THAM incompletely buffered metabolic acidosis, but it significantly improved contractility and relaxation in an isolated rabbit heart model.[107] A small adult study in the ICU setting, showed that THAM had an equivalent but shorter lasting alkalinizing effect in comparison to that of bicarbonate, but produced no decrease in potassium and did not elevated sodium, as occurs with bicarbonate.[222] The paucity of information and the report of several serious side effects, including hypekalemia, hypoglycemia, local extravasation injury, and hepatic necrosis in neonates, have limited its widespread use in the lactic acidosis setting.

Dichloroacetate

Of particular relevance for lactic acidosis is dichloroacetate (DCA), a simple compound that reduces plasma lactic acid concentration. DCA is not a buffer but a stimulator of pyruvate dehydrogenase, the enzyme that catalyzes the oxidation of pyruvate to acetyl–coenzyme A (CoA), facilitating its entry to the Krebs cycle and thus decreasing lactate production and promoting the clearance of accumulated lactate.[107,223] In addition, DCA promotes myocardial glucose utilization and contractility. Initial data from both children and adults were promising, but a large controlled clinical trial in adults with severe lactic acidosis showed that DCA treatment resulted in statistically significant but clinically unimportant changes in arterial blood lactate concentrations and pH. It also failed to alter hemodynamics or survival. Renewed interest in DCA has arisen from its potential application in attenuating lactic acidosis in certain congenital errors of metabolism,[224] and lactic acidosis due to severe malaria in children.[225] In regard to shock patients, the physiological "new paradigm" concerning the cell-to-cell lactate shuttle and its metabolic importance raises the possibility that targeting a specific pharmacological reduction of lactate levels through DCA might not be advantageous in this setting.[136-139]

Dialysis Management of Metabolic Acidosis

Dialytic procedures may be indicated in some cases of metabolic acidosis that are refractory to bicarbonate or in cases in which there are serious limitations in the amount of fluid or sodium load that can be administered to the patient, a common situation in the pediatric critical care unit (see Chapter 72) Uncompensated metabolic acidosis (pH <7.1) remains one of the acknowledged criteria for the initiation of renal replacement therapy in the pediatric ICU.[206] Peritoneal dialysis is often not the best choice, particularly in lactic acidosis associated with hypoperfusion. In this setting the hypoperfused peritoneal membranes may not be efficient for supporting enough peritoneal flux, and the increase in intraabdominal pressure may contribute to a further drop in cardiac output. If peritoneal dialysis is chosen, bicarbonate-buffered peritoneal dialysis solution provides some advantages over the conventional lactate-buffered peritoneal dialysis solution in terms of pH control, biochemical monitoring, and mesothelial cell preservation.

Most critically ill patients lack the hemodynamic stability to tolerate intermittent hemodialysis. Hemofiltration and hemodiafiltration are better options. Acute renal replacement therapy may be needed for critically ill patients with metabolic acidosis that is multifactorial in origin. Analysis of the acid-base status of these patients through Stewart-Figge methodology shows that acidemia is present despite the presence of hypoalbuminemic alkalosis, and that this acidemia is mostly secondary to hyperphosphatemia (mainly if there is concomitant acute or chronic renal failure), hyperlactatemia, and the accumulation of unmeasured anions. Once continuous hemofiltration is started, it becomes the dominant force in controlling metabolic acid-base status and profound changes are rapidly achieved. The result is the progressive resolution of acidemia and acidosis, with lowering concentrations of phosphate and unmeasured anions. If the patient stabilizes, this typically results in some degree of metabolic alkalosis, an effect the clinician must take always in account.

Hemofiltration techniques replace plasma water, which is low in bicarbonate concentration, with a solution that contains an above-normal bicarbonate (or lactate or acetate) concentration. Such weak anions free their sodium (which increases SID), buffer hydrogen ions, and then are transformed into CO_2 (lactate and acetate must convert first to bicarbonate in the liver), which is subsequently removed by ventilation. This exchange contributes to the correction of acidosis, along with the increase in SID through the sodium contribution. If such oxidizable anions are not fully extracted and metabolized by the liver and, therefore, accumulate in plasma, the ability to correct acidosis is lost, as they fail to increase the SID. Hence, hyperlactatemia with acidification of plasma occurs. Such iatrogenic hyperlactatemic acidosis is particularly frequent in lactate-intolerant patients (shock with lactic acidosis and/or liver disease), and it is specially marked if high-volume hemofiltration is performed, in which the associated high lactate load may easily overcome the patient's metabolic capacity for taking up lactate. In such patients, use of bicarbonate-based replacement fluids is mandatory.[226] In addition, the effect of lactate-based replacement fluid on blood lactate concentration can be misleading in patients who have sepsis with lactic acidosis. Additionally, it appears that lactate clearance through the hemofilter is small compared with endogenous clearance. Therefore, despite the fact that hemofiltration has been advocated for the treatment of lactic acidosis, kinetic studies of lactate removal do not suggest that such removal can counteract lactate production in any meaningful way.[140]

Metabolic Alkalosis

Metabolic alkalosis is defined as an elevation of plasma HCO_3^- with an arterial pH above 7.45. There is no accurate estimate of the incidence or prevalence of metabolic alkalosis. However, in the critical care setting, it is estimated that metabolic alkalosis is the more common form of acid-base disorder, as it may be present in about 50% of patients with acid-base disorders.

A study in pediatric patients undergoing open-heart surgery, found that 72% of children under 12 months of age developed metabolic alkalosis, in contrast with 30% of those older than 12 months of age. It is difficult to attribute a figure of mortality or morbidity directly to metabolic alkalosis. However, at least one study in adults found that mortality progressively rose with the pH: 47% with pH 7.57 to 7.59, 65% with pH 7.60 to 7.64, and 80% with pH 7.65 to 7.70. This does not necessarily indicate a cause-effect relationship.[227,228] Most of the clinical studies that have examined metabolic alkalosis are now somewhat old, and there is a need for prospective studies of updated design to reassess the incidence, consequences, and other aspects of metabolic alkalosis.

The increased incidence of metabolic alkalosis in patients with severe sepsis and trauma is due to factors related to a vigorous correction of shock, hypotension, and acidosis, where large quantities of citrated blood or lactated Ringer solution are given, as well as to the administration of bicarbonate itself (Table 68-8).[227] Other subsets of patients may arrive in the PICU already with metabolic alkalosis, associated with the chronic use of chloruretic diuretics, excessive exogenous or endogenous steroids, high doses of antacids, or related to elevated gastrointestinal fluid losses (emesis, suction, or chloride-rich diarrhea) or to the posthypercapneic state, the typical pattern of a chronic lung disease after the resolution of an acute episode of decompensation.[228,229] Alkalemia has been classified as mild (pH 7.45 to 7.50), moderate (pH 7.50 to 7.55), or severe (pH > 7.55).[227]

According to the physicochemical approach, metabolic alkalosis results from an increase in SID, or a decrease in A_{TOT}, due to a loss of anions (Cl^- from the digestive tract or through the kidneys, albumin from the plasma) or, rarely, to an excess of cations.[8,10] (see Table 68-6). In the classic approach to acid-base derangements, metabolic alkalosis is generated by net gain of base (primarily bicarbonate) or loss of nonvolatile acid from the extracellular fluid. Despite the fact that this model is not able to explain many of the electrolyte changes associated with metabolic alkalosis nor the reasons for the good results of some therapeutic interventions, it continues to be a practical way to approach metabolic alkalosis.[9,230] The excess of base may be gained through oral or parenteral bicarbonate administration, or by the administration of other weak anions such as lactate, acetate, or citrate, all of them as sodium salts. Thus it is actually the gain of strong cations (mainly sodium) that causes pH to increase. The acid deficit may be due to the hydrochloric acid loss by vomiting or enhanced renal acid excretion promoted by diuretics or aldosterone excess, and is often accompanied by hypochloremia and hypokalemia.[227-229] In a similar way, it is the loss of strong anions (mainly chloride), rather than the direct loss of hydrogen ions, that actually increases pH. There may also be a contraction of the extracellular fluid volume secondary to the chloride loss. Concomitant changes in the intracellular fluid do occur, including a loss of intracellular potassium along with a net gain of sodium and hydrogen. Hence, metabolic alkalosis in the extracellular fluid is usually accompanied by acidosis and potassium depletion in the intracellular compartment. Bicarbonate or base loading is rarely the single cause of metabolic alkalosis. Such a situation may transiently occur during and immediately after an IV infusion of $NaHCO_3$ or an equivalent base (e.g., citrate anticoagulant in transfused packed red blood cells). This situation may also occur after the successful treatment of ketoacidosis or lactic acidosis because these organic anions are metabolized to bicarbonate, and after the resolution of hypercapnia, either permissive or as a part of unintentional respiratory acidosis, before the kidney can excrete the bicarbonate previously "retained for compensation" (actually, HCO_3^- was increased because PCO_2 was increased). It is generally accepted that metabolic alkalosis involves a "generative" stage, during which the relative concentraton of alkali within the body increases, and a "maintenance" stage,[228,229] in which the kidneys fail to compensate by excreting strong cations and HCO_3^-.

Three major factors underlie the maintenance phase in most clinical situations: first, depletion in circulating volume and changes in generalized hemodynamics (e.g., heart failure) and in intrarenal hemodynamics, which combine to reduce the filtered load of bicarbonate traversing the proximal tubule despite the increase in bicarbonate concentration; second, increased aldosterone secretion (and probably endothelin-1), due to volume contraction and increased angiotensin-II, which stimulates acid secretion; and third, total potassium depletion and hypokalemia, which alter glomerular hemodynamics,

Table 68–8 Causes of Metabolic Alkalosis in Critically Ill Patients

I. Chloride-responsive (decreased urine [Cl^-]*)
  A. Gastrointestinal losses of Cl^-
    1. Gastric drainage or persisting vomiting
    2. Chloride-wasting acute diarrheas
  B. Renal losses of Cl^- and K^+
    1. Diuretics (mainly acute use)
    2. High dose of certain penicillin-derivative antibiotics
    3. Posthypercapnia
II. Chloride-resistant (increased urine [Cl^-]†)
  A. Excess mineralocorticoid activity: ongoing losses of K^+ and Cl^-
    1. Primary and secondary hyperaldosteronism
    2. Congenital adrenal hyperplasia (17α-hydroxylase or 11β-hydroxylase deficiency)
    3. Cushing syndrome
    4. Primary renin-secreting tumors
    5. Steroid treatment
  B. Genetic renal tubular defects of electrolyte transport
    1. Problem in chloride reabsorption
      a. Bartter and Gitelman syndromes
    2. Defective epithelial sodium channel (decreased sodium elimination)
      b. Liddle syndrome
  C. Drug-induced hypokalemic alkalosis
    1. Diuretics administered for prolonged time
    2. High-dose glucocorticoids
    3. Fludrocortisone
    4. Aminoglycosides
    5. Toxic effects of licorice (*Glycyrrhiza glabra*)
    6. Ion exchange resin
  D. Excess cation (alkali) gain
    1. Massive blood transfusion
    2. Massive infusion of lactated Ringer's solution
    3. Parenteral hyperalimentation with excessive sodium acetate
    4. Alkali ingestion/treatment and milk-alkali syndrome
    5. Magnesium depletion
III. Miscellaneous group (variable urine [Cl^-]†)
  A. Hypoproteinemia
  B. Cystic fibrosis
  C. Congenital chloride diarrhea
  D. Salt-losing nephropathy

*<20 mEq/L, usually <15 mE/L.
†>20 mEq/L, usually >40 mEq/L.

stimulate the renal H^+-K^+-ATPase, and secondarily increase renal acid secretion in the presence of aldosterone.[230] In other words, the regulation of pH through strong cation (mainly sodium) and bicarbonate elimination, is sacrificed to preserve volume and potassium stores. If volume and potassium are equilibrated, metabolic alkalosis self-corrects.

Metabolic alkalosis has been classified by the primary organ system involved, the response to therapy, or the underlying disease.[229,231] In the critical care setting, it may be more convenient to classify it according to the response to therapy, and use the serum chloride concentration (the most commonly anion involved) as the key variable for such a classification.[8-10,43] Sometimes the loss of Cl^- is temporary and can be treated effectively by replacing it; this type of metabolic alkalosis is known as *chloride responsive*. This represents the most frequently encountered metabolic alkalosis in the pediatric critical care unit, and it is also the most severe.[227-231] This group of disorders is usually the result of Cl^- losses from gastric drainage or persisting vomiting, as in pyloric hypertrophy and other causes of upper gastrointestinal obstruction.[8,98,227-229] Chloride loss also may occur as a consequence of the administration of diuretics.[10] Both persistent vomiting and excessive diuretics generate some degree of dehydration, with volume contraction and secondary stimulation of aldosterone release, which in turn leads to increased tubular Na^+ reabsorption—an alkalinizing process, because it increases the SID and increases urinary loss of K^+, which may yield hypokalemia.[229]

In other cases, hormonal mechanisms leading to an excess of mineralocorticoid activity directly produce ongoing losses of K^+ and Cl^-. Similar urinary losses may be associated with genetic renal tubular defects of electrolyte transport, mainly in chloride reabsorption. Decreased plasma levels of Cl^- and K^+ lead to an increased SID, which in turn yields metabolic alkalosis. In this setting, the Cl^- deficit can be offset only temporarily, at best, by Cl^- administration. Therefore this form of metabolic alkalosis is said to be *chloride resistant*.[8,10,227-231] (see Tables 68-6 and 68-8). The hallmark of this group of disorders is an increased urine Cl^- concentration, more than 20 mEq/L (usually >40 mEq/L).[227-231] Treatment requires a search for the underlying disorder and, if possible, a specific therapeutic intervention. Among the most important causes of chloride-resistant disorders are: (1) diseases with mineralocorticoid excess, including primary and secondary aldosteronism, congenital adrenal hyperplasia (17α-hydroxylase deficiency), renin-secreting tumors, and Cushing syndrome; (2) tubulopathies, including chloride-wasting tubulopathies (Bartter and Gitelman syndromes, and defective epithelial sodium channels (ENaC) leading to a decreased sodium elimination (Liddle syndrome); (3) drug-induced hypokalemic alkaloses, including those caused by diuretics, high-dose glucocorticoids, fludrocortisone, aminoglycosides, and toxic effects of licorice (*Glycyrrhiza glabra*); and (4) the miscellaneous group, which includes 11β-hydroxysteroid dehydrogenase deficiency, salt-losing nephropathy, cystic fibrosis, and congenital chloride diarrhea, among others. For further details about these specific disorders, the reader is referred to other sources.[98,228-235] Random urine chloride may suffice for a quick clinical orientation: uCl^- less than 20 mEq/L (usually <15 mEq/L) is consistent with chloride-responsive metabolic alkalosis; uCl^- greater than 20 mEq/L (usually >40 mEq/L) is consistent with chloride-unresponsive metabolic alkalosis.[228-230] However, this general rule may not apply to other special causes of metabolic alkalosis, which include the extrarenal chloride-resistant forms, such as cystic fibrosis,[234] and congenital chloride diarrhea, which is a recessively inherited disorder of chloride transport in the distal ileum and colon.[235] In both disorders, huge extrarenal chloride loss occurs (through sweat or diarrhea), and urine chloride may be low, normal, or high, depending on the patient's renal function and clinical situation.

Finally, metabolic alkalosis may occur as the SID increases as a consequence of the gain of cations rather than anion depletion. The most common clinical situation in the critical care setting is the IV administration of strong cations without strong anions, such as with massive blood transfusion. In this case, sodium is administered predominantly with citrate (a weak anion) instead of chloride. A similar mechanism of metabolic alkalosis occurs when parenteral nutrition contains excess sodium acetate (another weak anion) and insufficient chloride to balance the sodium load.[8] Excessive infusion of some gelatins used as plasma volume expanders and sodium lactate (as in Ringer's solution) can also cause metabolic alkalosis. The milk-alkali syndrome is now a rare cause of this derangement.

Treating Metabolic Alkalosis

Many clinicians have the perception that metabolic alkalosis is a mild, self-limited acid-base derangement. This can be true in some settings, such as post-hypercapnia and post-citrate or lactated Ringer's infusion in patients with normal renal and hepatic function, but it is not true in all cases. Alkalosis and alkalemia are important because they may increase morbidity and mortality. Increase in blood pH increases neuromuscular excitability, probably related to a decrease in ionized calcium concentration and potassium shifts, leading to alteration of consciousness, increased seizure activity, increased cardiac arrhythmia, decreased oxygen release to tissue from hemoglobin, tetany secondary to hypocalcemia, increased ammonia generation by the kidney, and, in some instances, depression of the respiratory drive. Because mortality is especially high when a pH in excess of 7.6 develops, intervention at a pH of 7.55 and greater is recommended.[227,230]

Regardless of the type of metabolic alkalosis, the first step for its proper management is to moderate or stop the process that generated the problem, even if only temporarily.[227] For example, if continuation of gastric drainage is required, the loss of gastric fluid can be reduced though the administration of H_2-receptor blockers or inhibitors of the gastric H^+/ K^+-ATPase. If it is not possible to withdraw diuretics, it may be possible to use potassium-sparing compounds (e.g., spironolactone, amiloride), that decrease distal acidification and curtail potassium excretion. Administration of bicarbonate or its precursors such as lactate, citrate, and acetate should be discontinued; these compounds are commonly present in IV and dialytic solutions, transfused blood and blood derivatives, and parenteral nutrition. If drugs with mineralocorticoid activity are being administered, their indication and dose should be reassessed.

Up to 10% of the total bicarbonate filtered is reabsorbed or lost to urine in the distal renal tubule. In most patients with metabolic alkalosis, extracellular fluid, altogether with chloride, potassium, and magnesium concentrations, is decreased.

Hence, the blood flow to the kidneys is also decreased, and secretion of both aldosterone and endothelin-1 is stimulated, bicarbonate urine loss is reduced, chloride wasting increases, and urinary hydrogen ions and potassium are decreased even more.

Because potassium, chloride, and magnesium concentrations limit bicarbonate excretion, their low concentrations will make metabolic alkalosis refractory to correction. Thus the restoration of circulating volume and electrolyte composition will allow renal excretion of bicarbonate and the correction of metabolic alkalosis[227] or, in agreement with the physicochemical approach, it really does not matter if the bicarbonate excretion is enhanced, but it is the replacement of Cl^- that corrects the increased SID.[8] Saline plus KCl infusion are usually the best choice because of the typical coexisting volume depletion and hypokalemia. Administration of normal saline is effective despite the release of equal amounts of $Na^+$and Cl^- because it results in larger relative increases in Cl^- concentration compared with Na^+ concentration. Treatment of severe chloride-responsive metabolic alkalosis can be a real challenge without the presence of either volume depletion or hypokalemia as well as in patients with cardiac or renal dysfunction and in the hepatic disease patient with ascites.

It is quite common that this group of patients had been receiving aggressive diuresis. Hence, more often, these patients have developed metabolic alkalosis as a result of the effects of diuretics and will be better treated by the provision of potassium chloride, because their previous treatments have rendered them potassium depleted. However, potassium chloride can induce hyperkalemia in patients with renal failure. In these patients, decreasing or adjusting the diuretic regimen, adding acetazolamide (a carbonic anhydrase enzyme inhibitor that enhances renal sodium bicarbonate loss, increasing urinary SID and decreasing blood SID),[201] and cautiously administering NaCl and potassium chloride may suffice.[9,227] If the pace of correction of the alkalemia needs to be accelerated, hydrochloric acid (HCl) can be infused intravenously as a 0.1 to 0.2 N solution (i.e., one containing 100 to 200 mmol of H^+ per liter). This intervention, which is rarely needed, is safe and effective for the symptomatic rapid relief of severe metabolic alkalosis. Because of its sclerosing properties and its hyperosmotic concentration, HCl must be infused through a central venous line at an infusion rate of no more than 0.2 mmol/kg/hr, up to 20 to 50 mmol/h maximum,[227] with arterial pH monitoring every hour. Although an alternative infusion through a peripheral IV line was described decades ago, this route is not advisable in the pediatric population. Calculation of the amount of HCl solution to be infused is based on a distribution volume equivalent to 30% of the body weight. Thus HCl dosage can be calculated with either the SBE or the bicarbonate difference in a manner similar to the bicarbonate administration formula (Equations 18A and 18B):

$$\text{Total body BE} = \text{SBE} \times \text{Body weight(kg)} \times 0.3 \quad (19A)$$

$$HCO_3^- \text{ excess} = 0.3 \times \text{Body weight (kg)} \times [HCO_3^- \text{ observed} - HCO_3^- \text{ desired}] \quad (19B)$$

In both formulas, the result is expressed in millimoles of HCl to be administered. If this intervention is contraindicated, not effective, or not available, and the alkalemia is severe with no hope of quick control, hemodialysis or hemodiafiltration can rapidly correct severe alkalemia and volume overload, but a dialysis solution low in lactate or bicarbonate must be used to prevent worsening of the alkalemia. Ammonium chloride has similarly been employed to correct chloride in patients with normokalemia or hyperkalemia. In this case ammonium represents a weak cation that does not increase the concentration of strong cations. The only specific treatment for metabolic acidosis available to date is for Liddle syndrome, which is responsive to a decreased dietary sodum intake and to a sodium channel blocker, such as amiloride or triamterene.[230]

Respiratory Acid-Base Derangements

Although the underlying pathological process may vary, the respiratory acid-base derangements always have the same mechanism: alveolar ventilation is increased or decreased out of proportion to CO_2 production. Carbon dioxide arises either from the cellular metabolism or by the titration of HCO_3^- by metabolic acids. Normal CO_2 production by the body (and its excretion by the lungs) is impressive (about 220 mL/min or about 317 L/day in a 70-kg adult, equivalent to 15,000 mmol of carbonic acid per day) compared with the 500 mmol/day of all nonrespiratory acids that are handled by the kidneys and gut.[10] Pulmonary ventilation is adjusted by the respiratory center in the brainstem in response to changes in P_aCO_2, pH, and P_aO_2, although respiratory drive can be influenced by other neural (anxiety, wakefulness) and nonneural factors (e.g., exercise, muscle strength) and can also be altered in some pathological situations (cystic fibrosis, asthma, and congenital central hypoventilation syndrome) (see Chapter 38).[236] The precise and real-time match of alveolar minute ventilation to CO_2 production allows stable P_aCO_2 levels of 35 to 45 mm Hg at sea level. Accuracy of the central control allows the body to adjust P_aCO_2 in compensation for alterations in arterial pH produced by metabolic acidosis or alkalosis in predictable ways (see Tables 68-2 and 68-3). When this normal respiratory system is disrupted or overwhelmed, P_aCO_2 deviates from normal and the respiratory acid-base disturbances are initiated.

Respiratory acidosis is produced by CO_2 retention, leading to hypercapnia (elevation of P_aCO_2). Respiratory alkalosis is produced by hyperventilation, leading to a drop in P_aCO_2 (i.e., hypocapnia). As soon as P_aCO_2 increases or decreases, plasma and intracellular buffers change their dissociation to maintain a stable pH, the effect of which is fully manifested within 15 to 30 minutes. If the alteration in P_aCO_2 is sustained for more than 6 to 12 hours, renal mechanisms induce far larger changes in bicarbonate concentration, reaching maximal impact within 3 to 5 days. These renal effects lead to a new steady state for the pH. The two responses to the primary alterations in P_aCO_2, plasma plus tissue buffers and the renal response, permit description of the respiratory acid-base derangements as acute and chronic phases.[10] Thus acute respiratory acidosis or alkalosis involves the immediate plasma and intracellular buffer response to hypercapnia or hypocapnia, whereas chronic respiratory acidosis or alkalosis involves the renal response.

Respiratory Acidosis

Respiratory acidosis occurs whenever the CO_2 elimination by the lungs is lower than the CO_2 production by the tissues, resulting in a positive balance of CO_2, which in turn increases

P_aCO_2 to a new equilibrium determined by the altered relationship between CO_2 production and alveolar ventilation. Because the increase in CO_2 production alone is not sufficient to overcome the normal ability of the lungs to increase alveolar ventilation,[10] what is central to all forms of respiratory acidosis is a failure of alveolar ventilation and CO_2 excretion to increase in response to a rising P_aCO_2. However, an increase in CO_2 production in the face of fixed ventilation can also result in respiratory acidosis. For example, this may occur in the critical care setting in patients receiving mechanical hypoventilation and a high load of carbohydrates in their parenteral nutrition. This may also happen if a patient with hypoventilated lungs becomes febrile (acute hypermetabolism). Immediately, the increase in P_aCO_2 increases both the hydrogen ion and bicarbonate concentrations in blood (Equations 3 to 5). Here the increase in $[HCO_3^-]$ occurs as a consequence of physicochemical principles and not as a consequence of an adaptive response in order to buffer the increase in H^+.[5,8,13] The only immediate buffering activity in hypercapnia comes from the nonbicarbonate plasma and intracellular buffers.[208]

Because of the increase in bicarbonate (a weak anion), no change in the SID is produced, and thus no change occurs in the SBE. Because CO_2 is produced within the cells and can freely diffuse across the lipophilic cellular membranes, intracellular acidosis always occurs with respiratory acidosis.[208,209] If the P_aCO_2 remains increased, active compensatory mechanisms are activated, and the SID increases to restore H^+ toward normal. Primarily, respiratory acidemia compensation is accomplished by removal of CL^- from the plasma space. Because movement of Cl^- into the tissues or red blood cells results in a drop of intracellular pH, Cl^- must be removed from the body to achieve a lasting effect on the SID. The kidneys are the most important organ for this task. Because every chloride ion that is filtered and not reabsorbed increases the SID (and the pH), Cl^- removal by the kidney must be highly accurate. The role of ammonium in this process is preeminent, not as a hydrogen ion carrier or a potential buffer, but for the excretion of Cl^- without losing Na^+ or K^+.[8,54] Thus when renal function is intact Cl^- is eliminated in the urine, and after a few days, the SID increases to the level necessary to return blood pH near 7.35. This amount of time is required by the physiological constraints of the system, but that is not entirely a disadvantage because this rate of response is useful in order to avoid being oversensitive to transient changes in alveolar ventilation. In any case, the compensation results in an increased pH for any degree of hypercarbia.

According to the Henderson-Hasselbalch equation (Equations 4 and 5), the increased pH will result in an increased HCO_3^- concentration for a given P_aCO_2. Therefore the so-called *adaptive increase* in HCO_3^- to hypercapnia actually results *from* the increase in pH, and *is not the cause of* the increase in the pH, which actually occurred from the increase in the SID as a consequence of the removal of chloride. Although the change in HCO_3^- concentration is a convenient and reliable marker for the metabolic compensation (see Tables 68-2 and 68-3), it is not the mechanism.

Acute respiratory acidosis develops as a consequence of the impaired function of one or more of the three participants in the ventilatory function: central nervous system; neural (peripheral), muscular, and skeletal structures; and lungs (airway and alveoli) (Table 68-9). Airway and parenchymal lung disease are the most common causes of acute CO_2 retention. This last group of conditions not only produces hypercapnia, but also primary hypoxemia. It is hypoxemia, not hypercapnia or acidemia, that poses the principal threat to life. The already mentioned conditions that cause the failure of the lungs to eliminate CO_2 can also be grouped into two types of ventilatory disorders.[10] The first, or "pure," hypoventilation occurs as a result of brainstem or neuromuscular dysfunction or because of extrapulmonary restrictive lung compromise. In this setting, the lung simply fails to move enough air in and out to exchange CO_2 and oxygen. As a result, PaO_2 falls in proportion to the rise in P_aCO_2. In the second and more common situation in the critical care setting, alveolar hypoventilation is the result of the imbalance between perfused and hypoventilated segments of a damaged lung (i.e., ventilation-perfusion [V/Q] inequality; see Chapter 40). In this case, a fall in P_aCO_2 often precedes hypercapnia, and when hypercapnia finally develops, the reduction in P_aO_2 is proportionally greater than the rise in P_aCO_2. With both types of ventilatory defects, however, hypoxemia is a concurrent finding when hypercapnia is present.[10]

Chronic respiratory acidosis is most often associated with chronic lung disease (e.g., bronchopulmonary dysplasia) or chest diseases with abnormal chest wall mechanics (chest congenital deformities, kyphoscoliosis), but it can also be

Table 68–9 Causes of Respiratory Acid-Base Derangements

ACIDOSIS (↑ P_aCO_2)	ALKALOSIS (↓ P_aCO_2)
Central nervous system depression	Hypoxemia
Severe head trauma, brain edema, metabolic diseases, infectious diseases, intentional sedation, pharmacological effect of drugs	High altitudes, pulmonary disease
Neural (peripheral), muscular, and skeletal structures	Pulmonary disorders
Electrolyte disturbances: hypophosphatemia, hypokalemia	Pneumonia, interstitial pneumonitis, fibrosis, edema, pulmonary embolism, vascular disease, bronchial asthma, pneumothorax
Specific diseases: myasthenia gravis, Guillain-Barré syndrome, spinal cord injury, Werdnig-Hoffmann disease, Duchenne muscular dystrophy, etc.	Cardiovascular disorders
	Congestive heart failure, hypotension
	Metabolic disorders
Ventilatory restriction: rib fractures and flail chest, patients with intraabdominal hypertension from ascites, from closure of congenital abdominal wall defects, etc.	Acidosis (diabetic, renal, or lactic), hepatic failure
	Central nervous system disorders
Lungs (airway and alveoli):	Psychogenic or anxiety-induced hyperventilation, central nervous system infection, central nervous system tumors
Respiratory obstructive disease, either acute or chronic: croup, asthma, bronchiolitis, bronchopulmonary dysplasia	Drugs
	Salicylates, methylxanthines, β-adrenergic agonists, progesterone
Alveolar injury: pneumonia, acute lung injury, acute respiratory distress syndrome, cardiogenic pulmonary edema	Miscellaneous
	Fever, sepsis, pain, pregnancy

caused by chronic upper airway obstruction (e.g., obstructive sleep apnea syndrome and craniofacial disorders),[237] chronic neuromuscular diseases, or chronic central nervous system problems (congenital central hypoventilation syndrome).[236] Respiratory decompensation in patients with these conditions usually results from recently acquired infection, use of narcotics, or uncontrolled oxygen therapy.[238] These additional factors superimpose an acute element of CO_2 retention and acidemia on the already elevated CO_2 baseline. Progressive narcosis and coma (i.e., hypercapnic encephalopathy) may ensue. On the basis of the preeminent renal participation in the ultimate compensation of hypercapnia, one should expect that patients with renal disease (with difficulties excreting chloride) will have a defective adaptation to chronic hypercapnia.

Treating Respiratory Acidosis

As the main threat to life in respiratory acidosis comes from associated hypoxemia, and not from the level of hypercapnia or acidemia, oxygen administration represents a critical element in the management of respiratory acidosis. Caution must be taken when uncontrolled concentrations of oxygen are administered to some patients with hypercarbia, particularly those with chronic lung disease, in whom exaggerated oxygen supplementation could depress respiratory drive and provoke further increase in P_aCO_2.[238] This occurs because chronic hypercapnia is thought to downregulate CO_2 chemoreceptor sensitivity, which means that these patients are more dependent on hypoxic drive to maintain adequate spontaneous ventilation. Thus hypoventilation (and hypercapnia), may worsen if unrestricted (and excessive) oxygen is administered. This phenomenon has been described mainly in adults with chronic obstructive pulmonary disease and acute asthma, but it may also occur in children with chronic lung disease. It should be emphasized, however, that the correction of hypoxia overrides strategies to avert oxygen-related hypercapnia, which normally tends to be of little clinical significance in children. Thus, immediate actions should focus on securing a patent airway and restoring adequate oxygenation by delivering an oxygen-enriched gas mixture.

Oxygen administration alone, however, is almost never enough as a single therapeutic measure. Hence hypoventilation must be treated directly. Whenever feasible, treatment must be directed to the underlying cause. Sometimes it is possible to solve the primary cause of hypoventilation rather quickly (e.g., relief of obstruction from croup with racemic epinephrine, reversal of narcotics with naloxone, resolution of bronchial spasm with some β_2 agonist). In such cases, it may be possible to avoid positive pressure ventilation. Generally speaking, mechanical ventilation is indicated when the patient is at risk of instability, the patient is already unstable, or the central nervous system function shows a trend toward deterioration. When respiratory muscle fatigue is impending, further deterioration must be avoided by using positive pressure ventilation. The classic "rule of the 50s" (i.e., 50 mm Hg of P_aO_2 and P_aCO_2 as a guide for endotracheal intubation) should not be interpreted literally. It is not the absolute value of P_aCO_2 (or P_aO_2) that is important but rather the clinical condition and perceived trend of the patient. In chronic hypercapnia, management of the respiratory decompensation depends on the cause, severity, and rate of progression of the hypercapnia. Immediate treatment of pulmonary infection with proper antibiotics, bronchodilator therapy, and removal of secretions can offer considerable benefit. The ventilatory drive can be optimized by minimizing the use of tranquilizers and sedatives, by gradually reducing supplemental oxygen (aiming for a P_aO_2 of about 60 mm Hg), and by correcting a superimposed metabolic alkalosis.

The "aggressive" approach that favors the early implementation of positive pressure ventilation is often appropriate for patients with acute respiratory acidosis[239] (see Chapter 49). For those patients with chronic diseases that limit pulmonary reserve, however, a more conservative approach is often advisable and possible because of the great difficulty often encountered in weaning such patients from ventilators. If the patient is obtunded or unable to cough and if hypercapnia and acidemia are worsening, mechanical ventilation should be instituted. Noninvasive mechanical ventilation (NIV) with a nasal or facial mask is being used with increasing frequency in children, both with moderately severe acute respiratory failure and with hypercapnic respiratory failure resulting from acute exacerbations of chronic lung disease (see also Chapter 50). Despite the limited pediatric experience,[240] its application in children is growing both in acute situations within the critical care unit, even in small children, and in cases of chronic hypercapnic and hypoxemic respiratory failure of various causes that are encountered in intermediate care wards and in children's home environments. When P_aCO_2 is high and minute ventilation is normal or increased, the respiratory muscles are already failing to generate sufficient alveolar ventilation to eliminate the CO_2 being produced. The general strategy for the correction of this problem is to decrease the work of breathing by reducing CO_2 production and to improve alveolar ventilation by increasing tidal volume or respiratory rate through whatever mode of assisted ventilation is appropriate for the patient. Respiratory muscle failure can occur when the work of breathing is normal (e.g., numerous acute or chronic neuromuscular problems) or increased (e.g., patients with asthma or the obesity hypoventilation syndrome), and presumably because of inadequate delivery of oxygen to the respiratory muscles (e.g., patients with cardiogenic pulmonary edema). When P_aCO_2 is increased and minute ventilation is low, the level of consciousness is generally impaired. Such patients usually require intubation for airway protection in addition to ventilatory assistance, unless the hypercapnia can be reversed within minutes with NIV.[241]

Hypoxemia is treated with FiO_2 augmentation (the lower the V/Q, the less the effectiveness) and through the recruitment of air spaces with an increase of the transpulmonary pressure applied at end-expiration. The usual ventilatory strategy for hypercapnia is to increase minute ventilation, which should gradually return the P_aCO_2 toward baseline values, while the excretion of excess bicarbonate by the kidneys is accomplished (on the assumption that chloride is provided). When the ventilator is used to correct respiratory acidosis, the end-inspiratory plateau and auto-PEEP pressures should be monitored routinely to detect any adverse effects of hyperventilation. An overly rapid reduction in the P_aCO_2 risks the development of posthypercapnic alkalosis, with potentially serious consequences. Should posthypercapnic alkalosis develop, the parameters of the mechanical ventilation must be readjusted immediately in order to reduce the minute volume. In addition, the alkalosis can be ameliorated with chloride in the form of sodium or potassium salt with

the aim of decreasing the SID. It is always beneficial to reduce CO_2 production. This can be achieved through reduction of the carbohydrate load in parenteral and enteral nutrition, through aggressive control of hyperthermia, and through adequate sedation or analgesia in anxious or combative patients. What alternatives are there for those patients with intractable hypercapnia? One possible option not yet routinely available is intratracheal pulmonary ventilation, a method in which an intratracheal catheter with a reversed continuous flow of gas at its tip (away from the lungs) facilitates flushing of CO_2 from the proximal dead space. Marked reductions in P_aCO_2, ranging from 37% to 71%, and improvement in baseline pH were achieved with this intervention in five moribund neonatal and pediatric patients with uncontrollable hypercapnia,[242] but major clinical experience is still lacking. Another possible approach is the extracorporeal removal of CO_2. After promising initial experiences in the adult population, successful pediatric case reports have begun to appear.[243]

Permissive Hypercapnia

The ultimate treatment for respiratory acidosis is to increase minute ventilation, a measure that often requires mechanical ventilation support. Because in many patients with respiratory acidosis lung dysfunction already exists, it is usually not possible to achieve normocapnia values without producing ventilator-associated lung injury (see also Chapter 51). More specifically for the critically ill patient with some sort of lung disease, normalization of the P_aCO_2 may come at the cost of volutrauma or barotrauma, that is, the alveolar distension and collapse cycle that is now known to be associated with tissue injury, increased microvascular permeability, and lung rupture.[112] Thus, the current practice for both adults and children favors the use of lower tidal volumes (5 to 8 mL/kg or less), with plateau or peak pressures no higher than 20 cm H_2O above the baseline. With this approach, there is increasing evidence that the lungs may have a better outcome, although a rise in the P_aCO_2 may ensue. This controlled hypoventilation is known as *permissive hypercapnia* (see also Chapter 52).[112,244] A significant body of literature, both clinical and preclinical, confirms the beneficial effects of hypercapnic acidosis in the setting of acute lung injury. Therefore the use of permissive hypercapnia as part of a lung-protective strategy in children should be accepted, and perhaps even desired, provided it does not result in significant hemodynamic instability and there is no coexisting contraindication such as intracranial hypertension (see the section Does Abnormal pH Harm? in this chapter).[244,245]

The "optimal" P_aCO_2 target has not been determined in clinical practice. It has been suggested that hypercapnia be limited to a degree that maintains pH greater than 7.20.[244] Hypercapnic acidosis (HCA) seems to be safe at any age, from preterm newborns to adults.[244-248] Small randomized clinical trials and large amounts of observational data from preterm infants have demonstrated that permissive hypercapnia does not increase risk for brain injury, intraventricular hemorrhage, and impairment among very low birth weight infants, with comparable survival rates and sensorineural outcome in comparison with infants treated with the traditional mechanical ventilation approach. The hypercapnic groups had lower incidence of bronchopulmonary dysplasia and respiratory deaths than that reported with conventional treatment.[247,248] Permissive hypercapnia in the preterm newborn may also protect against hypocapnia-induced brain hypoperfusion and subsequent ventricular leukomalacia.

However, extreme hypercapnia may be associated with an increased risk of intracranial hemorrhage. It may therefore be important to avoid large fluctuations in P_aCO_2 values. It was found that for infants whose Apgar scores were 4 or less, a permissive hypercapnea strategy was associated with a higher risk of intraventricular hemorrhage, whereas for Apgar scores 5 or greater, a permissive hypercapnia strategy was protective. Although this finding is not conclusive due to methodological limitations of the study,[248] it certainly underscores the need to individually assess every case for the potential risk versus benefit of HCA.

In sedated and intubated adults with ARDS, rapid intentional hypoventilation (pH falling from 7.40 to 7.26 in 30 to 60 minutes) lowered systemic vascular resistance and increased cardiac output, while mean systemic arterial pressure and pulmonary vascular resistance did not change.[249] In children, it was shown that hypoventilation improves arterial oxygenation after bidirectional superior cavopulmonary anastomosis.[250] In these patients, moderate hypercapnia with respiratory acidosis was also shown to reduce oxygen consumption and arterial lactate levels.

How low can the pH drop? How high can the P_aCO_2 rise? Actually, in many studies of adult patients undergoing permissive hypercapnia, a pH well below 7.20 has been tolerated.[249] The feared consequences of acidemia, projected from the experience with patients having lactic acidosis, failed to materialize. Available data from adults under consented hypoventilation show that the systemic hemodynamic effects are small, even as the pH falls to 7.15. Patients whose pH falls below 7.0 are fewer in number, so firm conclusions cannot be drawn, but they similarly seem to tolerate their respiratory acidemia. What is the limit of hypercapnia for pediatric patients? In a classical report, supercarbia was defined as P_aCO_2 150 mm Hg or higher.[251] In that study, the time course to development of maximal P_aCO_2 (mean, 206 mm Hg) was between 35 minutes and 2 days. Despite supercarbia, the only pathophysiologic change found was temporary neurologic depression, without consequences on the follow-up. Another report described an episode of near-fatal asthma in which P_aCO_2 rose to 293 mm Hg,[115] with a pH of 6.77 and a P_aO_2 of 65 mm Hg. Despite this supercarbia lasting more than 14 hours, no hemodynamic instability was seen. This case illustrates the cardiovascular and neurological tolerance to prolonged supercarbia in a child with previously healthy cardiovascular and neurological systems. This might not be the case for the typical scenario of a critically ill child with multiple system involvement, particularly one with brain injury, who can tolerate only mild hypercapnia, if any.[252] High levels of P_aCO_2 may cause increased respiratory drive and discomfort in the neurologically intact patient, necessitating heavy sedation and sometimes neuromuscular blockade.

Multiple inflammatory, ischemia-reperfusion, and septic animal models models have repeatedly demonstrated that acute HCA may protect against lung and systemic organic injury independently of ventilator strategy, even when it is instituted after the initiation of the lung or systemic injury process.[245,249] This protective effect has been associated with: (1) inhibition of xanthine oxidase and free radical production; (2) down-regulation of inflammatory cells, as HCA inhibits the release of tumor necrosis factor-α and interleukin-1 from stimulated macrophages; and (3) modulation of endothelial

cell and neutrophil expression of interleukin-8, selectins and intercellular adhesion molecules, attenuating lung neutrophil recruitment after both ventilator- and endotoxin-induced ALI. The mechanism underlying the inhibition of cytokine and chemokine production seems to be mediated, at least partially, through the inhibition of nuclear factor-κB (NFκB).[245,249,253]

Benefits of HCA have been demonstrated throughout the body: (1) attenuation of the stretch component of lung injury; (2) provision of protective effects on the myocardium, with better recovery after prolonged cold cardioplegic ischemia, which attenuates hypoxic/ischemic injury in the immature brain; (3) protection of the porcine brain from hypoxia/reoxygenation-induced injury; (4) modulation of neuronal apoptosis, and reduction of lipid peroxidation.[245,249] Hypercapnic acidosis has also been demonstrated to reduce injury initiated by bacterial endotoxin.[253]

The antiinflammatory effects of HCA underlie its protective effects. This powerful antiinflammatory action may reduce the magnitude of the host inflammatory response, thereby ameliorating host-induced tissue damage, as it occurs in non-sepsis models of lung and systemic organ injury.[253]

However, because immunocompetence is essential to an effective host response to microbial infection, concern have been raised with regard to the safety of hypercapnia and/or respiratory acidosis in the sepsis setting. Hypercapnic acidosis produces a broad-based suppression of proinflammatory events that contribute to microbial killing after phagocytosis, which could be detrimental to the host by facilitating bacterial spread and replication. In addition, HCA inhibits repair of pulmonary epithelial wounds,[254] a fact that raises the potential that it could reduce the barrier to access of bacteria from the lung to the bloodstream. At the present time, evidence from relevant preclinical studies supports the notion that the ultimate effect of HCA on bacterial injury may vary from beneficial to harmful, depending on the stage of injury process, that is, depending whether it is an early, an established, or a prolonged infection.[253,255,256]

Recent studies suggest that HCA is protective in the earlier phases of bacterial pneumonia-induced sepsis but may worsen injury in the setting of prolonged lung sepsis. These findings are possibly related to the fact that, in the setting of an early or established bacterial infection, HCA may reduce lung and systemic organ injury by ameliorating host-induced tissue damage. In contrast, in late or prolonged bacterial infection, it is likely that a large bacterial load may exist and hence direct bacterial tissue invasion and spread may play a greater role in tissue damage. Therefore antiinflammatory and immunosuppressive effects of HCA, particularly neutrophil inhibition, might impair bactericidal host responses and prevent any protective effects of reduced host-mediated tissue damage. However, the use of appropriate antibiotic therapy abolished the deleterious effects of HCA in prolonged infection, reducing lung damage and lung bacterial load.[253,255,256] In contrast to the findings in prolonged pulmonary infection, HCA reduced the severity of early, established, and prolonged systemic sepsis. There is evidence that the protective effects of HCA in acute lung injury are more a function of the acidosis than of elevated carbon dioxide per se. It has been showed that both HCA and buffered hypercapnia attenuate the hemodynamic consequences of systemic sepsis,[257] but only HCA, not buffered hypercapnia, reduced the severity of sepsis-induced lung injury. The conclusion so far is that buffering of HCA seems to confer little or no benefit in the setting of experimental sepsis and worsens pneumonia-induced lung injury.[253,257,258]

Therefore buffering HCA is generally not recommended. If it is decided that a specific patient needs some buffering for the respiratory acidemia, perhaps for associated hemodynamic depression, then THAM could be more useful than bicarbonate because it will not increase the P_aCO_2.[259]

The common knowledge states that the clinician must avoid hypercapnia after global cerebral ischemia in order to prevent secondary brain injury and uncontrolled intracranial hypertension. In immature animals, however, several studies consistently report that hypercapnia is neuroprotective after ischemia. In a recent and elegantly designed animal experiment,[260] it was found that mild-to-moderate hypercapnia (P_aCO_2 60 to 100 mm Hg) is neuroprotective after transient global cerebral ischemia/reperfusion injury, with better protection in the group of animals with moderate hypercapnia (P_aCO_2 80 to 100 mm Hg and pH 7.13 ± 0.09). The protective effect was attributed to the modulation of apoptosis-regulating proteins. In contrast, severe hypercapnia (P_aCO_2 100 to 120 mm Hg, pH 7.05 ± 0.1) increased brain injury, which could potentially be attributed to more pronounced brain edema formation. These results suggests a potential role for therapeutic HCA after global cerebral ischemia, a potential paradigmatic change. However, much experimental and preclinical work is still necessary before a clinical application can be considered.

Respiratory Alkalosis

If alveolar ventilation rises out of proportion to CO_2 production, then arterial PCO_2 falls. For any given rate of CO_2 production, an increase in alveolar ventilation always reduces PCO_2. In the ICU environment, hyperventilation occurs in a number of pathological conditions, including salicylate intoxication, early sepsis, hypoxic respiratory disorders, hepatic failure, fever, certain central nervous system alterations, and pain or anxiety (see Table 68-9). The sole presence of respiratory alkalosis is a bad prognosis sign, because mortality increases in direct proportion to the severity of the hypocapnia.[261] The detrimental effects of hypocapnia have been described in many settings: in premature infants in whom it has been associated with poor neurological outcome; in children after severe traumatic brain injury, in whom a relationship between hypocarbia and cerebral ischemia and infarcts have been described[261]; and in children after a cardiopulmonary bypass procedure.[262]

As in acute respiratory acidosis, acute respiratory alkalosis elicits a secondary change in plasma bicarbonate, which has two components. The first is the occurrence of a small-to-moderate acute decrease in the bicarbonate concentration; this fall is dictated by the Henderson-Hasselbalch equation (Equations 4 and 5) and is also due to some tissue buffering.[8,261,263] With the persistence of the hypocapnia, the second component appears: SID will begin to decrease as a result of renal chloride reabsorption, which is associated with a greater decrease in bicarbonate and a rise in urine pH.[5,9,10] By 48 to 72 hours, SID assumes a new, lower, steady state. This occurs because renal adaptation to hypocapnia "backtitrates" the nonbicarbonate buffers, an action that decreases SID and tends to return pH toward normal values, usually with an increased chloride serum concentration.[5]

Usually, blood pH does not exceed 7.55 in most cases of respiratory alkalosis, and severe manifestations of alkalemia are

unusual. Therefore management is directed at the underlying cause. Marked alkalemia can occur in certain circumstances: inappropriate mechanical ventilation parameters, central nervous system disorders, and some psychiatric diseases, not often seen in children. Typically, mild acid-base changes are clinically more important for what they can alert the clinician to, in terms of the underlying disease, than for any threat they may pose to the patient. Accordingly, specific measures directed to compensate the pH are not usually required. The anxiety-hyperventilation syndrome, more commonly seen in adolescents in the emergency department than in the critical care unit, can be an exception. In such cases, an active therapeutic approach with assistance from the hospital's psychological team is required. In rare cases, sedation may be necessary.

Pseudorespiratory Alkalosis

Arterial hypocapnia does not necessarily imply respiratory alkalosis or the secondary and compensatory response to metabolic acidosis. The presence of arterial hypocapnia in patients with profound circulatory shock has been termed pseudorespiratory alkalosis or, simply, venoarterial carbon dioxide gradient.[124] This condition can be seen when alveolar ventilation is relatively preserved but profound cardiovascular depression exists. In such conditions, the severely reduced pulmonary blood flow limits the CO_2 delivered to the lungs for excretion. On the other hand, the increased ratio of ventilation to perfusion and the increased pulmonary transit time result in the removal of a larger-than-normal amount of CO_2 per unit of blood traversing the pulmonary circulation.[264] Thus, despite decreased CO_2 delivery to the lungs, a situation that provokes a significant elevation of the mixed venous blood CO_2, arterial normocapnia, or frank hypocapnia may be noted. Overall CO_2 excretion is markedly decreased, however, and the CO_2 balance of the body is positive, a phenomenon that is the hallmark of respiratory acidosis. Marked tissue acidosis is reflected in mixed venous blood acidemia, usually involving both metabolic and respiratory components. The metabolic component derives from tissue hypoperfusion and hyperlactatemia. This is accompanied by an arterial pH that ranges from mildly acidic to frankly alkaline. This venous-arterial PCO_2 gradient increases as cardiac index decreases.[124,264,265] In animal models, both venous-arterial PCO_2 gradient and venous-arterial pH difference increase as oxygen delivery declines. In septic shock, an elevated venous-arterial PCO_2 gradient is seen in both those patients with low cardiac output and those with pulmonary disease who cannot eliminate CO_2.[266] In patients with cardiogenic shock, the venous-arterial PCO_2 gradient decreases as hemodynamic variables improve with dobutamine, a phenomenon also seen in pediatric septic shock with myocardial depression. In this setting, arterial oxygen saturation may appear to be adequate despite tissue hypoxemia because of the shift to the left of the oxygen-hemoglobin dissociation curve caused by hypocapnia. This condition may be rapidly fatal unless cardiac output is rapidly corrected.

Mixed Acid-Base Derangements

Coexisting metabolic acidosis and respiratory acidosis can be seen in several clinical conditions, for example during cardiopulmonary arrest, in bronchopulmonary dysplasia complicated with pneumonia and septic shock, in renal and pulmonary insufficiency, and as a consequence of certain toxic agents that may provoke both neural depression (and hypoventilation) and cardiocirculatory collapse (and metabolic acidosis).[10,24,43,51] As usual, treatment must be targeted to the underlying causes. In addition, both components of the acid-base derangement must be addressed. The first step will always be the ABCs: to secure the airway, to provide oxygenation and controlled hyperventilation, and to infuse fluids or vasoactive-inotropic agents according to the clinical condition of the given patient. Administration of an alkalinizing agent should be considered only after ventilation has begun and on the basis of results of the arterial blood gas analysis.

Alkalemia of both metabolic and respiratory origin may occur in several complex settings, such as in patients with chronic liver disease in whom hyperventilation ensues as the initial manifestation of pneumonia.[267] This hypocapnia appears in patients in whom metabolic alkalosis is common because of vomiting or gastric drainage, hypokalemia, diuretics, or alkali administration.[43,267] Mixed alkalosis may also occur in patients with chronic renal insufficiency in whom primary hypocapnia develops. In this setting, inappropriately high plasma bicarbonate levels occur as a consequence of the nonexistent renal adaptive response. This situation is seen despite the patient's dialysis program, because the dialytic procedures exert an alkalinizing influence and are much less effective in compensating alkalemia than acidemia.[226,268] This effect can be minimized by switching the patient from peritoneal dialysis to hemodiafiltration or hemodialysis.

Both the physicochemical (SIG and SID_{EFF}) and the modified SBE approaches are well suited for unmasking coexisting mixed acid-based disorders.

Acid-Base Balance in Special Situations

Hypothermia

Systemic hypothermia is one of the strategies employed for brain preservation and end-organ protection in global ischemia scenarios. Hypothermia is routinely applied in cardiopulmonary bypass for cardiac surgery, and thus anesthesiologists deal with most acid-base derangements during profound hypothermia in the operating room (see Chapter 30).[269] However, pediatric intensivists need to master these concepts, too; therapeutic hypothermia may become more widely used in the management of anoxic neurologic injury, such as after cardiopulmonary arrest or in traumatic brain injury with intracraneal hypertension.[270,271] Hypothermia has also been applied in adult patients with large ischemic stroke, and can occur accidently after near-drowning in ice water, or with other environmental exposures.

As temperature decreases, the dissociation constant ($pK_a = -\log_{10}K_a$) of aqueous systems, such as plasma and cytoplasma, increases. This results in a reduction in the concentration of OH^- and H^+ ions; that is, as temperature drops, H^+ decreases, and pH increases. Hence, the measured pH in an electrochemically neutral cell at 37° C is 7.40, whereas in an electrochemically neutral cell at 20° C, the measured pH will be 7.80. Changes in cellular pH during hypothermia are mediated through PCO_2 homeostasis. As temperature decreases, the solubility of CO_2 in blood increases, which in turn yields a reduction in PCO_2. For example, if the total CO_2 content is held constant, and the measured PCO_2 at 37° C is 40 mm Hg, then the measured PCO_2 at 20° C will be 16 mm Hg. This phenomena causes pH to increase

as temperature decreases and electrochemical neutrality is maintained. When a blood sample is introduced in a blood-gas analyzer, the sample is warmed to 37° C before measurement. The values obtained at 37° C are called the *temperature-uncorrected* values. These values are converted by the blood-gas analyzer to *temperature-corrected* values (actual patient's temperature) using a nomogram that accounts for temperature-induced changes in pH, and in O_2 and CO_2 solubility. If pH and PCO_2 are measured at 37° C, and then corrected to a lower temperature, the corrected pH will be higher and the corrected PCO_2 will be lower than the values at 37° C.

Alpha-Stat and pH-Stat

Alpha-stat and pH-stat are acid-base management methods that directly influence blood flow to the brain and other organs, and they can both be applied using either corrected or uncorrected blood gases. At a patient temperature of 37° C, there is no difference between alpha-stat and pH-stat management. The difference between these two strategies becomes apparent as patient temperature progressively decreases below 37° C, and is not clinically relevant until patient temperature is around 30° C and below. Alpha-stat strategy has solid theoretical foundations. It is well known that functions of proteins are critically dependent on their tertiary and quaternary structures, which in turn depend on the ionic charges of individual amino acid constituents. Thus, intracellular proteins must have a buffer of their own to keep a constant ionizing state in spite of pH change. The imidazole moiety of the amino acid histidine has a pK_a that is similar to pK_a of the water, and hence undergoes ionization with temperature changes in a similar proportion as water. The portion of the histidine imidazole group that loses a proton, acting as a buffer to maintain electrical neutrality is designated alpha-imidazole. Thus while changes in temperature will affect the degree of dissociation (i.e., pH) of water, the ionization state of the proteins will remain the same because it will adapt to the new temperature-influenced pH. Hence, proteins will maintain their structure and function regardless of the temperature.

According to the alpha-stat hypothesis, alpha-stat management is quite simple: electrochemical neutrality is maintained by keeping pH in the alkalotic range in temperature-corrected blood gases and normal in temperature-uncorrected gases. For practical purposes, it is easier to use uncorrected gases and make any necessary adjustment in order to keep pH at 7.4 and P_aCO_2 at 40 mm Hg at 37° C, regardless of the patient's body temperature. On the contrary, in the pH-stat approach, interventions are directed toward maintaining pH 7.4 and P_aCO_2 40 mm Hg, irrespective of patient's core body temperature. This means that the goal is to keep pH and PCO_2 at normal values for 37° C when the patient's body-temperature-corrected gases are used, and at acidotic values when temperature-uncorrected gases are used. For practical purposes, pH-stat is maintained by adding CO_2 to the ventilating gas during hypothermic cardiopulmonary bypass to increase PCO_2 and decrease the pH. In contrast to alpha-stat approach, in which CO_2 content is held constant, pH-stat regulation results in an increase in total CO_2 content.

There is still debate as to whether pH-stat or alpha-stat management should be used during deep hypothermia and circulatory arrest in neonates, infants, and children. Based on the theoretical advantages of maintaining electrochemical neutrality during hypothermia, in the early 1980s, the strategy at Boston Children's Hospital switched from pH-stat management to alpha-stat management. Within a short period, the incidence of severe neurologic injury in the form of choreoathetosis increased markedly following procedures under deep hypothermia cardiac arrest.[269,272] After this negative experience and the clinical trial that resulted from it, and on the basis of other preclinical and clinical data, the current best evidence suggests that the best technique to follow in the acid-base management of patients undergoing deep hypothermic circulatory arrest during cardiac surgery is dependent upon the age of the patient, with better results using pH-stat in the pediatric patient and alpha-stat in the adult patient.[272,273] This is not surprising, as the mechanisms of cerebral injury between adults and young children are quite different. Intraoperative cerebral injury in adults primarily relates to atheromatous emboli or fixed vascular stenoses. In contrast, in neonates and infants, brain injury more commonly results from global hypoperfusion. There are no studies assessing the age in which the switch from pH-stat to alpha-stat approach should occur, nor which type of acid balance management should be used in other scenarios in which therapeutic hypothermia is applied.

Summary

When one approaches a critically ill child with an acid-base imbalance, the first step is to define the nature of the disorder: acidosis versus alkalosis, acidemia versus alkalemia, simple versus mixed, acute versus chronic, severe and harmful versus neither severe nor harmful. The available tools for answering these questions are numerous. The easiest way to screen the acid-base status is to take a glimpse at venous bicarbonate (or CO_{2TOT}) concentration. However, a normal concentration (22 to 26 mEq/L) does not rule out the possibility of an acid-base derangement. So, if the clinical setting raises the suspicion of an illness known to be associated with acid-base imbalances, at the very least plasma electrolyte concentrations must be obtained, along with albumin levels, to calculate the AG_{CORR}. If bicarbonate (or CO_{2TOT}) or AG_{CORR} is abnormal, or a complex, potentially harmful, mixed acid-base disorder is suspected, an arterial blood analysis must be done, which will provide information on pH, $Paco_2$, and SBE. The classical bicarbonate-centered observational patterns must be applied. If available, lactate levels must be obtained too. This is mandatory if metabolic acidosis exists (with or without acidemia). If there is the suspicion of the presence of unmeasured anions and/or a mixed acid-base problem, it is advisable to calculate SID_{APP}, SID_{EFF}, and SIG, to delve deeper into the possible pathophysiological mechanisms underlying the acid-base unbalance. Care must be taken to review the patient's history for hemodynamic resuscitation with large volumes of normal saline solutions. If that is the case, special attention must be given to chloride levels and to analyzing the effect of the different components of acid-base physiology on SBE ("partitioned SBE"). The severity, potential harm of the acid-base derangement, and probable therapeutic intervention must be all defined. There is compelling evidence that abnormal pH by itself may not be as dangerous as once thought. However, an individualized approach must be taken in order to decide if a given patient has the chance of benefit or not from the attempt to modify his/her pH and acid-base status.

References are available online at http://www.expertconsult.com.

V

Chapter 69

Tests of Kidney Function in Children

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PEARLS

- As a marker of glomerular function, serum creatinine provides a crude assessment because it is influenced by several factors other than glomerular filtration, of which the amount of muscle mass is clinically most significant.
- Prediction formulas in children provide a better estimate of glomerular filtration rate GFR than serum creatinine alone because they incorporate surrogate variables for muscle mass.
- Neither serum creatinine nor the prediction formula is valid when renal function changes rapidly, yet both are used clinically as better alternatives are not available. It is essential to recognize that use of serum creatinine or creatinine-based equations in the setting of developing acute kidney injury (AKI) and prior to the establishment of a new steady state will result in an overestimation of GFR. On the other hand, in the recovery phase of AKI, their use will result in an underestimation of GFR.
- Formal clearance studies are still clinically essential to assess renal function in select patients with atypical body habitus or diet.
- Novel biomarkers for AKI, when grouped in a panel, may provide improved sensitivity to acute and small changes in renal function, but further studies to validate these markers are still needed.

Renal dysfunction and injury are not unusual in the critically ill child and may develop as a consequence of the underlying disease process (e.g., hypoperfusion secondary to sepsis, progressive glomerulonephritis) or its therapy (e.g., aminoglycoside toxicity). The ability to accurately, precisely, and rapidly assess renal function is essential for the early detection of acute kidney injury (AKI), for dose adjustments of medications excreted by the kidney, in risk assessment for imaging studies involving intravenous contrast agents or gadolinium, and for monitoring for medication-related nephrotoxicity. Until recently, a consensus for defining acute kidney injury (AKI) did not exist. AKI is now recognized to encompass a spectrum of disease ranging from mild, reversible, renal dysfunction to severe, potentially irreversible organ failure with need for dialysis support. In 2004, the Acute Dialysis Quality Initiative proposed the RIFLE (Risk, Injury, Failure, Loss, and End Stage Renal Disease) classification scheme for defining AKI in adults based on changes in serum creatinine or urine output.[1] This has since been modified for use in children (pRIFLE), in whom the severity of AKI is stratified based on changes in estimated GFR or urine output (Table 69-1).[2] The true incidence of AKI in the pediatric intensive care unit (PICU) is not well established due to the absence of a consensus definition, but recent studies suggest it is increasing.[3] Despite advances in pediatric critical care and dialysis, morbidity and mortality rates associated with AKI remain high.[4] Therapeutic intervention trials for AKI have had disappointing results, which can be attributed in part to delays in diagnosis as well as to the heterogeneity of patients enrolled.[5,6] Earlier recognition and intervention for AKI may provide a greater potential for recovery and/or stabilization of renal function. However, the early detection of impending AKI is severely limited by the lack of sensitive and specific tools currently available to assess renal function.

Assessment of Glomerular Function and Injury

Glomerular filtration rate (GFR) is considered the best overall indicator of kidney function but remains challenging to accurately and efficiently measure in clinical practice. Functionally, the total kidney GFR is determined by the cumulative number of nephrons and the GFR within each nephron (single nephron glomerular filtration rate, or SNGFR). Conceptually, it represents the volume of plasma that could be completely cleared of a substance per unit of time. Kidney function may therefore decline due to hypoperfusion, resulting in a decrease in SNGFR, or due to nephron injury, resulting in fewer functioning nephrons. The kidney has a certain degree of reserve and attempts to adapt to nephron loss by increasing the SNGFR of the remaining nephrons, thus maintaining total kidney GFR initially and masking early renal injury. Indeed, by the time the GFR actually falls, significant injury has already occurred. Loss of this renal reserve is one of the earliest manifestations of renal injury but is even more challenging to measure than GFR.[7-9]

Glomerular filtration is a dynamic variable that can fluctuate in a given individual by as much as 7% to 8% from day to day based on differences in hydration status and protein consumption.[10,11] GFR is also influenced by age, gender, and body size and therefore varies between individuals as well. Therefore, to facilitate comparison of GFR amongst children

Table 69–1 Pediatric Modified RIFLE Criteria

	Estimated CCl	Urine output
Risk	eCCl decrease by 25%	<0.5 mL/kg/h for 8 h
Injury	eCCl decrease by 59%	<0.5 mL/kg/h for 16 h
Failure	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m²	<0.5 mL/kg/h for 24 h *or* anuric for 12 h
Loss	Persistent failure >4 wk	
End stage	End-stage renal disease (persistent failure >3 mo)	

eCCl, Estimated creatinine clearance.
Modified from Akcan-Arikan A, Zappitelli M, Loftis LL, et al: Modified RIFLE criteria in critically ill children with acute kidney injury, *Kidney Int* 71(10):1034, 2007.

Table 69–2 Normal GFR Values for Children

Age	GFR (mL/min/1.73 m²)	Range (mL/min/1.73 m²)
Preterm (<34 wk)		
2–8 days	11	11–15
4–28 days	20	15–28
30–90 days	50	40–65
Term (>34 wk)		
2–8 days	39	17–60
4–28 days	47	26–68
30–90 days	58	30–86
1–6 mo	77	39–114
6–12 mo	103	49–157
12–19 mo	127	62–191
2–12 yr	127	89–165

Modified from Heilbron DC, Holliday MA, al-Dahwi A, et al: Expressing glomerular filtration rate in children, *Pediatr Nephrol* 5(1):5-11, 1991.

and adults of considerably different size, absolute GFR is normalized to body surface area (BSA), which correlates well with kidney weight, the most direct standard of reference.[12] Appreciation of the maturational increase in GFR that occurs during infancy is also necessary for proper assessment of kidney function in children. At birth, the mean GFR is quite low (20.3 mL/min/1.73 m^2 in term infants), due to renal immaturity, but yet sufficient to meet the metabolic demands of a healthy infant. The GFR doubles within the first 2 weeks of life and then continues to gradually increase to reach a mean of 77 mL/min/1.73 m^2 between 1 and 6 months of age and adult levels of 120 to 130 mL/min/1.73 m^2 by approximately 2 years of age (Table 69-2).[13]

GFR itself cannot be directly measured but can be assessed by measuring the clearance of an ideal filtration marker, or estimated using predictive formulas. Urinary or plasma clearance studies provide the greatest accuracy but are expensive, time-consuming, and labor-intensive. Consequently, they are used mainly for research and in select clinical situations where a very accurate assessment of kidney function is needed (e.g., chemotherapy dosing). For the daily clinical management of patients, serum creatinine and GFR estimating equations are used most commonly. They offer the advantage of being convenient, noninvasive, and inexpensive with timely accessibility of results. However, accuracy and sensitivity to small changes in renal function are sacrificed, making the detection of acute, early renal dysfunction difficult. The search for novel biomarkers of renal function (such as cystatin C) and early renal injury (e.g., neutrophil gelatinase-associated lipocalin [NGAL]) has therefore been a major focus in the field of AKI. However, data regarding these markers have been somewhat conflicting.

Renal Clearance Techniques

Inulin

The renal clearance of inulin remains the gold standard for measuring GFR. Inulin is an uncharged 5.2 kDa polymer of fructose that possesses many characteristics of an ideal filtration marker. It is not protein-bound and is freely filtered at the glomerulus without being reabsorbed, secreted, or metabolized by the kidney. Further, it is eliminated exclusively by the kidney.[14] The filtered load of inulin (GFR × P_{in}) is therefore equal to its urinary excretion ($U_{in} \times V$) where P_{in} and U_{in} are the plasma and urine concentrations of inulin (mg/dL), respectively, and V is the urine flow rate (mL/min). The renal clearance of inulin (C_{in}) can be calculated:

$$C_{in} = GFR = (U_{in} \times V) / P_{in}$$

When used for children, however, this must be scaled for BSA:

$$C_{in} = GFR = [(U_{in} \times V) / P_{in}] \times [1.73\ m^2 / BSA]$$

The classic protocol for inulin clearance is cumbersome, involving an intravenous infusion of inulin over several hours and serial timed blood and urine specimens. Properly done, inulin clearances provide the most accurate measure of GFR; however, the complexity of the protocol introduces a potential for significant error. Incomplete urine collections, for example, diminish the accuracy of the test and can be particularly problematic in children who are not yet toilet-trained or who have urologic disease (e.g., vesicoureteral reflux, bladder dyssynergia) affecting their ability to spontaneously void to completion. Placement of a bladder catheter or use of a bladder scanner may therefore improve accuracy, although the former may pose a small risk of infection and the latter may be of limited benefit in children with vesicoureteral reflux. Limited availability of inulin, technical issues pertaining to its assay, and the laborious nature of the protocol make it impractical for routine clinical use.

Iothalamate

Iothalamate (MW 614 Da) is also freely filtered by the glomerulus and has been studied extensively as an alternative exogenous marker for GFR measurements. Unlike inulin, however, iothalamate has some protein binding (<8%) and proximal tubular secretion (10%) raising concern for overestimation of GFR. Reported correlations between iothalamate and inulin renal clearances in the literature have been variable, with some studies demonstrating good correlation, whereas most suggest that iothalamate overestimates inulin clearance.[15-17]

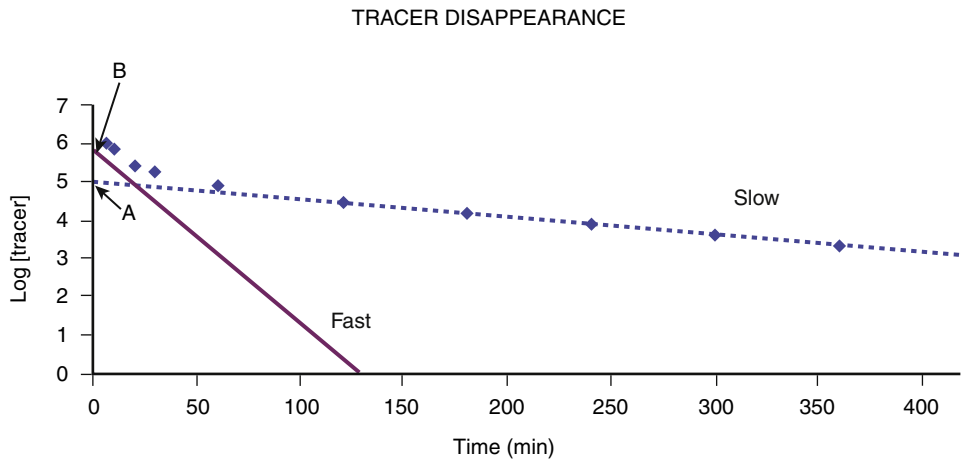

Figure 69–1. Plasma disappearance of filtration marker as a function of time after injection into blood. The curve is composed of two components: the slow curve with slope α and intercept A and the fast curve with slope β and intercept B. *(Modified from Schwartz GJ, Furth SL: Glomerular filtration rate measurement and estimation in chronic kidney disease,* Pediatr Nephrol *22[11]:1839-1848, 2007.)*

Creatinine Clearance

Clearance studies that make use of endogenous markers such as serum creatinine obviate the need for a constant infusion and make the study more amenable to clinical practice. However, the problems associated with timed urine collections persist and accordingly limit the usefulness of this technique, particularly in children. Further, creatinine is a flawed filtration marker. Although it is predominantly eliminated by glomerular filtration, a small but variable amount (~10%) is eliminated by tubular secretion. As renal function deteriorates, the proportion of secreted to filtered creatinine progressively increases, leading to an overestimation of GFR and making creatinine clearance a more unreliable measure of GFR.[11] Administration of oral cimetidine beginning 2 days prior to the study can at least partially circumvent this issue by inhibiting the tubular secretion of creatinine.[18] Although timed urine collections are still necessary, they are typically obtained over a 2-hour period facilitating performance in a monitored clinic setting.

Guidelines from the National Kidney Foundation no longer recommend routine performance of creatinine clearance studies to estimate GFR, as prediction formulas are now felt to be more accurate.[19] Nonetheless, creatinine clearance-based studies can still be helpful when assessing renal function in individuals with atypical body composition (e.g., anorexia, malnutrition) or dietary intake (e.g., vegetarian diet).[20]

Plasma Disappearance Techniques

Plasma disappearance techniques further simplify the measurement of GFR and avoid the need for urine collections. They are most commonly performed using a single intravenous injection technique, although constant infusion and subcutaneous protocols are also available.[15,21,22] Serial blood samples collected at specified times over a several-hour period following injection of the filtration marker are used to generate a plasma disappearance curve. This curve can be well approximated by a double exponential curve that is characterized by an initial "fast" curve and a later "slow" curve as illustrated in Figure 69-1. The initial "fast" curve represents the distribution phase and reflects renal elimination as well as diffusion of the marker into the extravascular space, whereas the late "slow" curve reflects only the renal elimination phase. Renal clearance can be calculated by dividing the delivered dose by the entire area under the plasma disappearance curve.[23] Modification from a two-compartment model to a one-compartment model focusing on the renal elimination phase simplifies the procedure, reducing the number of required blood specimens to two. GFR can then be derived from the slope of the slow curve but requires incorporation of a correction factor to compensate for overestimation of the GFR, which results from exclusion of the area under the fast curve.[23-26] Appropriate timing of the specimens is critical to ensure an accurate estimation of GFR. The first sample must be obtained after the marker has equilibrated, typically 2 hours after injection. The second specimen is obtained approximately 5 hours after injection but, in subjects with more advanced chronic kidney disease, this may need to be delayed further to minimize overestimation of the GFR, which can result from an inaccurate depiction of the lower slope of the plasma disappearance curve.[25] The validity of the single-compartment model may also be compromised in edematous states where the volume of distribution is increased, or with extravasation of the tracer at the injection site, as this decreases the actual dose delivered.[24] Unfortunately, when performed correctly, plasma disappearance studies are time-consuming and perhaps too complex for routine clinical care.

Radioisotopes

Plasma clearance studies are most commonly performed with radioisotopes that are more readily available and easier to assay than inulin. Their major disadvantage is, of course, radiation exposure, which limits their use, particularly in children.[27] ^{51}Cr-EDTA, ^{99m}Tc-DTPA, and ^{125}I-Iothalamate have been extensively studied and compared to inulin renal clearance.[15,28] All are low-molecular-weight compounds that are freely filtered by the glomerulus but which differ slightly in protein binding and renal handling. ^{51}Cr-EDTA (292 Da), appears to have little protein binding, and its plasma clearance correlates well with inulin clearances. It is commonly used in

Europe but is unavailable in the United States.[25] ^{99m}Tc-DTPA (393 Da) is most frequently used in the United States but demonstrates variable accuracy in GFR measurements based on product source, differences in protein binding, and potential dissociation of the chelate ($t_{1/2}$ = 6 hours) during the study.[29] ^{125}I-Iothalamate (614 Da) is a high-osmolar anionic contrast agent with some protein binding that also undergoes active secretion by the proximal tubule, contributing to overestimation of plasma clearance compared to inulin or EDTA.[17] Nuclear GFR studies can also be performed using a gamma camera, which measures the renal uptake of the tracer 2 to 3 minutes after injection and which can provide information regarding differential kidney function; however, the estimated GFR obtained this way is not as accurate as with the plasma-sampling technique.[25] To reduce radiation exposure, plasma clearance studies can also be performed using nonradiolabeled iothalamate which can be measured by high-performance liquid chromatography (HPLC).[30, 31]

Iohexol

Iohexol is emerging as an excellent alternative to inulin and radioisotopes for clearance studies. Iohexol (Omnipaque) is a low-molecular-weight (821 Da), nonionic, low-osmolar intravenous contrast agent used routinely in the United States for radiologic studies at doses appreciably higher than that required for GFR studies.[32,33] It is almost entirely eliminated through glomerular filtration and is not reabsorbed, secreted, or metabolized by the kidney, thus fulfilling many of the desired traits of an ideal filtration marker. Further, it has minimal protein binding and negligible extrarenal elimination even in advanced chronic kidney failure.[32,34] Though it can easily be measured by x-ray fluorescence or high-performance liquid chromatography, the latter is more sensitive and, therefore, requires a significantly lower dose of iohexol for the study.[33,35] Iohexol has been safely used for clearance studies for many years in Scandinavia.[32,36,37] Its excellent safety profile has recently been confirmed in the United States in over 1000 GFR estimations performed as part of the Chronic Kidney Disease in Children (CKiD) study, a multicenter, prospective, observational, cohort study of the progression of chronic renal failure.[26,38] (G.J.S., unpublished observations). Iohexol plasma clearance results appear to be comparable to renal inulin clearance and plasma EDTA disappearance studies across a broad range of GFR.[33,39,40]

Plasma Markers

Creatinine

Serum creatinine is the most commonly used laboratory study to assess renal function in clinical practice. It is simple, convenient, and practical—requiring a single blood sample—and therefore well suited for serial examination. However, the relationship between serum creatinine and GFR is quite complex, being influenced by several factors other than GFR. Therefore, at best, creatinine provides a crude estimate of the GFR. As illustrated in Figure 69-2, serum creatinine bears an inverse, nonlinear relationship with GFR and lacks sensitivity to acute and small changes in GFR. Notably, at low levels of serum creatinine corresponding to normal renal function, a substantial decrease in GFR may occur before being reflected by even a small increase in serum creatinine. In contrast, at higher levels of serum creatinine associated with renal failure, the same absolute rise in creatinine reflects a much smaller loss of remaining renal function. To a first approximation, every doubling of the serum creatinine represents a 50% decline in remaining GFR.

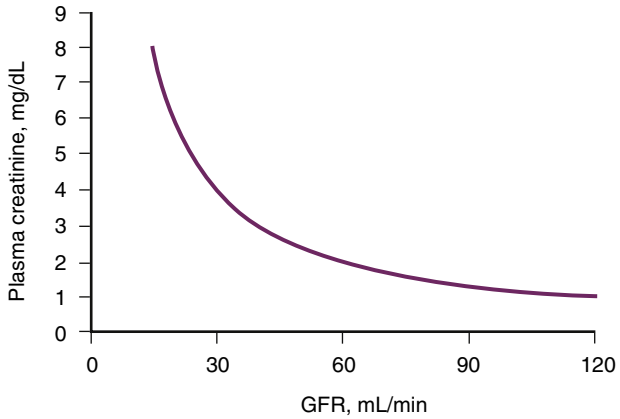

Figure 69–2. Idealized relation between the steady-state levels of serum creatinine and GFR in adults. When renal function is normal, a marked decrease in GFR can be associated with only a mild increase in serum creatinine.

Ideally, an endogenous marker such as creatinine can serve as a useful surrogate for GFR if it is produced at a constant rate and eliminated only via the kidney at a rate equivalent to its production rate such that a steady state exists. Figure 69-3 illustrates the relationship between the plasma level of an endogenous filtration marker, its generation (from cells and diet), and its elimination (renal and extrarenal). Ideally, elimination of the marker must occur exclusively by glomerular filtration. The serum level of the marker would then be expected to rise with renal impairment. Serum creatinine, however, does not strictly fulfill these criteria. Although creatinine production is relatively constant, it varies amongst and within individuals.[41] It is derived from the nonenzymatic dehydration of muscle creatine and hence is highly dependent on muscle mass. Consequently, in children, creatinine generation fluctuates with growth in addition to diet and illness, as seen with adults.[41] The reference range for serum creatinine levels representing normal GFR will thus vary with age, size, and gender after puberty. The relationship between GFR and serum creatinine is therefore particularly complex in children. Maturational changes in serum creatinine and GFR do not parallel one another. GFR is physiologically low at birth, whereas serum creatinine is elevated; however, because of fetal-maternal placental equilibration of creatinine, the elevated creatinine is not indicative of the infant's renal function but rather the mother's. Following birth, GFR steadily increases, reaching adult levels over the next 2 years. Serum creatinine, on the other hand, declines over the first few weeks, becoming reflective of the infant's renal function. The creatinine level then remains stable until approximately 2 years of age as muscle mass accrues proportionally to the increase in GFR. Beyond 2 years of age, when GFR per BSA has fully matured, the ongoing accretion of muscle results in a progressive rise in serum creatinine until adolescence, when adult levels are achieved (0.7 mg/dL for adolescent females and 0.9 mg/dL for adolescent males). Superimposition of a severe or chronic illness associated with malnutrition and muscle wasting makes the interpretation of GFR from serum

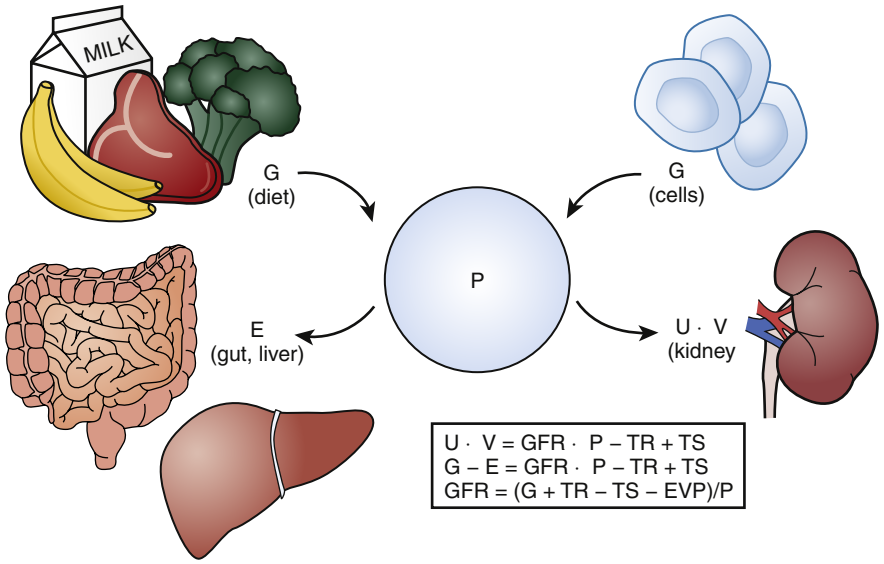

Figure 69–3. Determinants of the serum level of endogenous filtration markers. The plasma level (*P*) of an endogenous filtration marker is determined by its generation (*G*) from cells and diet, extrarenal elimination (*E*) by gut and liver, and urinary excretion (*U* + *V*) by the kidney. Urinary excretion is the sum of filtered load (*GFR* × *P*), tubular secretion (*TS*), and reabsorption (*TR*). In the steady state, urinary excretion equals generation and extrarenal elimination. By substitution and rearrangement, GFR can be expressed as the ratio of the non-GFR determinants (G, TS, TR, and E) to the plasma level. *(Modified from Stevens LA and Levey AS: Measured GFR as a confirmatory test for estimated GFR,* J Am Soc Nephrol *20:2305-2313, 2009.)*

creatinine alone even more difficult in the pediatric patient. For example, at first glance, maintenance of a stable creatinine in a patient with a prolonged ICU course may be reassuring for preservation of renal function; however, if significant muscle atrophy has occurred, this actually suggests deterioration of renal function.

The second requirement, that excretion of the marker occurs only by glomerular filtration, is also flawed in the case of creatinine. Although the majority of serum creatinine is eliminated by glomerular filtration, a small but unpredictable amount is eliminated by tubular secretion and gastrointestinal degradation. Proximal tubular secretion of creatinine typically accounts for approximately 10% of its elimination, although considerable inter- and intra-individual variability exists.[42] At normal levels of GFR, the impact of tubular secretion on GFR is minimal. However, with deteriorating renal function, the proportion of secreted versus filtered creatinine increases, resulting in a lower serum creatinine than predicted for the true level of GFR, thus decreasing the sensitivity for serum creatinine to detect mild decreases in renal function.[42] A similar phenomenon occurs in the setting of moderate-to-severe renal failure, when the bacterial degradation of creatinine within the gastrointestinal tract can become clinically significant, leading to a decrease in serum creatinine concentration.[43,44] Failure to recognize the influence of tubular secretion and gastrointestinal elimination on serum creatinine values can result in overestimation of renal function and may lead to higher, inappropriate dosing of medications. Conversely, in patients with advanced kidney failure, administration of medications (e.g., cimetidine, trimethoprim) that inhibit the tubular secretion of creatinine or administration of antibiotics that mitigate the gastrointestinal degradation of creatinine may result in an elevation of serum creatinine and subsequent underestimation of GFR without any true change in renal function. If not appreciated, this may be misconstrued as worsening renal function and lead to potential underdosing of medications.

Third, the requirement for a steady state cannot be overemphasized. When GFR abruptly declines with AKI, the production rate of creatinine exceeds its clearance rate leading to a gradual rise in serum creatinine that lags behind the true GFR. (Figure 69-4) During this period, serum creatinine does not accurately reflect the true GFR, which is unknown. Nonetheless, serum creatinine is still typically used to crudely estimate renal function as better alternatives do not currently exist. However, it must be recognized that use of the serum creatinine or creatinine-based estimating equations (see below) to estimate GFR prior to the establishment of a new steady state will result in overestimation of the renal function. Similarly, during the recovery phase of AKI, serum creatinine cannot be used to estimate GFR as it will again lag behind the true GFR until the kidney clears the accumulated creatinine and reaches a new steady state. Use of serum creatinine to estimate GFR during the recovery phase of AKI will therefore result in an underestimation of true GFR.

Finally, analytical factors related to the creatinine assay itself provide another potential source of error when assessing GFR. True creatinine levels can be measured by isotope dilution mass spectroscopy (IDMS) or HPLC, but these are expensive and not readily available for routine clinical use.[45] Enzymatic creatinine assays exhibit greater specificity for creatinine than the conventional Jaffe alkaline picrate method, and are now available in many laboratories. Due to the enhanced specificity, enzymatic creatinine levels run closer to HPLC values and approximately 10% to 30% lower than Jaffe creatinine levels. However, enzymatic assays differ in their performance, some being more influenced by interfering substances than others. Although problems with accuracy and precision still persist, the coefficient of variation using new autoanalyzers is now approximately 3%, and significantly lower than for the Jaffe assay.[41,46] Nonetheless, according to the 2007 College of American Pathologists, many laboratories still use a modified version of the Jaffe

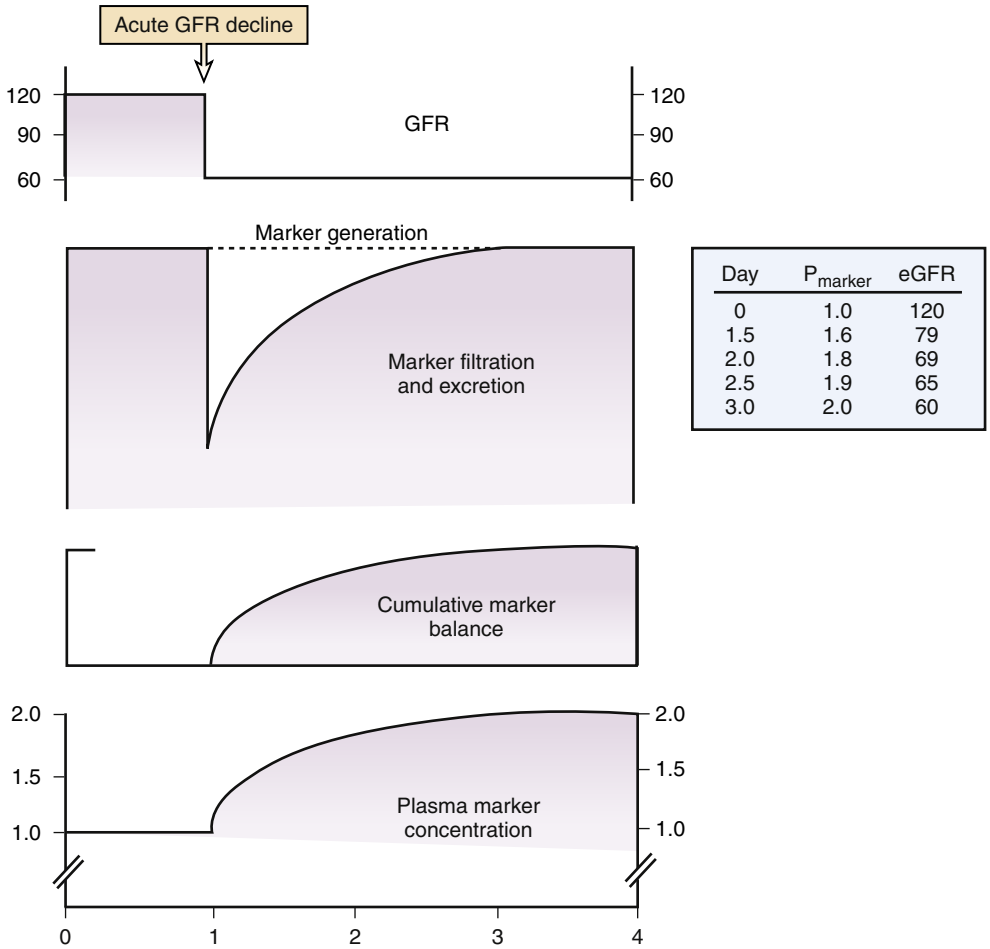

Figure 69–4. Following an acute decline in GFR, filtration and excretion of an endogenous marker (e.g., creatinine) decrease while production of the marker remains constant, leading to a gradual rise in serum marker concentration over several days. During this period, use of the serum level of the marker to assess GFR will result in an overestimate, as illustrated above (where eGFR is expressed in mL/min/1.73 m^2). The increase in serum marker level results in a higher filtered load until a new steady state is achieved such that the production and filtration rates of the marker are again equivalent, assuming tubular secretion and extrarenal elimination are negligible. Once a new steady state is achieved, eGFR approaches GFR. *(Modified from Stevens LA, Levey AS: Measured GFR as a confirmatory test for estimated GFR,* J Am Soc Nephrol *20:2305-2313, 2009; and Kassirer JP: Current concepts: clinical evaluation of kidney function: glomerular function,* N Engl J Med *285[7]:385-389, 1971.)*

assay because it is less expensive than enzymatic assays.[47] The Jaffe method is based on an alkaline picrate colorimetric reaction that tends to falsely elevate the true creatinine by up to 20% (for creatinine ~1 mg/dL) due to the presence of interfering, noncreatinine chromagens. This effect is greatest at the lower levels of creatinine typically observed in children.[48] By falsely elevating the true creatinine, the Jaffe creatinine underestimates the GFR. Indeed, analytical variability is believed to play a greater role than biologic variability in the day-to-day fluctuations of creatinine measurements.[41] An international effort to standardize creatinine measurements in clinical laboratories through use of a uniform assay and calibration materials has recently been launched.[49] Unfortunately, neither a standardized assay for creatinine nor standardized pediatric reference material for use by manufacturers to improve the accuracy and precision of assays in the pediatric range exists at this time.[45]

Proper interpretation of the serum creatinine as a measure of GFR, therefore, requires the physician to be knowledgeable about the clinical variables, physiologic processes, and analytical factors that can affect creatinine levels (Table 69-3). Although the clinical laboratory provides normative reference ranges alongside the results, clinicians should confirm that the reported references are age-appropriate and also realize that if the patient has decreased muscle mass (e.g., spina bifida, anorexia), even these age-appropriate reference ranges will be incorrect.

Cystatin C

The well-established limitations of serum creatinine highlight the critical need to identify alternative biomarkers of renal function that have improved sensitivity and specificity. Low-molecular-weight proteins have been considered potential candidate markers as they are excreted primarily by glomerular filtration. Several low-molecular-weight proteins have been considered but cystatin C, a 13-kDa cationic cysteine protease inhibitor produced at a constant rate by all nucleated cells, has shown the greatest promise. Like creatinine, it is freely filtered at the glomerulus[50] but, unlike serum creatinine, it is not secreted by the tubules; rather, it is completely reabsorbed and metabolized by the proximal tubule epithelial cells.[51] In most studies, the production of cystatin C is not significantly affected by age, gender, and muscle mass, making it

Table 69–3 Non-GFR Factors Affecting Creatine Levels in Children

	SERUM CREATININE LEVEL	
Factor	**Increase**	**Decrease**
Affecting creatinine generation	Age (infancy through adolescence)	Chronic illness Anorexia, malnutrition Neuromuscular disease (spina bifida, muscular dystrophy) Liver disease
	Male gender (after puberty)	Body habitus (amputation)
	Body habitus (muscular)	Diet (vegetarian)
	Diet Consumption of cooked meat Creatine supplements	
Affecting creatinine elimination	Impaired tubular secretion (trimethoprim, cimetidine)	Tubular secretion
	Impaired extrarenal elimination (sterilization of gastrointestinal flora by antibiotics)	Extrarenal elimination (gastrointestinal degradation)

a particularly attractive marker in growing children, subjects with atypical body composition (e.g., malnutrition, anorexia, spina bifida, neuromuscular disease), and subjects experiencing rapid changes in muscle mass.[52-54] Furthermore, in young children, the maturational changes associated with serum cystatin C follow those of GFR better than serum creatinine. Serum cystatin C levels are elevated at birth, presumably due to the physiologically lower GFR. However, cystatin C, unlike creatinine, does not equilibrate across the placenta; hence, the levels early after birth are more representative of the infant's renal function than are creatinine levels, and thus may facilitate the evaluation of renal function in newborns.[55] Concurrent with the GFR increasing after birth, cystatin C levels decline to reach a plateau 0.8 to 1 mg/L by approximately 1.5 to 2 years of age.[56] Beyond this age, serum cystatin C levels remain constant (until age 50 years) as does GFR.[52] Serum cystatin C levels may, therefore, potentially facilitate the recognition of abnormal renal function, as growth is no longer a confounding variable.[54] Furthermore, cystatin C has a shorter half-life than serum creatinine, making it more sensitive to acute and subtle changes in GFR.[57,58]

Studies comparing the use of cystatin C to serum creatinine as a diagnostic marker of kidney function have yielded conflicting results. Nonetheless, two recent meta-analyses including adult as well as pediatric studies suggest cystatin C is superior or equivalent to serum creatinine as a marker of renal function.[59,60] Specifically, cystatin C may be advantageous in populations with low or atypical muscle mass (e.g., spina bifida)[61,62] and mild renal impairment.[63] Changes in serum cystatin C levels may also potentially allow earlier detection of AKI. Herget-Rosenthal[64] found that cystatin C levels rose 1 to 2 days earlier than serum creatinine in patients with AKI. Further investigation in this area is needed. In renal transplant recipients, however, cystatin C levels may underestimate GFR.[56,65]

Although promising, cystatin C is also not a perfect marker for estimating GFR. Data emerging from several recent studies suggest cystatin C levels can be affected by several potentially confounding variables including age, gender, race,[66] obesity,[67] nonrenal elimination,[68] glucocorticoids,[56] and thyroid dysfunction,[56] as well as differences in cystatin C assays.[69] Two automated immunoassays are now available (particle-enhanced turbidometric immunoassay [PETIA] and particle-enhanced nephelometric immunoassay [PENIA]) but differ by as much as 20% to 30% in reported values.[69] This is thought to contribute to the variability in assays for cystatin C concentration.[52,53] Because cystatin C is completely reabsorbed by the proximal tubular cells, urinary clearance studies are not possible. However, cystatin C has been noted in the urine of patients with glomerular and tubular disease, raising questions about its accuracy in estimating GFR.[70]

Estimating Equations

Empirical formulas (Cockcroft-Gault for adults; Schwartz and Counahan-Barratt for children) were developed in the 1970s to enhance the physician's ability to estimate GFR (eGFR) and in particular, to facilitate the recognition of chronic renal impairment.[71-73] The equations were developed in chronic kidney disease populations and based on serum creatinine, but incorporate clinical variables such as height, weight, age, and gender as surrogates for muscle mass. However, because they are creatinine based, they are subject to some of the same constraints as use of serum creatinine alone (for example, physiologic processes such as tubular creatinine secretion and analytical factors related to the creatinine assay itself will influence eGFR results). Nonetheless, these equations perform better than serum creatinine alone, and therefore current national guidelines recommend that estimated GFR (eGFR) be reported alongside the creatinine value.[20] This has recently been implemented for adults and is soon to be available for children.[57]

In pediatrics, the Schwartz formula has been most commonly used to predict GFR. The original Schwartz formula was developed in the 1970s and based on a modified Jaffe creatinine, using inulin clearance as the reference standard. GFR is related to serum creatinine, using length as a surrogate for muscle mass and an empirical constant to account for age- and gender-related differences in body composition:

$$\text{eGFR} = k \times L / S_{Cr}$$

where eGFR is estimated GFR in mL/min/1.73 m^2, L is length in cm, S_{Cr} is serum creatinine in mg/dL, and k is an empirical constant (i.e., 0.45 for term infants through the first year of life, 0.55 for children and adolescent females, and 0.7 for adolescent males).[48,73] The simplicity of the formula makes it convenient and practical for use at the bedside, although knowledge of the patient's height is required. Counahan-Barratt developed a similar formula using ^{51}Cr-EDTA plasma disappearance as the reference standard.[72] This formula, however, uses a single constant with a lower value, attributed to a difference in creatinine assays:

$$\text{eGFR (mL/min/1.73 m}^2) = 0.43 \times L / S_{Cr}$$

It is now well-recognized that Schwartz's original formula systematically overestimates GFR, most likely due to a change in creatinine methodology over the years from the Jaffe assay to an IDMS referenced enzymatic assay.[38] As noted above, enzymatic creatinine levels run approximately 0.2 mg/dL lower than Jaffe creatinine levels.

Other formulas (Leger and British Columbia Children's Hospital) designed to improve the accuracy of eGFR have also been recently proposed for use in children with chronic kidney disease but are considerably more complex, not more accurate, and not as easily utilized at the bedside.[74,75] The adult formulas, Modification of Diet in Renal Disease and Cockcroft-Gault, have also been studied in children but are not accurate.[76,77]

Recently, an updated "bedside" Schwartz formula, based on an enzymatic creatinine assay and using the plasma disappearance of iohexol as the reference standard, was developed using data from the CKiD Study:

$$\text{eGFR} = 0.413 \times \text{L} / \text{S}_{\text{Cr}}$$

where length is in cm and serum creatinine is in mg/dL.[78] Notably, this is the first multicenter study to generate an estimating formula in children. Using the updated Schwartz formula, approximately 80% of eGFR values fell within 30% of the GFR measured by iohexol plasma disappearance and 37% fell within 10%.[57]

Given the limitations of creatinine, cystatin C-based GFR-estimating equations have also been developed in an effort to improve accuracy. Several have been published both for use in adults as well as children. They vary in terms of accuracy and precision, but appear at least as good as the creatinine-based equations. However, cystatin C is not readily available in many hospital laboratories.[56] Incorporation of both creatinine and cystatin C into the formula appears to provide a better estimate. Using data from the CKiD study, Schwartz et al. recently developed a new eGFR equation incorporating both cystatin C and serum creatinine in addition to height, BUN, and gender:

$$\text{eGFR} = 39.1 \times [\text{height (m)} / \text{S}_{\text{Cr}}\ (\text{mg/dL})]^{0.516} \times [1.8 / \text{cystatin C (mg/L)}]^{0.294} \times [30 / \text{BUN (mg/dL)}]^{0.169} \times [1.099]^{\text{gender}} \times [\text{height (m)} / 1.4]^{0.188}$$

where gender = 1 for male and 0 for female. Using this formula, over 85% of the eGFRs were within 30% of the GFR measured by iohexol, the reference standard for this study, and 45% were within 10%.[78] The equation is valid in the range of 15 to 75 mL/min/1.73 m^2 and uses the DAKO cystatin C assay.[57]

As noted above, several creatinine-based as well as cystatin C-based formulas to estimate GFR have been published. Proper use of the prediction formulas to obtain a meaningful eGFR, however, requires the clinician to be cognizant of the specific creatinine assay (or cystatin C assay) used to create the equation as well as that used in one's hospital lab, as levels obtained by different methodologies are not interchangeable, and the coefficients derived for each equation are critically dependent on the assay methodology. Clinicians must also be knowledgeable about the clinical characteristics of the study population to determine whether or not generalizability of the equation is appropriate.

Other Novel Biomarkers of Acute Kidney Injury Under Investigation

Clearly, the currently available tools for assessing AKI are inadequate, both in terms of detecting the onset of renal cellular damage as well as for detecting the onset of renal functional impairment. Recent advances in molecular biology have significantly enhanced our understanding of the pathogenesis of AKI, leading to the identification of several potential candidate biomarkers for AKI. NGAL is the most extensively studied and one of the most promising. NGAL is a ubiquitous 25 kDa protein bound to gelatinase from human neutrophils and constitutively expressed at low levels in the kidneys as well as lung, liver, and gastrointestinal tract.[79] Following ischemia and epithelial cell injury, the expression of NGAL is upregulated, leading to marked increases in serum and urine NGAL levels that precede a rise in serum creatinine.[80,81] Studies of urine NGAL in adults and children following cardiac bypass surgery found a rise in urine NGAL expression beginning 2 to 6 hours after bypass, which was higher and more sustained in those who developed AKI.[81,82] However, the sensitivity and specificity of urinary NGAL as a predictor of AKI was higher in the pediatric study. More recently, studies have focused on the utility of urine and serum NGAL to predict AKI in a heterogeneous group of critically ill children and adults in the ICU for whom the onset of renal injury is unknown. Zappitelli et al.[83] found that urine NGAL concentrations increased 48 hours prior to a serum creatinine increase of 50% or more. They also found that children with sepsis-related AKI had higher urinary NGAL levels than those with AKI unrelated to sepsis. Similarly, Bagshaw et al.[84] found higher levels of plasma and urine NGAL levels in adult patients with sepsis-related AKI versus non-sepsis-related AKI. These studies suggest urinary NGAL may have variable specificity for predicting AKI based on the subtype of AKI. A recent meta-anlaysis including more than 19 studies (adult and pediatric) concluded that despite the variability in predictive value reported for NGAL to diagnose early AKI, NGAL levels appear to have diagnostic value.[85]

Kidney injury molecule-1 (KIM-1) is a transmembrane receptor with unclear function whose expression also appears to be significantly upregulated in proximal tubular cells following ischemia or nephrotoxic injury. After subsequently undergoing cleavage, the extracellular domain is shed into the urine, where it can be detected about 12 to 24 hours following some forms of renal injury. Recent studies suggest urinary KIM-1 is more specific for acute kidney injury secondary to renal ischemia and nephrotoxins.[86] Urinary interleukin-18 (IL-18), a proinflammatory cytokine induced in proximal tubular cells following AKI, is another promising biomarker that also appears to be more specific to ischemic AKI and other types of acute tubular necrosis than to other forms of acute renal disease (e.g., urinary tract infection or prerenal azotemia).[86]

To improve the sensitivity and specificity of these biomarkers, the development of an AKI blood panel (NGAL and cystatin C) and urine panel (NGAL, IL-18, and KIM-1) has been proposed.[86]

Tubular Function

Disorders of electrolyte balance, acid-base homeostasis, and volume regulation are also encountered in the ICU and require assessment of renal tubular function. Although the techniques required to assess tubular function may be easier to perform than techniques needed to assess GFR, the interpretation of test results is not always straightforward. It is essential for physicians to recognize that although lab results may fall within the usual limits reported by the laboratory, this may not represent an appropriate response given the clinical context.

Urine Electrolytes (Sodium and Chloride)

Urine sodium (U_{Na}) and chloride (U_{Cl}) are commonly used to assess intravascular volume status and to help differentiate prerenal azotemia from acute tubular necrosis (ATN). With the prerenal azotemia, U_{Na} is typically less than 20 mEq/L and U_{Cl} less than 15 mEq/L as the kidney avidly tries to reclaim sodium and chloride in addition to water in an effort to restore the extracellular fluid volume, whereas with ATN, the U_{Na} is typically greater than 40 mEq/L due to structural tubular damage. However, overlap can occur as the final concentration of sodium in the urine will depend not only on the amount of sodium reclaimed by the tubules but also on the amount of water reabsorbed in the distal tubule under the influence of antidiuretic hormone. Thus the U_{Na} could exceed 20 mEq/L even in a prerenal state, particularly if oliguria is present. The fractional excretion of sodium (FE_{Na}) accounts for this differential degree of water reabsorption and therefore provides a more accurate reflection of the kidney's ability to conserve sodium. FE_{Na} represents the fraction of filtered sodium that is excreted into the urine: $FE_{Na} = (U_{Na}/S_{Na})/(U_{Cr}/S_{Cr}) \times 100$, where U_{Na} and S_{Na} correspond to the urine and serum sodium (mmol/L), respectively, and U_{Cr} and S_{Cr} (mg/dL) correspond to the urine and serum creatinine, respectively. With prerenal azotemia, the FE_{Na} is generally less than 1%, whereas with ATN it is greater than 1%. In premature infants, due to tubular immaturity, this threshold for FE_{Na} is approximately 3%, not 1%. It should be noted that FE_{Na} is really only meaningful in the setting of oliguric AKI. In euvolemic patients, the urinary excretion of sodium will be more dependent on dietary sodium intake. The accuracy of U_{Na} and FE_{Na} is further compromised when urinary salt-wasting conditions are present (e.g., diuretic use, renal dysplasia, chronic renal failure, cerebral salt wasting, as well as mineralocorticoid deficiency such as congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency). These conditions are associated with elevated urinary chloride levels as well.[87]

Urine Concentration Capacity

The urine specific gravity (U_{SG}) and urine osmolality (U_{Osm}) assess the kidney's ability to concentrate the urine. Urine specific gravity and osmolality bear a linear relationship, with urine specific gravity rising approximately 0.001 for about every 30 to 40 mOsm/kg. When urine is iso-osmotic to serum, the U_{SG} is approximately 1.010. In a healthy kidney, the limits of U_{SG} range from 1.003 to 1.035 and U_{Osm} from 50 to 1400 mOsm. However, due to renal immaturity, infants have a reduced urinary concentration capacity of about 600 mOsm for preterm and 800 mOsm for full term infants. U_{SG} can be easily measured by refractometer and is therefore clinically used more often than U_{Osm}, which requires an osmometer. In general, U_{SG} provides a good estimate of the kidney's concentration ability. However, because U_{SG} compares the density of urine to that of water, the presence of heavier solutes such as glucose and/or protein can increase the urine specific gravity without affecting the urine osmolality. Urine osmolality therefore provides a more accurate assessment of the kidney's response to antidiuretic hormone (ADH). With prerenal azotemia, the appropriate renal response is to retain sodium and water. Classically, the U_{SG} exceeds 1.020, U_{Osm} exceeds 500, and the urine output decreases, with the patient often becoming oliguric (urine output <1 mL/kg/h). With ATN, on the other hand, the conservation of water is impaired secondary to tubular injury resulting in isosthenuria (U_{SG} ~ 1.010, U_{Osm} ~300 to 350 mOsm). It is crucial to remember, however, that children with underlying urinary concentration defects and tubular resistance to ADH (e.g., renal dysplasia, nephrogenic diabetes insipidus, chronic kidney failure) may have a low U_{SG}, low U_{Osm}, and high urine output despite life-threatening intravascular volume depletion.

Urine osmolality is also helpful in evaluation of the child with polyuria. A low osmolality (<150 mOsm/kg) suggests a urine concentration defect such as central or nephrogenic diabetes insipidus whereas a urine osmolality of 300 to 350, associated with a high specific gravity, suggests an osmotic diuresis. The urinary concentrating capacity can be assessed by (1) checking the osmolality of a first morning urine after overnight fluid restriction or (2) by a water deprivation test.

Serum Blood Urea Nitrogen/ Creatinine Ratio

The ratio of serum blood urea nitrogen (BUN) to creatinine is also frequently used to help differentiate prerenal AKI from ATN. Urea, like creatinine, is freely filtered at the glomerulus but, unlike creatinine, has significant tubular reabsorption that further increases with hypovolemia. In prerenal states, therefore, the BUN/creatinine ratio generally exceeds 20 to 1, while it is lower than this with ATN. However, this ratio becomes inaccurate in clinical conditions where the BUN is elevated for nonrenal reasons such as a gastrointestinal bleed, catabolic state, or corticosteroid use; nor is it accurate in clinical conditions associated with a low BUN, such as protein calorie malnutrition or liver disease. The ratio may also be misleading in conditions associated with a particularly low muscle mass and serum creatinine such as muscular dystrophy.

Urine Microscopy

Urine microscopy can aid in determining the etiology for AKI. The presence of muddy brown or renal cellular casts and renal tubular epithelial cells is consistent with ATN. However, the absence of such findings does not rule out less severe ATN. In the setting of prerenal azotemia, urine microscopy is bland; hyaline and granular casts may be seen. Hematuria with dysmorphic red blood cells (RBCs) and red cell casts is consistent with glomerulonephritis, whereas hematuria in the absence of RBCs on a freshly examined urine suggests hemoglobinuria or myoglobinuria. Leukocyturia with white cell casts suggests pyelonephritis or

interstitial nephritis. Eosinophils in the urine can be detected using special stains and are classically associated with interstitial nephritis but can also be seen with pyelonephritis and urinary tract obstruction.[88] Examination of a fresh, concentrated urine specimen optimizes the opportunity for detecting these cellular elements.

Proteinuria

Protein excretion in healthy individuals is minimal (<4 mg/m^2/h in children) but can increase with renal injury. Glomerulopathies are associated with albuminuria and nonspecific proteinuria, while tubulointerstitial disease results in low-molecular-weight proteinuria. Urinary protein excretion can be detected qualitatively by reagent strips. However, these strips detect primarily albumin and are therefore helpful for assessing glomerular proteinuria but not tubular or low-molecular-weight proteinuria. Low-level false-positive results (30 to 99 mg/dL) can be obtained with the dipstick if the urine is very alkaline. Low levels of protein detected by dipstick (30 to 99 mg/dL or 100 to 299 mg/dL) can, however, also represent heavy proteinuria if the patient is polyuric. Quantitative assessments of proteinuria can be obtained using a random urine total protein/creatinine ratio (normal <0.2 for children older than 3 years) measured by the biuret method[89] and are preferred for following glomerular as well as tubular proteinuria. Twenty-four-hour urine collections for protein and creatinine can also be performed but are not believed to be advantageous over the random urine protein/creatinine ratio, particularly in children.

In diabetics, the development of overt proteinuria detectable by reagent strips is preceded by the presence of microalbuminuria, defined as persistent albumin excretion between 30 and 300 mg/g creatinine.[90] Use of the microalbumin/creatinine ratio allows for early detection of glomerular damage.[20]

Renal Acidification

Metabolic acidosis is also commonly encountered in the PICU. When associated with a normal serum anion gap, the major diagnostic consideration is renal tubular acidosis versus gastrointestinal loss of bicarbonate. The appropriate renal response to a metabolic acidosis is to increase proton secretion and ammonium production, which will allow increased net acid excretion (also see Chapter 68). The urine pH in this case should fall below 5.3, ideally measured with a pH meter after collecting a fresh specimen in an airtight syringe. Whereas a urine pH greater than 5.3 in the setting of systemic acidemia is consistent with renal tubular acidosis, a urine pH less than 5.3 does not exclude the diagnosis. Proximal RTA is characterized by bicarbonaturia secondary to a reduced threshold for bicarbonate reabsorption. At low levels of serum bicarbonate (<14 mEq/L), the filtered bicarbonate is able to be reabsorbed, resulting in a low urine pH. However, under conditions of bicarbonate loading, the reabsorptive capacity of the proximal tubule is exceeded leading to fractional excretion of bicarbonate greater than 15% to 20%:

$$FE_{bicarb} = (U_{HCO3}/S_{HCO3})/(U_{Cr}/S_{Cr}) \times 100$$

where U_{HCO3} and S_{HCO3} are the urine and serum bicarbonate concentrations in millimoles per liter and U_{Cr} and S_{Cr} are the urine and serum creatinine concentrations in milligrams per deciliter. Assessment of distal acidification includes calculation of the urine net charge and osmolal gap, both of which provide an indirect assessment of ammonium production, which cannot be routinely measured. The former is simpler to calculate:

$$\text{Urine net charge} = (U_{Na} + U_K - U_{Cl})$$

where U_{Na} is the urine sodium concentration (mEq/L), U_K is the urine potassium concentration (mEq/L), and U_{Cl} is the urine chloride concentration (mEq/L). Assuming chloride is the major anion excreted, an appropriate urine net charge in the setting of acidosis should be negative (−30 to −50), indicating the presence of ammonium, an unmeasured cation. A positive net charge would therefore suggest impaired ammonium production or proton secretion. The urine net charge, however, has limited utility when the urine sodium concentration is low (<25 mEq/L) as occurs with hypovolemia. In this setting, the kidney avidly conserves sodium and chloride (urine chloride <15 mEq/L) leaving less anion available for excretion with ammonium and resulting in a reversible impairment of urinary acidification. The urine net charge is also misleading in the presence of unmeasured anions (e.g., beta hydroxybutyrate and acetoacetate in diabetic ketoacidosis, hippurate from toluene ingestion/glue sniffing, or penicillins). In this setting, the urine net charge is positive and underestimates ammonium excretion because the cations—ammonium, sodium, and potassium—are excreted with the unmeasured anion instead of chloride. In infants, the validity of the urine net charge is also compromised due to considerable variability in the unmeasured ionic composition of the urine.[91] The urinary osmolal gap is more informative because it accounts for the excretion of the unmeasured anions. It represents the difference between the measured and calculated urine osmolalities where the calculated $U_{Osm} = \{2 \times [U_{Na}\ (mmol/L) + U_K\ (mmol/L)]\} + [U_{urea}\ (mg/dL)/2.8] + [U_{glucose}\ (mg/dL)/18]$.[92] Assuming urinary ammonium is the predominant unmeasured cation, the concentration of excreted ammonium is approximately half of the urine osmolal gap. During periods of systemic acidosis, urinary ammonium excretion increases to concentrations greater than 75 mEq/L; a level less than 25 mEq/L in this setting suggests impaired ammoniagenesis.[93]

More sophisticated tests are available to assess distal tubular acidification (proton secretion). Traditional tests include (1) measuring the difference in PCO_2 between the urine and blood during bicarbonate loading and (2) an NH_4Cl loading test. However, these can be difficult to perform and may not be well tolerated. More recently, simultaneous administration of furosemide to enhance distal sodium delivery and fludrocortisone to enhance distal sodium reabsorption as well as stimulate proton secretion has been used as an alternative test for distal acidification. In the presence of intact distal acidification, the urine pH should decrease to less than 5.3. This test has the advantages of being easy to perform and is well tolerated.[94]

Potassium Regulation

Assessment for an appropriate renal response in the setting of hypokalemia or hyperkalemia can also be challenging. Unlike urine sodium, which can be extremely efficiently reclaimed by the tubules, there is an obligate K excretion of at least 5 to 10 mmol/day due to K secretion that occurs in the distal tubule.

Potassium excretion is primarily dependent upon the aldosterone activity and serum K concentration but also requires an adequate urine flow rate and delivery of sodium to the distal nephron. The TTKG (transtubular potassium gradient) provides an assessment of potassium excretion secondary to mineralocorticoid activity and is calculated:

$$TTKG = [U_K S_{Osm}] / [S_K U_{Osm}]$$

where U_K and S_K represent urine and serum concentrations of potassium (mEq/L) respectively and S_{Osm} and U_{Osm} represent serum and urine osmolalities (mOsm/kg). In the setting of hyperkalemia, the TTKG should be elevated; therefore a low TTKG (<4.1 in children; 7 in adults) suggests hypoaldosteronism. In the setting of hypokalemia, on the other hand, the TTKG would be expected to be quite low; levels greater than 2 suggest aldosterone activity is not appropriately suppressed.[87,95]

Generalized Proximal Tubulopathy

Generalized proximal tubulopathies (Fanconi syndrome) can be congenital (i.e., cystinosis, tyrosinemia) or acquired (e.g., aminoglycoside toxicity, ifosfamide, severe ATN) and may be partial or complete. Biochemical abnormalities associated with a complete Fanconi syndrome include hypokalemia, metabolic acidosis, hypophosphatemia, hypouricemia, and low serum carnitine associated with urinary wasting of sodium, potassium, bicarbonate, phosphorus, uric acid, carnitine, glucose, amino acids, and low-molecular-weight proteins. A generalized proximal tubulopathy should be suspected when electrolyte wasting is profound and/or involves several electrolytes.

References are available online at http://www.expertconsult.com.

Renal Pharmacology

Douglas L. Blowey

PEARLS

- For situations when the goal is the maintenance of a serum concentration close to the steady state level throughout the dosing interval, a decrease in the size of the dose while the normal dosing interval is maintained will decrease the variation between the serum drug concentration peak and trough.
- With the exception of spironolactone and arginine vasopressin antagonists, diuretics must reach the renal tubular fluid to produce a pharmacologic effect.
- Loop diuretics decrease sodium reabsorption by inhibiting the electroneutral $Na^+/K^+/2Cl^-$ cotransporter located on the apical cell membrane in the ascending limb of Henle.
- Spironolactone prevents the binding of aldosterone to a cytosolic receptor resulting in decreased activity of Na^+/K^+-adenosine triphosphatase and a decrease in the number of apical sodium channels.
- The continuous infusion of a loop diuretic is more efficient than intermittent high doses and avoids the high and low serum concentrations associated with toxicity and resistance.

The kidney plays a central role in many physiological processes that have a direct impact on drug action and disposition, and the kidney is also an important target for drug therapy in the critically ill child. The key functions of the kidney are the elimination of endogenous and exogenous substances from the body, including drug and drug metabolites, and the maintenance of body fluid composition and volume. The glomerular and tubular mechanisms that carry out these functions are directly and indirectly influenced by the function of other organs. For example, congestive heart failure decreases the adequacy of arterial blood flow and is detected by sensors located throughout the circulatory system. The sensed reduction in effective arterial blood volume triggers a complex neurohormonal response that decreases kidney blood flow, increases sodium and water retention in the kidney, and further aggravates the edema associated with congestive heart failure. Conversely, the accumulation of drugs, drug metabolites, metabolic waste products, and alterations in body fluid composition and volume associated with kidney failure may have deleterious effects on the function of other vital organs and physiological systems.

Kidney Function and Drug Disposition

Many drugs are eliminated by the kidney, and abnormal kidney function can affect the amount of drug present at the site of action and the magnitude of the drug response. A clear understanding of the effects of abnormal kidney function on drug disposition and action is important because abnormal kidney function is common in the critically ill child and alterations in drug disposition or action may result in suboptimal therapeutic efficacy or serious adverse events.

The pharmacologic effect of a therapeutic agent is determined by the amount, and time, that the active drug component (e.g., parent drug or drug metabolite) is present at the site of action and the responsiveness of the target organ to the drug. Only the free, unbound form of a drug can exert a pharmacologic effect through interaction with receptors. The disposition of a drug after administration is determined by the formulation and route of administration, the rate and extent of absorption from the site of administration, the extent of distribution in the body fluids and tissues, the rate and extent of metabolism, and the rate and route of elimination. Drug disposition and response are further influenced by the genetic, physiologic, and pathologic constitution of the ill child.[1,2] Pharmacokinetics is the mathematic expression of drug disposition, and pharmacodynamics describes the magnitude of response to a drug. The determination of pharmacokinetic parameters is an invaluable tool for designing individualized drug-dosing regimens in children with kidney failure or critical illnesses that may alter drug disposition (see also Chapter 116).

Although decreased kidney elimination of drugs and drug metabolites is the most obvious consequence of altered kidney function, kidney failure or the associated coexisting conditions may affect drug absorption, distribution, and metabolism (Table 70-1).[3-5] The mechanisms that govern drug removal by the kidneys are glomerular filtration, tubular secretion, and tubular reabsorption. These processes are altered in children with kidney disease, as well as other organ dysfunction. Each of the kidney's one million nephrons consists of a tuft of capillaries (glomerulus) enveloped by an epithelial-lined capsule (Bowman's space) that drains into a contiguous tubular system. As blood flows through the glomerular capillaries, fluid and small solutes, including drugs and drug metabolites not bound to plasma proteins, pass through the glomeruli into Bowman's space. The volume of water and accompanying solute that is filtered through the glomeruli per unit time is the glomerular filtration rate (GFR) and is the most important measure of kidney function (see Chapter 69). The GFR

Table 70–1 Potential Alterations of Drug Distribution in Kidney Failure

PK PARAMETER	EFFECT	PROPOSED MECHANISM
Absorption	↓	Edema of GI tract, uremic N/V, delayed gastric emptying Drug interaction—phosphate binders, H2blockers Altered GI pH
Distribution	↑	Increased unbound drug fraction Hypoalbuminemia (nephrosis, malnutrition) Uremic changes in albumin structure
Metabolism	↓	Inhibition of CYP 450 metabolism (liver, intestine, kidney) Drug interaction
	↑	Direct inhibition by "uremic" milieu Induced CYP 450 metabolism
Excretion	↓	Decreased GFR Decreased tubular secretion Increased tubular reabsorption

CYP 450, Cytochrome P450; *GFR,* glomerular filtration rate; *GI,* gastrointestinal; *N/V,* nausea and vomiting; *PK,* pharmacokinetic.

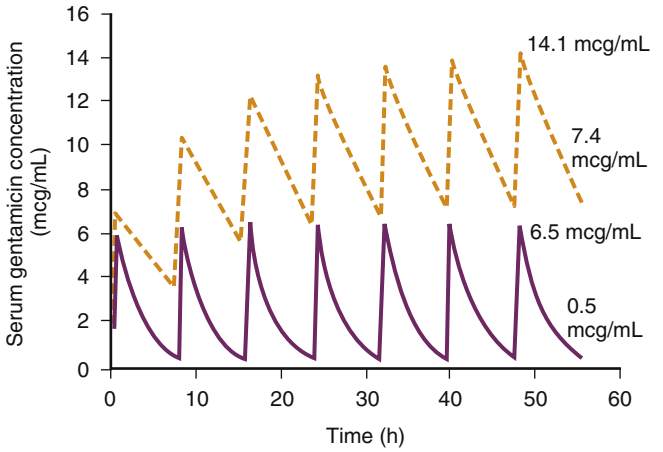

Figure 70–1. Gentamicin time-concentration profile in a 5-year-old child receiving 2.5 mg/kg intravenously every 8 hours. The *solid line* represents the plasma concentration-time profile in a child with normal kidney function (e.g., 120 mL/min/1.73 m^2) and the *dashed line* represents the plasma concentration-time profile in a child with a creatinine clearance of 30 mL/min/1.73 m^2.

is estimated with the measurement of the rate that the kidney removes a substance from the blood (e.g., renal clearance). The measured substance may be an endogenous compound (e.g., creatinine [Cr] or cystatin C), an exogenous compound that is specifically administered to measure the GFR (e.g., inulin, isotope, or iohexol), or a compound primarily eliminated by glomerular filtration that is administered as part of clinical care (e.g., gentamicin).[6] The clearance of Cr corrected for body surface area is the most common method used to estimate the GFR. Creatinine clearance (C_{Cr}), expressed in mL/min/1.73 m^2, is calculated with the measurement of the amount of Cr in an accurately timed urine collection and a mid collection plasma Cr.

$$C_{cr} = \frac{[\text{Urine CR (mg/dL)} \times (\text{Urine volume [mL]/Time [min]})]}{\text{Plasma Cr (mg/dL)}} \times \frac{1.73\ m^2}{\text{BSA } (m^2)}$$

C_{Cr} is low at birth and rapidly increases during the first 2 weeks of life, followed by a steady rise until adult values are reached by 8 to 12 months.[7,8]

Although not as accurate as a timed urine collection, for children aged 1 to 18 years, C_{Cr} can be quickly estimated with the measurement of the child's serum Cr and length with the following equation[9]:

$$C_{cr} = \frac{\text{Length (cm)} \times 0.41}{\text{Plasma Cr (mg/dL)}}$$

where the plasma creatinine is calibrated to the isotope-dilution mass specrometry method of measuring serum creatinine. It is important to understand that the normal relationships among serum Cr, length, and GFR are altered in disturbances of Cr biosynthesis (e.g., muscular disease and malnutrition) or in clinical settings where the serum Cr is rapidly changing (e.g., acute renal failure, recovery from renal failure, and dialysis). In these situations, a timed urine collection is required for an accurate estimate of the GRF.

The total amount of drug eliminated from the body by the kidneys is a composition of the amount of drug filtered across the glomeruli, the amount actively secreted into the filtrate by the renal tubules, and the amount reabsorbed by the renal tubules. Because albumin and other large molecules do not pass through the glomeruli, large drugs and drugs bound to plasma proteins normally do not pass through the glomeruli and are not effectively removed by glomerular filtration but may be efficiently eliminated by the kidney through renal tubular secretion (e.g., furosemide). For drugs and drug metabolites that are primarily eliminated by glomerular filtration, the rate of elimination mirrors kidney function (C_{Cr}). As such, when kidney function declines, the reduced drug elimination results in drug accumulation in the body. For example, gentamicin is an aminoglycoside that is eliminated primarily by glomerular filtration with an elimination half-life of around 2 hours in children and adults with normal kidney function and 4 to 12 hours in infants because of the well-characterized developmental immaturity of kidney function.[7,8] A 75% reduction of the GFR (e.g., C_{Cr} = 30 mL/min/1.73 m^2) in a 5-year-old child receiving intravenous (IV) gentamicin will prolong the elimination half-life to 8 hours. Unless adjustments are made in the dosing regimen to account for the decreased kidney elimination, gentamicin will accumulate to toxic serum concentrations (Figure 70-1).

The active renal tubular secretion of drugs and drug metabolites by relatively nonspecific anionic and cationic transport systems in the proximal tubule can contribute substantially to the amount of drug eliminated by the kidney. The renal tubular secretion of a drug may be inhibited by other

Box 70–1 Guidelines for Drug Dosing in Kidney Failure

1. Estimate the glomerular filtration rate
2. Determine the percentage of drug eliminated by the kidney
3. Calculate the dosage adjustment factor (Q)
4. Adjust the dose size or dosing interval
5. Monitor response
6. Monitor therapeutic drug (when available)

drugs or endogenous substrates that use the same nonspecific transport systems. For example, probenecid blocks the tubular secretion of many drugs by the organic anion transporter and is of clinical utility as an adjuvant to antibiotic therapy and the prevention of drug-induced nephrotoxicity.[10-12] For example, the coadministration of probenecid and penicillin-type antibiotics results in higher and more prolonged serum penicillin levels because of the inhibition of penicillin secretion by the renal tubule. The increased penicillin exposure may enhance the therapeutic efficacy of penicillin.[13,14] Nephrotoxicity is the major dose-limiting adverse effect of the antiviral agent cidofovir and is in part mediated by the proximal tubular transport of cidofovir by the organic anion system. Coadministration of probenecid restricts the proximal renal tubular uptake of cidofovir and decreases the incidence of nephrotoxicity.[11] Reabsorption is the passive diffusion of non-ionized (noncharged) drug from the filtrate into the renal tubular cell. Basic urine (e.g., urine pH >7.5) favors the ionized form of acidic drugs and limits reabsorption, whereas reabsorption of basic drugs is enhanced in basic urine because the non-ionized form of the drug is favored. Urinary alkalinization is used to enhance the renal elimination of salicylates and possibly barbiturates in overdose situations (see Chapters 105 and 106).[15]

Drug Dosing in Kidney Disease

Drugs and drug metabolites that are predominately eliminated by the kidney will accumulate to higher serum drug concentrations in patients with decreased kidney function if adjustments are not made to the drug-dosing regimen. A systematic approach to individualized drug therapy in children with kidney failure will ensure maximal therapeutic efficacy and minimize toxicity (Box 70-1). The first step in designing a rational individualized dosing regimen is an estimation of the child's kidney function with measurement of the C_{Cr} as described in the previous section. The next step is to evaluate the effect of kidney failure on the drug disposition characteristics for all of the drugs prescribed to the child. Reference books such as the *Pediatric Dosage Handbook*,[16] *Physicians Desk Reference*, and *Micro Medex* are excellent beginning sources for information about drug disposition in kidney failure. Unfortunately, because there is little pharmacokinetic information about drug disposition in children with kidney failure, estimates from adult patients with kidney failure are cautiously used, keeping in mind the potential changes in drug disposition that occur with development.[17] The most important information for designing an optimal dosing regimen is the amount of drug that is eliminated by the kidneys in persons with normal kidney function. If one assumes that drug protein binding, distribution, and metabolism are not greatly altered in kidney failure, an assumption that is likely true for most drugs,[5] then a dosage adjustment factor (Q) can be estimated:

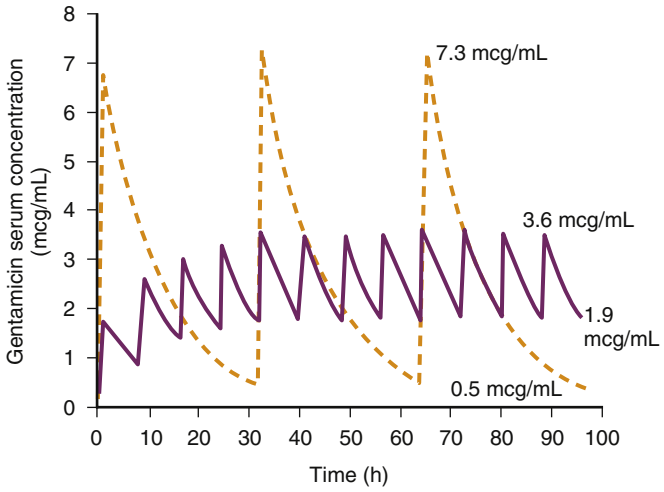

Figure 70–2. Gentamicin concentration-time profile in a child with a creatinine clearance of 30 mL/min/1.73 m^2 receiving intravenous gentamicin. The *solid line* represents the plasma concentration-time profile when the dose remains unchanged (2.5 mg/kg) and the dosing interval is adjusted to 32 hours [normal dosing interval (8 hour) ÷ dosing adjustment factor (0.3)]. The *dashed line* represents the plasma concentration-time profile if the dosing interval remains unchanged (8 hours and the dose is adjusted to 0.625 mg/kg [normal dose (2.5 mg/kg) × dosing adjustment factor (0.3)].

$$Q = 1 - [\%\ \text{excreted unchanged} \times 1 - \frac{(\text{Child's creatine clearance [mL/min/1.73 m}^2])}{\text{Normal creatine clearance (120 mL/min/1.73 m}^2)}]$$

Once the need for a dosage adjustment has been established and the adjustment factor (Q) calculated, the best method of adjustment, whether it be a change in the size of the dose or the length of the dosing interval, is selected on the basis of the known relationships between the peak and trough drug concentrations and clinical response or toxicity. Figure 70-2 shows the concentration-time profiles for two different IV gentamicin dosing regimens in a child with a measured C_{Cr} of 30 mL/min/1.73 m^2. About 95% of gentamicin is excreted unchanged in the urine, and the dosage adjustment factor is calculated as:

$$Q = 1 - [0.95 \times 1 - \frac{(30\ \text{mL/min/1.73 m}^2)}{120\ \text{mL/min/1.73 m}^2}] = 0.30$$

When the dosing interval is increased and the size of the drug dose remains unchanged (see Figure 70-2, *solid line*), the steady state peak and trough drug concentration are similar to those seen in children with normal renal function; however, there is a prolonged period when the serum gentamicin concentration is above and below the average steady state concentration. This dosing regimen may be inappropriate for drugs that should be maintained at a relatively stable serum concentration, such as cephalosporins or antihypertensive medications. For situations when the goal is the maintenance of a serum concentration close to the steady state level throughout the dosing interval, a decrease in the size of the dose while the normal dosing interval is maintained will decrease the variation between the serum drug concentration peak and

trough (see Figure 70-2, *solid line*). The dosing adjustments are estimates based on many assumptions, and the final step in individual therapy is close monitoring of clinical efficacy and toxicity. When available, the measurement of serum drug concentrations and determination of pharmacokinetic parameters is invaluable for individual drug therapy, especially in agents with a narrow therapeutic index.

Dialysis

Some form of dialysis is used in about 3% of children admitted to the intensive care unit. Drug elimination in children receiving dialysis is a composite of nonrenal drug elimination, residual kidney elimination, and the added elimination provided by dialysis. The efficiency of a given dialysis modality to eliminate a drug depends on the physiochemical characteristics of the drug and the form and characteristics of the dialysis procedure. Hemodialysis, peritoneal dialysis, and the varied forms of continuous renal replacement therapies that include continuous veno-venous hemodialysis and continuous veno-venous hemodiafiltration are all used in the intensive care setting (see Chapter 72). It is beyond the scope of this chapter to detail drug disposition in the various forms of dialysis, and the reader is referred to other excellent sources for further information.[4,18] In general, highly protein-bound drugs and drugs with a large volume of distribution are not well removed by dialysis.

The Kidney as a Therapeutic Target: Diuretics

Diuretics are a diverse group of drugs that act on the kidney to increase salt and/or water excretion. In the intensive care setting, diuretics are commonly prescribed for mobilization of excess body fluid and treatment of cerebral edema, ascites, and hypertension. Less common indications include congestive heart failure, disorders of calcium metabolism, glaucoma, and drug overdoses. Diuretics are grouped into six classes according to the primary site of action: osmotic diuretics and carbonic anhydrase inhibitors act in the proximal tubule; loop diuretics act in the thick ascending limb of Henle; thiazide and thiazide-like diuretics act in the distal tubule; potassium-sparing diuretics act in the cortical collecting ducts; and vasopressin receptor antagonists act in the medullary collecting duct.

Renal tubular cells transport solute and water from the apical cell membrane (tubular fluid) to the basolateral cell membrane (blood side). The reabsorption of sodium is central to the kidney's ability to reabsorb water and other solutes (e.g., glucose, amino acids, and bicarbonate). Apical cell sodium entry is mediated by channels that permit sodium to enter by diffusion or transported by specific proteins located on the apical cell membrane. In all renal tubular cells, the sodium-potassium adenosine triphosphatase (ATPase) located on the basolateral membrane maintains the low intracellular sodium concentration that favors sodium movement from the tubular fluid into the renal tubular cell. Diuretics inhibit sodium reabsorption by blocking sodium channels or sodium transport proteins located on the apical cell membrane at discrete sites along the nephron. Because sodium reabsorption occurs in a sequential manner along the nephron, the combination of diuretics with different sites of action (e.g., loop diuretic plus a thiazide diuretic) has a synergistic effect on sodium reabsorption. The additional osmotic force associated with the increased urinary sodium causes a rise in urine volume. The diuresis is associated with a decrease in vascular volume that stimulates movement of sodium and water from the interstitial space into the vascular space, as well as stimulation of counterregulatory pathways (e.g., the renin-angiotensin-aldosterone system) that serve to maintain an adequate extracellular fluid volume.

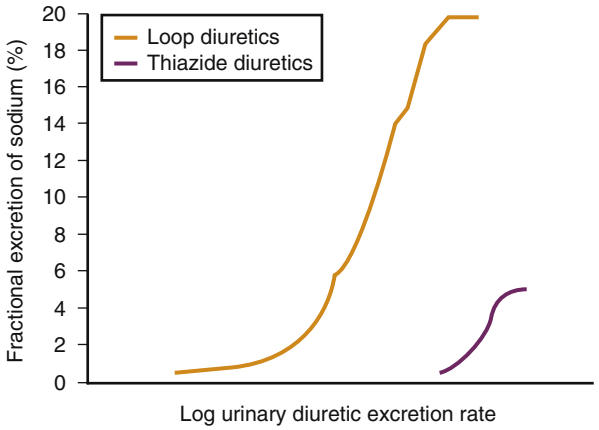

Figure 70–3. Concentration-response curve depicting the relationship between the urinary diuretic excretion rate and the excretion of sodium in the urine.

With the exception of spironolactone and the vasopressin receptor antagonists, diuretics must reach the renal tubular fluid to produce a pharmacologic effect. Because diuretics are extensively bound to plasma proteins, their entry into the tubular fluid depends primarily on proximal tubular secretion. The organic anion transporters actively secrete carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics, whereas the organic cation transporters actively secrete amiloride and triamterene. Mannitol is freely filtered at the glomerulus, and spironolactone has a complex mechanism of action that does not require entry into the tubular fluid for pharmacologic effect. Finally, the nephron delivers a hypotonic fluid to the medullary collecting duct where water is either excreted or reabsorbed based on the presence or absence of apical water channels (e.g., aquaporins). In response to increased plasma osmolality or reduced plasma volume, the posterior pituitary releases vasopressin into the blood that interacts with vasopressin receptors on the basolateral membrane of the collecting duct. Vasopressin mediates the insertion of water channels and the reabsorption of water.

The response to diuretics is determined by the amount and time course of drug reaching the site of action and the sensitivity of the active site to the diuretic. The concentration-response curve (Figure 70-3) depicts the relationship between the urinary excretion rate of loop and thiazide diuretics and diuretic response. The S-shaped curve indicates that for each diuretic there is a minimal concentration that must be reached at the site of action before any response is noted (therapeutic threshold) and that there is a maximal response (ceiling) above which no further response will occur even if more drug reaches the site of action. The amount and time course of drug reaching the site of action, and thus effect, are influenced by the route and frequency of administration, as well as drug and disease states that modify the amount of diuretic reaching the tubular fluid or the tubular response to the diuretic. An example is the twofold to threefold increase in loop diuretic dosage required for response in patients with decreased kidney

function. In kidney failure, the entry of loop diuretics into the tubular fluid is limited by decreased drug delivery to the organic anion transporters due to decreased renal blood flow and competitive inhibition of diuretic transport by "uremic toxins." Adequate tubular fluid diuretic concentration and response can be achieved with the administration of high doses of diuretic[19] but at the risk of increasing ototoxicity, particularly with concurrent aminoglycoside administration.[20,21]

Loop diuretics, such as furosemide, bumetanide, and torsemide, are the most potent diuretics because a large percentage of the filtered sodium is reabsorbed (25%) in the ascending limb of Henle. Loop diuretics decrease sodium reabsorption by inhibiting the electroneutral $Na^+/K^+/2Cl^-$ cotransporter located on the apical cell membrane in the ascending limb of Henle. Loop diuretics increase sodium delivery to the distal tubular segments and diminish water reabsorption by increasing the tubular fluid osmotic force and disrupting the generation of a hypertonic medullary interstitium. The potential for profound fluid and electrolyte loss with loop diuretics mandates close monitoring of body fluid volume and serum electrolytes during therapy.

The increased delivery of sodium to the distal nephron segments has three significant physiologic consequences. First, because sodium reabsorption in the thick ascending limb results in a lumen-positive transepithelial voltage that drives passive magnesium and calcium reabsorption, inhibition of sodium reabsorption by loop diuretics diminishes the transepithelial voltage and causes an increase in the urinary excretion of calcium and magnesium. Long-term use of loop diuretics is associated with hypomagnesaemia, hypercalciuria, and calcium-based kidney stones.[22-24] On the other hand, the enhanced urinary excretion of magnesium and calcium observed with loop diuretics is clinically beneficial in the treatment of hypercalcemia and hypermagnesemia.[25,26]

The second physiologic consequence of increased sodium delivery to the distal nephron segments is enhanced potassium secretion. Sodium reabsorption by the principal cell in the collecting duct favors potassium secretion into the tubular fluid and promotes hypokalemia.[27,28] Finally, the increased sodium delivery to the distal nephron is associated with acute and chronic adaptive processes that enhance distal sodium reabsorption and diminish diuretic efficacy.[29]

Loop diuretics display similar efficacy but differ slightly in pharmacokinetic characteristics. Bumetanide and torsemide are almost completely absorbed after oral administration, whereas the absorption of furosemide is extremely variable, with an average bioavailability of 50%.[30,31] Therefore, when IV furosemide is switched to oral furosemide, the dose is increased to account for the decreased absorption. The onset of diuretic effect is within minutes of IV administration of a loop diuretic and 30 to 60 minutes after oral administration. The duration of diuretic effect is short (2 to 6 hours),[27,32,33] and this short duration often results in the need for multiple doses or a continuous infusion to achieve the desired effect.

Thiazide and thiazide-like diuretics, such as chlorothiazide, hydrochlorothiazide, metolazone, and chlorthalidone, decrease sodium reabsorption by inhibiting the Na^+/Cl^- cotransporter located on the apical membrane in the distal tubule. The thiazide diuretics are less effective than the loop diuretics (see Figure 70-3) because less sodium reabsorption occurs in the distal tubule (5% to 10%) compared with the ascending limb of Henle. Thiazide diuretics have a synergistic effect on fluid and electrolyte excretion when combined with loop diuretics.[34-36] The different thiazide diuretics have similar efficacy, and the main difference resides in potency and duration of action. Metolazone and chlorthalidone display a longer duration of effect than chlorothiazide and hydrochlorothiazide; however, the biologic effect of thiazide agents is prolonged compared with their elimination rates and thus doses usually are administered once or twice a day. Thiazide drugs are relatively ineffective in the setting of renal failure because of the decreased delivery of drug into the tubular fluid and the limited distal tubule sodium reabsorption. In contrast to the calcinuric effect of loop diuretics, thiazide diuretics enhance calcium reabsorption and may have a beneficial effect in children with nephrocalcinosis/nephrolithiasis and hypercalciuria. Thiazides have a greater propensity than other diuretics to cause hypokalemia.

The potassium-sparing diuretics triamterene and amiloride decrease sodium reabsorption by blocking the apical membrane sodium channel in the principal cells of the cortical-collecting duct. Sodium reabsorption in the cortical-collecting duct results in a transepithelial voltage that favors the secretion of potassium and hydrogen ions. Although potassium-sparing diuretics can enhance diuresis, particularly in patients receiving loop or thiazide diuretics, the main clinical benefit of these agents is a reduction in the potassium excretion induced by loop and thiazide diuretics. Spironolactone prevents the binding of aldosterone to a cytosolic receptor, resulting in decreased activity of sodium-potassium adenosine triphosphatase and a decrease in the number of apical sodium channels. Spironolactone is effective in primary and secondary hyperaldosteronism (e.g., liver disease). Potassium-sparing diuretics are not recommended in patients with renal failure because of the propensity for the development of hyperkalemia.

Osmotic diuretics are nonelectrolytes that are freely filtered at the glomerulus and poorly reabsorbed or, in the case of glucose, present in amounts that exceed the tubular reabsorptive capacity. Mannitol is the prototypical osmotic diuretic, and its therapeutic effectiveness is directly related to the mannitol dose being large enough to raise the plasma and tubular fluid osmolality. The extraction of water from the intracellular compartments to the extracellular fluid volume that is associated with mannitol administration is clinically useful in cerebral edema, glaucoma, and the prevention of dialysis dysequilibrium syndrome. The mannitol-induced expansion of the extracellular fluid volume may be sufficient to perpetuate congestive heart failure, pulmonary edema, and significant hyponatremia in patients with renal failure in whom the half-life of mannitol is prolonged and the ability to excrete free water is limited.[37]

Carbonic anhydrase catalyzes the dehydration of carbonic acid to water and carbon dioxide, as well as the reverse hydration reaction. Acetazolamide is the prototypical carbonic anhydrase inhibitor and is more clinically useful for its extrarenal effects than its diuretic effects. Acetazolamide is used to treat glaucoma, acute mountain sickness, and occasionally epilepsy. The effectiveness of the carbonic anhydrase inhibitor is limited by the metabolic acidosis that develops because of the bicarbonate loss in the urine.

The "vaptans" (e.g., conivaptan) are nonpeptide arginine vasopressin antagonists that inhibit the arginine vasopressin–stimulated absorption of free water in the medullary collecting duct. In contrast to other diuretics, the vasopressin antagonists

Box 70–2 Causes of Diuretic Resistance

Noncompliance
- Medication, salt restriction

Poor absorption of medication
- Poorly absorbed formulation (e.g., furosemide oral)
- Disease-induced changes in absorption

Impaired excretion of diuretic
- Renal failure, renal transplant
- Drug interactions: NSAIDs, probenecid

Protein binding in renal tubule
- Nephrotic syndrome

Hemodynamic
- Shock, hypoxemia
- Drugs: NSAIDs, antihypertensive drugs

Change in dose response
- CHF, nephrotic syndrome, cirrhosis

Adaptive responses

CHF, Congestive heart failure; *NS,* nephrotic syndrome; *NSAID,* nonsteroidal antiinflammatory drug.

Box 70–3 Intensive Diuretic Therapy

1. High-dose diuretic therapy
2. Combination of diuretic therapy
3. Continuous infusion diuretic therapy

Box 70–4 Common Adverse Effects Associated with Diuretics

1. Volume depletion
2. Electrolyte abnormalities
   - Hyponatremia
   - Hypokalemia (loop and thiazide diuretics)
   - Hypomagnesemia (loop diuretics)
3. Hypercalciuria (loop diuretics)
4. Ototoxicity (loop diuretics, especially furosemide)

increase urine flow without increasing the renal elimination of sodium. The current use of vasopressin antagonists has been in patients with euvolemic, or hypervolemic hyponatremia, associated with the inappropriate secretion of antidiuretic hormone or congestive heart failure.[38]

Diuretic Resistance

An inadequate diuretic response results from disease- or drug-related alterations in diuretic pharmacokinetics or pharmacodynamics, high dietary salt intake,[39] or adaptive processes[29] (Box 70-2). During diuretic-induced extracellular volume depletion, short-term and long-term adaptive processes serve to protect the intravascular volume; however, when these adaptive processes interfere with the diuretic responsiveness before the desired reduction in the extracellular fluid volume is achieved, they contribute to diuretic resistance.

Short-term adaptation results from enhanced postdiuretic sodium retention. The brisk diuresis associated with diuretics activates counterregulatory pathways that serve to enhance sodium reabsorption and maintain extracellular fluid volume. Counterregulatory mechanisms involved in the short-term adaptation to diuretics include a decrease in atrial natriuretic peptide, increased renal sympathetic activity, increased antidiuretic hormone, a stimulated renin-angiotensin-aldosterone system, and a reduced GFR. The balance favors sodium and water excretion when the diuretic concentration in the renal tubular fluid is sufficient to inhibit sodium reabsorption. When the concentration of diuretic in the tubular fluid is below the threshold needed to elicit sodium excretion, the balance favors sodium and water reabsorption. In patients receiving a generous salt intake, which may be either dietary or associated with obligate fluids or medications, the postdiuretic sodium reabsorption may compensate entirely for the diuretic-induced sodium losses with an end result of no change in the extracellular fluid volume. Long-term adaptation occurs after several days of diuretic use and is characterized by a diminished response to each successive dose of diuretic.[39] The adaptation occurs because of the persistence of short-term counterregulatory mechanisms, as well as functional and structural changes that enhance the sodium reabsorptive capability of the distal tubule.[40,41]

If the response to moderate doses of a diuretic fails to be adequate in patients, several dosing strategies may help overcome the apparent diuretic resistance. Intensive diuretic therapy is achieved through high-dose diuretic therapy, combination diuretic therapy, or a continuous diuretic infusion (Box 70-3).

In patients with edema, the dose-response curve may be shifted to the right so that a greater amount of drug is needed in the renal tubule to produce the desired diuretic response. In patients who have renal failure or patients who receive drugs that inhibit the secretion of diuretic from the blood into the renal tubule, the dose-response curve is normal, but the problem lies in the inability to get a sufficient concentration of diuretic into the renal tubule. In both situations, an intermittent high-dose diuretic regimen may overcome the impaired rate of tubular secretion and increase the urinary diuretic concentration in an amount sufficient to elicit a response. High-dose therapy is associated with an increased risk of fluid and electrolyte abnormalities and a risk of toxicity related to high blood concentrations. Loop diuretic ototoxicity is more common with rapid infusion of high doses, especially when furosemide is combined with other ototoxic drugs.[36]

Because sodium reabsorption in the kidney is sequential and many of the adaptive processes increase sodium reabsorption distal to the site of diuretic action, combination therapy with diuretics that inhibit the distal tubule with loop inhibitors is effective. Part of the effectiveness of combination diuretic therapy resides in the longer duration of effect for thiazides that prevents the postdiuretic sodium reabsorption noted with the shorter-acting loop diuretics. Fluid and electrolyte abnormalities are more common with combination drug therapy (Box 70-4).

The final strategy to overcome diuretic resistance is a continuous infusion of a loop diuretic. The continuous infusion of a loop diuretic is more efficient than intermittent high doses and avoids the high and low serum concentrations associated with toxicity and resistance.[42-45] Continuous infusions result in steady diuretic effect and may avoid the rapid hemodynamic changes and stimulation of counterregulatory process associated with rapid changes in extracellular fluid volume.

A loading dose of diuretic is recommended at initiation and with each upward dosing adjustment to ensure a prompt response. The diuretic response may be further augmented by the addition of a distally acting diuretic.

Prevention/Reversal of Acute Renal Failure

Acute renal failure in the pediatric intensive care unit is generally associated with diminished renal perfusion caused by hypovolemia, hypotension, or decreased cardiac output. In addition, acute renal failure is also associated with nephrotoxins such as radiocontrast agents, antibiotics (e.g., vancomycin), and chemotherapeutic agents (e.g., cisplatin). With the exception of simple saline hydration, little evidence suggests that in humans, mannitol, furosemide, or dopamine prevents the development of acute renal failure in high-risk patients or changes the outcome in patients with established acute renal failure.[46-49] Nevertheless, the use of high-dose furosemide alone or in combination with low-dose dopamine might increase urine output and ease patient care by improving fluid management and permitting increased nutrition.

References are available online at http://www.expertconsult.com.

V

Chapter 71

Glomerulotubular Dysfunction and Acute Kidney Injury

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PEARLS

- Acute kidney injury (AKI) has replaced the term *acute kidney failure*. There are over 30 definitions of AKI in children. Use of the RIFLE, the pRIFLE, and the AKIN defintions may help in streamlining the definition. In the future, biomarkers may further add clarity to this definition at an earlier time frame than they are presently used.
- In the critically ill child, AKI is often associated with cardiovascular instability, which, if prolonged, exhausts the normal kidney compensatory responses to maintain kidney blood flow and glomerular filtration.
- Because tubular blood flow, and thus oxygen delivery to this vital epithelium, depends on postglomerular blood flow, prolonged vasoconstriction of glomerular arterioles results in tubular necrosis.
- Nephrotoxic drugs, sepsis, and overzealous use of diuretics are common comorbid conditions that further contribute to AKI.
- Attention to cardiovascular status and the avoidance of unnecessary nephrotoxic agents such as aminoglycosides, nonsteroidal antiinflammatory drugs, and contrast agents may avoid further AKI.

Acute kidney injury (AKI) is a frequent problem in the pediatric intensive care unit (PICU), but an accurate incidence is difficult to establish due to the ongoing evolution of a clear definition of renal failure. The classic definition was a 50% reduction of glomerular filtration rate (GFR) accompanied by a 50% increase in creatinine. A RIFLE classification of renal injury to allow earlier appreciation of renal dysfunction is now utilized in adults and a modification of this system (pRIFLE) can also be applied to children.[1-3]

Early detection of renal dysfunction by biomarkers is needed, to allow a more timely awareness of injury and, thereby, modifications to alleviate the renal stress. Recent investigations in this area, although early in their development, postulate a panel approach (plasma panel of neutrophil gelatinase-associated lipocalin [NGAL] and cystatin C or a urine panel of NGAL, interleukin 18, and kidney injury molecule-1 [KIM-1]) may be of help in the future to provide more sensitive and specific detection of early AKI.[4-6]

Acute Kidney Injury Pathophysiology

Physiology of Glomerular Filtration

GFR is the product of the filtration rate of the individual nephron and the number of functioning nephrons.[7] A single nephron glomerular filtration rate (SNGFR), is defined by the Starling forces of the glomerular capillaries and the properties of the glomerular capillary wall.

$$\text{SNGFR} = \text{Kf}\,(\Delta P - \Delta\pi) = \text{Kf}\,P_{uf}$$

where *Kf* is a capillary wall property known as the ultrafiltration coefficient and is the product of the surface area available for filtration and the hydraulic conductivity of the membrane. The Starling forces (or pressures) that affect filtration are the hydraulic pressure in the glomerular capillary (P_{gc}), the hydraulic pressure in Bowman's space (P_{bs}), the oncotic pressure of the glomerular capillary (π_{gc}), and the oncotic pressure in Bowman's space (π_{bs}), which is usually zero because the ultrafiltrate is essentially protein-free.[8] P_{gc} favors filtration; Pbs and π_{gc} are opposing forces to filtration. The mean ultrafiltration pressure (P_{uf}) is the difference between the net change in hydraulic pressure and the net change in the oncotic pressure. Thus SNGFR may be modified by alterations in the glomerular capillary pressures, glomerular membrane characteristics, or the surface area available for filtration.

The kidneys are responsible for plasma water and electrolyte balance through filtration at the glomerular membrane and then reabsorption of this filtrate from the renal tubular epithelium. The loss of filtration and tubular reabsorption in AKI is the result of renal adaptive changes that initially function to preserve renal perfusion and glomerular filtration; however, when these are exhausted, the kidney's compensatory mechanisms fail and renal dysfunction ensues.

Glomerular filtration depends on adequate renal perfusion; the kidneys receive approximately 25% of total cardiac output. The fraction of cardiac output perfusing the kidneys is related to the ratio of renal vascular resistance (RVR) and systemic vascular resistance.[9] Renal blood flow (RBF) is determined by systemic blood pressure (SBP) and RVR, expressed by the formula RBF = SBP/RVR.[9] Kidney autoregulation, which maintains a constant renal perfusion pressure, occurs through alterations in RVR in response to changes in systemic

vascular resistance or intravascular volume. When SBP is within the normal physiological or autoregulatory range, the kidney can maintain constant blood flow and GFR by dilation of the preglomerular or afferent arteriole, which reduces RVR and increases RBF. This afferent arteriole dilation is accomplished by two known mechanisms, smooth muscle relaxation of the afferent arteriole in response to sensing a transmural pressure drop (the myogenic reflex[3]) and the tubuloglomerular feedback system. The tubuloglomerular feedback system is operational following a reduction of plasma flow. When solute and water delivery to the macula densa are reduced, the juxtaglomerular apparatus responds by relaxing the smooth muscle of the adjacent afferent arteriole. Thus a reduction in cardiac output or effective renal plasma flow is accompanied by vasodilation at the preglomerular arteriole, which in turn reduces RVR, thereby restoring RBF.

During states of reduced cardiac output or intravascular volume depletion, the systemic vasoconstrictors, angiotensin II and vasopressin, are released to help preserve vascular tone. The kidney counteracts the renal vasoconstrictor activity of angiotensin II and increased sympathetic tone through the intrarenal production of vasodilatory prostaglandins such as prostaglandin I2.[10] These locally produced substances may attenuate renal vasoconstrictive forces and help preserve renal perfusion. Animal model data of congestive heart failure have provided evidence that enhanced prostaglandin synthesis is required for preservation of renal perfusion and GFR. Patients receiving prostaglandin synthetase inhibitors such as nonsteroidal antiinflammatory drugs (NSAIDs) have potentiation of renal ischemia because of an increase in renal vasoconstriction not antagonized by intrarenal prostaglandin synthesis.[11] Endothelium-derived relaxation factors (EDRFs), which are vasodilatory, and the potent vasoconstrictor endothelin, produced by the endothelium, may also affect the regional vascular tone.[12]

Constriction of the postglomerular capillary sphincter, the efferent arteriole, in the face of reduced RBF serves to increase the filtration fraction and preserve GFR, although this occurs at the expense of renal plasma flow, which may be further reduced. Vasoconstriction at the efferent arteriole is mediated by angiotensin II and, to a lesser extent, by the action of the adrenergic system by epinephrine.[13] Elevation in postglomerular arteriolar resistance may be blocked by the angiotensin-converting enzyme inhibitors. When converting enzyme inhibitors are administered to the patient who requires efferent arteriolar constriction to maintain GFR, renal decompensation often results.[14]

As previously noted, reductions in effective intravascular volume and cardiac output are accompanied by increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system and increased circulating levels of vasopressin.[15] Hormonal and neural systems signal the kidneys to increase the reabsorption of sodium and water to help restore the deficient intravascular volume, increase cardiac output, and consequently improve RBF. These, and the kidney's homeostatic mechanism, by afferent arteriolar vasodilation and efferent arteriolar constriction, maintain the kidney's glomerular filtration. The kidney's homeostatic mechanisms, however, are not without limitation. The autoregulatory ability of the afferent arteriole is maximal once the mean SBP falls below 80 mm Hg. The renal autoregulatory range appears to be age-dependent, because younger animals can autoregulate over lower pressure ranges. The range of perfusion pressure over which the kidney can autoregulate may be limited in certain conditions so that vasodilation is maximal with a minor reduction in mean arterial blood pressure. Examples include extracellular fluid depletion, renal ischemia, or renal vascular disease (e.g., hypertension, diabetes, atherosclerosis).

As the stimulus for release of vasoconstrictors continues, afferent arteriolar constriction rather than vasodilation may predominate, and the result is a decrease in renal plasma flow and filtration rate.

Constriction of the afferent arteriole may be stimulated by increased sympathetic nervous system activity and increased levels of endogenous or exogenous circulating catecholamines such as dopamine or norepinephrine. Thus the administration of these vasoactive-inotropic agents may actually compromise the kidney's adaptive mechanisms. Excessive vasoconstriction eventually results in diminished filtration rate and oxygen delivery to the kidney.

Pharmacological agents may alter renal perfusion by changing SBP through an action on systemic vasculature or by direct effects on renal vasculature (Box 71-1). Vasodilators, such as hydralazine, lower SBP without changing renal perfusion pressure, because the decrease in SBP is accompanied by decreased RVR. Conversely, epinephrine increases SBP but decreases RBF by its vasoconstrictor effect on intrarenal blood vessels.

Box 71–1 Vasoactive Substances in the Kidney Vasculature

1. Kidney vascular resistance/F kidney blood flow
   - Epinephrine
   - Norepinephrine
   - Angiotensin II
   - Arachidonic acid
   - Thromboxane A_2
2. Kidney vascular resistance/F kidney blood flow
   - Prostaglandin E_1
   - Prostaglandin E_2
   - Dopamine
   - Furosemide
   - Angiotensin-converting enzyme inhibitors
   - Bradykinin
   - Isoproterenol
   - Acetylcholine

Data from Hostetter TH, Brenner BM: Kidney circulatory and nephron function in experimental acute kidney failure. In Brenner BM, Lazarus JM, editors: *Acute kidney failure*, ed 2, New York, 1988, Churchill Livingstone.

Morphologic Changes in Renal Injury

Morphologic changes seen in acute renal injury, especially those in the tubules, depends on the duration of injury as well the eliciting mechanism.

The kidney's complex structure, with heterogeneous segments within the kidney receiving differential regional perfusion and thereby oxygenation, sets up a common form of renal failure, that of the tubulointerstitium. This region is at greatest risk for ischemia because of its gradient of regional perfusion and oxygenation. In addition, vascular disease, including

glomerular disease, often occurs in children and results in AKI, but there are studies that suggest the extent of damage to the tubulointerstitium has the greatest prognostic implication to the degree of final renal recovery.[16]

Initial structural changes in tubular cells are seen as apical and basal surface changes of simplification, with microvilli of the brush border shortening and disappearing by either detachment from the apical surface or being internalized within the tubular cells.[17]

In this scenario, enzymes of the brush border (alkaline phosphatase and gammaglutamyl transpeptidase), may be found in the urine and may be used as markers of early tubular injury.[18] The loss of microvilli surface area leads to loss of enzymes and transport sites for transcellular absorption and apical uptake. Additionally, loss at the basolateral interdigitating infoldings of the tubular cells then results in further reduction of surface area for transport and loss of the Na-K-adenosine triphosphatase (ATPase) that is localized to this membrane and involved in many transport processes.[19]

Morphologic changes in distal tubules and outer medulla also occur and may be found even when proximal tubular injury is not readily identified on biopsy. Experimentally, the outer medulla has been identified as sensitive to hypoxia, including that induced by toxins such as radiocontrast agents and cyclosporine.[20]

Injury at this outer medulla region may be missed on biopsy since this site often is not sampled. Tubular cell detachment with exposed, denuded regions of the basement membrane can be found on biopsies, as a result of altered cell-matrix attachments.[21]

Renal tubular sensitivity to ischemic injury is primarily influenced by the individual renal cell's energy requirements, its glycolytic capacity, and the extent of hypoxic stress upon the cell. Glycolysis and oxidative phosphorylation both supply the ATP required by the cell to drive its metabolism, and it follows that cells with a greater capacity for glycolysis (distal tubular cells) are less sensitive to oxygen deprivation than the cells that rely mainly on mitochondrial derived energy, (proximal tubular cells).[22]

In vivo and in vitro studies may be discordant in identifying susceptiblity to hypoxia. Medullary straight portions of the proximal tubule have a higher glycolytic capacity than the cortical segments of the proximal tubule but, due to the regional distribution of perfusion within the kidney, the medullary portions operate in a lower oxygen-tension environment and therefore are more susceptible to hypoxia/ischemic injury.[23] The individual cell's energy requirements to conduct its transport activities further influences its risk to hypoxic injury. The outer medullary proximal tubular cell (pars recta), due to the high energy requirements for its transport functions, has a greater injury risk than the deep inner medullary tubular cell with its low-oxygen environment, but also a low energy requirement to maintain its transport function.[24]

When energy stores are rapidly depleted, the normal Na-K ATPase pump begins to fail and the most basic of cell function, membrane integrity, is jeopardized, with resultant accumulation of Na, Cl, and water within the cell; this cell swelling (oncosis) is a hallmark feature of necrosis.[25] Not all cells that fail to maintain their energy requirements die through necrosis; apoptosis, which appears morphologically as cell shrinkage, is also a result of inadequate energy support. Apoptosis is an asynchronous cell death triggered over hours to days, with the earliest cellular element involving mitochondrial changes including loss of transmembrane potential and release of mitochondrial cytochrome c into the cytosol.[30] It is mitochondrial function/dysfunction that primarily determines the fate of the cell for recovery and survival or death, and by what form: apoptosis or necrosis.

Pathogenesis of Reduced Glomerular Filtration Rate in Acute Kidney Injury

The mechanisms responsible for GFR reduction in acute renal injury have been studied extensively with experimental models of AKI. Multiple mechanisms are often operational in mediating hypofiltration. Whereas one factor may have greater importance in the initiation of injury and decreased filtration, others are involved in the sustained reduction in GFR during the maintenance phase of AKI. Four major mechanisms result in reduced GFR during AKI: reduced blood flow, decreased Kf, tubular obstruction, and backleakage of tubular fluid.[31] Each factor is discussed regarding its role in both the initiation and maintenance phases of AKI.

A reduction in RBF can be demonstrated during the initiation phase of many forms of AKI and seems to play a predominant role in ischemic injury and rhabdomyolysis.[31] Proposed theories for the reduction of RBF include (1) a proportional increase in the afferent and efferent arteriolar resistances in response to activation of the renin-angiotensin system; (2) vascular endothelial cell swelling and damage with release of vasoactive peptides such as endothelin; and (3) hyperemic congestion of the medullary peritubular capillaries.

Kf may be reduced in both nephrotoxic and ischemic forms of renal failure. Endothelial or mesangial cell swelling reduces the surface area available for filtration; altered permeability induced by humoral factors such as angiotensin II and vasopressin may also decrease Kf. Circulating levels of both hormones are increased during AKI.

Renal tubular cells are the primary site of injury in both ischemia and nephrotoxin-induced renal injury. Tubular cell injury may be sublethal or lethal and result in cell necrosis or apoptosis. Once this injury occurs, cells detach from the supporting basement membrane and obstruct the tubule lumen. In addition, even with sublethal injury, tight junctions may be disrupted, and the intact layer may be lost. The loss of epithelial integrity allows backleakage of ultrafiltrate, which contains creatinine and urea, through paracellular pathways into the renal interstitium, creating further diminution of excretory function and reduced urine formation. Necrosis of a selected region of the renal tubule is accompanied by tubular obstruction and eventual filtration failure by that entire unit or nephron.

Intratubular obstruction occurs in most forms of acute renal injury, either as a contributing factor in the initiation phase or during the maintenance phase.[31] Tubular obstruction with cellular debris and precipitated protein is a prominent finding in both the initiation and maintenance phases of ischemic injury. In the case of nephrotoxic injury, the degree of injury may determine the extent of tubular obstruction. In an experimental model of gentamicin nephrotoxicity, the drug dose was positively correlated with the contribution of tubular obstruction to reduced GFR.[31] Tubular obstruction and loss of epithelial integrity caused by tubular cell injury result in the backleakage of tubular fluid and solutes. Excretion of solute

and fluid is decreased, and this decrease possibly signals a further reduction in the GFR by stimulation of the tubuloglomerular feedback mechanism.[31] Backleakage of fluid involves tubular factors and is not a result of hypofiltration, although it does impair the excretory function of the kidney. Consequently, a falsely low estimation of actual GFR may occur because tubular fluid containing urea and creatinine leaks back into the vascular space and interstitium. Prevention of the tubular obstruction may alter the course of renal failure, even in those states in which the primary mechanism of injury is not obstruction.

AKI may be viewed as an evolving process into three phases[32]: (1) an initiation phase in which the primary mechanism of injury is operational; (2) a maintenance phase during which renal function remains poor and other factors may contribute to sustained injury; and (3) a recovery phase during which there is regeneration of cells and restoration of function. Although the primary initiating event may be hypoperfusion with ischemia, often it involves multiple contributing factors that mediate additional cellular damage, usually through alterations in energy supply. From a clinical perspective, it may be most helpful to consider acute renal dysfunction syndromes according to the cause of the inciting event; however, it is equally vital to understand the other contributing mechanisms that ultimately affect outcome.

Recently, endothelial injury and vascular dysfunction have been postulated to occur during the initiation and particularly during the maintenance phases of AKI. Although most studies have focused on the tubular cell as the primary site of injury leading to dysfunction, recent studies have provided insight into the potential role for endothelial injury in continued reduced RBF and altered vascular function.[33] Sutton et al. propose that an additional phase be added to the current model for AKI: after the initiation phase, an extension phase occurs that is due to microvascular injury related to ischemic damage to endothelial cells, infiltration of leukocytes, and activation of the coagulation system. This process is thought to predominate in the corticomedullary and outer medullary microvessels and may occur in the face of early tubular cell regeneration so that limiting the extension process provides a potential mechanism for aiding recovery.

Mechanisms of Renal Cell Injury

The renal tubular cell expends energy in the form of ATP to maintain a high intracellular concentration of potassium and a low intracellular concentration of sodium. This concentration gradient depends on the continuous activity of the Na^+/ K^+-ATPase and is the driving force for the reabsorption of sodium. Active reabsorption of sodium is the primary driving force for water reabsorption and the coupled transport of amino acids, carbohydrates, organic acids, and other compounds. Thus all transport functions, as well as many other vital cell functions, depend on normal activity of the Na^+/K^+ pump, which, in turn, depends on an adequate supply of energy. In addition, membrane fluidity or integrity is important to transport functions in tubular cells. Processes that result in alterations in the membrane or in the supply of energy are common final pathways for renal tubular cell death.

A decrease in the cellular ATP content occurs in many forms of renal injury, possibly as the result of primary alterations in the cell's ability to perform oxidative phosphorylation or as the end result of other perturbations. Heterogeneity exists in the susceptibility of nephron segments to oxygen deprivation with more distal segments being relatively resistant. This is related to the greater glycolytic capacity of the distal tubule compared with the proximal tubule, which relies on oxygen-consuming pathways for ATP generation. Therefore the net result of renal injury is usually a depletion of energy in the form of ATP, with the inability of the cell to perform vital functions, including transport and maintenance of cell integrity.

Cellular injury may be modified by the requirements made on its energy stores. If more transport is required of the cell, more energy is consumed, and less energy is left for cell maintenance. Evidence exists to support this theory. If transport requirements are reduced by the administration of diuretics or by the stimulation of the glomerulotubular feedback mechanism, then further injury may be attenuated. The feedback mechanism, whereby there is reduction of GFR in the face of reduced reabsorption by the proximal tubule, is a protective signal that conserves cell energy by reducing metabolic demands made on the cell.

Heat shock proteins (HSPs) are a family of proteins that appear to protect cells from injury as a result of hyperthermia, ischemia, or toxins. The HSP induction by sublethal thermal stress has been found to attenuate subsequent injury in the kidney.[34] Renal transplants from animals that underwent short-term hyperthermia had better initial function and subsequent survival. Furthermore, in cultured inner medullary collecting-duct cells, induction of HSP-1 by preconditioning hyperthermia attenuated the alterations in mitochondrial function and glycolysis that were observed after cells were exposed to high temperatures. Investigations into potential mechanisms to use this natural cell defense mechanism are under way.

The ability of renal tubular epithelial cells to undergo regeneration determines in large part the degree of renal recovery. Therefore much work has recently been done to study ways that cells regenerate and mechanisms that might enhance recovery. Early in ischemic injury there is induction of early response genes such as c-fos and Egr-1.[35] By 2 days after ischemia, the proliferating cell nuclear antigen is detected, followed by expression of other dedifferentiated cell markers, which seem to be a sign of early recovery. Other cells appear to undergo apoptosis or cell death. Postischemic regeneration seems to be a recapitulation of early renal tubular cell development. Growth factors such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor 1 (EGF-1) have been associated with enhanced recovery as well. Renal levels of hepatocyte growth factor (HGF) increase after two models of renal failure, postnephrectomy, and following CCL4 (chemokine [C-C motif] ligand 4) injection, and this increase supports a role for HGF in renal repair.[36] Exogenous EGF has been shown to enhance renal tubular cell regeneration and to lessen the severity and duration of hypoxia and toxin-induced renal failure. EGF receptor levels increase within hours of ischemic injury in the rat. Elevation of soluble EGF occurs along with morphological evidence of tubular injury within 12 hours of ischemia, which is followed by cell proliferation and a decrease in soluble EGF by 24 to 48 hours after ischemia.

Alterations in Cell Membranes

Membrane phospholipids have a structural function and affect membrane permeability, as well as the activity of membrane transport systems.[37] These compounds are regulated in part by

the activity of phospholipases, which release free fatty acids from phospholipids. Several mechanisms related to acute cell injury may alter phospholipase activity and thereby change membrane phospholipids and membrane integrity: altered intracellular calcium homeostasis, depletion of ATP, and lipid peroxidation.[33] Increased phospholipase activity has been associated with an abnormal increase in permeability of the inner mitochondrial membrane, which ultimately results in disruption of mitochondria and loss of the ability to produce adequate energy.

Cellular Calcium Homeostasis

Increased intracellular calcium is commonly found in cell injury. It is not, however, a consistent finding in all models of renal injury.[38] Techniques to study changes in the subcellular distribution of calcium have allowed time-related changes to be assessed. In the rat proximal tubule, steady-state hypoxia is accompanied by a prompt increase in cytosolic free calcium that precedes the appearance of membrane damage. The increase in calcium is reversed with reoxygenation. Increased cellular calcium may activate phospholipases, as previously mentioned; alter the cytoskeleton and cause injury by allowing cell swelling; or affect membrane permeability at the plasma membrane, the mitochondrial membrane, or the endoplasmic reticulum. Alterations in mitochondrial function that occur as a result of calcium loading of this organelle have been extensively studied. Excess mitochondrial calcium is associated with changes in the permeability of the inner mitochondrial membrane with loss of the electrochemical gradient and the capacity for oxidative phosphorylation. In addition, changes in enzyme activity and mitochondrial levels of nucleotides may exist.

Production of Free Radicals

Renal cell damage induced by inflammation or oxygen deprivation may be mediated, in part, by oxygen free-radicals that are generated by several cell processes, including accumulation of long chain acyl CoA as a result of mitochondrial dysfunction. The net result is increased intracellular calcium and ultimately, changes in membrane-related functions.[32]

Tubular Cell Energy Metabolism

After exposure to a variety of nephrotoxins or ischemia, renal cortical ATP levels are reduced even before changes in membrane integrity and cell death occur.[39] In ischemic injury, alterations in renal perfusion may result in decreased oxygen delivery to tubular epithelium. Direct mitochondrial damage has been postulated to be the primary event in many forms of nephrotoxic injury.[32] Other nephrotoxins interfere with energy production by the inhibition of enzymes along the citric acid cycle. In this way, toxins impair energy production. ATP levels decrease immediately after ischemia, with concomitant increases in ATP hydrolysis products. Reflow is associated with a gradual increase in cell ATP levels.

Classification of Acute Glomerulotubular Dysfunction

Hemodynamically Mediated Acute Kidney Injury

Renal hypoperfusion with ischemia is a common form of acute renal damage, especially in the setting of the ICU. This form of renal injury is often accompanied by oliguria and results from alterations in renal perfusion after a period of hypoxia, hypotension, cardiac dysfunction, or any condition that promotes hemodynamic instability, decreased effective plasma volume, or both states. This condition is commonly referred to as acute tubular necrosis because it is characterized by necrosis of tubule cells; however, this is a nonspecific term that may also define nephrotoxic injury. A preferred term is vasomotor nephropathy or hemodynamically-mediated renal failure.[40] The same physiological alterations that initiate renal injury in this form of nephropathy may potentiate renal failure in conditions whose primary inciting event may not have been vascular.

Vasomotor nephropathy commonly follows a period of renal compensatory changes that may be termed prerenal failure,[9] which are discussed in the preceding section on physiology. When the kidney has fully used normal compensatory mechanisms, renal oxygen delivery is critically impaired, and this impairment results in cell damage or tubular cell necrosis. Thus it is apparent that acute tubular necrosis is the end result of a continuum of renal adaptive mechanisms. Acute cortical necrosis is an exaggerated and more advanced form of renal ischemia.

When vascular or hemodynamic abnormalities persist or are profound, renal compensatory mechanisms are unable to preserve RBF and maintain sufficient oxygen delivery and GFR. At a mean renal perfusion pressure of 80 mm Hg, afferent, arteriolar dilation is maximal, and below these systemic pressures, RBF dramatically declines.[9,40] In addition, loss of the ability to autoregulate as a result of ischemia may cause further damage. Renal cell injury develops as the result of deficient oxygen delivery, depletion of cellular energy, loss of membrane integrity, and release of reactive oxygen species. Without sufficient oxygen, the kidney cannot support cell functions that maintain architectural integrity and complex transport functions.

Although total RBF is decreased in vasomotor nephropathy, outer cortical blood flow is preferentially reduced. The medulla is not spared, however, because of its increased susceptibility to alterations in renal perfusion.[41] Oxygen delivery to this segment of the kidney is precarious. Medullary partial pressure of oxygen (PO_2) is approximately 10 mm Hg in the rat and dog. This oxygen level approaches the critical minimum level required to support oxidative phosphorylation and ATP synthesis for cell function. In general, however, the proximal tubule sustains the greatest injury. The renal arteriogram of human subjects with vasomotor nephropathy reveals marked narrowing of the arcuate arteries and absence of peripheral vasculature, providing further evidence for the marked vascular resistance enhancement.[40]

The primary event in vasomotor nephropathy is injury of the renal tubule. The initiation of this injury, however, is microvascular in origin. Maximal renal compensation with marked efferent and afferent arteriolar vasoconstriction reduces glomerular plasma flow with resulting hypofiltration and compromises postglomerular blood supply to the renal tubule. Tubular cell necrosis with sloughing of tubular cells into the lumen results in obstruction of flow and backleakage of filtrate through the injured epithelium. Alterations in tubular cell function in cells receiving sublethal or lethal injury increase fluid and salt delivery distally, and this increase signals the glomerulotubular feedback system to cause vasoconstriction of the afferent arteriole and limit the fraction of plasma filtered at the glomerulus.[40] Although the initial reduction in

GFR is the result of decreased RBF and tubular factors such as obstruction and backleakage, continued hypofiltration during the maintenance phase is related primarily to continued vasoconstriction and renal hypoperfusion.[40] Recovery from postischemic AKI is biphasic. Initially, an increase in GFR occurs with relief of tubular obstruction and subsequently, improved filtration in association with renal vasodilation.

Oliguria in the presence of renal hypoperfusion has been referred to as acute renal success by investigators who propose that the response of an intelligent organ to a perceived reduction in blood flow is to reduce fluid and electrolyte losses by vasoconstriction to reduce the fraction of plasma filtered and by maximal reabsorption of fluid and salt to restore the circulation. In addition, increased distal delivery of water and solutes because of tubular cell necrosis reflects failure of the renal tubule to absorb what is filtered. The appropriate response of an intact nephron is to reduce filtration by release of angiotensin II into the interstitium. Angiotensin II mediates arteriolar vasoconstriction, which decreases glomerular plasma flow, and retraction of the glomerular tuft, which reduces Kf, the net effect being decreased glomerular filtration.[41]

The classic form of hemodynamically-mediated AKI was oliguric, by definition; however, nonoliguric acute vasomotor nephropathy is increasingly recognized.[41,42] This form of less severe disease has been referred to as attenuated acute tubular dsyfunction and has allowed the recognition of three stages of AKI that actually represent a continuum of worsening disease: first, abbreviated renal insufficiency occurs after a single event of renal hypoperfusion, such as aortic cross-clamping, in the face of adequate volume repletion and SBP. This syndrome is characterized by an acute drop in the GFR with gradual return to normal within a few days. The inability to concentrate the urine or to conserve sodium provides evidence of tubular injury. The second phase or form is referred to as overt renal failure. An example of this situation is aortic cross-clamping followed by continued renal hypoperfusion because of poor cardiac function. A more prolonged period of hypofiltration lasts for several days to weeks with a gradual return of the GFR. If recovery of renal perfusion is impaired by repeated episodes of ischemia/hypotension, sepsis, or hypoxia, the third pattern may be observed in which a protracted course may be observed and chances for recovery may be doubtful.[42] One situation in which the last example could exist is aggressive hemodialysis (ultrafiltration) with hypovolemia and, consequently, renal hypoperfusion in the recovering phase of renal failure. Clinical experience has supported this theory. Patients with multiple renal insults have a more protracted course and increased morbidity.[43]

Using the Schwartz formula for estimate of creatinine clearance (GFR) in infants and children, a modified RIFLE classification (pRIFLE) has been developed.

$$\text{Schwartz Formula: eGFR} = \text{eCrCl} = K \times \text{Height (cm)} / \text{serum creatinine (mg/dL)}$$

[K value of premature infants (0.33), infants (0.45) and children > 1 year of age of 0.55][44,45]

The pRIFLE classification is defined by the percent reduction in eCrCl and/or the amount of diminishing urine output[2] (Table 71-1).

Table 71–1 pRIFLE Classification

pRIFLE	Estimated CrCL	Urine Output
Risk	25% decrease	< 0.5 mL/kg/h for 8 hours
Injury	50% decrease	< 0.5 mL/kg/h for 16 hours
Failure	75% decrease	< 0.3 mL/kg/h for 24 hours or anuric for 12 hours
Loss	Persistent failure >4 weeks	
End-stage renal disease	Persistent failure >3 months	

Treatment of Acute Kidney Injury

Prevention/Attenuation of Acute Renal Failure

Prevention or attenuation of ARF has been the subject of numerous studies, as most agree that protection of the kidney from damage or enhancing recovery after damage would be preferable to the currently available supportive therapies. Primary prevention of AKI in the ICU is limited to those conditions in which the timing of injury is predictable, such as exposure to radiocontrast dye, cardiopulmonary bypass, nephrotoxic medications, or chemotherapy. In contrast to most cases of community-acquired AKI, nearly all cases of ICU-associated AKI result from more than a single insult.[46] Protective agents have been studied extensively with animal models of acute renal injury. Some of these agents have ultimately been used in clinical situations with variable success. In general, methods to reduce renal injury have been aimed at manipulation of RVR or alteration of the metabolic processes of the renal tubular cell.

Dopamine

Dopamine, when infused in low intravenous doses, increases RBF, increases GFR, and increases sodium excretion. In the past, clinicians frequently used "renal dose" dopamine in the hopes that such a maneuver might attenuate renal injury and improve survival. In addition, clinicians often interpret an increase in urinary output as proof that these two assumptions are valid. Dopamine stimulates both dopaminergic and adrenergic receptors. As such, dopamine may affect renal blood flow by direct vasodilation (dopamine receptors), by increasing cardiac output (β-receptors), or by increasing perfusion pressure. Of particular interest are its action on Dopamine 1 (D1) receptors, which are abundantly distributed throughout the renal vasculature.[47] Stimulation of D1 receptors results in vasodilation by means of receptor coupling with cyclic adenosine monophosphate (cAMP) and calcium flux generated by protein kinase A. In addition, D1 receptors are also found within the brush border and basolateral membranes of the proximal tubule; medullary ascending limb of the loop of Henle; distal tubule; and cortical collecting ducts where agonist induces decreases in sodium, phosphate, and bicarbonate absorption. D1 receptors have also been localized to the macula densa where they may modify renin production.[47] Dopamine inhibits the Na/K-ATPase along the nephron. Interestingly, this action would be expected to decrease

the oxygen consumption of the renal tubule; thus it would be less susceptible to ischemic or hypoxic injury. Dopamine 2 (D2) receptors are present along the renal tubule. In the inner medulla, a subclass, D2k is coupled to prostaglandin E2 and attenuates the action of antidiuretic hormone (ADH) in this segment.

Dopamine in the dosage range of 0.5 to 2 μg/kg/min increases RBF by 20% to 40%. The GFR increases by 5% to 20%, an effect related to enhanced glomerular ultrafiltration by a preferential vasodilation at the afferent arteriole. This is thought to be related to a dopamine-induced increase in local angiotensin production, which attenuates the dopamine-induced vasodilation at the efferent but not the afferent arteriole. The increase in medullary blood flow observed with dopamine results in a decrease in the urea concentration within the medullary interstitium and contributes to the limited concentrating ability of the dopamine-stimulated renal tubule.

The observed increase in urinary flow is thought to be related primarily to the tubular actions rather than the vascular actions of dopamine. At higher doses, dopamine stimulation of receptors results in decreased sodium and fluid excretion, as well as renal vasoconstriction. Dopamine clearance is decreased in the presence of renal or liver dysfunction.

However, dopamine does have noncardiac effects that complicate its use and should make clinicians rethink its previous role as a vasoactive agent. The group that formulated the 2008 International Guidelines for Management of Severe Sepsis and Septic Shock does not recommend the use of low-dose dopamine as a renal agent, based on available data.[48] They also noted that dopamine may inhibit thyrotropin hormone release from the hypothalamus and have immunosuppressive effects through its inhibition of release of the lymphotropic factor prolactin. Dopamine should be used cautiously in neonates because the renal vascular response to dopamine is age dependent,[49] although administration of dopamine (0.5 to 2 μg/kg/min) to premature neonates with respiratory distress syndrome and renal insufficiency was reported to result in improved creatinine clearance without major side effects.

Diuretics

Intravenous diuretics have been frequently used in the intensive care unit to ameliorate fluid overload by increasing urine output.[50] This widespread use of loop diuretics in the face of impending renal failure has been ascribed to a combination of animal and human data. Loop diuretics decrease renal vascular resistance and increase renal blood flow.[51] In addition, loop diuretics inhibit the sodium/potassium chloride cotransporter system (NKCC2), thereby reducing active oxygen transport and potentially reducing oxygen consumption, and thus limiting ischemic injury to the outer medullary tubules. Indeed, furosemide has been shown to decrease renal oxygen consumption in critically ill patients.

Mannitol may attenuate renal failure if it is given before the insult or immediately afterward.[52] Loop diuretics, such as furosemide, if given along with a potentially nephrotoxic agent, may increase the renal excretion of the agent and reduce associated nephrotoxicity. Mannitol has been shown to ameliorate nephrotoxicity related to gentamicin, amphotericin B, cisplatin, and myoglobin. A specific beneficial effect is doubtful, however, because acute saline loading alone provides similar protection. When tubular obstruction plays a major role, mannitol may increase tubular flow enough to wash obstructing debris downstream. It seems reasonable to use mannitol and potentially furosemide in the initial phases of oliguria when AKI may not be established; however, these agents provide little benefit and may increase toxicity in sustained oliguria as a result of tubular necrosis.

Calcium Entry Blockers

These agents may prevent renal insufficiency through their vasodilatory action on renal vasculature, as well as inhibition of calcium entry. The calcium channel blockers verapamil, nitrendipine, diltiazem, and nisoldipine have been administered to various animal models of ischemic injury with some success in the prevention or attenuation of renal failure. Minimal protection is observed, however, if they are administered after ischemia.[52] Calcium entry blockers had a beneficial effect in endotoxin-mediated AKI. This effect was postulated to be a result of an antagonism of platelet-activating factor.[53] The perfusion of cadaveric renal grafts before transplantation with diltiazem was associated with improved graft survival compared with control subjects.[54] Preoperative administration of calcium channel blockers to adults undergoing cardiac surgical procedures did not provide any obvious protection from the development of AKI.[55]

Prostaglandins

Vasoconstrictive forces in the renal vasculature may result from the action of vasoconstrictor prostaglandins and are counteracted by the vasodilatory substances.[56] Infusion or stimulation of the vasodilatory prostaglandins or inhibition of the vasoconstrictor prostaglandins seems to be a reasonable approach. Prostacyclin provided protection during ischemia in a rat model.[56] Administration of the thromboxane synthetase inhibitor OKY-046 partially ameliorated hypofiltration in a rat model of ischemic renal failure.[57] In addition, the administration of the free radical scavenger's dimethylthiourea and superoxide dismutase attenuated renal insufficiency and reduced thromboxane levels.

Renin-Angiotensin Antagonists

Administration of saralasin, an angiotensin II receptor antagonist, either before or after ischemia was not beneficial in the rat model. Blockade of angiotensin production by the conversion of enzyme inhibition with enalapril or captopril was not successful in preventing AKI.[58] Although captopril did prevent a fall in RBF, in one study the GFR actually dropped.

Adenosine and Adenosine Triphosphate

Renal ischemia results in the depletion of cellular adenine nucleotides and increased levels of adenosine, an agent implicated as a mediator of local renal vasoconstriction.[59] Adenosine may also have protective tubular effects during ischemia because it inhibits solute reabsorption in the medullary thick ascending limb of the loop of Henle. Theophylline, a competitive inhibitor of adenosine receptors, partially prevents the hypofiltration following ischemia in the rat.

Infusion of ATP-magnesium chloride (ATP-$MgCl_2$) after renal ischemia promotes more rapid cellular recovery and attenuates renal injury.[59] In animal models exogenous ATP, adenosine diphosphate (ADP), adenosine monophosphate

(AMP), and adenosine preserve renal tubular cell metabolism during anoxia by protecting the membrane from disruption and providing precursors for rapid synthesis of ATP during reperfusion.

Atrial Natriuretic Factor

Atrial natriuretic factor (ANF) has direct effects on glomerular hemodynamics and GFR.[60] ANF dilates arcuate, interlobular, and proximal afferent arterioles, and it relaxes mesangial cells.[61] In a rat model of rhabdomyolysis, administration of ANF improved GFR and enhanced sodium and water excretion. In addition, ANF improved GFR and maintained cell energy levels during ischemic injury.[62] ANF preserves glomerular filtration and cellular ATP levels in experimental models of AKI by its effect on glomerular hemodynamics.

Free Radical Scavengers

Reactive oxygen species have been proposed as a cause of cellular injury in many forms of AKI. The conversion of xanthine to hypoxanthine during reoxygenation produces reactive oxygen species. Antioxidants and xanthine oxidase inhibition (allopurinol) have proved to attenuate renal injury in many models of ARF.

Thyroxine

Thyroxine reduces renal injury in a number of experimental models when given before the injury, immediately after, or 24 hours after ischemia. The mechanism by which thyroxine preserves both glomerular and tubular function is not completely understood; however, the rate of recovery of cellular ATP levels was much more rapid in animals given thyroxine after ischemic AKI. Isolated mitochondria from rats subjected to 45 minutes of ischemia exhibited decreased mitochondrial ADP transport. Administration of thyroxine was associated with significantly enhanced ADP transport.[63] The investigators speculated that part of the ATP depletion associated with ischemic injury might be the result of decreased mitochondrial uptake of the ATP precursor, ADP. The administration of thyroxine at 5 to 6 ng/kg/day for 5 to 10 days in eight children with AKI resulted in the recovery of renal function in all but one child, who died of the original disease.[64]

Glycine and Alanine

The amino acids glycine and alanine have recently been shown to have cytoprotective effects against injury in anoxia-hypoxia and chemotherapy-induced renal failure. The mechanism of cytoprotection is not understood but does not appear to involve preservation of intracellular ATP levels. Studies performed in cultured proximal tubular cells indicate that glycine and alanine may stimulate the expression of hsp genes and increase HSP proteins, which protect cells from injury. The cytoprotective effect was not observed with other amino acids and was independent of cellular ATP levels in this model of renal injury.[65] Incubation of isolated renal tubules with glycine during hypoxia was associated with increased levels of glutathione, as well as increased cell ATP, although these did not appear to account fully for the protective effect of glycine. In addition, administration of glycine prevented renal injury in rats treated with nephrotoxic doses of cisplatin.[66]

Acute Kidney Injury: Clinical Impact

Severe deterioration of kidney function can have a profound effect on body fluid homeostasis and on blood pressure. The nature of these alterations often requires intensive care management regardless of the precise underlying diagnosis. A wide variety of kidney diseases may result in AKI. The most urgent aspects of AKI are (1) hyperkalemia, (2) severe hypertension, (3) severe plasma and extracellular volume expansion leading to heart failure and pulmonary edema, (4) unremitting metabolic acidosis, (5) hypocalcemia/hyperphosphatemia. Each of these can be viewed as an indication for intensive care and consideration of dialysis.[67] Additionally, over the past decade, the presence and degree of fluid overload (FO) has been shown to be a predictor of survival at the initiation of renal replacement therapy (RRT), and is now considered as an important indication for intervention.[68,69,70,71]

Hyperkalemia

The major reason for the development of hyperkalemia (serum potassium concentration more than 6 mEq/L) is the release (or infusion, or both) of potassium into the extracellular space at a rate greater than the kidney's ability to excrete potassium. Further the intracellular potassium is in the concentration range of 140 to 150 mEq/L, adding to the total source of potassium. The fact that AKI and oliguria have developed does not mean that hyperkalemia will develop. By the same token, hyperkalemia may develop rapidly in situations of extensive tissue destruction even without oliguria and "full-blown" AKI. Thus in the clinical situation of a crush injury or the tumor lysis syndrome, hyperkalemia should be anticipated and careful anticipatory monitoring begun.

Severe Hypertension

Hypertension is frequently associated with kidney disease. The two main mechanisms by which kidney disease leads to hypertension, especially accelerated hypertension, are (1) plasma volume expansion caused by the failure to excrete sodium chloride and water and (2) hyperreninemia associated with decreased kidney perfusion.

Plasma and Extracellular Volume Expansion

Plasma and extracellular volume expansion are associated with kidney failure. With an abrupt decline in GFR, even "normal" amounts of sodium and water intake expand the extracellular and plasma volumes. Depending on the cardiac status of the patient, the serum albumin level, and the degree of capillary permeability, this extracellular and plasma volume expansion may be manifest as peripheral edema, hypertension, or congestive heart failure and pulmonary edema. In situations of hypertension or congestive heart failure, the treatment involves two principles. The first is to reduce to as low a level as possible the amount of sodium and fluid the patient receives. This requires attention to diet, intravenous or hyperalimentation solutions, and drugs. The second principle is to remove extracellular fluid. If the patient's kidney

function permits (glomerular filtration of approximately 15 mL/min or higher), then diuretics, especially loop diuretics such as furosemide, bumetanide, or ethacrynic acid, will help to stimulate a diuresis that should improve the blood pressure or the congestive heart failure. The addition of thiazide diuretics prior to the use of loop diuretics may potentiate the effectiveness of loop diuretics allowing for a greater diuresis.[72] In children with more severe kidney disease, diuretic therapy does not result in diuresis, and dialysis will be necessary.

Severe Metabolic Acidosis

The kidney is responsible for the excretion of hydrogen ion and the regeneration of bicarbonate. When kidney function rapidly deteriorates, then the extracellular concentration of hydrogen ion increases, and this increase leads to acidosis and low serum bicarbonate concentrations. This problem is exacerbated by conditions that increase the production of hydrogen ion and its release into the extracellular fluid. Conditions such as sepsis, severe trauma, burns, extensive abdominal disease or surgery, high chloride-containing intravenous fluids, and hemolysis are all examples in which hypoxia, high hydrogen ion production and/or release into the extracellular space, and a decline in RBF and the GFR are combined. The result is severe metabolic acidosis.

Hypocalcemia/Hyperphosphatemia

Hypocalcemia arises from hyperphosphatemia as a result of dietary load, cellular breakdown, and reduced kidney phosphate excretion; reduced synthesis of calcitriol; downregulation of skeletal cell receptors for PTH; and acidosis.[73]

Hyperphosphatemia may not be recognized, for the plasma phosphorus level is not contained on any of the classic "lab panels" as directed by Medicare; it therefore needs to be thought of and sought out for identification.

Uremia

The symptoms of uremia are frequently vague and difficult to quantitate. They include central nervous system (CNS) manifestations such as lethargy, confusion, seizures, and obtundation and also gastrointestinal manifestations such as anorexia, nausea, and vomiting. These symptoms plus metabolic derangements often lead to the initiation of dialysis.

Renal Disposition of Endogenous and Exogenous Compounds

An important consideration in AKI is the role of the kidney in the metabolism, elimination, and detoxification of endogenous and exogenous materials. Any drugs given must be reviewed because the dosing interval or the dose of drug may need to be altered in AKI. Endogenous substances generally are more slowly metabolized or excreted. For example, the hormone gastrin is metabolized by the proximal tubule after being filtered by the glomerulus. The resultant persistent high circulating levels of gastrin may explain the higher incidence of gastritis and ulcer disease seen in patients with kidney failure.

Specific Kidney Diseases that May Lead to Acute Kidney Injury

Hemolytic-Uremic Syndrome

Hemolytic uremic syndrome (HUS) is considered to be the most common cause of AKI in children in the world.[74] Whereas this may be correct, it should be recognized that within "westernized" medical systems, AKI due to sepsis and cardiac disease as well as in children with other comorbid and chronic underlying conditions are more likely the cause of AKI.[75]

HUS is characterized by thrombotic microangiopathy with platelet aggregation and fibrin deposition in small vessels in the kidney, gut, CNS, and elsewhere. The hemolytic anemia is related predominantly to shearing of red blood cells as they pass through involved vessels. In the typical form of the disease, a triggering infectious agent has frequently been reported. The syndrome is defined by the presence of anemia (hemolysis), thrombocytopenia, and impaired kidney function. *Escherichia coli* (0157:H7) has been implicated in a large number of cases of typical (epidemic) forms of HUS.[76] It should be understood that there exist a myriad of causes of HUS and that in the absence of verotoxin-secreting *E. Coli*, HUS can still occur.

Clinical Signs

Typical HUS usually presents in "epidemics" and is characterized by a prodrome of bloody diarrhea. Children with HUS are older than 1 year and younger than 10 years (typically, 18 months to 3 years). The important presenting features of bloody diarrhea, fever, lethargy, decreased urine output, and paleness should lead to a suspicion of HUS. Laboratory evaluation will verify the diagnosis.

The development of HUS has been associated with bacterial and viral infections, oral contraceptives, cyclosporin A, and complement abnormalities.[76,77] The final common pathway, regardless of the initiating agent, is endothelial cell injury.

Once the endothelium is injured and the subendothelial region is exposed, a sequence of events is set into motion that serves to amplify the initial endothelial damage. Platelets adhere to the subendothelial space, and a release reaction follows that activates additional platelets and initiates fibrin deposition. Both endothelial cell and platelet factors are involved in the propagation of intraglomerular fibrin deposition and coagulation. Direct injury of the endothelial cell may initiate coagulation by release of tissue factor or exposure of the basement membrane. Evidence suggests that the endothelial cells in patients with HUS have reduced ability to produce prostacyclin (PGI_2), a potent vasodilator and inhibitor of platelet aggregation. Some patients with HUS lack a plasma factor that stimulates PGI_2 production. In addition, there is decreased glomerular fibrinolytic activity because of a circulating inhibitor of plasminogen activator. Interestingly, this fibrinolysis inhibitor is removed from the circulation by dialysis.[78] Platelet count and survival time is decreased in patients with HUS, and occasionally there is evidence of platelet activation.

HUS is a heterogeneous group of disorders that have a common result. As a means of differentiating the pathogenesis and

clinical outcome, the following classification scheme has been proposed[79]:

1. The classic form presents in infants or small children after a prodrome of bloody diarrhea that may involve the verotoxin-producing strain of bacteria such as *E. coli*.
2. The postinfectious form is associated with an identified infectious agent such as *Shigella* or *Salmonella* or with endotoxemia.
3. Hereditary forms have been recognized that have both autosomal dominant and recessive modes of inheritance. These patients probably lack a plasma factor necessary for PGI_2 production or have a prostacyclin inhibitor.
4. An immunologically mediated form is characterized by low plasma C3 and activation of the alternative complement pathway. This form may also be familial.
5. A so-called secondary form is related to known predisposing conditions such as lupus, scleroderma, chemotherapy, malignant hypertension, and kidney irradiation.
6. A form related to pregnancy or use of oral contraceptives is characterized by arterial microangiopathy.

Hemolysis may be brisk and may require transfusions on a daily basis. The aim of transfusions during the period of hemolysis should be to prevent heart failure and not to return the hematocrit value to normal. Thrombocytopenia may be severe but only rarely results in significant bleeding, and therefore platelets should not be given unless clearly needed to stop bleeding or in anticipation of invasive (especially vascular) procedures. Some have suggested that platelets play an important role in the pathophysiology of this disorder. It is further suggested that infusing platelets may actually prolong or worsen the intravascular deposition characteristic of HUS.

Complications

Other organ system involvement may lead to serious complications. CNS involvement may reflect the metabolic effects of uremia and can be manifested by lethargy, somnolence, stupor, coma, or seizures. Seizures, paresis, and even CNS hemorrhages can result from vascular damage and CNS vessel occlusion. Gastrointestinal involvement has also been well documented.[79] Liver enzyme elevations; abdominal pain, intestinal obstruction, and bowel perforation have all been reported. These possibilities must be considered and evaluated when appropriate. In some instances, the diagnosis of HUS has been made after abdominal exploration.

Therapy

In recent years therapy has been conservative, aimed at preventing deterioration and carefully managing such complications as AKI, anemia, and CNS and abdominal symptoms. Furthermore, any therapy would have to show a dramatic benefit to improve on a complete recovery rate of more than 90%.

Comprehensive supportive care has clearly resulted in a dramatic decline in the mortality from HUS (40% in the 1950s to 5% to 10% in the 1980s).[77] Nevertheless, therapy specifically aimed at HUS has been attempted because vascular platelet plugging and fibrin deposition in arterioles is part of the pathophysiology.

Heparin, fibrinolytics, and antiplatelet drugs (aspirin, dipyridamole) have all been attempted. In general, reports demonstrate lack of benefit and, in the cases of heparin and fibrinolytics, increased harm from increased bleeding. Fresh-frozen plasma infusion was suggested because of the finding that serum from some patients with HUS cannot generate normal amounts of prostaglandin or does not demonstrate normal antithrombotic and antiplatelet function.[80] All these defects could account for the thrombotic microangiopathy of HUS. Fresh-frozen plasma might provide the missing factors that could ultimately reduce microangiopathy. Unfortunately, studies in patients did not demonstrate a beneficial effect. Plasmapheresis has not been tested as carefully as fresh-frozen plasma infusion in patients with typical HUS.[81]

Vitamin E therapy has been proposed after findings of abnormal lipid peroxidation and low vitamin E activity in patients with HUS. Anecdotal studies suggested some benefit, but controlled, albeit small, studies have not shown benefit.[82]

Further, intravenous immunoglobulin G (IgG) infusions have received attention on the basis of studies in adults that showed IgG can inhibit platelet aggregation.[83] This presumably would diminish thrombotic microangiopathy and reduce the period of time of thrombocytopenia. Controlled studies have not been completed. The preliminary data suggest a shorter period of thrombocytopenia but, as yet, little information on reductions in other morbidities of HUS.

Prognosis

The prognosis for the "typical" form of HUS is good. Most series report 3% to 5% mortality rates and an additional 3% to 5% with chronic changes such as chronic kidney disease, persistent hematuria/proteinuria, and chronic hypertension. Thus more than 90% of children with the typical form of HUS recover completely.

In the face of AKI, many of the therapies (RBC, platelet infusion, fresh frozen plasma) result in volume to the children, potentially increasing the risk of fluid overload. Further, the plasma components of PRBCs are hyperkalemic, acidotic, and hypocalcemic. Therefore, transfusing PRBCs to a patient with AKI may induce not only fluid overload but also significant and even lethal electrolyte disbranches. The use of RRT may be needed to offset these potential risks.

Acute Glomerulonephritis

Nearly every form of glomerulonephritis has been reported to present as AKI (Box 71-2). In some instances the kidney insufficiency may be the result of an immunological process leading to acute inflammation (e.g., acute postinfectious glomerulonephritis). In others, intravascular volume depletion may play a prominent role in AKI (e.g., minimal change nephrotic syndrome).

In general, glomerulonephritis is initiated by immunological events within the glomerulus followed by mechanisms that result in damage to the glomerulus.[84] Glomerular disease results from the deposition of immune complexes composed of (1) antibodies to nonkidney antigens that localize within the glomeruli and form in situ immune complexes; (2) circulating soluble immune complexes that are trapped within the mesangium or subendothelial space; or (3) antibody to antigens within the glomerulus, either as normal glomerular antigens or as neoantigens induced by inflammation or infection.

Box 71–2 Glomerular Disease Associated with AKI

Hypocomplementemic (low C3)
- Acute postinfectious glomerulonephritis
- Membranoproliferative glomerulonephritis
- Systemic lupus erythematosus

Normocomplementemic (normal C3)
- Henoch-Schönlein purpura
- Immunoglobulin A nephropathy
- Wegener granulomatosis
- Goodpasture syndrome
- Membranous nephropathy

Hemolytic-uremic syndrome
Minimal-change nephrotic syndrome

Box 71–3 Classification of Rapidly Progressive Crescentic Glomerulonephritis

Pulmonary renal syndromes
- Antiglomerular basement membrane antibody-mediated (Goodpasture syndrome)
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Wegener granulomatosis
- Churg-Strauss syndrome

Postinfectious
Henoch-Schönlein purpura
Immunoglobulin A nephropathy
Membranoproliferative glomerulonephritis

Antibody deposits promote injury by activation of inflammatory cells or by their direct interaction with glomerular cells. The result is mesangial cell proliferation, capillary wall and basement membrane injury, and extracapillary proliferation of epithelial cells, a process known as crescent formation.

Immune complexes mediate glomerular injury in two ways: through direct membrane damage by the membranolytic membrane attack complex (involving complement components, C5b-9) or by stimulation of glomerular localized inflammatory cells.

Salt and water retention commonly observed with acute glomerulonephritis is the result of a decreased GFR, not increased tubular reabsorption, as once proposed. The renin-angiotensin system is thought not to play a role in the positive salt and water balance. In general, the presentation of glomerulonephritis as AKI implies a virulent form of disease known as rapidly progressive or crescentic glomerulonephritis. Although rapidly progressive refers to a clinical characteristic and crescentic to a pathological feature, the two are commonly coincidental in the presentation of AKI. A classification of rapidly progressive glomerulonephritis is presented in Box 71-3. Four prototypical conditions serve as examples of acute kidney disease that may result in the need for intensive care.

Acute Postinfectious (Streptococcal) Glomerulonephritis

This condition is well known to pediatricians. An association between glomerulonephritis and scarlet fever was known in the eighteenth century. In the early twentieth century, however, a clear connection between streptococcal infections and glomerulonephritis was established. The disease most frequent occurs between the ages of 2 and 12 years. It is seen as a sporadic event or in epidemics. It appears that only certain strains of streptococci lead to glomerulonephritis, thus the term nephritogenic streptococcus.[85] Over the past decade the more recent term has moved to postinfectious glomerulonephritis (PIGN) due to the fact that no longer does *Streptococcus* cause the majority of the cases of PIGN.

The mechanism(s) by which nephritogenic streptococci cause glomerular injury is similar to that seen with "shunt nephritis." It is generally accepted that immune complexes, with the participation of complement and other inflammatory mediators, cause glomerular inflammation. The precise nature of the bacterial antigen and its site of formation (circulation compared with in situ in the glomerulus) remain areas of study.

Clinical Signs. The usual sites of infection are the upper respiratory tract, skin, or both. A longstanding observation is that the latent period is 7 to 14 days if the infection is in the upper respiratory tract and 21 to 40 days if the infection is on the skin. Subclinical cases may be common; they are estimated to be 2 to 19 times as frequent as clinical cases. Symptomatic cases usually present with an acute nephritic syndrome: edema, hypertension, hematuria, and oliguria. Other important clinical features include proteinuria, red cell casts, and abnormal urinary red cell morphological findings, all markers of glomerular injury. Pulmonary edema may also be present, especially if significant salt and water retention are present and if hypertension is severe. Nonspecific findings include malaise, anorexia, abdominal pain, nausea, and vomiting. (This presentation is seen with other forms of acute glomerulonephritis.) Patients may have AKI.

Laboratory Findings. Laboratory findings at the time of presentation or early in the course include high serum IgG levels and low serum complement levels, especially C3 and CH50. In general, the alternate pathway of complement is the mechanism of complement activation, although on occasion C2 and C4 may be depressed as well. Complement levels return to normal in 4 to 6 weeks. Therefore if complement levels remain depressed for 6 to 8 weeks after the onset of acute glomerulonephritis, another diagnosis should be strongly entertained (systemic lupus erythematosus or membranoproliferative glomerulonephritis). The definitive diagnosis is based upon renal biopsy that can be performed easily adding clarity to the diagnosis.

Treatment. Treatment is based on the patient's symptoms and is directed at preventing or reducing salt and water retention and hypertension. All patients should have salt and water restriction unless dehydration is obvious (an unusual situation). Approximately 50% to 60% of patients require treatment for hypertension. Diuretics, angiotensin-converting enzyme inhibitors, and potent vasodilators should be considered. Five percent of patients may require dialysis for congestive heart failure, hypervolemia, or encephalopathy.

Prognosis. The long-term prognosis in acute postinfectious glomerulonephritis is a matter of debate. The mortality rate

is approximately 0.5%, and death usually results from severe hypertension and encephalopathy or heart failure. Studies by Baldwin et al.[86] suggested that the long-term prognosis generally thought to be excellent was in fact not necessarily so. They suggested 50% of patients had evidence of kidney disease in long-term studies. Studies with follow-up of 10 to 15 years suggest that chronic AKI develops in approximately 1% of patients. A second consensus conclusion is that the prognosis is better in children than in adults. Longer-term follow-up is needed.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a protean illness affecting many organ systems. In some instances, intensive care is needed for such aspects of SLE as nephritis, cerebritis, carditis, serositis, or sepsis.

Even within a relatively narrow aspect of SLE such as nephritis, great heterogeneity exists. Glomerulonephritis develops in approximately 75% of patients with SLE.[87] This may range from mild hematuria and proteinuria to nephrotic syndrome and rarely to rapidly progressive kidney failure. The patterns of lesions in lupus nephritis are varied. The World Health Organization (WHO) has classified lupus nephritis based upon light microscopy into five categories: (1) minimal disease; (2) mesangial disease; (3) focal proliferative glomerulonephritis; (4) diffuse proliferative glomerulonephritis; and (5) membranous nephropathy. These five categories have been further subdivided to reflect activity (e.g., cellular proliferation, crescents, thrombi, presence of tubulointerstitial disease) and chronicity (e.g., sclerosis, fibrosis, tubular atrophy). Combining these pathological categories with a small number of clinical predictors of poor outcome such as age younger than 24 years, male gender, and decreased kidney function on presentation has permitted a more careful assessment of therapeutic interventions.

Clinical Signs. The broad variation in clinical manifestations may reflect individual expression of similar immunopathological mechanisms or different immunopathological mechanisms presenting as a similar constellation of clinical manifestations.[88] It is clear that SLE represents the overproduction of antibodies against multiple "self"-antigens. Patients with lupus have high titers of antinuclear antibodies and in particular anti-double-stranded DNA antibodies, which are often seen in SLE nephritis. Recent work by the author's group demonstrates a high presence of antiphospholipid antibodies placing the child at risk for clotting. This clotting risk may be accentuated in the face of nephrotic syndrome or the use of birth control pills.[89] The factors that lead to the abundant production and activation of relevant B cells are unclear. Certainly hormonal influence must be important because most patients with SLE are women. Environmental factors may be important in cases of SLE induced by drugs or viruses and the known association of SLE with ultraviolet light exposure. Other important factors are suggested by the higher than normal T helper/T suppressor cell ratio. Many of these act in concert to result in abundant antibody production and the deposition of complexes in target organs such as the kidney.

Clinically, patients with SLE nephritis who require intensive care probably have rapidly progressive glomerulonephritis or AKI. Their presentation includes many of the following features: hypertension; active urinary sediment with proteinuria, hematuria, and casts; oliguria or rarely anuria; intravascular volume expansion; and declining kidney function with rising serum creatinine, hyperkalemia, and metabolic acidosis. Unlike the glomerulonephritis described previously, treatment should include management of kidney dysfunction as previously outlined and management aimed at the SLE itself. Kidney biopsy is useful.[90] When in doubt; a biopsy specimen may help distinguish acute tubular necrosis from glomerulonephritis. A biopsy specimen will ascertain the degree of interstitial involvement, which may suggest drug toxicity. Biopsy can be useful in determining long-term treatment and prognosis.

Treatment. In the intensive care setting, treatment directed at rapidly progressive or diffuse proliferative SLE nephritis consists of high-dose bolus corticosteroid (usually methylprednisolone) at a dosage of 10 to 20 mg/kg intravenously (IV) given 3 to 5 times in a daily or every-other-day regimen.[91] This therapy is associated with hypertension. Other treatments have included plasmapheresis; antiplatelet drugs such as dipyridamole; and immunosuppressives including azathioprine, cyclophosphamide, mycophenolate mofetil or other alkylating agents, and methotrexate. Recent data from the National Institutes of Health and others have suggested significant benefit from cyclophosphamide or mycophenolate mofetil in maintaining kidney function.[92]

Prognosis. The long-term prognosis for children with SLE nephritis is unclear.[88] Regardless, patients and families must expect persistent evidence of kidney injury such as hematuria, proteinuria, hypertension, and even reduced kidney function such as a diminished GFR. Further, patients may have relapsing episodes of nephrotic syndrome or acute glomerulonephritis.

Other Glomerulonephritides

Two other forms of glomerulonephritis may result in the need for intensive care therapy. These are antiglomerular basement membrane (anti-GBM) antibody disease (Goodpasture syndrome) and Wegener granulomatosis. Although rare in children, both conditions can result in AKI. Therapy should be directed at the general condition of AKI as discussed previously in addition to specific therapy.

In the case of anti-GBM antibody disease, patients may have both kidney disease and pulmonary disease, often pulmonary hemorrhage. Treatment includes corticosteroids, plasmapheresis, and immunosuppressives, mainly alkylating agents. Despite therapy, end-stage kidney disease develops in some patients. Recurrences of anti-GBM antibody disease in kidney allografts have also been reported.[93] Vasculitic syndromes associated with kidney disease include Wegener granulomatosis and so-called antineutrophil cytoplasm antibody (ANCA) associated diseases.[94] ANCA is an autoantibody that is found in one of two patterns in many forms of vasculitis and which serves as a potentially useful diagnostic tool. Wegener granulomatosis is characterized by granulomatous vasculitis that attacks the lungs, the respiratory tract including sinuses and trachea, and the kidneys. This condition may be difficult to diagnose, and biopsy may be the only means of determining the diagnosis if the plasma ANCA is negative. Five children with ANCA-associated glomerulonephritis and AKI have been described. Nonspecific systemic illness commonly preceded the presentation of AKI. In two of the five, kidney

function recovered; the other three required long-term dialysis. Cyclophosphamide has been shown to be beneficial in the treatment of the kidney disease of Wegener granulomatosis, and plasmapheresis is also of potential benefit in crescentic forms, although it is not widely used because of frequent complications.

Nephrotic Syndrome and Acute Kidney Failure

AKI is an uncommon complication of primary nephrotic syndrome in children but may occur as a result of intravascular volume depletion, bilateral kidney venous thrombosis, or drug-induced kidney toxicity.[95]

The clinical scenario is one in which the child has a low serum albumin level and edema (increased extracellular volume). These patients have stable and often normal plasma volumes despite low oncotic pressure. Should an acute illness (e.g., gastroenteritis) occur, however, intravascular volume depletion and AKI may develop rapidly. Patients with nephrotic syndrome who have fluid losses or are unable to take in fluids should be admitted to the hospital, and intravenous administration of albumin plus maintenance and replacement fluids should be considered. The use of intravenous albumin helps to maintain the intravascular volume and reduces the edema that might develop during fluid therapy. In some children with nephrosis and AKI, no cause for reduced GFR can be found. In a recent report of four children with idiopathic AKI associated with primary nephrotic syndrome, three had evidence of peritonitis at presentation, two had minimal-change nephrotic syndrome, and two had focal segmental glomerulosclerosis. All four children required dialysis for treatment of marked anasarca. Kidney biopsies performed during AKI in three of the four children showed tubular ischemic injury. Removal of fluid with diuretics or dialysis/hemofiltration was associated with recovery of function. Placing a vascular access for dialysis in a child with nephrotic syndrome is not without risk. In general, children with nephrotic syndrome have a high risk of clotting, independent of vascular access. The large bore vascular access commonly used for dialysis may potentiate this risk. Use of heparin for thrombosis prevention should be considered in certain high-risk situations.

Tubulointerstitial Disease

Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (ATIN) is a clinical syndrome characterized by inflammation of the kidney interstitium accompanied by interstitial edema and kidney tubular injury. ATIN may be caused by numerous drugs, infectious agents, and systemic illnesses.[96] A partial list of causes can be found in Box 71-4.

In most cases, ATIN is immunological in origin. Most of understanding of the pathogenesis has been obtained from animal models. Three phases have been described for ATIN. The initial phase involves recognition of a nephritogenic antigen located in the interstitium. The antigen may be a normal component of the interstitium, a modified constituent, drug-induced, or infection-induced. Loss of host tolerance is thought to be required for the initial phase to occur. The immune regulatory phase is characterized by the activation of T-helper lymphocytes, which induce differentiation of T and B cells that directly injure the interstitium. The inability of the host to counteract this response with T-suppressor cells permits T- and B-cell activation to go unabated. In the effector phase, both humoral and cell-mediated components contribute to tissue injury. Antibodies to tissue antigens promote injury by activation of the complement cascade, chemotaxis, and cell-mediated cytotoxicity. IgE is also produced, that may recruit eosinophils or mast cells. Mononuclear cell infiltration produces tissue injury by release of proteases and lymphokines. Eosinophils also damage surrounding tissue by release of proteases, leukotrienes, and toxic oxygen species.

Box 71–4 Primary Causes of Acute Tubulointerstitial Nephritis

Drugs
Infections
Septicemia
Leptospirosis
Candidiasis
Malignant infiltration
Lymphoma
Leukemia
Systemic diseases
Systemic lupus erythematosus
Sarcoidosis

Data from Grunfeld J, Kleinknecht D, Droz D: Acute interstitial nephritis. In Schrier RW, Gottshalk CW, editors: *Diseases of the kidney*, ed 4, Boston, 1988, Little, Brown.

Several theories have been proposed to explain the reduced GFR: (1) the "clogged drain," (2) the capillary bed, and (3) vascular tone hypotheses. The clogged drain theory proposes that tubular obstruction caused by luminal debris and interstitial edema results in increased pressure in Bowman's space and decreased pressure favoring filtration. Interstitial inflammation results in injury to the blood supply of the tubules (capillary bed hypothesis). Because these vessels are postglomerular, the increased resistance and reduced surface area associated with vessel injury result in an increase in efferent arteriolar pressure and a reduction in the pressure gradient across the glomerulus with a resultant drop in the GFR. Decreased sodium reabsorption by injured proximal tubular epithelial cells reduces the medullary interstitial osmolality, and impairs the ability to concentrate the urine. Thus an increased volume of filtrate is delivered distally, stimulating the juxtaglomerular apparatus to increase angiotensin II production (vascular tone hypothesis). The net result is vasoconstriction and a diminished GFR.

Pathologically, diffuse or patchy infiltration of the kidney interstitium by lymphocytes, plasma cells, and eosinophils, and edema of the interstitial space is observed. Eosinophils are usually indicative of an acute phase, whereas epithelioid granulomas with giant cells and fibroblasts or fibrosis indicate chronic disease. Tubules may have mild structural alterations or marked necrosis with loss of brush border. Drug-induced interstitial nephritis is the most common form of ATIN in adults and children. Eight of 13 pediatric patients described in one series[96] and 38 of 57 in another series of children[97] with interstitial nephritis had drug-related causes of ATIN. Numerous drugs have been associated with ATIN. The β-lactam antibiotics are the most frequently associated with

ATIN with methicillin being the prototype, although ampicillin is the most common offending drug in pediatric series. NSAIDs are increasingly recognized as a cause of acute kidney dysfunction.

Clinically apparent disease usually develops days to weeks after exposure to the inciting drug or agent but may be immediate.[98] Drug-induced tubulointerstitial disease is localized predominantly to the cortex, whereas infectious or infiltrative disorders more commonly localize to the medulla. The functional abnormality often indicates the primary site of tubular injury. Damage involving mainly the proximal tubule results in the wasting of bicarbonate, phosphate, glucose, amino acids, and uric acid. Distal tubular involvement may be manifest as hyperkalemic kidney tubular acidosis as a result of impaired secretion of both K^+ and H^+. Nephrogenic diabetes insipidus can result with medullary involvement.

Although ATIN is primarily a disease of the kidney interstitium and tubule with lack of glomerular structural alterations, the GRF may also be reduced. Of 13 children described by Ellis et al[96] and Andreoli,[99] 12 had a creatinine clearance of less than 50 mL/min/1.73 m^2. AKI resulting from ATIN may be oliguric. Other clinical signs of ATIN are fever and rash. ATIN usually resolves with removal of the offending agent, although occasionally chronic kidney insufficiency may result.

Cardiorenal Syndrome

Renal insufficiency occurs commonly in adult and pediatric patients with heart failure. Although the mechanisms are not fully understood, diminished cardiac function coupled with renal dysfunction, or the cardiorenal syndrome, has been observed in both the acute and chronic care settings. The phenomenon remains better characterized in adult medicine. Decreased urine output and resultant fluid retention can aggravate heart failure symptoms and contribute to clinical deterioration. Even a modest increase in serum creatinine (i.e., >0.2 mg/dL) can predict mortality in adult patients hospitalized for heart failure.[100] The relationship of renal function and heart failure in children has not been well examined. Retrospective data analysis have shown a high incidence of cardiac disease among children who exhibit renal insufficiency while hospitalized, and clinical experience suggests that as in adults, worsening renal function is associated with worse outcomes among children with heart failure.[101]

Basis for Deteriorating Renal Function

The physiologic interaction of the heart and kidney is complex and not well understood, although it is recognized that disease of one organ system frequently complicates the other. Some have termed this combined cardiac and renal dysfunction the cardiorenal syndrome. Renal insufficiency occurring in heart failure patients is usually attributed to a "prerenal state" resulting from diminished cardiac output and renal perfusion. It is hypothesized that deteriorating cardiac output and decreasing renal blood flow trigger neurohormonal activities that lead to fluid retention and increased systemic vascular resistance, causing further progression of ventricular dysfunction. Data from animal studies show that isolated renal ischemia leads to increased pulmonary vascular permeability, suggesting a bidirectional pathophysiologic interaction between the renal and cardiopulmonary systems.[102] Other mechanisms may also contribute to a decline in a renal function, including medications being used to support cardiovascular function, such as vasoactive drugs. A study by Price et al.[103] reported worsening renal function with the use of dopamine and nesiritide.

There is evidence that right ventricular dysfunction may be associated with the renal venous congestion. Using echocardiographically derived measurements, Testani et al. showed that in 151 patients, RV dysfunction remained a significant predictor of change in glomerular filtration rate after controlling for heart rate, hemoglobin, admission serum urea nitrogen, B-type natriuretic peptide level, diuretic dose, length of stay, ejection fraction, cardiac output, tricuspid regurgitation severity, and inferior vena cava inspiratory collapse.[104]

Cardiac Surgery–Related Acute Kidney Injury

AKI is not uncommon following cardiac surgery, and its presence portends a worse prognosis. In a survey of 542 patients who underwent cardiopulmonary bypass to fix their congenital cardiac disease, the rate of acute kidney injury after congenital cardiac surgery was shown to be about 11%.[105] Other studies have found mortality rates to be four times higher in patients with renal failure compared to those without. Studies have shown that a small rise (less than 50%) in creatinine in the first 48 hours could predict a greater than 50% increase in serum creatinine in the next 48 hours. Significant independent risk factors for AKI were bypass time and longer vasopressor use; there was a tendency toward younger age as a risk factor.[106] Cardiac surgery-related AKI has been characterized and described in adult medicine; however, at this time it remains difficult to characterize the exact nature of the injury in the pediatric population. Cardiac surgery-associated acute kidney injury (CSA-AKI) is a significant clinical problem. It results from the interactions between the complicated interventions required in the process of congenital cardiac surgery such as cardiac bypass, use of blood products, the anatomical variability of the congenital cardiac abnormality such as single ventricles, and the surgical correction/palliation of the lesion. It likely involves at least six major mechanisms: exogenous toxins and cytokines, metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation, and oxidative stress.[107] These mechanisms of injury are likely to be active at different times with different intensity, and probably act synergistically. There are also some data that suggest that at least some of the injury may be pigment-related, but this is yet to be substantiated.[108] There have also been attempts at ameliorating the injury with interventions such as *N*-acetyl cysteine, but this has resulted in an increase in bleeding with any benefit yet to be established.[109]

There are, however, newer markers of renal injury such as plasma neutrophil gelatinase-associated lipocalin (NGAL) that are more sensitive than serum creatinine in predicting acute kidney injury. In fact, plasma NGAL at 2 hours after cardiopulmonary bypass (CPB) was the most powerful independent predictor of AKI in patients post-CPB.[110,111] Serum creatinine is an inadequate marker because nearly 50% of renal function has to be lost before its levels are elevated, and serum creatinine does not accurately depict kidney function until a steady state has been reached, which may require

Table 71–2 Patient Stratification by Risk

	Risk		
Type of Cancer	**High**	**Intermediate**	**Low**
NHL	Burkitt lymphoblastic, B-ALL	DLBCL	Indolent NHL
ALL	WBC ≥100,000	WBC 50,000–100,000	WBC ≤50,000
AML	WBC ≥50,000, monoblastic	WBC 10,000–50,000	WBC ≤10,000
CLL		WBC 10,000–100,000 Tx w/fludarabine	WBC ≤10,000
Other hematologic malignancies (including CML and multiple myeloma) and solid tumors		Rapid proliferation with expected rapid response to therapy	Remainder of patients

NHL, Non-Hodgkin lymphoma; *B-ALL,* Burkitt acute lymphoblastic leukemia; *DLBCL,* diffuse large B-cell lymphoma; *ALL,* acute lymphoblastic leukemia; *AML,* acute myeloid leukemia, *CLL,* chronic lymphocytic leukemia; *Tx,* treatment; *CML,* chronic myeloid leukemia
Data from Coiffier BJ: Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review, *Clin Oncol* 26(16):2767–2778, 2008.

several days. Biomarkers such as plasma NGAL may provide for earlier clinical intervention, thereby preventing significant mortality or morbidity. The renal histological changes in cardiac surgery-related AKI are yet to be well characterized.

Porcine data utilizing experimental cardiopulmonary bypass revealed higher tubular injury scores in kidneys post-CPB relative to controls (median score 1.0 [IQR 1.0-1.0], $P = .019$). AKI was associated with endothelial injury and activation, as demonstrated by reduced DBA (*Dolichos biflorus* agglutinin) lectin and increased endothelin-1 and vascular cell adhesion molecule (VCAM) staining.[112]

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an oncologic emergency that is usually seen when tumor cells undergo rapid decomposition spontaneously or, more often, in response to cytoreductive therapy with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation. Catabolism of the nucleic acids to uric acid leads to hyperuricemia, and a marked increase in uric acid excretion can result in the precipitation of uric acid in the renal tubules and mediate acute renal failure. Despite advances in risk stratification, prophylaxis, and active interventions to reduce the incidence of TLS, up to 6% of at-risk pediatric and adult patients undergoing chemotherapy are believed to develop AKI.[113] Even mild AKI that does not require renal replacement therapy has been associated with increased long-term risk for renal failure and mortality. The levels of phosphorus in malignant cells can be up to four times the levels found in normal cells, and rapid release of these stores can result in hyperphosphatemia, with an increase in serum levels by as much as 2.1 mmol/L in children.[114] Initially, the kidneys respond by increasing urinary excretion and decreasing tubular resorption. However, tubular transport mechanisms eventually become saturated, leading to increasing serum phosphorus levels. Acute renal insufficiency caused by uric acid or other complications may further exacerbate the development of hyperphosphatemia. In 2008, a group of researchers published evidence-based guidelines for the prevention and treatment of tumor lysis syndrome.[115] Their recommendations were based on the type of tumor at the initiation of chemotherapy as discussed in the following section.

Management

Vigorous IV hydration with diuresis has long been the cornerstone to prevention and treatment of tumor lysis syndrome (to achieve urine output of 80 to 100 mL/m^2/h). Increasing intravascular volume and urine output increases the renal excretion of uric acid and phosphate. Alkalization of the urine is no longer recommended, due to the lack of supporting evidence and the potential for enhancing the precipitation of xanthine in the urine.[116] Allopurinol works to lower serum uric acid levels by reducing the production of uric acid from purine precursors by inhibiting xanthine oxidase. Because it does not alter the uric acid already formed, it works best when initiated at least 48 hours prior to chemotherapy.[117] It is generally well tolerated, and can be given orally or intravenously; the dose needs adjustment for preexisting renal impairment.

Rasburicase. Recombinant urate oxidase exerts it pharmacologic activity by enzymatic oxidation of uric acid into allantoin.[118] It works rapidly, often dropping the uric acid level to levels less than normal within hours. Although contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, it is overall well tolerated. The traditional recommended dosage is 0.15 to 0.20 mg/kg per dose IV daily for up to 7 days. Investigators recommend the use of rasburicase as the first line intervention for high-risk patients (see Box 71-1) and as backup therapy for moderate-risk therapy for those patients who go on to develop hyperuricemia despite allopurinol and hydration (Table 71-2).[115]

Rasburicase is remarkably well tolerated. The rare, but serious, adverse events that require prompt and permanent discontinuation of rasburicase are methemoglobinemia and hemolysis.[118] Glucose-6-phosphate dehydrogenase (G6PD) deficiency is regarded as the main predisposing factor for hemolysis and remains a contraindication to its use (the mechanism is related to oxidative stress from the hydrogen peroxide [H_2O_2] produced as uric acid is converted to allantoin), justifying, when possible, the screening for patients at high risk for G6PD deficiency (e.g., African or Mediterranean ancestry).

Recent work by the author's group eliminated reversible AKI in infants associated with elevated uric acid when treated with rasburicase.[119]

Role of Renal Replacement Therapy. The understanding of the optimal start time, method, and dosage of renal replacement therapies (RRT) has evolved. Early intervention is favored, because most AKI survivors leave the hospital with independent kidney function.[120] Once the process of cell turnover is uncoupled, the rapid release of intracellular contents into the bloodstream, including anions, cations, proteins, and nucleic acids occurs. In this clinical paradigm, the early institution of renal replacement interrupts the cascade before the occurrence of tumor lysis-related AKI with life-threatening complications Therefore, the group recommended that for pediatric patients at high risk of TLS, cytotoxic chemotherapy should only be administered in a facility with ready access to dialysis. Although dialysis usage has been reduced since the introduction of rasburicase, as many as 3% of patients (1.5% of pediatric patients and 5% of adult patients) still require RRT.[121] In line with this, the panel recommends that renal consultation be obtained immediately if urine output is low, if there are persistently elevated phosphate levels, or in the case of hypocalcemia.[115]

Pigment Nephropathy

Rhabdomyolysis is a dissolution of skeletal muscles that produces a nonspecific clinical syndrome that causes extrusion of toxic intracellular contents from myocytes into the circulatory system. The possible causes of rhabdomyolysis are myriad; with direct muscle injury remaining the most common cause of muscle injury, additional causes include hereditary enzyme disorders, drugs, toxins, endocrinopathies, malignant hyperthermia, neuroleptic malignant syndrome, heatstroke, hypothermia, electrolyte alterations, diabetic ketoacidosis and nonketotic hyperosmolar coma, severe hypothyroidism or hyperthyroidism, and bacterial or viral infections. Most of the data remains adult-based. In a study of 210 pediatric patients, the most common causes of rhabdomyolysis were viral myositis (38%), trauma (26%), and connective tissue disease (5%). Higher initial creatine kinase levels (>6000 IU/dL) and higher fluid administration rates were associated with higher maximal creatinine levels.[122]

Pathophysiology

Rhabdomyolysis, which literally means "dissolution of striped [skeletal] muscle," is the final pathway of many different processes. Regardless of the underlying mechanism, myocyte dissolution triggers a cascade of events that lead to the rapid release of calcium ions into muscle cells resulting in a pathological interaction between actin and myosin and activation of cell protease, with subsequent myocyte necrosis of muscle fibers, release of potassium, phosphates, myoglobin, creatine kinase (CK), and urates into the extracellular space and into the bloodstream. As such, myoglobin can precipitate in the glomerular filtrate, particularly in an acidic environment, causing tubular occlusion and severe kidney damage. Pigmented myoglobin casts, which characterize the rhabdomyolysis syndrome, are the result of the interaction between myoglobin and Tamm-Horsfall protein in an acid environment.[123] Additional mechanisms causing renal damage include (1) a direct cytotoxic effect of myoglobin on renal cells; (2) urate precipitation, leading to intraluminal casts, increased intratubular pressure, and subsequent decreased glomerular filtration rate; (3) renal vasoconstriction and ischemia due to the heme group of myoglobin causing activation of the cytokine cascade; and 4) oxidant injury through heme-induced reactive oxygen species such superoxide anion, hydrogen peroxide, or hydroxyl radicals causing direct oxidative damage.[124]

The classic triad of symptoms of rhabdomyolysis includes myalgia, weakness, and dark urine, although these findings may be inconsistent.[122]

The definitive diagnosis of rhabdomyolysis requires an elevation of CK levels to greater than five times normal in the absence of significant elevations of brain or cardiac CK fractions. The most dangerous sequela of rhabdomyolysis is AKI, the exact mechanisms of which are unclear but may be attributable to vasoconstriction/hypoperfusion, renal tubular dysfunction/cast formation, and/or myoglobin-induced tubular cytotoxicity. The mainstay of treatment for rhabdomyolysis, directed at preventing AKI, is fluid therapy.[122] Many clinicians advocate alkalinization of urine with sodium bicarbonate (sometimes with concomitant forced diuresis with mannitol). There are no data that suggest that this strategy prevents AKI in children with rhabdomyolysis.

Once the patient has reached the hospital, fluid infusion should be continued, with the goal of maintaining a brisk urinary flow and a urine pH above 6.5 and plasma pH below 7.50.[125] The rate of infusion should be at 150% of maintenance rate, with hemodynamic parameters and urine output monitored closely. Some authors also suggest administering mannitol. This is done to induce osmotic diuresis and to remove liquids from the damaged muscular interstitium, thus relaxing the compartments involved.[126] To force diuresis, some clinicians also recommend the addition of furosemide.

There is little clinical evidence to support the use of bicarbonate, mannitol, and furosemide. It is important to understand that the treatment benchmark is aggressive forced hydration with saline and glucose solutions. Studies in humans show that alkalinization and osmotic and diuretic treatment add little to the beneficial effect of hydration.[123] Forced hydration should be continued until the disappearance of myoglobinuria, which typically occurs after the third day. Hyperkalemia must be managed using the usual techniques, considering that treatment with glucose and insulin may prove to be ineffective in this context due to the damaged muscle's inability to capture potassium from the extracellular space. It is often necessary to treat severe hyperkalemia with renal replacement therapy.

Hypocalcemia

Secondary sequestration of calcium into damaged muscle cells must be viewed critically. Administration of intravenous calcium (either chloride or gluconate) should be used only to treat life-threatening electrocardiographic alterations, secondary to hyperkalemia or extreme hypocalcemia.

Drug-Induced Nephrotoxicity

Many different drugs and agents may cause AKI in children. In the ICU, factors such as age, pharmacogenetics, underlying disease, the dosage of the toxin and concomitant medication all interact and influence the severity of nephrotoxic insults. Pediatric retrospective studies have reported incidences of AKI in PICUs of between 8% and 30%.[127] It is widely recognized that neonates have higher rates of AKI, especially following cardiac surgery, severe asphyxia, or premature birth. While

in most cases the etiology of AKI in the ICU is multifactorial (e.g., sepsis, ischemia/hypoperfusion), several recent large epidemiologic studies have shown that nephrotoxic drugs were contributing factors in 19% to 25% of cases of severe acute renal failure in critically ill adult patients.[128]

NSAIDs, antibiotics, amphotericin B, antiviral agents, angiotensin-converting enzyme (ACE) inhibitors, calcineurin inhibitors, radiocontrast media, and cytostatics are the most important drugs implicated in the etiology of AKI in children. The mechanisms of nephrotoxicity include constriction of intrarenal vessels, acute tubular necrosis, acute interstitial nephritis, and, more infrequently, tubular obstruction.[127]

Aminoglycoside Nephrotoxicity

Aminoglycosides (AGs) are non–protein-bound drugs that are primarily excreted unmetabolized by glomerular filtration. Their cationic nature facilitates binding to the tubuloepithelial membrane in the proximal tubule, resulting in rapid intracellular transport.[129] The molecular number of cationic groups determines the facility with which these drugs are transported across cell membranes and is an important determinant of toxicity[130,131] Neomycin is associated with the most nephrotoxicity; gentamicin, tobramycin, and amikacin are intermediate, and streptomycin is the least nephrotoxic.[132] Several hypotheses have been proposed to explain the nephrotoxic effects of aminoglycosides. Intracellular accumulation of AG within lysosomes is thought to interfere with normal cellular function such as protein synthesis and mitochondrial function, eventually leading to cell death.[133] Aminoglycosides also are known to stimulate the calcium-sensing receptor on the apical membrane thereby inducing cell signaling and eventual cell death.[134]

Risk factors for aminoglycoside nephrotoxicity include the type of AG, high peak serum levels, cumulative dose, the duration and frequency of administration, and patient-related factors such as age, preexisting renal dysfunction, hypoalbuminemia, liver dysfunction, decreased renal perfusion, and the concomitant use of nephrotoxic drugs.[132]

Several approaches have been evaluated in both animals and humans as potential treatments to attenuate the nephrotoxicity of aminoglycosides. Investigators have demonstrated that calcium supplementation reduces the nephrotoxic effect, likely through competitive inhibition of calcium channels in the proximal tubule.[135] Similarly, calcium channel blockers also have been shown to attenuate AG nephrotoxicity.[136] Also the protective effect of concomitant use of β-lactam antibiotics has been recognized for several years, although the mechanism by which this may occur is somewhat unclear.[137,138] More recent investigations have evaluated a possible role for antioxidants in renoprotection.[139] Once-daily dosing of aminoglycosides is the only clinical approach that is commonly used to reduce nephrotoxicity.[140] The rationale for the efficacy of consolidated AG dosing against gram-negative bacteria is based on two pharmacodynamic properties of aminoglycosides: (1) the bacteriocidal mechanism of action is concentration-dependent; and (2) prolonged postantibiotic effect.[132]

Clinical evidence of AG-induced acute tubular necrosis is seen within a week of initiation of aminoglycoside treatment. AG-induced acute renal failure is generally nonoliguric, and may be associated with decreased urine-concentrating ability and urinary magnesium wasting. It is generally reversible after discontinuation of the drug; however, supportive renal replacement therapy may be required. The authors recommend that alternative antimicrobials should be considered when possible in patients at high risk for AG nephrotoxicity. If required and consolidated AG dosing is used, renal function should be assessed daily to monitor for changes in renal function, and trough levels should be followed to guide dosage.

Amphotericin B

The use of antifungals has become more commonplace in intensive care units, as the prevalence of fungemia (specifically candidemia) has increased in critically ill patients. For decades, amphotericin B was the drug of choice because of its broad spectrum of activity and its wide availability; however, its use has been sharply curtailed in recent years because of its considerable side effects (specifically, nephrotoxicity) and the availability of newer, less-toxic agents.

Approximately 80% of patients who receive treatment with amphotericin B will experience some renal dysfunction.[141] There are several mechanisms by which amphotericin B is thought to induce renal dysfunction: (1) by directly binding to tubular epithelial cells in the cortical collecting duct, resulting in altered cell permeability; (2) by causing sodium, potassium, and magnesium wasting; and (3) by directly causing afferent arteriolar (preglomerular) vasoconstriction.[142] Risk factors for amphotericin B nephrotoxicity include preexisting renal insufficiency, hypokalemia, volume depletion, the use of concomitant nephrotoxins, and large individual and cumulative dosages.[143]

A number of strategies have been studied to minimize the associated nephrotoxicity, including sodium loading and longer infusion rates.[144] While some have shown a reduction in nephrotoxicity, these studies are very small and typically enroll low-risk patients. Lipid-based formulations of amphotericin B also are available, which may produce less nephrotoxicity. However, these agents are considerably more expensive. The recent introduction of alternative antifungal agents such as itraconazole, voriconazole, and caspofungin has largely supplanted the use of amphotericin B in high-risk patients with renal impairment; however, it continues to be used widely in patients with normal renal function because of its relatively low cost and broad spectrum of activity.

Given the presence of many underlying risk factors for nephrotoxicity in critically ill patients, it is recommended that amphotericin B should be avoided in this patient population if alternative therapies are available. When it is used, sodium loading with intravenous hydration is recommended to attenuate vasoconstrictive effects, and longer infusion times should also be considered. Renal function and serum electrolytes (specifically potassium) should be monitored during treatment.

Vancomycin

The use of vancomycin hydrochloride has increased considerably over the last decade as it has become the standard therapy for treatment of methicillin-resistant *Staphylococcus aureus* infections. Recent data from the 2004 Centers for Disease Control and Prevention, National Nosocomial Infections Surveillance System indicate that the prevalence of methicillin-resistant *S. aureus* exceeds 50% in U.S. hospitals. The synergistic nephrotoxicity of combination therapy involving vancomycin and aminoglycosides is well established,

with a reported frequency of acute renal failure in the range of 20% to 30%. However, the nephrotoxicity of vancomycin alone increasingly is being recognized as high-dose therapy has become more common for the treatment of methicillin-resistant *S. aureus*.[146]

Vancomycin is excreted by glomerular filtration, 80% to 90% in an unaltered form.[147] It is hard to determine the exact rates of vancomycin-related toxicity because most reported cases have had additional risk factors for acute renal failure, which makes it difficult to determine the true risk of treatment. The mechanism by which it exerts its nephrotoxicity is unknown. Independent risk factors for nephrotoxicity include the use of concomitant nephrotoxic agents, age, duration of therapy, and drug levels achieved.[147] Trough levels higher thank 15 μg/mL are associated with increased risk of nephrotoxicity, and peak levels also have been associated with increased nephrotoxicity. The dosing of vancomycin requires careful consideration of renal function and estimated glomerular filtration rate. Trough levels should be monitored frequently in patients with fluctuating renal function.

Calcineurin Inhibitors

The introduction of calcineurin inhibitors (CNIs) has led to dramatic improvement in both allograft and patient survival. The clinical use of CNIs often is limited by their nephrotoxic effect, which can present as two distinct and well-characterized forms: acute and chronic nephrotoxicity. Calcineurin inhibitor-induced AKI may occur as early as a few weeks or months after initiation of therapy. The clinical manifestations of CNI-induced renal dysfunction include reduction of GFR, hyperkalemia, hypertension, renal tubular acidosis, increased resorption of sodium, and oliguria. The acute adverse effects of calcineurin inhibitors on renal hemodynamics are thought to be directly related to the cyclosporine (CsA) or tacrolimus dosage and blood concentration and can be managed by dose reduction. This is in contrast to calcineurin inhibitor-induced chronic nephropathy, which is largely irreversible and can occur independently of acute renal dysfunction, CNI dosage, or blood concentration.

Although the exact mechanism of nephrotoxicity is not fully understood, several factors have been implicated in the pathogenesis of CNI nephrotoxicity.[148] Experimental models of acute CsA toxicity revealed that CsA administration is associated with afferent and efferent arteriolar vasoconstriction, which results in a significant reduction of renal plasma flow and GFR.[149,150] The precise mechanism by which CsA induces renal vasoconstriction has not been established clearly. Results from several studies indicate that vascular dysfunction induced by CsA results from an increase in vasoconstrictor factors that include endothelin, thromboxane, and angiotensin II, as well as a reduction of vasodilator factors such as prostacyclin and nitric oxide.[150,151]

Cyclosporine and tacrolimus differ with respect to side effects; however, the available data comparing nephrotoxicity are conflicting. While some studies have suggested that tacrolimus may be associated with a decreased severity of renal dysfunction in comparison to CsA[132] other investigators have demonstrated no difference between the two CNIs.[152]

Studies have been conflicting on the protective effect of calcium channel blockers on the preservation of renal function for patients receiving CNIs. In a multicenter, prospective, randomized, placebo-controlled study in 118 cadaveric renal transplant recipients receiving CsA, the use of a calcium channel blocker resulted in a significantly better allograft function at 2 years and demonstrated an improvement in graft function, as assessed by serum creatinine and GFR, that was independent of lowered blood pressure.[153] Currently, more research is being done with goals of improving the safety profile of CIs and identifying safer alternatives.

Sirolimus

Sirolimus is an mTOR (mammalian target of rapamycin) inhibitor that is becoming increasingly used in allograft preservation. Its target protein, mTOR, is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription in transplantation.[154] As its use in transplant medicine is increasing, it was hoped that its lack of nephrotoxicity in animal models would be translated in humans to improve immunosuppression with minimal effect on renal function. Unfortunately, several recent studies suggest that sirolimus has inherent nephrotoxicity, such as development of proteinuria and delay in recovery from ischemia-reperfusion injury. In addition, several studies have shown that the nephrotoxicity associated with CNIs is exacerbated when used in combination with sirolimus.[155]

Nonsteroidal Antiinflammatory Drugs

In most circumstances, NSAIDs do not pose a significant risk to patients with normal renal function. However, in situations in which renal perfusion is compromised (which are relatively common with critically ill patients), the inhibition of prostaglandin-induced vasodilation with the use of NSAIDs may further compromise renal blood flow and exacerbate ischemia.[156] The renal effects of NSAIDs do seem to be dependent on the type, dose, and duration of treatment.[156] Indomethacin is thought to be the most likely drug to impair renal function, and aspirin the least likely.[156] Patients at high risk of NSAID-induced nephrotoxicity include patients with preexisting renal dysfunction, severe cardiovascular or hepatic failure, or the concomitant use of other potentially nephrotoxic medications, such as aminoglycosides, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.[156]

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) acute kidney injury is an important complication in the use of iodinated contrast media that accounts for a significant number of cases of hospital-acquired AKI. The occurrence of AKI as a result of contrast will continue to increase, as there is growing use of imaging and interventional procedures in pediatric intensive care patients.[157] At the same time, many patients in intensive and critical care units have compromised renal function, representing the most important risk factor for contrast-induced AKI.

Three core elements are intertwined in the pathophysiology of CIN: (1) direct toxicity of iodinated contrast to nephrons; (2) microshowers of atheroemboli to the kidneys; and (3) contrast- and atheroemboli-induced intrarenal vasoconstriction.[158] Direct toxicity to nephrons with iodinated contrast has been demonstrated and seems to be related to the osmolality of the contrast.[159] Hence, low-ionic or nonionic,

and low-osmolar or iso-osmolar contrast agents were shown to be less nephrotoxic in vitro. Microshowers of cholesterol emboli are believed to occur in up to 50% of percutaneous interventions where a guiding catheter is passed through the aorta. Most of these showers are clinically silent; however, in approximately 1% of high-risk cases, acute cholesterol emboli syndrome (CES) can develop, which is manifested by AKI, mesenteric ischemia, decreased microcirculation to the extremities, and in some cases, embolic stroke.[160] Finally, intrarenal vasoconstriction as a pathologic vascular response to contrast media, and perhaps an organ response to cholesterol emboli, is a final hypoxic/ischemic injury to the kidney.[161] Hypoxia triggers activation of the renal sympathetic nervous system and results in a reduction in renal blood flow, especially in the outer medulla.[160] There is disagreement about the direct vasoconstrictor or vasodilator effects in the kidney of contrast agents when given to animals.[162] It is likely that in completely normal human renal blood vessels, contrast agents provoke a vasodilation and an osmotic diuresis. When there is vascular disease, endothelial dysfunction, and glomerular injury, however, contrast and the multifactorial insult of renal hypoxia provoke a vasoconstrictive response, and hence mediate, in part, an ischemic injury.[162] The most important predictor of CIN is underlying renal dysfunction. The "remnant nephron" theory postulates that after sufficient chronic kidney damage has occurred, the remaining nephrons assume the remaining filtration load, require increased oxygen demands, and are more susceptible to ischemic and oxidative injury. Understanding the pathophysiology of CIN is key to devising a preventive strategy.

Role of Renal Replacement Therapy. Contrast media is removed by dialysis, but there is no clinical evidence that prophylactic dialysis reduces the risk of AKI, even when carried out within 1 hour or simultaneously with administration. Hemofiltration performed before and after contrast adminstration deserves further investigation given reports of reduced mortality and need for hemodialysis but the high cost and need for prolonged ICU care will also limit the utility of this prophylactic approach.[163]

There are no currently approved pharmacologic agents for the prevention of CIN AKI. With iodinated contrast, the pharmacologic agents tested in small trials that deserve further evaluation include theophylline, statins, ascorbic acid, and prostaglandin E_1.[164] Although popular, N-acetylcysteine has not been consistently shown to be effective. Nine published meta-analyses document significant heterogeneity between studies and pooled odds ratios for *N*-acetylcysteine approaching unity.[165] Importantly, only in those trials in which *N*-acetylcysteine reduced serum creatinine below baseline values because of decreased skeletal muscle production did renal injury rates seem to be reduced. Thus *N*-acetylcysteine seems to falsely lower creatinine and not fundamentally protect the kidney against injury. However, a recent study suggested that the use of volume supplementation with sodium bicarbonate together with *N*-acetylcysteine was more effective than *N*-acetylcysteine alone in reducing the risk of CIN. Fenoldopam, dopamine, calcium channel blockers, atrial natriuretic peptide, and L-arginine have not been shown to be effective in the prevention of contrast-induced AKI. Furosemide, mannitol, and an endothelin-receptor antagonist are potentially detrimental.[165]

Acute Renal Failure After Stem Cell Transplantation

One of the most frequent complications of bone marrow transplant (BMT) is renal failure, with 5% to 15% of all BMT patients developing AKI and 5% to 20% of the survivors developing chronic renal failure (CRF).[166] Hematopoietic stem cell transplantation is a common procedure for the treatment of malignancies and some nonmalignant hematologic disorders. The process of stem cell transfusion predisposes these patients to renal failure because of prior chemotherapy, irradiation, sepsis, and exposure to nephrotoxic agents. Complicating outcomes are newer conditioning regimens which allow for reduced intensity and nonmyeloablative regimens, thereby allowing patients with significant comorbidities to undergo transplantation with reduced morbidity and mortality. These have led to challenges in the ICU management of these patients, because they already have residual organ injury. A recent study of 29 pediatric patients who required CRRT in the ICU showed an almost 100% mortality at 6 months post-ICU admission due to transplant-related illness. This study demonstrated the management and ethical difficulties being posed by hematopoietic stem cell transplant patients becoming critically ill and requiring organ support at tertiary care centers. In contrast with the improving survival rates following stem cell transplantation, there are a greater numbers of children surviving and progressing to end-stage renal disease (ESRD). Some of these patients are being treated with renal transplantation.[167]

A better understanding of the underlying histopathologic changes in renal morphology would perhaps lead to a better control of the renal insults that occur during the process of stem cell transfusion. Some histopathology-based studies have shown a variety of findings in patients post-stem cell transplantation, including features of tubulitis and peritubular vasculitis. These studies also show that kidneys from adult patients who had grade III-IV GVHD were more likely to have tubulitis and peritubular capillaritis.[168] Other studies have shown membranous glomerulonephritis and thrombotic microangiopathy to be common histologic features post-stem cell transplantation.[169] However, there still remains a paucity of pediatric studies examining renal histopathology in patients posttransplantation.

Urinary Tract Obstruction

Obstruction of urine flow may result in AKI, although unilateral obstruction rarely causes AKI unless there is a single kidney or disease in the other kidney. Both unilateral and bilateral ureteral obstruction is accompanied by an initial increase in RBF caused by afferent arteriolar vasodilation.[170] Relaxation of the preglomerular capillary sphincter is mediated by the local release of vasodilatory prostaglandins.[171] Administration of indomethacin, a cyclooxygenase inhibitor, results in a marked reduction in the GFR after a decrease in glomerular plasma flow and an increase in both afferent and efferent arteriolar resistances.[172] This indicates an important role of vasodilatory prostaglandins in the maintenance of the GFR.

If the obstruction persists, RBF progressively decreases as afferent arteriolar resistance increases because of the overriding action of angiotensin II and thromboxane. This vasoconstriction may actually protect the kidney from damage during

Table 71–3 Management of Electrolyte Abnormalities

Abnormality	Management Recommendation
HYPERPHOSPHATEMIA	
Moderate (≥2.1 mmol/L)	Avoid IV phosphate administration Administration of phosphate binder
Severe	Dialysis, CAVH, CVVH, CAVHD, or CVVHD
Hypocalcemia (≤1.75 mmol/L)	
Asymptomatic	No therapy
Symptomatic	Calcium gluconate 50–100 mg/kg IV administered slowly with ECG monitoring
HYPERKALEMIA	
Moderate and asymptomatic (≥6.0 mmol/L)	Avoid IV and oral potassium ECG and cardiac rhythm monitoring Sodium polystyrene sulphonate
Severe (>7.0 mmol/L) and/or symptomatic	Same as above, plus: Calcium gluconate 100–200 mg/kg by slow IV infusion for life-threatening arrhythmias Regular insulin (0.1 U/kg IV) + D25 (2 mL/kg) IV Sodium bicarbonate (1–2 mEq/kg IV push) can be given to induce influx of potassium into cells. However, sodium bicarbonate and calcium should not be administered through the same line. Dialysis
Renal dysfunction (uremia)	Fluid and electrolyte management Uric acid and phosphate management Adjust renally excreted drug doses Dialysis (hemodialysis or peritoneal) Hemofiltration (CAVH, CVVH, CAVHD, or CVVHD)

Data from Zaffanello M, Antonucci R, Cuzzolin L, et al: Early diagnosis of acute kidney injury with urinary biomarkers in the newborn, *J Matern Fetal Neonatal Med* 3(suppl 22):62-66, 2009; and Coiffier BJ: Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review, *Clin Oncol* 26(16):2767–2778, 2008.

the period of obstruction. Intratubular pressure rises after ureteral obstruction; this pressure is translated to the glomerulus as increased pressure in Bowman's space. The contribution of this increased force opposing filtration to the decrease in the GFR is probably inconsequential because the intratubular pressure rise is transient.[170] In addition, the elevation in Bowman's space pressure is negated by an increase in the glomerular capillary pressure that increases the GFR. RBF is redistributed from the outer to the inner cortex and results in relative ischemia of the kidney medulla.[170]

Various clinical causes of urinary tract obstruction are listed in Table 71-3. The most important factors determining recovery of kidney and tubular function are the degree and severity of the obstruction. Treatment consists of decompression of the urinary collecting system by removal of the obstruction or by urinary diversion. Relief of obstruction is accompanied by a marked diuresis resulting from increased RBF and abnormal tubular function. The increase in urine volume is related to a concentrating defect caused by loss of the medullary gradient and unresponsiveness of the kidney tubule to vasopressin.[173] Hydrogen ion and potassium secretion may also be impaired, and the result is a distal type of kidney tubular acidosis with hyperkalemia.[174]

This chapter has reviewed the major factors that contribute to the development of AKI, both in its oliguric and nonoliguric forms. Also indicated are the clinical settings in which AKI may occur. In addition, treatment modalities have been discussed. Clearly, the challenge in AKI is the development of novel therapeutic strategies that will more directly intervene in the disease process and which can have an impact on the cellular and metabolic mechanisms that contribute to kidney cell injury. Certain current investigations were discussed because they may lead to clinical trials during the next 10 years. Included among these agents are calcium channel blockers, adenine nucleotides, thyroid hormone, and oxyradical scavengers because they may modulate the full expression of kidney cell injury. Only with understanding of the pathophysiological mechanisms in AKI can these potential therapeutics be applied in a clinical setting to the care of pediatric patients.

References are available online at http://www.expertconsult.com.

V

Chapter 72

Pediatric Renal Replacement Therapy in the Intensive Care Unit

Jordan M. Symons and Stuart L. Goldstein

PEARLS

- Patients receiving renal replacement therapy require careful monitoring of fluid and electrolyte balance and nutritional needs.
- Coordination between the critical care and nephrology staff is essential for the successful care of patients requiring renal replacement therapy.
- Earlier initiation of renal replacement therapy may improve outcome.
- Peritoneal dialysis remains an excellent form of acute pediatric renal replacement therapy.
- Hemodialysis is the modality of choice for rapid correction of fluid or metabolic imbalance.
- Continuous renal replacement therapy can establish and maintain fluid and metabolic control in unstable patients.

Renal replacement therapy has an established role in the pediatric intensive care unit (ICU).[1] Volume overload and metabolic imbalance can complicate the course of critically ill patients, especially those with multiorgan dysfunction.[2] Some patients with normal kidney function may have metabolic imbalance or intoxication that overwhelms baseline endogenous clearance capacity, necessitating extracorporeal clearance techniques. Improvement of techniques coupled with the realization that early supportive therapy may improve outcomes have led to expanded use of renal replacement therapy for critically ill pediatric patients.

Renal Failure and Other Indications for Renal Support

Acute Kidney Injury

Acute kidney injury (AKI) can be defined as an acute decrease in the glomerular filtration rate. Oligoanuria is a frequent, but not essential, component of AKI. Common causes of AKI in the critically ill patient include renal hypoperfusion (leading to so-called *prerenal azotemia*), hypotension or shock causing renal ischemic injury or acute tubular necrosis, nonspecific renal involvement as part of a sepsis syndrome or multiorgan dysfunction, and renal injury from nephrotoxins such as antibiotics and radiocontrast media (see Chapter 71).

Patients with even mild AKI can have volume overload, electrolyte imbalance, and metabolic derangement with associated poor outcomes.[3-5] Such complications can be particularly detrimental to the care of the critically ill patient. While all modalities of renal replacement therapy can correct these abnormalities, certain modalities may be better suited for specific pediatric clinical situations.

Acute Intoxication and Metabolic Disorders

Hemodialysis can rapidly remove many exogenous toxins (e.g., as the result of poisonings and drug overdoses) and endogenous toxins (such as those seen in persons with inborn errors of metabolism), and it is often the therapy of choice for severe life-threatening intoxication. Hemodialysis can be followed by continuous renal replacement therapy (CRRT) for intoxications where a rebound phenomenon may occur (see Chapters 76 and 105).

Renal Support

Diminished renal function is a common component of multiorgan dysfunction syndrome. AKI is highly correlated with poor outcome in hospitalized adults and children.[4,6] In pediatric patients, studies demonstrate increased mortality in critically ill children with excessive levels of fluid overload in the setting of concomitant AKI.[7-10] These observations, coupled with advanced capabilities for renal replacement therapy, lead many clinicians to consider early initiation of renal support. In this model, traditional indicators for dialysis, such as profound azotemia, oligoanuria, massive fluid overload, or significant electrolyte imbalance, may occur too late in the clinical course to alter outcome. Earlier intervention, either with renal replacement therapy or perhaps through careful conservative management, may prevent complications associated with serious metabolic disarray and volume overload and permit vigorous nutritional and medical support. The concept of early "renal support" for patients in the ICU to limit metabolic derangement and prevent volume overload has gained wider acceptance in both the adult and pediatric critical care arenas.

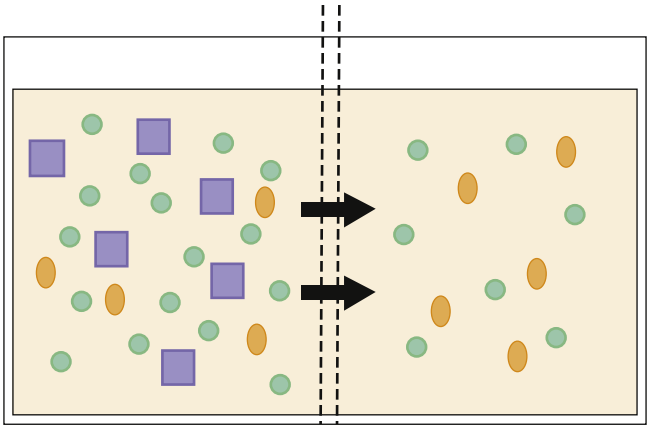

Figure 72–1. Diffusion. Particles move across the semipermeable membrane from an area of higher concentration to an area of lower concentration. Smaller particles diffuse more freely, whereas larger particles are relatively restricted.

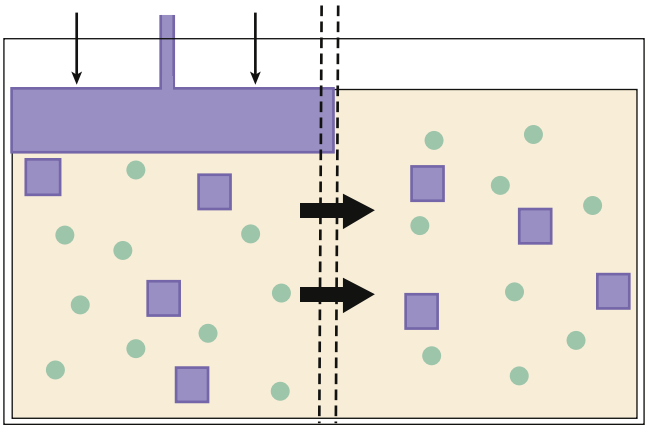

Figure 72–2. Convection. Particles move across the semipermeable membrane, carried by ultrafiltered water, because of the effect of pressure. All particles up to the cutoff size of the membrane move relatively equally. The concentration of the effluent is equal to that of the original solution.

Conservative Management

Conservative management of AKI includes optimization of clinical status with the maintenance of fluid balance, renal perfusion, cardiac output, and adequate blood pressure. Nephrotoxin exposure should be limited. Judicious use of diuretics can greatly augment the patient's ability to maintain fluid homeostasis. After initial early and goal-directed fluid resuscitation in patients with hemodynamic shock, fluids may need to be restricted to prevent worsening degrees of fluid overload.[11,12] Patients require careful dietary management to provide sufficient nutrition in a smaller daily fluid volume and to avoid excess delivery of substances normally cleared through the kidney (e.g., potassium and phosphorus).

Conservative management avoids the potential risks associated with renal replacement modalities; the cases of many pediatric patients with milder renal dysfunction can be managed successfully without renal replacement therapy. As noted previously, however, support exists for the use of renal replacement early in the ICU course. Data show improved outcomes for pediatric patients receiving CRRT who demonstrated less fluid overload at initiation of therapy,[7-10,13] suggesting a survival advantage for patients who begin CRRT earlier rather than later. Although the best time to initiate renal replacement for the patient in the ICU remains unclear, there is a growing consensus to avoid unnecessary delay.[14]

Basic Physiology of Dialysis and Ultrafiltration

The physical principles of molecular movement across a semipermeable membrane underlie peritoneal dialysis, hemodialysis, and CRRT modalities. The following brief review summarizes the basic mechanisms of particle and water removal for all forms of renal replacement therapy.

Diffusion describes the movement of dissolved particles across a semipermeable membrane from an area of high concentration to an area of low concentration (Figure 72-1). This physical principle operates in all renal replacement modalities in which dialysis fluid is used. Diffusion favors the movement of smaller particles and is most rapid when the concentration gradient across the semipermeable membrane is greatest; diffusion stops when the concentrations achieve equilibrium.

Convection occurs when dissolved particles pass across a semipermeable membrane because of the effects of a pressure gradient (Figure 72-2). Particles that are smaller than the pores of the membrane can pass freely, whereas larger particles are restricted. Because particles and water are moving together, the removed solution is isotonic to the original.

Ultrafiltration describes the movement of water across the semipermeable membrane due to pressure. Convection occurs with ultrafiltration.

Peritoneal Dialysis

Peritoneal dialysis (PD) has been a standard form for renal replacement therapy for many years. Despite improving techniques that permit the application of other modalities to even the smallest patients, PD remains an effective method of renal replacement therapy and may represent the best choice in selected cases.[15] Even the most experienced centers may have difficulty achieving vascular access in some patients. Children with vascular abnormalities, certain types of cardiac disease, or hemodynamic issues may be suboptimal candidates for extracorporeal perfusion through a hemodialysis or hemofiltration circuit. In such circumstances, PD can be the best choice for renal replacement therapy.

Physiology

It has been known for many years that the peritoneum can be used as a dialyzing membrane.[16] Instillation of a dialysis fluid into the peritoneal space permits diffusion of particles out of the blood and into the dialysis fluid across the peritoneum, which acts as a semipermeable membrane. Through the use of a hypertonic solution, water also passes across the membrane, generating an ultrafiltrate. Water movement will also tend to drag particles across the peritoneum by convection. After the dwell is complete, the spent dialysate is drained from the abdomen and fresh dialysis fluid is introduced.

Indications

PD can remove excess fluid and provide volume control in patients with oligoanuria. Compared with fluid removal with intermittent hemodialysis, fluid removal with PD is much

slower. Manipulation of dialysis fluid osmolality and dwell time can adjust the quantity of volume removed. The slow, steady ultrafiltration achieved with PD may be preferable to the rapid fluid removal that occurs in intermittent hemodialysis, particularly in unstable, critically ill patients.

Similar to volume control, PD provides slow and relatively continuous metabolic control. It is an effective method for correction of uremia. Manipulation of the PD prescription can improve clearances.

Technique

The basic technique for PD involves instilling a sterile dialysis fluid into the peritoneal cavity and allowing it to dwell for a specified period, during which particles diffuse across the peritoneal membrane and water moves across by ultrafiltration. At the end of the dwell time, the fluid is removed from the peritoneal space and the process is repeated.

Flexible catheters are most often used for chronic PD in pediatric patients. For acute PD, either this form of a surgically placed catheter or percutaneously inserted temporary PD catheters may be used; some data suggest that fewer complications occur with surgically placed catheters.[17] Catheters come in a variety of sizes, depending on the size of the patient. Local practice often determines who will insert the catheters when they are needed; the procedure requires expertise to ensure proper functioning of the catheter.

PD fluid comes in standardized, sterile bags with premixed formulations, and thus pharmacy preparation is unnecessary. Because most patients with renal failure have metabolic acidosis, the dialysis fluid contains base, usually in the form of lactate. Thus the PD system will remove unwanted particles and also can act as a source of electrolytes. Lactate absorption can lead to confusion regarding acid/base interpretation, especially in critically ill infants. In such settings bicarbonate-based dialysis fluid may be preferable,[18] although this fluid may require extemporaneous preparation by the local pharmacy.

Ultrafiltration in PD is accomplished by osmotic pressure, usually through the presence of dextrose in the dialysis fluid. Dialysis fluids contain standardized concentrations of dextrose; the choices vary somewhat between the United States and other countries. Dialysis fluid with higher concentrations of dextrose will cause greater ultrafiltration for each exchange of fluid.

Dialysis fluid should be warmed to body temperature before instillation. This step is particularly important in small patients, in whom hypotension associated with cold dialysis fluid infusion can develop.[19]

Initial exchanges with a new PD catheter should use relatively lower volumes of dialysis fluid (10 to 20 mL/kg; <500 mL/m^2) to limit the chance of leakage from the catheter entrance operative site. Volumes may increase gradually during the next few days or weeks to 1100 mL/m^2.[19]

Longer dwell periods between exchanges provide more time for equilibration of dialyzable particles and for ultrafiltration. Although shorter dwell times may not maximize mass transport for given dwell periods, they may permit more dialysis and ultrafiltration in a 24-hour period by allowing more exchanges per day. Initial dwell periods of 30 to 60 minutes can be adjusted later on the basis of clinical status.

PD fluid can be instilled by hand or with the use of a cycler, a device that will automatically fill and empty the patient's abdomen with dialysis fluid on a preprogrammed schedule. The cycler also contains a warmer for the dialysis fluid and monitoring systems to record effluent volumes. Several brands of cyclers are currently available. Programming limitations may prevent the use of a cycler for some patients who require very small fill volumes or very short dwell times.

Disadvantages and Complications

The PD technique requires placement of a peritoneal catheter and a sufficiently maintained intraabdominal status to permit infusion of dialysis fluid with successful diffusion and ultrafiltration. Patients who have undergone an abdominal operation or have had abdominal complications may be poor candidates for PD.

Invasion of the peritoneal space puts the patient at risk for peritonitis, a potentially serious complication. The importance of sterile technique when performing PD cannot be overemphasized. Appropriate technique limits the risk of infectious complications, which could be fatal in a critically ill patient.

Peritonitis must always be considered in a patient undergoing PD who has a fever or cloudy effluent. Dialysate should be analyzed for cell count, Gram stain, and bacterial culture if infection is suspected. Empirical or specific antibiotic therapy can be placed in the dialysate to treat peritonitis via the intraperitoneal route.[20]

Dialysate can fail to fill or drain through the PD catheter because of a number of potential problems, including kinking of the catheter, fibrin plugs, omental obstruction, or catheter malposition. Percutaneously inserted temporary dialysis catheters are more prone to malfunction than are surgically placed catheters.[21] Abdominal x-ray images can confirm appropriate positioning and permit checks for kinks in the catheter. Some success has been reported with thrombolytic agents to treat fibrin plugging.[22-24] Revision or replacement of the catheter may need to be considered if simple maneuvers do not correct the malfunction.

Perforation of abdominal or pelvic structures can occur, either at the time of initial catheter placement or later.[21] Although this event is relatively uncommon, significant morbidity can result.

PD is a suboptimal choice for patients who require rapid correction of metabolic abnormalities, immediate removal of circulating toxins, or rapid ultrafiltration for acute complications of fluid overload. For the latter indications, hemodialysis would be the preferred modality. Effectiveness of PD may be suboptimal in settings of low cardiac output where splanchnic circulation is compromised. However, this does not preclude the use of PD in selected cases, such as for infants following surgery for congenital heart disease.

Fluid leakage is seen most often with dwell volumes that are too large, especially in the period immediately after catheter placement.[25] Lower fill volumes should be used. Fluid leakage into the thorax can compromise respiration. External fluid leakage around the catheter increases the risk of infection.

Intensive Care Unit Issues

Patients undergoing PD can lose protein into the dialysate. Nutritional support must provide sufficient protein to compensate for this loss. High dextrose concentrations in the

dialysis fluid can cause hyperglycemia; administration of insulin may be necessary. Indwelling dialysis fluid causes increased intraabdominal pressure that can complicate care of the critically ill patient. Diaphragmatic excursion may be limited, and venous return can be reduced. Stomach compression can lead to gastroesophageal reflux. Although patients undergoing long-term PD who receive fewer daily exchanges usually require maximal fill volumes to achieve adequate dialysis, patients undergoing short-term PD may do better using submaximal fill volumes with more frequent exchanges provided around the clock.

Intermittent Hemodialysis

Intermittent hemodialysis (IHD) has been the traditional form of renal replacement therapy in the ICU. The technique is well established for pediatric patients.[26] IHD offers the advantages of high efficiency for rapid metabolic correction and fluid removal. Its very advantages, however, may limit IHD's usefulness in the critically ill patient. IHD for infants and small children can be technically difficult and demanding. IHD may be the preferred modality for some critically ill pediatric patients; successful treatment in this setting requires experienced personnel.

Physiology

The dialyzer used in IHD is an artificial semipermeable membrane. The most common design used today is the hollow-fiber dialyzer. It consists of a plastic cartridge traversed by several thousand thin hollow fibers, each with microscopic fenestrations that permit the passage of water and other small molecules. Dialyzers vary in their surface area, permeability, priming volume, and membrane composition; numerous dialyzers are available commercially. Choosing different dialyzer characteristics permits adjustment of the dialysis prescription to the clinical situation.

Successful hemodialysis requires sufficiently high blood flow to allow adequate dialysis and ultrafiltration with a minimal risk of clotting. Dialysis efficiency falls off dramatically with lower blood pump speeds; this may require extended time on dialysis to compensate. Consequently, high-quality vascular access is essential for successful hemodialysis.

While blood flows through the hollow fibers of the dialyzer, dialysis fluid flows through the cartridge in the space surrounding the hollow fibers. Particles move by diffusion from the blood across the semipermeable membrane into the dialysate. Use of high-flow dialysis fluid with maximal blood flow through the dialyzer permits intermittent hemodialysis to remove particles more efficiently than any other renal replacement therapy.

Increasing blood flow, dialysis fluid flow, or dialyzer size will increase the rate of diffusion. Because diffusion favors the movement of small particles over large particles, large molecules or small molecules bound to larger molecules (such as albumin) will not dialyze well. In addition, intracellular particles will move into the vascular compartment on the basis of individual cell membrane transport characteristics, which may limit the rate at which dialysis can remove particles that do not reside within the vascular compartment.

Ultrafiltration on hemodialysis occurs because of hydrostatic pressure across the membrane that forces water out of the blood. Dissolved particles will travel with the water, leaving by convection. With use of IHD, dialysis staff can control the rate of ultrafiltration with precision and can achieve high rates of ultrafiltration.

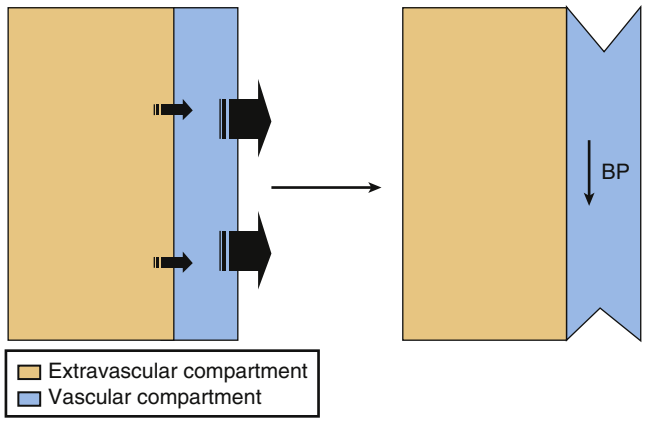

Figure 72–3. Two-compartment model of ultrafiltration. The rate of water removal from the vascular compartment by ultrafiltration (*large arrows*) exceeds the rate of refilling from the extravascular compartment (*smaller arrows*), and this process leads to relative vascular volume depletion and hypotension.

Analogous to the process of diffusion, ultrafiltration during IHD removes fluid only from the vascular compartment. Extravascular or "third space" fluid must move into the vascular compartment for removal by ultrafiltration. When the rate of movement from the extravascular space is slower than the rate of ultrafiltration, intravascular depletion can occur even though total body water remains elevated (Figure 72-3). This "two-compartment" model represents a potential limitation of rapid ultrafiltration during IHD, especially in the critically ill patient.

Indications

Thanks to its high efficiency, hemodialysis is the best modality for rapid particle removal. IHD is indicated for the treatment of toxic ingestions, many serious drug overdoses, and metabolic derangements that lead to the overproduction of endogenous toxins such as ammonia (see Chapters 76 and 105).[27-30]

The IHD system can perform ultrafiltration more rapidly than any other renal replacement modality. Consequently it is often the best choice for the treatment of critical volume overload but may be limited by the patient's ability to tolerate rapid fluid removal. Recent technology to guide ultrafiltration by the noninvasive monitoring of hematocrit changes during IHD may prevent and/or mitigate hypotension associated with ultrafiltration.[31]

Profound metabolic imbalance, such as that seen with critical hyperkalemia, can be corrected most quickly with IHD. Patients with oncologic problems such as tumor lysis syndrome may require IHD to rapidly correct the multiple metabolic abnormalities and to aid clearance of uric acid, which can cause renal failure (see Chapters 81 and 83).[32,33]

Technique

Vascular access is the first step for successful hemodialysis. Double-lumen catheters for hemodialysis come in a variety of sizes; occasionally, two single-lumen catheters at separate

sites are needed for small infants, although recent data suggest that these catheters do not perform as well.[34] Catheters can be placed in jugular, femoral, or subclavian positions (see Chapter 15). The internal jugular vein is preferred for access that will be required for more than a few sessions. Surgical support may be needed for patients when percutaneous placement is difficult.

Most patients receiving IHD will require heparin for anticoagulation. Some may be able to undergo successful dialysis with little or no heparin because of coagulopathy related to their systemic disease. Staff members often monitor clotting times during the IHD session to determine the need for heparin.

The blood pump rate is chosen based on the patient's clinical status and the quality of the vascular access. In smaller patients with smaller catheters, blood pump speeds often must run at less than 100 mL/min; in infants, speeds may run as low as 25 to 50 mL/min. Larger patients can tolerate faster blood pump speeds. Higher blood flow rates permit greater mass transfer of particles out of the patient in a given period.

The chosen dialyzer should provide sufficient clearance to achieve the goals of the dialysis session. Smaller patients receive dialysis with smaller dialyzers to limit extracorporeal blood volume and reduce the risk of dialyzer clotting with slower blood flow rates.

Small patients or those with unstable blood pressure may require priming of the IHD circuit with saline solution, albumin, or reconstituted whole blood. Dialysis machines with precise volumetric ultrafiltration control permit accurate and safe IHD in neonates and infants, for whom small inaccuracies in ultrafiltration volumes could potentially lead to severe fluid imbalances. Dialysis fluid concentrations of electrolytes can be adjusted to some extent on the basis of the clinical situation. The length of the IHD session will vary depending on the clinical situation and goals of the therapy. Mathematical models permit estimation of dialytic clearance and can be used to structure session length. The rate at which the patient can tolerate ultrafiltration is often the limiting factor in IHD for critically ill patients. Sessions may need to be extended to achieve ultrafiltration goals without significant hypotension.

Disadvantages and Complications

The principal disadvantage of IHD is the requirement for vascular access. Acceptable access can be difficult to achieve in critically ill children. Complications related to the access can include infection, bleeding, and thrombosis.

IHD's benefit of high efficiency with rapid fluid and particle removal can lead to difficulties in the ICU setting. Critically ill patients may not tolerate the rapid ultrafiltration and metabolic shifts of IHD.

Smaller patients or those with unstable blood pressure may require priming of the extracorporeal circuit to limit hemodynamic stress at dialysis initiation. For infants in whom the extracorporeal volume is relatively much larger, priming may need to be done with a blood/albumin mix, which exposes the patient to blood products.

Most IHD sessions require systemic anticoagulation with heparin, which can be difficult to manage in a critically ill child. Heparin exposure can complicate bleeding and cause heparin-induced thrombocytopenia. With careful monitoring of clotting times and circuit performance during the session, it is possible to perform IHD without heparin. The risk of clot formation in the IHD circuit rises, however, when heparin is not used.

Intensive Care Unit Issues

Patients receiving IHD as ongoing renal replacement therapy in the ICU require special attention to fluid and electrolyte balance. One should limit potassium and phosphorus delivery and may need to limit total daily fluids because ultrafiltration only occurs intermittently. Medication doses and schedule may require adjustment because of poor excretion with renal failure and subsequent rapid removal with dialysis (see Chapter 70).

Continuous Renal Replacement Therapy

CRRT is a generic term applied to several techniques of extracorporeal renal support. Similar to IHD in the use of a blood pump and hemofilter, the various subcategories of CRRT differ in their reliance on diffusion, convection, or a combination of the two for molecular clearance.

CRRT is becoming more popular as a method of renal support for pediatric patients.[1,35] Technological improvements in catheters, blood pumps, and ultrafiltration control mechanisms permit the application of CRRT to even the smallest infants.[36,37]

Physiology

The CRRT hemofilter is similar to that used for IHD. CRRT membranes traditionally have been more porous to permit greater removal of water. Numerous hemofilters are available commercially.

Both convection and diffusion can be used to remove particles during CRRT. Dialysis fluid allows diffusion, which favors the movement of smaller molecules. High rates of ultrafiltration will remove both small and larger particles by convection, up to the limits of the membrane. With high ultrafiltration rates to achieve better convective clearance, the patient may need to receive replacement of volume and electrolytes to compensate for that lost in ultrafiltrate.

Because of slower flow rates, the clearance achieved with CRRT may be lower than that of IHD. Continuous therapies, however, make up for this lower efficiency through the extended time of the treatment. Compared with a 3- or 4-hour IHD session, CRRT running 24 hours a day can achieve equivalent daily clearance with less metabolic variation. Newer CRRT devices can run at flow rates approaching those seen in IHD, greatly increasing the potential for rapid molecular clearance.

Nomenclature for the various subcategories of CRRT is based on the vascular access and the primary method of particle clearance (convection, diffusion, or both). Because most CRRT in pediatric patients uses a pump-assisted venovenous method, the most commonly used terms are continuous venovenous hemofiltration, which uses high convective clearance requiring replacement fluids; continuous venovenous hemodialysis, which uses dialysis fluid for diffusion, but minimal additional convection; and continuous venovenous hemodiafiltration, which uses both dialysis fluid and replacement fluids for combined diffusion and high-grade convection.

Indications

As a result of the slow, continuous removal of fluid, CRRT is particularly well suited to the treatment of volume overload in critically ill patients. Whereas IHD will attempt to reach an ultrafiltration goal within a relatively short therapeutic session, CRRT allows continuous ultrafiltration that can help maintain cardiovascular stability.

CRRT is useful to maintain metabolic balance through ongoing removal of unwanted particles. Although it is less efficient than IHD, CRRT's continuous nature can avoid daily fluctuations inherent in the use of an intermittent modality. In addition, CRRT can be used as a secondary method to maintain metabolic balance after rapid correction with IHD.[38]

For patients with diminished renal function and decreased urinary output, CRRT can allow administration of the daily load of fluids required to deliver medication and nutrition. With this modality the patient can be maintained in a more stable balance compared with IHD, in which the patient has progressive volume overload between IHD sessions and then must achieve the ultrafiltration goal in a brief treatment period.

Technique

As in IHD, successful CRRT requires adequate vascular access (see Chapter 15). Given the relatively large extracorporeal volume, smaller patients may require priming of the CRRT circuit with blood/albumin mix. In larger, more stable patients, CRRT can be initiated successfully with saline prime.

Earlier methods that entailed arteriovenous access have largely been abandoned in favor of venovenous CRRT. Older systems with adapted blood and fluid pumps linked together extemporaneously have been replaced by dedicated CRRT machinery. Several CRRT systems are available at this time; this latest generation of CRRT machines permits much greater accuracy for blood pump speed, fluid delivery, and ultrafiltration control.

Anticoagulation

Adequate anticoagulation is essential for successful CRRT. Currently, most patients treated with CRRT receive systemic heparin, regional citrate, or no added anticoagulation.

Systemic heparinization has been the traditional form of anticoagulation used in CRRT. This method is proven and functions well. Disadvantages include systemic anticoagulation with risk of bleeding, risk of heparin-induced thrombocytopenia, and the need for frequent monitoring and adjustment of the heparin dose.

Regional citrate anticoagulation has become popular for CRRT in both adult and pediatric patients. Citrate, introduced into the CRRT circuit, chelates calcium, which is a required cofactor in both the intrinsic and extrinsic arms of the clotting cascade. Calcium is infused back into the patient through a central access to prevent systemic hypocalcemia. Citrate is metabolized to bicarbonate, acting as a source of base. Several protocols have been developed for regional citrate anticoagulation in CRRT.[39-42] The systems are stable and require less monitoring than heparin-based anticoagulation. Disadvantages include the potential for acid/base imbalance, the risk of hypercalcemia or hypocalcemia, citrate overload due to poor metabolism or diminished clearance, and the need for additional central access for high rates of calcium delivery.

Many critically ill patients have disorders of coagulation as a part of their multiple organ system injury and can undergo CRRT without exogenous anticoagulation. Increased clotting of the CRRT circuit in such patients may be a sign of improving clinical status. A study of pediatric CRRT suggested that circuits that are run without anticoagulation have a significantly shorter life span; thus it may be appropriate to consider the use of anticoagulation even in the coagulopathic patient to ensure continued delivery of the therapy.[43]

Patient and vascular access size can limit blood pump rate. The current generation of CRRT machines can run at lower blood pump speeds with greater accuracy than did earlier systems.

Many brands of hemofilter are available for CRRT. Larger surface areas will permit more rapid ultrafiltration and clearance by convection. Of particular interest in the pediatric patient are reports of profound hypotensive events related to the use of a type of polyacrylonitrile hemofilter known as the AN-69 membrane.[44] This reaction, occurring rapidly when the patient's blood comes in contact with the hemofilter, is thought to be related to the release of bradykinin in response to the low pH of blood used to prime the CRRT circuit. Smaller patients and those with metabolic acidosis seem to be at greatest risk. Maneuvers to adjust pH within the circuit and limit this reaction have been described.[44-46] Some practitioners prefer to avoid use of the AN-69 membrane to limit the risk of complication, while others choose to tolerate this potential complication in patients with sepsis in light of the relatively high IL-6 clearance provided by AN-69 membranes.[47]

Dialysis Fluid and Infused Fluids

Nearly all of the current CRRT machines use premade, fully compounded dialysis or hemofiltration fluid rather than generating dialysis fluid online from concentrates (during IHD the dialysis fluid is generated online). Commercially available dialysis and hemofiltration fluid, compounded under quality-controlled conditions and delivered in premixed sterile bags, has largely replaced the use of extemporaneously prepared dialysis fluid from local pharmacy services. Several manufacturers offer dialysis fluid for CRRT; the products come in a variety of electrolyte concentrations to suit differing clinical needs. Commercially prepared options are also available for replacement fluids in CRRT. It has been suggested that the use of commercial CRRT solutions, rather than those made by a local pharmacy, can reduce the likelihood of errors related to solution preparation.[48]

Replacement fluids are infused to the CRRT system either before the hemofilter ("prefilter" or "predilution") or after ("postfilter" or "postdilution"). Prefilter delivery will reduce convective clearance at a given ultrafiltration rate because the blood entering the hemofilter will be diluted by the replacement fluid. This reduction, however, can be easily overcome with an increase of the ultrafiltration rate. Furthermore, prefilter replacement may permit higher ultrafiltration rates because it limits hemoconcentration within the hemofilter and thus lessens the chances of filter clotting. Some CRRT machines will permit either prefilter or postfilter delivery of replacement fluids, whereas others have a fixed location for replacement fluids.

Clearance

CRRT blood pump, dialysis fluid, and replacement fluid rates traditionally have been lower overall than those used in IHD. Consequently, clearance rates are lower but total daily clearance increases because the therapy is continuous. In most prescriptions, the limiting factor in CRRT clearance is the dialysis fluid or replacement fluid flow rate; greater rates of clearance

often can be achieved with an increase in the rate of dialysis fluid or replacement fluid. Newer CRRT machines are capable of higher dialysis and replacement fluid rates than in the past. Slower blood pump speeds can also potentially limit clearances; some newer devices are capable of higher blood pump speeds. Controversy exists in adult patients regarding appropriate goals for clearance. An influential single-center study suggested better outcomes with higher rates of clearance, [49] but this finding has not been reproduced in subsequent multicenter trials.[50,51] This question has not been fully studied in children.

Slow, steady ultrafiltration to gradually achieve fluid balance and then maintain it is the hallmark of CRRT. Slow ultrafiltration can permit movement of extravascular fluid into the vascular space at a rate roughly equal to the ultrafiltration rate, which allows greater mobilization of fluid while the risk of acute intravascular volume depletion and hypotension is limited. Ultrafiltration rates must be chosen on the basis of clinical status of the patient and fluid balance goals; frequent reevaluation is often necessary.

Disadvantages and Complications

Like IHD, CRRT requires vascular access, which can be difficult to obtain in infants and small children. Recent data can provide guidance regarding catheter size choice based on patient size and suggest that 5 Fr single-lumen catheters should not be used for CRRT because they are associated with significantly shorter functional CRRT circuit survival.[34] Continuous extracorporeal perfusion and anticoagulation carry risks of bleeding and infection. Some patients experience blood pressure instability despite the slow method of ultrafiltration. Continuous exposure to heparin can lead to heparin-induced thrombocytopenia. Patients receiving citrate anticoagulation are at risk for acid/base disturbance or hypocalcemia. Citrate overload can cause low patient ionized calcium with normal or high total calcium levels, the so-called *calcium gap* or *citrate lock*,[40,52] which occurs when excess citrate binds free calcium in the patient. Under these circumstances, citrate delivery should be reduced or clearance through the CRRT system should be increased.

Intensive Care Unit Issues

Continuous clearance on CRRT, particularly with convective modalities, can cause profound electrolyte deficiencies. Careful attention must be paid to appropriate replacement of electrolytes lost through CRRT. Similarly, nitrogen losses on CRRT can be high.[53] Patients require increased nutritional support during CRRT therapy, and careful consideration of the nutritional prescription is required.[54] Medication dosages often require adjustment because of losses through the CRRT system. Coordination between the ICU staff and nephrology staff is essential to establish appropriate goals for fluid removal and metabolic control.

Extended Daily Dialysis

IHD sessions can be extended in length to provide therapy that approaches CRRT. Variously referred to as slow low-efficiency dialysis or slow extended daily dialysis, such techniques can provide improved molecular clearance with better tolerance of ultrafiltration when compared with conventional schedules for IHD. Sessions may run 6 to 8 hours or more on a daily basis.[55]

Some institutions may prefer extended daily dialysis methods because they obviate the need to purchase and maintain separate, dedicated CRRT equipment, using instead standard IHD machines that have been adapted for longer session length. In addition, disposable materials for IHD are usually less expensive than are those for CRRT, potentially leading to cost savings. Because the patient is not connected to the device 24 hours a day, patient mobility for tests or surgical procedures may be facilitated and risk of treatment-related complications may be reduced. Online generation of dialysis fluid, as for standard IHD, greatly simplifies the question of solutions compared with premixed bags that must be frequently exchanged for CRRT. However, most online dialysis fluid is not sterile, raising a theoretical risk for the critically ill patient. Newer devices capable of extended therapies can be adapted to provide ultrapure dialysis fluid, which may mitigate this potential concern. Individual institutions may need to consider staffing requirements related to tending an IHD device for extended sessions.

While use of extended daily dialysis techniques for both adult and pediatric patients is growing, the literature has a dearth of information regarding efficacy in the pediatric population. This modality is often chosen for pragmatic reasons rather than because of proven superiority. It remains a reasonable option under the appropriate circumstances.

Outcomes of Renal Replacement in Critically Ill Children

Outcome data comparing modalities for pediatric renal replacement are sparse. The majority of studies are from single centers and are limited by small numbers of subjects.

The most recent studies in pediatric renal replacment therapy have centered on CRRT. Findings from five studies, comprising an aggregate of more than 400 patients, demonstrate an association of higher mortality for patients with more severe levels of volume overload.[7-10,13] A multicenter observational registry has provided insight on outcomes in pediatric CRRT.[37] Overall survival on CRRT in this cohort of more than 300 critically ill children was 58%; this percentage is superior to previously reported outcomes and likely represents improvement in CRRT techniques as well as overall critical care for the pediatric patient. Outcomes in the subpopulations of children with multisystem organ dysfunction and stem cell transplant who required CRRT also were noted to be improved compared with historical reports.[7,56] Because these studies did not compare CRRT to other interventions, no specific evidence-based comments can be made regarding choice of modality in the modern era, and this decision is largely based on experience and opinion.

Summary

Pediatric patients who require renal replacement therapy represent a special challenge. Multiple modalities are available, and the best choice may be dictated by the clinical situation and local expertise. Careful attention to fluid and electrolyte balance and appropriate nutritional support and close interaction between critical care and nephrology personnel will yield the best outcomes.

References are available online at http://www.expertconsult.com.

Hypertension in the Pediatric Intensive Care Unit

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PEARLS

- Systemic hypertension, an often underappreciated condition that is increasing at an alarming rate in part because of the obesity epidemic, leads to long-term morbidity, mortality, and poor quality of life.
- A hypertensive emergency exists when there is evidence of end organ damage along with a severely elevated systolic or diastolic blood pressure. Consequently, prompt therapy and intensive monitoring are required.
- Treatment of a hypertensive emergency requires balancing the desire to quickly lower pressure against the potential harm from dropping pressure and thus organ blood flow too rapidly (e.g., cerebral, coronary, or renal ischemia). In clinical practice, mean arterial pressure during a hypertensive crisis should be lowered no more than 25% within the first hour.
- Although hypervolemia is a common cause of hypertensive urgencies or emergencies, the high perfusion pressure that occurs during a hypertensive emergency can lead to pressure diuresis, rendering some patients relatively hypovolemic, with hemoconcentration and activation of the renin-angiotensin-aldosterone system. Consequently, persistent hypovolemia may trigger a vicious cycle of further stimulation of the renin-angiotensin-aldosterone system, thus increasing systemic vascular resistance.
- Hypertension, when present in children in the pediatric intensive care unit, is most often related to pain, anxiety, positive fluid balance, drug effect (e.g., steroids or immunosuppression), or occasionally unrecognized seizure activity. In children with long-standing hypertension admitted to the pediatric intensive care unit, renal causes are most frequent and may be clinically silent, such as renovascular hypertension.

When confronted with a child with abnormally "high" blood pressure (BP) in the medical setting, the pediatrician is immediately confronted with two vexing issues. One is whether this abnormality will lead to immediate organ- or life-threatening consequences, and the second is whether the potential intervention itself will result in a worse outcome. Systemic hypertension (HTN) is a major lifelong condition that begins in childhood and is one of the leading causes of premature death in developed countries and developing nations.[1] The current obesity epidemic along with other lifestyle choices have likely led to the increasing numbers of children now being diagnosed with HTN.[2] Current estimates suggest that up to 5% of children have HTN compared with estimates of approximately 1% just a decade ago, while another 10% to 25% have prehypertension.[3-13] If untreated, HTN is associated with a 10-year survival rate of about 50% in adults depending on the degree of retinal changes and/or level of diastolic pressure.[14,15]

Several questions are commonly posed to the intensivist when managing the case of a child with acute HTN: What is acute HTN in the pediatric intensive care unit (PICU)? Is this level of HTN dangerous? Does the HTN represent a transient acute response? Is it important to manage high BP at this moment? How aggressive do I need to be in monitoring and managing it? It is the objective of this chapter to set the foundation for understanding the deleterious effects of systemic HTN, recognize when invasive versus noninvasive monitoring is warranted, and appreciate the importance of a prompt but measured response in management.

Definition of Terms

The most recent recommendations for diagnosing HTN in children were published in 2004 by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (Task Force) and were designed to mirror recommendations for diagnosing HTN and pre-HTN in adults according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. However, unlike adult definitions that are based on the observations reported by Volhard and Fahr in 1914 as well as epidemiologic studies showing a clear risk for cardiovascular morbidity and mortality with BPs at a certain level, pediatric definitions are based on epidemiological thresholds generated from a population of more than 60,000 children and adolescents across the United States.[16,17] Therefore in children systemic hypertension is defined as an average systolic BP (SBP) and/or diastolic BP (DBP) that is ≥95th percentile for gender, age, and height on three or more separate occasions[16,18] (see Appendix at www.expertconsult.com). In addition, children with an average SBP and/or DBP that is at the 90th percentile or higher (or ≥120/80 mm/Hg when a patient's 90th percentile exceeds this value) should be considered prehypertensive.[16] This classification of prehypertension is not meant to be considered

Table 73–1 Description of Youngest Patients Diagnosed with Malignant Hypertension

Age (Yr)	Gender	Blood Pressure (mm Hg)		History of Present Illness	Survival After Admission (Mo)
9	Female	190/130	180/130	Periodic attacks of headache and projectile vomiting ×5 years; nine convulsions 5 months ago	Alive
15	Female	200/140	170/115	Headache ×4 years, albuminuria ×2 years; left facial paralysis ×2 months	11
18	Male	240/180	220/140	Periodic severe headache ×3 years; convulsions; blurred vision; albuminuria ×8 months	Alive
19	Female	270/150	220/150	Headache, hypertension, and periodic blurring of vision ×2 years; dyspnea and nervousness ×1 year; albuminuria ×8 months	1.5

Modified from Keith N, Wagener H, Kernohan J, et al: The syndrome of malignant hypertension, *Arch Intern Med* 41:141-188, 1928.
DBP, Diastolic blood pressure; *SBP*, systolic blood pressure.

Box 73–1 Common Sequelae of End-Organ Damage During Hypertensive Emergencies

Encephalopathy
Acute left ventricular failure
Myocardial infarction
Unstable angina
Pulmonary edema
Eclampsia
Stroke
Head trauma
Life-threatening bleeding
Aortic dissection

a definitive diagnosis such as with HTN. Rather, the goal of classifying children as prehypertensive is to identify those who may be at risk for developing HTN in the near future in the hopes that interventions may prevent its establishment. Note that these definitions refer to threshold BPs measured in a resting, nonstressed child; elevations in BP are commonly associated with a patient's stress response, which will normalize when the stress is eliminated. Nevertheless, the health care community has performed poorly in managing patients who have already been diagnosed with HTN, and vigilance must be practiced across all age groups.[19-21]

The clinical state of a "malignant sclerosis" or "bösartig hypertension" was first reported by Volhard and Fahr in 1914 in patients with mainly HTN and "hypernephrosclerosis."[17] In 1928, Keith et al: described 81 cases of what was termed "the malignant hypertension syndrome" that was a diagnosis made before end-stage damage of retinal, cerebral, cardiac or renal function occurred.[22,23] It was also the first description of pediatric patients with significantly uncontrolled hypertension (Table 73-1). The term "hypertensive crisis or emergency" is defined as a rapid and elevated level of either systolic or diastolic BP that is associated with end-organ damage (Box 73-1).[24-26] The terms "hypertensive crisis" and "hypertensive emergency" have been used interchangeably in the literature; "hypertensive emergency" is used in this chapter. Organs commonly affected include the central nervous system (CNS) (hypertensive encephalopathy, retinal vasculopathy-induced visual changes, cerebral infarction, and hemorrhage); the cardiovascular system (congestive heart failure, myocardial ischemia, aortic dissection); and the kidneys (proteinuria, hematuria, and acute renal insufficiency). The term "hypertensive urgency" is reserved for the condition where end-organ damage has not yet occurred despite an increase in BP.[25,26] Historically, a patient with a hypertensive urgency could be managed with oral medications and the BP corrected over a 24-hour period.[27] In contrast, a patient with a hypertensive emergency requires parenteral therapy and continuous BP monitoring.[27]

Etiology and Evaluation

Hypertension may be either primary (essential) or secondary to another underlying medical condition. While primary HTN is unusual in the PICU, its frequency is increasing with the current epidemic of obesity, although hypertensive urgency and emergency are almost always secondary to another condition.[16] Children with primary HTN are frequently overweight and have positive family histories for HTN and cardiovascular disease. The prevalence of HTN increases progressively with a rise in body mass index, with approximately 30% of overweight children (body mass index >95th percentile) exhibiting hypertension.[28] Being overweight and hypertensive are signs of the insulin-resistance syndrome or metabolic syndrome, a condition associated with multiple metabolic risk factors for cardiovascular disease as well as type 2 diabetes.[29]

Secondary causes of HTN can be both transient and sustained. The most common reasons for elevated BP in a critical care unit are inadequately treated pain and agitation. Without a high degree of suspicion, this can be difficult to detect, particularly if neuromuscular blockade is administered. Tachycardia as well as eye tearing with noxious interventions are two useful clues to this condition. Drug-induced HTN is also common in the critical care setting, especially when high-dose corticosteroids are used in patients with organ transplantation and other immunologic conditions. A number of other drugs associated with elevated BP are listed in Box 73-2. A review of all medications taken by the patient, as well as considering illicit drug use, is indicated for all patients with an elevated BP. A patient's fluid balance for several days also should be reviewed when HTN develops while in the ICU. Apparently innocuous discrepancies between input and output for a single day can cumulatively produce significant fluid overload after several days, although this alone is not typically enough to cause HTN in the absence of other renal, cardiovascular, or CNS problems that raise systemic vascular resistance

Box 73–2 Causes of Hypertension in Children

Error in BP reading
Essential hypertension
Secondary hypertension
Renal diseases
- Acute GN (postinfectious, tubulointerstitial, rapidly progressive GN)
- Acute tubular necrosis
- Chronic glomerulonephritides
- Chronic pyelonephritis and reflux nephropathy
- Chronic renal failure
- Congenital renal anomalies (dysplasia)
- Hemolytic uremic syndrome
- Henoch-Schönlein purpura nephritis
- Nephrotic syndrome (if hypervolemic)
- Inherited parenchymal disease (ADPKD, ARPKD)
- Obstructive uropathy
- Renal trauma
- Relapse of nephritis associated with systemic disease (lupus, vasculitis)

Vascular disorders
- Arteriovenous fistulae
- Coarctation of the aorta
- Neurofibromatosis
- Patent ductus arteriosus
- Renal artery compression (abdominal compartment syndrome)
- Renal artery stenosis (fibromuscular dysplasia, congenital)
- Renal transplant arterial stenosis
- Renal vein/artery thrombosis/embolization
- Trauma

Neurologic causes
- Dysautonomia (Riley-Day syndrome)
- Guillain-Barré syndrome
- Increased intracranial pressure (tumor, hydrocephalus)
- Poliomyelitis
- Seizures
- Spinal cord injury

Endocrine disorders
- Adrenal hemorrhage
- Congenital adrenal hyperplasia (11-hydroxylase deficiency, 17-hydroxylase deficiency)
- Conn syndrome
- Cushing disease and syndrome
- Hyperparathyroidism
- Hyperthyroidism

Renal tumor associated
- Wilms tumor
- Hamartomas
- Hemangiopericytoma

Catecholamine-secreting tumors
- Neuroblastoma
- Paraganglioma
- Pheochromocytoma

Low-renin hypertension
- Apparent mineralocorticoid excess
- Glucocorticoid remediable aldosteronism
- Gordon syndrome
- Liddle syndrome

Drug-induced hypertension
- Drug withdrawal (narcotic, benzodiazepine)
- Cyclosporine and tacrolimus
- Erythropoietin
- Glucocorticoids and mineralocorticoids
- Heavy metals
- Maternal drug use (cocaine, heroin)
- Nonsteroidal antiinflammatory agents
- Oral contraceptive agents
- Rebound after withdrawal of antihypertensives (especially clonidine and β-blockers)
- Sympathomimetic drugs (amphetamines, cocaine, ephedrine, lysergic acid diethylamide, phenylephrine)
- Theophylline/caffeine

Diet-mediated causes
- Alcohol
- Caffeine
- Licorice

Miscellaneous disorders
- Bronchopulmonary dysplasia
- Burns
- Congenital rubella syndrome
- Hypercalcemia
- Orthopedic procedures (leg traction)
- Polycythemia
- Preeclampsia/eclampsia
- Sickle cell anemia
- Stevens-Johnson syndrome
- Williams syndrome

ADPKD, Autosomal dominant polycystic kidney disease; *ARPKD,* autosomal recessive polycystic kidney disease; *BP,* blood pressure; *GN,* glomerulonephritis.

(SVR), cardiac output (CO), or both. Finally, postoperative HTN is common in the ICU setting, occurring in up to 75% of patients. Initially, factors such as hypoxia, hypercarbia (through its sympathomimetic effects), and pain should be promptly and adequately addressed.[30] Afterward, pharmacotherapy is indicated if HTN is refractory or sustained despite adequate ventilation, sedation, and analgesia.

Box 73-2 shows a list of other potential causes of transient and sustained HTN in children. Evaluation should be targeted at both identifying the etiology as well as any potential signs of injury to the cardiovascular, neurologic, renal, or ocular systems. A detailed history and thorough examination should be obtained for all patients, with special care paid to findings suggestive of an underlying hypertensive disorder or end-organ damage (Table 73-2). Signs and symptoms are often reflective of the severity and rapidity of onset of HTN. Chronic HTN is more commonly asymptomatic or characterized by low-grade generalized symptoms such as fatigue and recurrent headaches. Neurologic symptoms, however, are the most common presenting complaints in children with hypertensive emergency; congestive heart failure and renal insufficiency also are reported.[16] Hypertensive encephalopathy typically manifests as a severe headache with dizziness and changes in mental status ultimately culminating as seizures; other reported symptoms include facial palsies and visual changes that may lead to blindness and coma.[31-33] An abrupt presentation of chest or back pain along with HTN should trigger the consideration of aortic dissection.[34] Rarely, children can present with abdominal pain or vomiting as the only symptoms of a hypertensive emergency.[35]

Table 73–2 History and Physical Examination Findings in HTN

Finding	Possible Significance
HISTORICAL FINDINGS	
Complaint/Review of Systems	
Headaches, dizziness, epistaxis, visual changes	Nonspecific with respect to etiology of HTN
Abdominal/flank pain with hematuria	Renal artery or vein thrombosis
Hematuria, swelling, decreased urine output	Acute glomerulonephritis
Dysuria, frequency, urgency, nocturia, enuresis	Underlying renal disease
Joint pains/swelling, edema, rashes	Autoimmune mediated disease/glomerulonephritis
Weight loss, sweating, flushing, palpitations	Pheochromocytoma or hyperthyroidism
Muscle cramps, weakness, constipation	Hypokalemia associated with hyperaldosteronism
Delayed puberty	Congenital adrenal hyperplasia
Snoring	Sleep apnea
Prescription, over-the-counter, or illicit drug use	Drug-induced HTN
Medical History	
Umbilical artery catheterization	Renal artery thrombosis/renal embolus
Previous urinary tract infections	Renal scarring
Thyroid cancer, neurofibromatosis, von-Hippel Lindau disease	Pheochromocytoma
Family History	
HTN	Inherited forms of hypertension (AME, Gordon syndrome, Liddle syndrome, GRA), essential HTN
Renal disease	Polycystic kidney disease, Alport syndrome
Tumors	Familial pheochromocytoma, multiple endocrine neoplasia type II
PHYSICAL EXAMINATION FINDINGS	
Vital Signs	
Tachycardia	Hyperthyroidism, pheochromocytoma, neuroblastoma, primary HTN
Bradycardia	Increased intracranial pressure (tumor, hydrocephalus)
Drop in blood pressure from upper to lower extremities	Coarctation of aorta
General	
Growth retardation	Chronic kidney disease
Truncal obesity	Cushing disease, insulin resistance
Head and Neck	
Moon facies	Cushing disease
Elfin facies	Williams syndrome
Proptosis/goiter	Hyperthyroidism
Web neck	Turner syndrome
Adenotonsillar hypertrophy	Sleep disorders
Fundal changes	Chronic or severe HTN
Cardiovascular	
Friction rub	Systemic lupus erythematosus, collagen vascular disease, uremia
Apical heave	Left ventricular hypertrophy
Disparity in pulses	Coarctation
Lungs	
Crackles/rales	Heart failure
Abdomen	
Masses	Obstructive nephropathy, Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidney disease
Hepatomegaly	Heart failure

Continued

Table 73–2 History and Physical Examination Findings in Hypertension—cont'd

Finding	Possible Significance
Bruit	Renal artery stenosis, abdominal coarctation
Genitalia	
Ambiguous, viralized	Congenital adrenal hyperplasia
Extremities	
Edema	Underlying kidney disease
Joint swelling	Autoimmune disease
Rickettsial changes	Chronic kidney disease
Dermatologic	
Neurofibromas	Neurofibromatosis
Tubers, ash leaf spots, adenoma sebaceum	Tuberous sclerosis
Bronzed skin	Excessive adrenocorticotropic hormone
Acanthosis nigricans	Insulin resistance/metabolic syndrome
Striae, acne	Cushing disease
Rashes	Vasculitis/nephritis
Needle tracks	Drug-induced HTN
Neurologic	
Mental status changes	Severe HTN
Cranial nerve palsy	Severe HTN

AME, Apparent mineralocorticoid excess; *GRA,* glucocorticold-remediable aldosteronism.

Physical examination should include BP measurements in all four extremities as a screening for coarctation of the aorta, which should be suspected if upper extremity pressures are higher than lower extremity pressures and lower extremity pulses are weak or absent. Special attention also should be paid to pulse rate because HTN with associated bradycardia is suggestive of increased intracranial pressure (ICP). Rapidly lowering BP in this scenario could lead to decreased cerebral perfusion and its associated sequelae. A thorough cardiac examination to identify signs of heart failure, a search for carotid or abdominal bruits, a funduscopic examination, evaluation of cutaneous lesions, and a neurologic examination also are essential in the initial evaluation of patients with severe HTN.

Initial laboratory studies for all patients should include electrolytes, blood urea nitrogen, creatinine, complete blood cell count with peripheral smear, and urinalysis. Renal disease is the most common cause of secondary HTN in children, and both chronic and acute renal conditions may present with severe HTN. Anemia associated with chronic disease or a microangiopathic anemia resulting from disseminated activation of the coagulation system or hemolytic uremic syndrome may be seen as well. Finally, a hypokalemic metabolic alkalosis may develop with volume depletion and secondary hyperaldosteronism. This condition also may be seen in children with inherited monogenic forms of HTN.[36]

Renal ultrasonography is indicated for most patients to evaluate for renal parenchymal lesions such as small scarred kidneys, polycystic kidney disease, or other structural anomalies. Doppler evaluation of blood flow to the kidneys also should be performed, although this evaluation is less sensitive than in adults at identifying subtle renal artery stenosis in smaller children. Although both computed tomography (CT) and magnetic resonance angiography have shown some promise as a screening tool for renal artery stenosis, angiography remains the gold standard for identifying this lesion.[37-39] Further imaging such as a dimethylsuccinic acid (DMSA) scan may be indicated in children who are suspected of having renal scarring; plasma renin and aldosterone levels also may help discern the etiology of HTN, although typically they are not rapidly available.

A chest radiograph and electrocardiogram should be done at presentation to look for signs of heart failure and electrocardiographic evidence of ventricular hypertrophy, strain, or both. An echocardiogram is now recommended for all children with HTN to assess for congenital anomalies such as a coarctation of the aorta as well as for left ventricular hypertrophy, a common finding in children with long-standing HTN that correlates with blood pressure severity.[40-42] An echocardiogram may not need to be performed emergently if the child has no other signs of heart failure.

A head CT scan should be done in patients with concern for increased ICP. In children with cerebral edema or increased ICP, increased BP may develop as a strategy to preserve cerebral perfusion due to the increased resistance to cerebral blood flow. Initially, a child with traumatic brain injury will often maintain sufficient cerebral blood flow over a range of BPs because of the brain's capacity for autoregulation, as depicted in Figure 73-1.[43] However, if the resistance to cerebral blood flow increases, such as when ICP rises from swelling, then the patient may compensate through cerebral vasodilation or increased CO to meet the metabolic needs of the brain. Cerebral vasodilation, however, will only increase ICP further. To attempt to maintain adequate cerebral blood flow, the perfusion pressure must increase as noted in the following mathematical relationship: Cerebral perfusion pressure = Mean arterial pressure (MAP) − ICP. In such situations, it is prudent to undertake measures

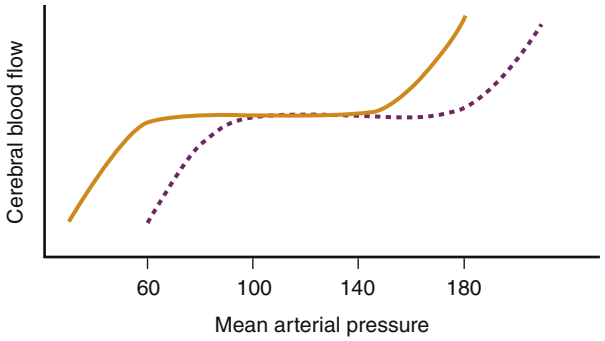

Figure 73–1. Cerebral blood flow autoregulation. Schematic representation of autoregulation of cerebral blood flow (CBF) in normotensive (*solid line*) and hypertensive (*dashed line*) patients. In both groups, within a range of about 100 mm Hg, increases or decreases in mean arterial pressure are associated with maintenance of CBF because of appropriate changes in arteriolar resistance. Changes in blood pressure outside this range lead to reduction (hypotension) or an elevation (with marked hypertension) in CBF. It is important to understand that hypertensive encephalopathy (increased blood flow with pressures exceeding the autoregulatory range) may occur with a mean arterial pressure below 200 mm Hg in the normotensive individual, but it may require a much higher mean arterial pressure in patients who have sustained hypertension. Conversely, lowering blood pressure to the "normal range" of a mean arterial pressure of 80 mm Hg (equivalent to 120/80 mm Hg) may produce a clinically significant decrease in CBF, especially in patients with preexisting cerebrovascular stenosis. *(Modified from Posner J, Saper C, Schiff N, et al: Examination of the comatose patient. In* Plum and Posner's diagnosis of stupor and coma, *ed 4, Oxford, UK, 2007, Oxford University Press. Reprinted by permission of Oxford University Press, Inc.)*

to control brain edema through hyperosmolar therapy, judicious sedation/analgesia, and minimizing the noxiousness of laryngoscopy while securing the airway to control oxygenation and ventilation. Efforts to directly lower systemic BP can undermine the patient's ability to support injured but viable cerebral tissue.

A magnetic resonance image also may be considered for patients with other neurologic symptoms. The most common brain-associated finding in children with a hypertensive emergency is posterior reversible encephalopathy syndrome (PRES). PRES is a syndrome characterized by the sudden onset of HTN, headaches, altered mental status, seizures, visual loss, and even cortical blindness.[156] Neuroimaging studies during PRES typically demonstrate cerebral edema affecting the white matter in a parieto-occipital distribution.[157] PRES is associated with immunosuppressive therapy (especially cyclosporine and tacrolimus), acute glomerulonephritis, eclampsia of pregnancy, and hypertensive encephalopathy (Figure 73-2).[44] Hypertensive emergencies and tonic-clonic seizures were presenting features in 59% of renal transplant patients who were found to have PRES on further work-up.[45] In addition, nearly half of the patients with PRES had no history of uncontrolled chronic HTN.[45] This constellation of symptoms and pathology, which has also been called reversible posterior leukoencephalopathy by other authors,[46] typically resolves once the HTN is treated, but it may take weeks to months for the imaging abnormalities to normalize.[45]

Pregnancy associated with preeclampsia also must be considered in patients experiencing a hypertensive emergency. Preeclampsia is a state of hypertensive proteinuria in a

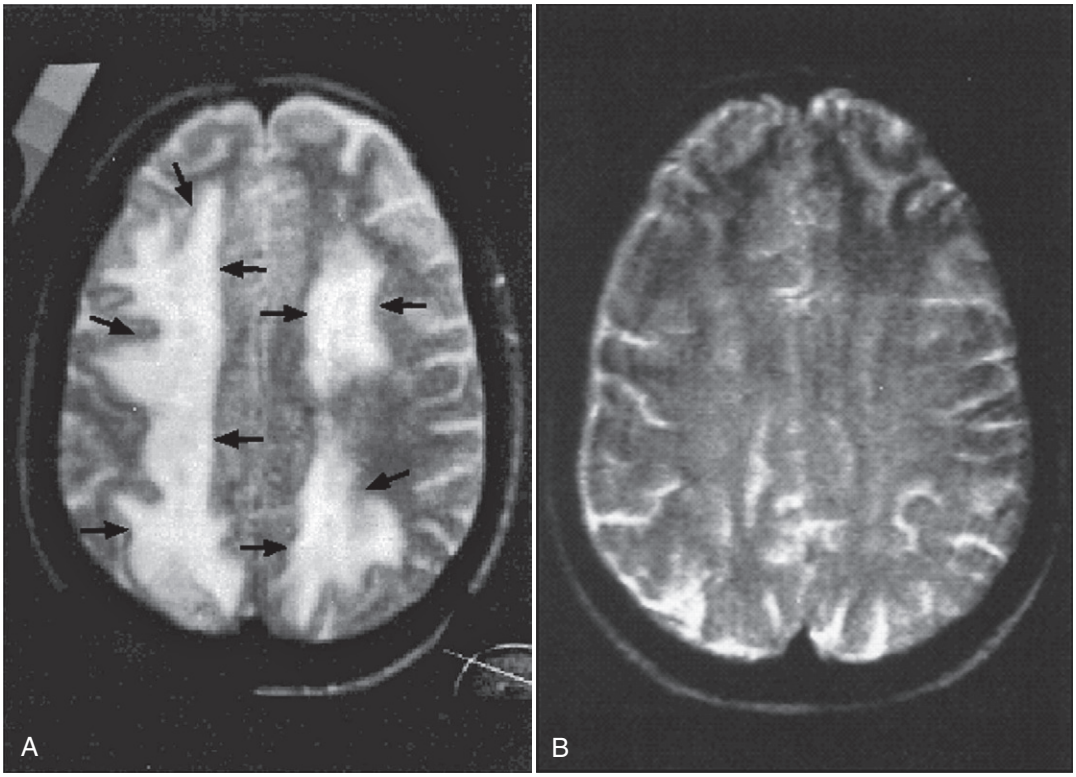

Figure 73–2. Posterior reversible encephalopathy in a patient with a renal transplant receiving cyclosporine and experiencing severe hypertension. **A**, The initial image shows widespread white-matter signal abnormalities (*arrows*). **B,** A follow-up scan shows that the abnormalities have resolved. *(From Hinchey J, Chaves C, Appignani B, et al: A reversible posterior leukoencephalopathy syndrome,* N Engl J Med *334[44]:494-500, 1996. Copyright 1996 Massachusetts Medical Society. All rights reserved.)*

pregnant woman who is at greater than 20 weeks' gestation.[47] Clinically, the classic triad of preeclampsia consists of HTN, proteinuria, and edema, although now it is accepted that edema should no longer be considered a prerequisite for making the diagnosis of preeclampsia.[47] Under these circumstances, an elevated BP separated by a minimum of 4 hours (maximum 7 days) is considered adequate for making a diagnosis for HTN (>140/90 mm Hg) or severe HTN (>160/100 mm Hg). Proteinuria is considered significant when two random urine samples collected at least 4 hours (but <7 days) apart have a level of 30 mg/dL or higher (1+) or 300 mg or more of protein are present in a 24-hour urine collection.[47] In the absence of proteinuria, pregnancy-induced HTN, gestational HTN, or chronic HTN must be considered. The goal of managing preeclampsia is to meticulously control the blood pressure in order to protect the fetus from insufficient placenta-utero blood flow (via overly aggressive antihypertensive therapy) and to avoid eclampsia (the condition characterized by tonic-clonic seizure activity culminating in coma).

Further evaluation for the cause of symptomatic HTN should be targeted based on history and physical findings. In many cases thyroid studies, a drug screen, cortisol levels, and plasma or urinary catecholamines/metanephrines may help elicit the cause of elevated BP.

Pathophysiology

MAP is approximately equal to the product of CO and SVR, as expressed mathematically by the following equation: MAP ≅ CO × SVR, where *MAP* is the mean arterial pressure, *CO* is the cardiac output, and *SVR* is the systemic vascular resistance (central venous pressure should be subtracted from the MAP in this equation but is usually so small it can be ignored). Organ-specific blood flow can be substituted for CO, such as considering the effects of increased resistance to flow from intracranial HTN in the CNS. Thus factors that increase either CO or SVR lead to elevated BP if the other does not decrease proportionally. In addition, chronically, these factors have an interdependent interaction that is still poorly understood. For example, while the initiating event leading to HTN may cause a rise in CO, a compensatory rise in peripheral vascular resistance often develops that may persist even after CO returns to baseline.

A hypertensive emergency can occur in patients with essential HTN, secondary HTN, or without any history of HTN.[24] The mechanisms responsible for generating and maintaining a hypertensive crisis continue to be elucidated. What seems plausible is that there is a triggering event that precipitates a dramatic increase in BP over a short period in a patient who is hypertensive at baseline. This event then leads to further arteriolar damage that prolongs the hypertensive state. The foundation for understanding this process can be drawn from knowledge regarding the existence of arteriolar damage caused by the mechanical stresses of long-standing HTN.[48] In the presence of systemic HTN, endothelial cell damage occurs, encouraging platelet activation, aggregation, and fibrin deposition followed by intravascular hemolysis.[48] Over time, the arterioles exhibit fibrinoid necrosis with fine subendothelial lipid inclusions and hyaline thrombi formation with little evidence of an inflammatory infiltrate.[49]

Endothelial Homeostasis

Endothelial health plays a central role in the HTN continuum. The endothelium is on the receiving end of the excessive pressures and shear stress generated from high blood flows along with concomitant increased resistance imparted by the vascular architectural scaffolding and surrounding smooth muscle cells. Aside from structural trauma, endothelial cell function is also affected. For instance, the stressed endothelial cell increases intracellular levels of nuclear factor-κB (NF-κB).[50] In turn, NF-κB results in expression of vascular cell adhesion molecule-1 that binds to monocytes and T-lymphocytes (facilitating invasion through the vascular wall that normally does not occur) and contributes to the inflammatory state.[50,51] The proinflammatory mediators interleukin-1β and tumor necrosis factor-α also induce vascular cell adhesion molecule-1 expression in endothelial cells through the NF-κB pathway.[50] In addition to vasoconstrictor mediators, the coagulation system also has been implicated in the HTN story; injured endothelial cells locally activate the coagulation cascade and promote platelet aggregation that leads to a prothrombotic surface.[24,50,52,53]

Adults with essential HTN who experienced a hypertensive emergency demonstrated a significant decline in BP when given L-arginine (a precursor of nitric oxide [NO]) compared with patients who also had essential HTN but had not experienced a hypertensive emergency event. This observation underscores the importance of the endothelium in the pathogenesis of a hypertensive emergency because an intact functional endothelial cell surface is necessary to respond to L-arginine.[54] Von Willebrand factor (a surface marker of endothelium), P-selectin (platelet activation), and fibrinogen serum levels were all increased in hypertensive adult patients with a hypertensive emergency compared with control subjects with HTN, suggesting that alterations in the homeostasis of the endothelial and/or the coagulation system occur during a hypertensive emergency.[55]

Hemodynamics of the Kidney

Regulation of sodium, the principal extracellular solute, controls extracellular fluid volume. As extracellular fluid volume increases, BP increases, particularly if SVR simultaneously increases in response to angiotensin II, sympathetic nervous system activation, and increased vasopressin release that often accompany renal dysfunction. In the normal kidney, an increase in BP augments renal excretion of sodium and water, which are respectively termed *pressure natriuresis* and *pressure diuresis*. With prolonged HTN, extracellular fluid may be depleted, leading to a somewhat paradoxical state of HTN and hypovolemia. In addition to the hydrostatic effects of increased BP on the glomerulus, a number of vasoactive substances may alter the glomerular filtration rate and renal blood flow by modulating resistances of the afferent and efferent arterioles, which affects the hydrostatic driving pressure at the glomerulus level.

The Autonomic System: Sympathetic Activation

A common cause of increased CO is activation of the sympathetic nervous system, often in concert with an increase in intravascular volume. At the same time, sympathetic nervous

system activation further increases SVR, exacerbating the rise in BP. The therapeutic approach to HTN depends on reducing SVR and often suppressing or reducing sympathetic nervous system activation. Without the latter being suppressed, the drop in SVR mediated by a vasodilator may be compensated by an increase in sympathetic activation with a resultant increase in CO and no net reduction in BP.

Renin-Angiotensin System

The renin-angiotensin system is thought to play a prominent role in many patients during a hypertensive emergency.[48,52,56] Renin is a proteolytic enzyme synthesized in the juxtaglomerular cells of the afferent renal arterioles that cleaves angiotensinogen (an α_2 globulin synthesized in the liver) to create angiotensin I (a decapeptide). In turn, angiotensin-converting enzyme (ACE) coverts angiotensin I to angiotensin II (an octapeptide), which acts at the angiotensin type 1 receptor (a G-coupled receptor found in renal afferent and efferent arterioles) to cause vasoconstriction, increased aldosterone release, and enhanced sodium and water reabsorption.[57] Interestingly, ACE also degrades the vasodilator bradykinin. Increased serum renin levels can reflect a primary condition, such as renovascular disease, or be secondary to renal parenchymal ischemia, hypotension, hypovolemia, increased sympathetic effects, β-adrenergic agonists, or a combination of these factors.[56,57] Ultimately, increased renin levels raise BP through a number of mechanisms primarily mediated through angiotensin II. Aside from its vasoconstrictive properties, angiotensin II increases the expression of aldosterone that leads to increased renal sodium and water retention, thus augmenting CO by increasing intravascular volume. Angiotensin II also induces the expression of interleukin-6 and NF-κB that in turn leads to elevated levels of tumor necrosis factor-α and increases nicotinamide adenine dinucleotide phosphate oxidase activity; the latter generates reactive oxygen species, promoting oxidative stress, and inhibits the cytokine-mediated activation of inducible-nitric oxide synthase (iNOS) that attenuates vasodilation.[58-61] Over time the collective result of these processes is enhanced and sustained endothelial cell trauma, vascular dysfunction, and ultimately end-organ damage.

Focal impairment of renal blood flow with release of renin and a subsequent increase in circulating angiotensin II underlie many types of childhood HTN.[62] For example, thromboemboli from umbilical or central vascular catheters may impair renal perfusion, and coarctation of the aorta is associated with high peripheral renin activity.[62,63]

Nitric Oxide

NO, now recognized as a ubiquitous biologic effector, is a labile, short-lived chemical produced from arginine via NO synthases.[64-66] These synthases are distinguished by cellular distribution and by the requirement for calcium as a cofactor. The constitutive isoform of NOS is believed most responsible for basal vasomotor tone, although iNOS may have a role. NO is released continuously from arteries and arterioles but not from veins. In addition, other mediators function through the NO system. For instance, bradykinin stimulates the release of NO to produce vasodilation. NO diffuses from the endothelium to the vascular smooth muscle cell, where it produces its vasodilatory effect in part by increasing the intracellular concentration of cyclic guanosine monophosphate (cGMP) through stimulation of soluble guanylate cyclase. NO that diffuses from the local endothelial environment reacts with hemoglobin, forming nitrosohemoglobin and methemoglobin. Thus HTN need not be attributed only to a direct vasoconstrictor effect but also may be related to loss of basal NO vasodilation. Therapeutic agents such as sodium nitroprusside and nitroglycerin produce their systemic vasodilator action by stimulating NO production (see HTN management section that follows).

Hypervolemia

An acute increase in intravascular volume is a frequent cause of acute decompensation of BP control in a patient with chronic HTN, particularly in the setting of stimuli that increase sympathetic nervous system and/or renin-angiotensin-aldosterone system activation. Although hypervolemia is a common cause of hypertensive urgencies or emergencies, pressure diuresis may render some patients relatively hypovolemic, producing hemoconcentration and further marked activation of the renin-angiotensin-aldosterone system.[56] Further volume depletion may actually worsen HTN by stimulating a further increase in SVR with the potential for organ ischemia. Thus diuretics and fluid restriction are not standard therapy for patients who present in hypertensive crisis; they are reserved for patients with clinically apparent fluid overload.[53,56,67]

Clinical Symptoms

The presentation of a patient with a hypertensive emergency depends on underlying medical conditions, baseline systemic BP, rate of rise and degree of BP elevation, as well as effects on end organs. The range of both SBPs and DBPs can be quite large in patients with hypertensive emergency, but long-standing baseline systemic HTN is a common attribute in many cases.[48] Headache is a common presenting complaint in patients with a hypertensive emergency. Approximately 60% of patients had a headache during presentation and an additional 28% reported dizziness.[68] Visual impairment is another common presenting complaint in patients with a hypertensive emergency. In children, essential HTN was associated with some form of retinopathy diagnosed by means of retinal photographs in up to 50% of patients[69]; however, in a separate study, only 8.6% had evidence of retinopathy diagnosed with an ophthalmoscope.[70] Nevertheless, evidence indicates that the pattern of retinal lesions can offer some information related to the onset of HTN. For instance, generalized arteriolar narrowing and arteriovenous nicking were associated with long-standing systemic HTN, whereas focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton-wool spots were indicative of recent significant increases in BP.[71]

From a pathophysiological perspective, the retinal changes associated with HTN can proceed through a few stages. The first stage (vasoconstrictive stage) is characterized by vasospasm (i.e., increased arteriolar tone and narrowing of arterioles). In time, the retinal vasculature undergoes intimal thickening, medial wall hyperplasia, and hyaline degeneration.[71] If allowed to progress, then the damage proceeds to the sclerotic stage, which is represented by generalized narrowing of retinal arterioles, arteriovenous nicking (restricted junctions between the arterioles and venules), and an abnormal arteriolar light

reflex characterized as "copper wiring" or widening and accentuation of the central light reflex.[71] Some cases evolve into the exudative stage that is attributed to a breakdown of the blood-retina barrier with smooth muscle and endothelial cell necrosis, ischemic changes, and extravasation of blood. Clinically this results in microaneurysms, hemorrhages, hard exudates, and cotton-wool spots.[71] During a hypertensive emergency, papilledema may be evident.

Perhaps the strongest link between HTN and consequent retinal changes has to do with their relationship with stroke risk. The retinal blood flow shares embryologic, anatomic, and physiologic attributes with the cerebral circulation.[71] In fact, some retinal lesions such as retinal hemorrhages, microaneurysms, and cotton-wool spots were associated with newly diagnosed strokes in one multicenter cohort trial of adults.[72]

In children with HTN left ventricular hypertrophy (LVH) often commonly develops, with obesity being the most prevalent associated factor.[73,74] The incidence of LVH is higher in children with established HTN as well as in patients who have HTN confirmed with 24-hour ambulatory BP monitoring.[42] The correlation between HTN and LVH is lower when only casual BP measurements are used to diagnose HTN.[75] Fifteen percent to 41% of children with essential HTN have LVH, depending on whether one uses adult or pediatric criteria, respectively.[41] Furthermore, geometric features of the left ventricle demonstrate ethnic tendencies such as concentric LVH that occurs more frequently in Hispanic and African American children.[41] Eight percent of patients with a hypertensive emergency experienced other cardiac manifestations, such as acute heart failure with pulmonary edema.[76]

Children with HTN can exhibit evidence of renal damage such as hematuria, albuminuria, and uremia. In fact, the degree of proteinuria can be correlated with the severity of HTN, as seen in Figure 73-3. Attempts to determine the renal effects of severe HTN is fraught with difficulties because of the frequent association of renal parenchymal and/or renovascular disease with systemic HTN. Moreover, hypertensive pathology is not usually limited to a single organ like the kidney; other end-organ abnormalities usually can be seen, such as left ventricular hypertrophy and neurologic sequelae (such as mental status changes, seizures, and cerebrovascular accidents).[77] Nevertheless, children with HTN resulting from vasculitis have been found to have nephrotic range proteinuria, microscopic hematuria, elevated creatinine levels, and diminished glomerular filtration rates.[77-79] Renal pathology may reveal renal arterial stenosis and small kidney as well as histologic evidence of arteriolar sclerosis and focal glomerulosclerosis.[77]

Illicit cocaine abuse in adults has provided an interesting window on the acute renal effects associated with a hypertensive emergency.[80] Clinically, elevated serum creatinine and urea nitrogen levels were found to be accompanied with segmental glomerular fibrinoid necrosis and prominent fibrinoid necrosis of afferent and efferent arterioles on biopsies.[80]

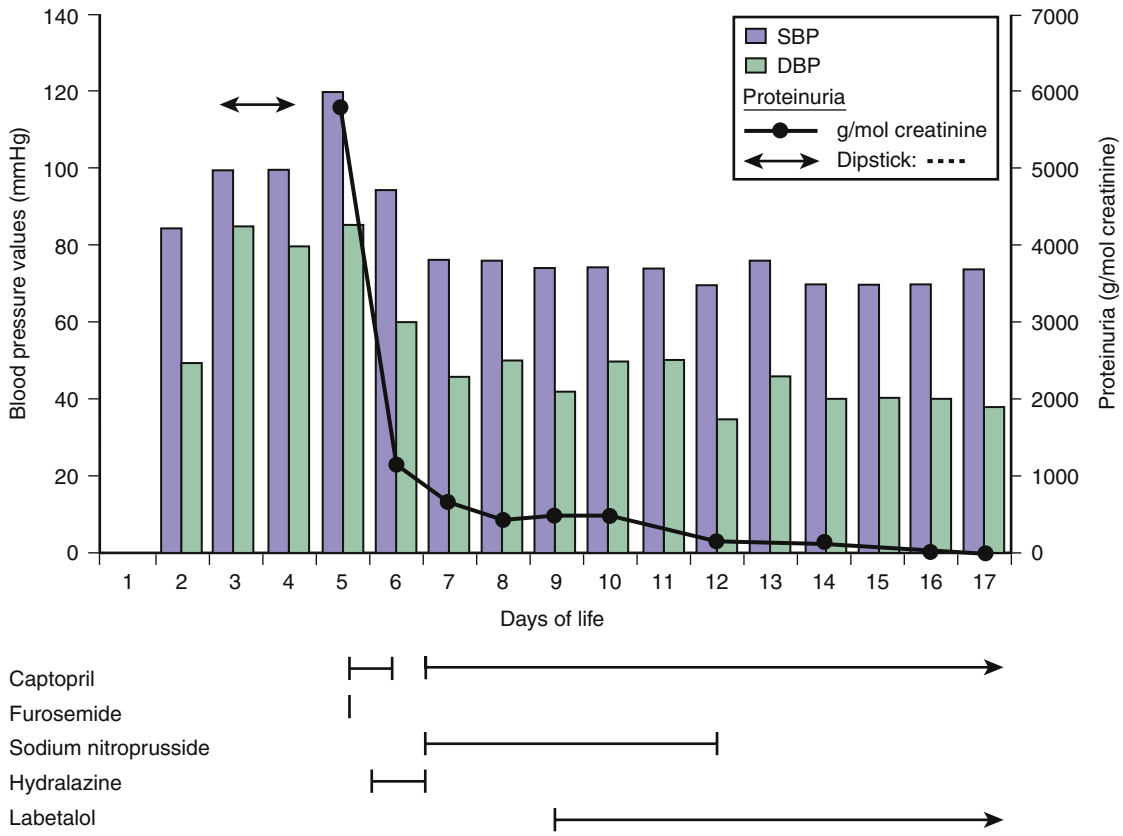

Figure 73–3. Variation of proteinuria with blood pressure control. Effects of nitroprusside in conjunction with other agents in the control of systemic hypertension in an infant with renal artery stenosis. The infant also had left ventricular failure that resolved according to echocardiography performed 3 months after discharge. *(From Cachat F, Bogaru A, Micheli JL, et al: Severe hypertension and massive proteinuria in a newborn with renal artery stenosis,* Pediatr Nephrol *19:544-546, 2004.)*

Management Strategy

Monitoring

The most critical component of identifying and monitoring hypertensive emergencies is accurately measuring BP. Both noninvasive and invasive techniques may be used in the ICU setting and are commonly used together to complement the strengths and weaknesses of each method. The main techniques used to determine BP in the ICU are the auscultatory method, oscillometric method, Doppler method, and invasive hemodynamic monitoring.

Auscultatory, oscillometric, and Doppler BP methods are noninvasive techniques that are based on the return of blood flow through a major artery after compressing it with an inflatable cuff. *Auscultatory methods* require an observer to listen to the Korotkoff sounds generated as the cuff deflates. Korotkoff sounds 1 and 5 should be used to represent SBP and DBP, respectively. It should be noted that current normal values were generated using this technique over the brachial artery and it is thus the preferred method for diagnosing chronic HTN. To obtain accurate measurements, it is important that the appropriate cuff size be utilized, and it should cover approximately 75% of the upper arm.[16] *Oscillometric techniques* utilize a similar technique except that a MAP is determined from oscillometric wave forms generated as blood flow returns through the artery. SBP and DBP are then calculated using a proprietary formula specific to the monitor. For this reason, it is important to ensure that the specific oscillometric device has been validated in the patient population in which it is being used.[16] *Doppler devices* use changes in ultrasound frequency to infer velocity of blood flow. The Doppler shift corresponds to the turbulent flow, as signified by the Korotkoff sounds, that diminishes as laminar flow predominates.[81] As with the auscultatory method, selection of an appropriate cuff size is paramount.

Invasive arterial lines are fluid-filled tubes attached to a pressure transducer, a device consisting of a thin flexible diaphragm connected to a strain gauge and capable of converting the pressure transmitted to an electrical signal (see Chapter 21). The most common source of inaccuracy is the influence of electrical damping on reported BP. An overdamped signal underestimates both SBP and DBP, although MAP may be accurate. On the other hand, an underdamped system overestimates SBP, especially with a hyperdynamic circulation, but does not affect MAP.[82] This phenomenon is recognized as a narrow peaked pressure wave and wide pulse pressure. Moreover, invasive blood pressure measured in the lower extremity is higher than in the upper extremities because of the nature of BP wave transmission, which results in an increase in SBP reading the further away from the heart it is measured.[83]

Generally, children with sustained levels of HTN as seen in hypertensive emergencies need to be closely monitored in a controlled setting such as the ICU, and the ideal way to continuously follow BPs is with the aid of an indwelling arterial catheter. Arterial lines can be placed in a variety of locations, but usually they are placed in peripheral arteries that supply areas with robust collateral blood flow; common sites include the radial, dorsalis pedis, and posterior tibial arteries. As a rule, patients experiencing a hypertensive crisis need to have continuous intra-arterial BP monitoring because of the lability of BP when continuous medications are utilized. However, using noninvasive techniques to confirm that transduced values are accurate is a quite common practice because electrical damping of the transduced signal can cause inaccuracies in SBP and DBP, although MAP is likely to be less affected.

Pharmacotherapy

The therapeutic strategy for hypertensive emergencies depends on the clinical context of elevated BPs. Hypertensive children returning from surgery need to be adequately sedated and given sufficient analgesia postoperatively for comfort and to control sympathetic activation. It is not uncommon for children to return to recovery areas, floors, and ICUs with variable levels of anesthetics still circulating that can permit pain, anxiety, and emergence phenomena that could be accompanied with elevated BPs. This situation by no means minimizes the potential detrimental effects of severely elevated systolic or diastolic pressures if they are inadequately treated or ignored.

Initially, it is prudent to ascertain fluid status while determining the best approach to a hypertensive child. Some situations, such as the presence of pulmonary edema and renal failure, clearly identify the child with probable fluid overload conditions. On the other hand, other children with significant HTN exhibit a pressure-induced diuresis associated with secondary activation of the renin-angiotensin system during HTN, and these patients may need judicious volume replenishment while managing their HTN.

The child with altered mental status, unequal (anisocoric) pupils, and systemic HTN needs agents directed at managing increased ICP such as mannitol or hypertonic saline solution, along with careful rapid sequence intubation and controlled ventilation. The goal here is to prevent cerebral herniation and not to directly lower BP too rapidly, which may be deleterious.

Finally, the strategic pharmacologic goal for a patient experiencing a hypertensive crisis is to aim for a controlled decrease in BP as opposed to a sudden rapid fall. As a rule, one should aim to promptly lower the BP no more than 20% to 25% over 60 minutes in acute situations.[1] One group reported the occurrence of permanent neurologic deficits in adults treated with bolus antihypertensive therapy resulting in rapid BP reduction,[84] and similar catastrophes have occurred in children as well.[85,86]

Table 73-3 lists the attributes of specific antihypertensive medications while Table 73-4 suggests choices based on the etiology of HTN. The indications, pharmacology, adverse effects, and dosage are reviewed for the medications commonly used to treat hypertensive emergencies and urgencies in children.

Sodium Nitroprusside

Sodium nitroprusside (SNP) lowers systemic BP as an arteriolar (peripheral resistance vessel) and venous (peripheral capacitance vessel) dilator. Consequently, this effect often results in a reflexive tachycardia because of the fall in arteriolar BP. SNP lowers right atrial pressures through relaxation of venous capacitance vessels, thus increasing venous compliance. In addition, SNP reduces right ventricular afterload through its pulmonary arterial vasodilator activity.[87] Its potent pulmonary vasodilation inhibits hypoxic-mediated pulmonary vasoconstriction.[88] Generally, when used in a hypertensive emergency, SNP reduces CO in patients with normal left ventricular function through its venous pooling (e.g., increased

Table 73–3 Overview of Antihypertensive Agents

Drug	Mechanism	Dose	Route	Comments
Captopril	ACE inhibitor	Infants: 0.1–0.5 mg/kg/dose Child: 0.3–0.5 mg/kg/dose	Oral every 6–12 h	Contraindicated if obstruction to renal blood flow Monitor potassium (hyperkalemia risk) Cough and angioedema
Clonidine	Central α_2-adrenergic agonist	3–10 μg/kg/dose up to 25 μg/kg/day	Oral every 6–8 h	Caution if altered mentation Frequently causes sedation Useful when high sympathetic activity contributes to HTN
Diazoxide	Direct vasodilator	1–3 mg/kg (maximum 150 mg)	IV infusion; may repeat in 5–15 min	Hypotension and reflex tachycardia Hyperglycemia (inhibits insulin release)
Enalapril/ enalaprilat	ACE inhibitor	Enalapril: 0.1–0.5 mg/kg/day Enalaprilat: 5–10 μg/kg/dose	Oral: every 12 h IV: repeat every 6–8 h as needed	Same as captopril, except cough and angioedema are rare
Esmolol	Selective β_1-adrenergic blocker	500 μg/kg bolus followed by infusion of 125–250 μg/kg/min	IV bolus and infusion	Avoid in patients with asthma, chronic obstructive pulmonary disease, bradycardia and heart failure May cause profound bradycardia
Fenoldopam	Dopamine receptor agonist	0.2–1.2 μg/kg/min	IV infusion	Increases renal perfusion and urine output
Hydralazine	Direct vasodilator	0.1–0.2 mg/kg/dose initially (maximum initial dose 20 mg) up to 1.7–3.5 mg/kg/day divided in 4–6 doses	IV, IM	Give every 4 h by IV bolus Associated with lupus-like reaction in slow acetylators Reflex tachycardia and fluid retention common
Isradipine	Inhibition of L-type calcium channels	0.05–0.1 mg/kg/dose 3 to 4 times a day (maximum dose 0.8 mg/kg/day up to 20 mg/day)	Oral	Adverse effects include headache, dizziness, flushing, and tachycardia
Labetalol	Combined α- and β-adrenergic receptor blocker (7:1 relative potency for β- over α-antagonism)	0.2–1 mg/kg bolus (up to 40 mg initial dose); repeat 0.15 mg/kg every 5–15 min Infusion of 0.25–3 mg/kg/h	IV bolus or infusion	Contraindicated in asthma and overt heart failure May cause infusion-limiting bradycardia
Nicardipine	Inhibition of L-type calcium channels	0.5–5 μg/kg/min; increase by 0.5 μg/kg/min every 10–15 min as needed	IV infusion	May cause reflex tachycardia Should be infused centrally (high incidence of phlebitis peripherally)
Nifedipine	Inhibition of L-type calcium channels	0.25 mg/kg (maximum dose 10 mg)	Oral or feeding tube (not sublingual)	May cause significant decrease in blood pressure
Nitroprusside	Stimulation of NO in both arterial and venous circulation	0.5–10 μg/kg/min	IV infusion	Reflex tachycardia occurs frequently Monitor cyanide levels (or lactate) Consider coadministration of sodium thiosulfate
Nitroglycerin	Relatively selective NO stimulation in veins	0.5–5 μg/kg/min	IV infusion	No active metabolite, but relatively weak arterial dilator
Phentolamine	Nonselective α-adrenergic receptor blocker	0.05–0.1 mg/kg IV bolus 5–15 mg in adults	IV bolus	Used for pheochromocytoma
Trimethaphan camsylate	Blocks acetylcholine in both sympathetic and cholinergic ganglia reducing sympathetic activity; also a peripheral vasodilator	50–150 μg/kg/min	IV infusion	Reflex tachycardia May cause weakness and apnea with high doses

Medications are listed alphabetically and compiled from several sources.[16,152-155]
ACE, Angiotensin-converting enzyme; *IM,* intramuscular; *IV,* intravenous; *NO,* nitric oxide.

Table 73–4 Drug Selection Based on Etiology of Hypertensive Emergency/Urgency

Type of Emergency	Drugs of Choice	Alternate Second Line	Relative Contraindications
Hypertensive encephalopathy	Nicardipine Nitroprusside	Labetalol	Trimethaphan, clonidine
Intracranial hemorrhage	Labetalol Nicardipine	Nitroprusside	Vasodilators with reflex sympathetic stimulation (e.g., hydralazine, diazoxide, short-acting nifedipine)
Left ventricular failure and pulmonary edema	Nitroprusside ± loop diuretics ± ACE inhibitor	Nitroglycerin, fenoldopam	Labetalol, β-adrenergic blockers, verapamil
Adrenergic crisis	Nitroprusside ± β-blockers, phentolamine Clonidine (if centrally mediated HTN such as narcotic withdrawal)	Labetalol	Monotherapy with β-adrenergic blockers Contraindicated with cocaine-induced HTN
Dissecting aortic aneurysm	β-adrenergic blockers ± nitroprusside, trimethaphan	Labetalol, verapamil	Vasodilators with reflex sympathetic stimulation
Eclampsia	Hydralazine, labetalol nicardipine	Nifedipine	ACE inhibitor, nitroprusside
HYPERTENSIVE URGENCIES			
Acute renal failure	Labetalol, minoxidil ± β-adrenergic blockers	Nicardipine, diuretics, or hemofiltration (if volume overloaded)	Nitroprusside (to limit risk of thiocyanate toxicity)
Perioperative HTN (if not a result of pain, agitation)	Nitroglycerin, nitroprusside ± β-adrenergic blockers Enalaprilat or nicardipine for coarctation of the aorta	Labetalol, nicardipine, fenoldopam	

venous capacitance) effects. On the other hand, SNP improves CO in patients with poor left ventricular function and diastolic ventricular distension mainly by decreasing afterload by means of relaxing arteriolar resistance vessels.[89]

SNP has a prompt onset of action and a very short half-life, making it ideal for meticulous titration. Its prowess as a BP-lowering agent was first observed in the 1920s through the 1950s, but it was not commercially available until the mid 1970s.[87] Later, SNP was used not only in patients with severe HTN but also in the operative theater to induce arterial hypotension and in the hospital setting to lower afterload in patients with heart failure.

SNP is an unstable compound that breaks down under alkaline conditions and when exposed to ambient light.[89] Immediately during infusion, SNP interacts with oxyhemoglobin to yield methemoglobin, cyanide, and NO. In contrast to the organic nitrates (e.g., nitroglycerin) that require thiol-containing compounds to generate NO, SNP spontaneously generates this chemical, thus functioning as a prodrug.[90] Once generated, NO activates the enzyme guanylate cyclase found within vascular smooth muscle, resulting in increased levels of cGMP, which inhibits calcium entry into vascular smooth muscle cells and may increase calcium uptake by the smooth endoplasmic reticulum to produce vasodilation. Its onset of action is 30 seconds, it peaks at 2 minutes, and it is eliminated 3 minutes after cessation.[89]

The cyanide that is produced is rapidly cleared by nonenzymatic means by reacting with sulfhydryl groups on proteins in surrounding tissue and in erythrocytes.[88] In addition, the liver enzymatically metabolizes cyanide to thiocyanate by means of rhodanese. Because the liver is the major source of rhodanese, in patients with liver failure, signs and symptoms of cyanide intoxication may develop upon nitroprusside administration. Adverse effects from methemoglobinemia generated by SNP metabolism are rare, even in patients with a congenital inability to convert methemoglobin to hemoglobin (i.e., methemoglobin reductase deficiency). In any event, any patient receiving SNP in whom CNS dysfunction, cardiovascular instability, and/or increasing metabolic acidosis develops should be evaluated for cyanide toxicity.[88] If cyanide toxicity is suspected, SNP infusion should be stopped and therapies directed toward cyanide toxicity should be considered. Because the rate-limiting step of cyanide detoxification to thiocyanate usually entails the need for a sulfur donor, coadministration of sodium thiosulfate as a sulfur donor increases the rate of reaction of rhodanese, removing cyanide from circulation so that it no longer binds to cytochrome C.[89] A solution of 0.1% sodium nitroprusside and 1% sodium thiosulfate or a 1:10 ratio by weight in light-protected tubing is administered according to the usual dosing guidelines for sodium nitroprusside.[91-93] Alternatively, hydroxocobalamin (vitamin B_{12a}) can be used to trap the cyanide ion by exchanging the hydroxyl group for cyanide and forming cyanocobalamin, which is excreted unchanged in the urine.[94] Cyanocobalamin is the synthetic form of vitamin B12 (cobalamin) that is used for food additives and is not harmful. Of note, intravenous (IV) methylene blue is contraindicated in treating methemoglobinemia attributable to cyanide toxicity because the conversion of methemoglobin to hemoglobin may liberate large amounts of cyanide.[94]

Thiocyanate is eliminated in the urine with an elimination half-life of 3 days in patients with normal renal function.[89] Because thiocyanate accumulates in patients with renal failure and can result in renal toxicity, nitroprusside is often used

only briefly and in limited doses in children with renal failure. Clinically, patients with thiocyanate toxicity exhibit anorexia, nausea, fatigue, disorientation, and psychosis.[89] Thiocyanate also inhibits iodine uptake by the thyroid and may produce hypothyroidism. Thus thiocyanate levels should be monitored with prolonged infusion (>24 hours).

In one study evaluating the effectiveness of nitroprusside in children presenting with hypertensive emergencies of renal origin, target levels of BP were achieved within 1 to 20 minutes in all patients. In addition, symptoms of cardiac failure resolved in all patients, and neurologic symptoms abated in 80% of children within 24 to 48 hours.[95] Even in neonates with structural causes of HTN such as renal artery stenosis, nitroprusside was shown to be a formidable adjunctive agent in controlling BP and reversing signs of heart failure and proteinuria.[96] The disadvantages of sodium nitroprusside include not only the potential for cyanide and thiocyanate toxicity but also acute hypotension, rebound HTN, increasing cerebral blood flow/ICP, oxygen desaturations (via inhibition of hypoxic vasoconstriction), and in time, tachyphylaxis.[52,89,97] However, it is important to note that nitroprusside was effective in children experiencing HTN after bidirectional superior cavopulmonary shunts without altering cerebral blood flow.[98] It should be started at doses of 0.3 to 0.5 μg/kg/min; the usual dose is 3 μg/kg/min and can be titrated up to 8 to 10 μg/kg/min if necessary.[16]

Nitroglycerin

Nitroglycerin is principally a venodilator, although arteriolar dilation occurs at higher doses. Once nitroglycerin is converted to NO, it activates guanylate cyclase within smooth muscle (like nitroprusside) and stimulates the production of cGMP. The result is venous capacitance pooling with a predictable decrease in myocardial preload.[99] In volume-depleted patients, a condition typical of hypertensive emergencies other than acute pulmonary edema or acute renal failure, a reduced myocardial preload reduces CO and is undesirable, especially in patients with compromised myocardial, cerebral, or renal perfusion.[100,101]

Onset of action of IV nitroglycerin is 1 to 2 minutes, with a duration of action of 3 to 5 minutes.[102] In adults and adolescents, nitroglycerin should be started at a low rate to avoid hypotension, typically 5 to 20 μg/min, and increased by 5 to 10 μg/min every 5 minutes up to a maximum of 200 μg/min.[102] In children, the initial recommended dose is 0.25 to 0.5 μg/kg/min and can be adjusted by 0.5 to 1 μg/kg/min every 3 to 5 minutes to a maximum of 5 μg/kg/min, although doses up to 20 μg/kg/min may be used.[103] Common adverse effects include headache, orthostatic hypotension, nausea, palpitations, and flushing.[102] The hemodynamic effects of nitroglycerin may be deleterious in patients with anatomically restrictive cardiac lesions such as aortic stenosis or other left-sided obstructive cardiac lesions. Furthermore, nitroglycerin should be avoided in patients with increased ICPs because of its cerebral vasodilatory properties.

Nicardipine

Nicardipine is a dihydropyridine calcium channel blocker that is specific for L-type calcium channels and is primarily an arteriolar vasodilator. It is selective for L-type calcium channels in vascular smooth muscle as opposed to cardiac myocytes. Moreover, nicardipine has profound coronary and cerebral vasodilatory activity.[104] Its potent BP actions are without negative inotropic effects or suppression of cardiac conduction; it has minimal effects on automaticity and no appreciable venodilation.[105-107]

Nicardipine is used increasingly for hypertensive urgencies and emergencies in children and was found to be both safe and effective. The vasodilatory effects appear to be greater in patients with HTN than in patients with normal BP.[108] In addition, it has gained a role in various cardiovascular, neurosurgical, and general surgery procedures as well as in the postoperative period.[108,109]

In head-to-head trials for treatment of hypertensive emergencies in adults, nicardipine was as effective as nitroprusside. Unlike nitroprusside, nicardipine does not pose the risk for cyanide or thiocyanate toxicity and can be used for a longer duration than nitroprusside. Plasma levels of nicardipine increase rapidly in the first few hours of a continuous infusion but then reach a steady state thereafter.[108] The elimination half-life is a few hours with normal renal function and prolonged with decreased clearance during renal failure.[110] It is highly protein bound,[107,108,111] a property that may be associated with increased cyclosporin levels and lower vecuronium requirements.[112,113] In children the recommended starting dose is 0.5 to 1 μg/kg/min, titrated in 0.5 μg/kg/min increments up to 5 μg/kg/min.[114,115] It is usually effective at 1 to 4 μg/kg/min with a slightly longer onset of action and a much longer elimination half-life compared with nitroprusside.[108]

Because nicardipine may cause thrombophlebitis when given through a peripheral intravenous line, central venous administration is recommended. Like other arterial vasodilators, nicardipine has the potential to increase ICP, although another dihydropyridine (nimodipine) is neuroprotective and is often used in patients with subarachnoid hemorrhage.

Esmolol

Esmolol is a pure β_1-blocker that decreases blood pressure by reducing CO. In a study of 17 children (6 months to 14 years), esmolol was shown to lower BP along with cardiac index, shortening fraction and heart rate, while SVR remained unaffected.[116] It has a rapid onset of action and short half-life (2 to 4 minutes), which makes it ideal for critically ill patients who require judicious titration for BP management.[116,117] Because esmolol is rapidly hydrolyzed by esterases in the cytosol of red blood cells, its clearance is not dependent on organ blood flow or function.[118]

Like labetalol, esmolol has the advantage of not increasing ICP. It should not be used in patients with obstructive lung disease, such as asthma, and should be used with caution if the patient has congestive heart failure. It can cause profound bradycardia.[16] In addition, the use of β-blockers alone should be avoided in children with suspected neuroendocrine catecholamine secreting tumors because the stimulation of α-receptors from these catecholamines without opposing β-stimulation can severely worsen BP.

Because of its short half-life, a loading dose of 300 to 500 μg/kg/min is followed by an infusion of 125 to 500 μg/kg/min in children.[16,119] In a small study examining seven children after they underwent a coarctation of the aorta repair, the mean dose was 173 μg/kg/min.[120] A larger multicenter,

double-blind, randomized, dose ranging study of 116 pediatric patients (younger than 6 years) with postoperative HTN after coarctation of the aorta repair revealed efficacy with doses ranging from 125 to 500 μg/kg/min.[119] Esmolol has been used successfully for the intraoperative management of HTN during pheochromocytoma resection in children.[121,122] Nevertheless, published experience on esmolol therapy in children without cardiovascular lesions is limited.

Labetalol

Labetalol is a combined α and β-blocker that can be given as a continuous infusion or as an IV bolus. It lowers systemic vascular resistance with minimal effect on CO.[123] It provides nonselective β-adrenergic blockade, which reduces reflex tachycardia and increased cardiac contractility that may be seen with vasodilators. β_2-Adrenergic blockade would increase SVR, but this effect is counterbalanced by α-adrenergic blockade, which is selective for the α_1-receptor, resulting in vasodilation. The α-to-β blocking ratio of the oral preparation is 1:3, whereas it is 1:7 for the IV form.[97] Labetalol is therefore most useful in situations where HTN is produced by excessive sympathetic nervous system activity. Labetalol has an onset of action of 2 to 5 minutes with a peak at 5 to 15 minutes, and it can last up to 4 hours. It is metabolized in the liver through glucuronide conjugation and excreted in the urine, bile, and stool.[124]

The infusion is effective at doses of 0.5 to 3 mg/kg/hr, and the agent has a longer duration of action than nitroprusside or nicardipine.[52] Adverse effects include bradycardia and bronchospasm, although in one report a pediatric patient with a history of asthma experienced no breathing problems when given labetalol for HTN.[124] Nevertheless, published experience in the use of labetalol in children is limited.

Hydralazine

Hydralazine causes direct relaxation of arteriolar smooth muscle. It does not dilate capacitance vessels or relax venous smooth muscle.[89] However, this arteriolar vasodilation triggers a compensatory sympathetic response characterized by tachycardia and increased contractility; it also increases renin levels leading to fluid retention.[125] The positive inotropic effects of hydralazine exhibit both cyclic adenylate monophosphate–dependent and independent mechanisms, yet the importance of each remains elusive.[126] Nevertheless, it is known that intracellular calcium homeostasis is altered when hydralazine mediates its effects.[125,127]

Hydralazine, when given orally, has low systemic bioavailability (16% in fast acetylators and 35% in slow acetylators). Consequently, the dose needed to achieve therapeutic levels is higher in fast acetylators because the acetylated form is inactive. *N*-acetylation of hydralazine occurs in the bowel and/or the liver.[125] The half-life is a function of genetically determined acetylation rates, but on average it is approximately 60 minutes; it is cleared hepatically, and elimination is a function of hepatic blood flow.

The initial dose of hydralazine in persons with acute HTN is 0.1 to 0.2 mg/kg/dose given slowly (maximum initial dose, 20 mg) every 4 to 6 hours as needed up to a total of 1.7 to 3.5 mg/kg/day divided in four to six doses.[100,128] BP begins to decrease within 10 to 30 minutes and lasts 2 to 4 hours.[100] Consideration should be given to add a β-blocker to attenuate reflex sympathetic activity. Hydralazine also may be given intramuscularly.[129] The onset of action after IV administration is 5 to 20 minutes, with a duration of 1 to 4 hours.[129] While hydralazine's half-life is variable, its effect on BP generally persists for 2 to 4 hours.[100] Adverse effects are related to the reflexive sympathetic activity and include tachycardia, palpitations, flushing, headache, and dizziness.

Clonidine

Clonidine is a mixed agonist that stimulates both central α_2 adrenergic and imidazoline (I_1) receptors.[130] The stimulation of α_2 adrenergic receptors in the CNS inhibits peripheral sympathetic activity that results in vasodilatation.[131] Its effects are targeted primarily toward arterioles at lower doses.[131] This centrally acting agent is known as an antihypertensive agent with a favorable hemodynamic profile, especially because of the infrequency of postural hypotension. Typically, it is given orally for the management of acute HTN and its onset is within 15 to 30 minutes.[97] It is metabolized hepatically into inactive forms and excreted unchanged in the urine with some gastrointestinal excretion because of enterohepatic recirculation.[132]

In children, the initial dose is 5 to 10 μg/kg/day in divided doses every 8 to 12 hours and, if needed, the dose can be increased to 5 to 25 μg/kg/day in divided doses every 6 hours to a maximum of 0.9 mg/day.[133] For adolescents (age ≥12 years), the recommended dose begins at 0.1 mg/dose orally twice a day and may be increased by 0.1 mg/day on a weekly basis to a total of 0.8 mg/day.[97,134] Adverse effects include bradycardia, dry mouth, and sedation.[130] In addition, severe rebound HTN may occur in patients treated chronically with clonidine if the drug is abruptly stopped.

Enalaprilat

Enalaprilat is an IV form of an ACE inhibitor that blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor.[135] Thus ACE inhibition leads to vasodilation because of decreased levels of angiotensin II.[135] Enalaprilat is also the active form of enalapril that is given by mouth and immediately hydrolyzed by hepatic esterases to the active dicarboxylic acid, enalaprilat.[135] Interestingly, ACE also metabolizes bradykinin; hence bradykinins increase during ACE inhibition, and this effect may contribute to vasodilation as well.[136] In any event, ACE inhibitors decrease systemic vascular resistance and thus afterload and systolic wall stress. Consequently, CO and stroke volume improve.[135] The rationale behind the use of an ACE inhibitor is to attenuate renal damage caused by hyperfiltration and subsequent proteinuria from activation of the renin-angiotensin system.[77]

ACE inhibitors are cleared predominantly by the kidneys. Therefore doses of these agents need to be reduced in patients with renal insufficiency.[135] ACE inhibitors are most potent in patients with high renin levels; significant decreases in BP can occur in this population. Thus patients with elevated renin levels need to be monitored closely after receiving IV enalaprilat. Enalaprilat should not be used in patients with myocardial infarction, bilateral renal artery stenosis, pregnancy, or preeclampsia/eclampsia.[137] Use in preterm infants before glomerular development is complete is also controversial.

The pediatric dose for enalaprilat is 5 to 10 μg/kg/dose IV every 8 to 24 hours as determined by BP response.[138] The adult dose for enalaprilat is 0.625 mg to 1.25 mg IV every 6 hours.[139]

Fenoldopam

Fenoldopam is the first available peripheral dopamine$_1$ receptor (DA1) agonist, the newest class of antihypertensive agents available to treat hypertensive crisis. Stimulation of the DA1 receptor causes vasodilation of peripheral arteries as well as the mesenteric and renal vasculature with less effect in the cerebral and coronary circulation. Thus it lowers BP and peripheral vascular resistance while maintaining renal blood flow.[140]

DA1 receptor stimulation leads to vasodilatation by increasing cAMP, which promotes smooth muscle relaxation. Interestingly, cAMP also inhibits the sodium-hydrogen exchanger and the sodium/potassium-adenosine triphosphatase pump in the renal tubule.[141,142] This feature gives fenoldopam the advantage of maintaining or increasing renal perfusion and is associated with short-term increases in urine output, sodium excretion, and creatinine clearance.

In one blinded, randomized, prospective study of children ranging from 3 weeks to 12 years of age who were scheduled for surgery with a planned induction of hypotension, fenoldopam rapidly lowered mean arterial BP compared with placebo at an infusion rate up to 1.2 μg/kg/min.[143] A retrospective analysis of 13 patients aged 4 months to 18 years with primarily cardiac lesions demonstrated increased urine output with fenoldopam without the need to increase fluid intake; no increase in serum creatinine levels or adverse hemodynamic effects were observed.[144]

Like other drugs that act through adrenergic receptor stimulation, tolerance develops in patients who take fenoldopam for longer than 48 hours. With respect to toxicity, fenoldopam has the potential to increase intraocular pressure and is known to cause a dose-dependent tachycardia.[140,143] It has a half-life ranging from 5 to 10 minutes.[140] It is usually effective at doses between 0.8 to 1.2 μg/kg/min and has an onset and duration of action similar to that of IV nicardipine.[52,143] There are few pediatric case reports of hypertensive urgencies and emergencies that have responded to fenoldopam.[145] In addition, one case has been reported of a child with severe HTN resulting from renal graft rejection who did not respond to fenoldopam.[146] Thus few data support the use of fenoldopam in the treatment of hypertensive emergencies in children.

Isradipine

Isradipine is a second-generation dihydropyridine calcium channel blocker that is specific for the L-type calcium channel found in smooth muscle. It lowers BP by relaxing arteriolar smooth muscle, leading to decreases in peripheral vascular resistance. As a result, the calcium channel blockers elicit a sympathetic discharge that causes stimulation of the sinoatrial node and consequent tachycardia.[147] It is an orally administered agent that has a rapid onset of action with a peak effect that can last as long as 3 hours. It has been reported to be effective in children with chronic HTN and secondary forms of HTN.[148,149]

In one retrospective study examining 80 children with secondary HTN over a 5-year period, isradipine was used individually or in combination with other antihypertensive medications. Isradipine monotherapy decreased SBP by a mean of 13 mm Hg and DBP by 10 mm Hg over a broad range of ages from 1 week to 16.8 years of age.[149] Adverse events attributed to isradipine occurred in 9.5% of patients and included headache, dizziness, flushing, and tachycardia.[149] Similar responses to isradipine (a decrease in systolic pressure of 11.8% and diastolic pressure of 17.4%) were seen retrospectively in 53 children (ages 1 day to 16 years) treated with an average dose of 0.4 mg/kg/day.[150]

Isradipine undergoes extensive first-pass metabolism in the liver by the cytochrome 450 isoenzyme CYP3A4.[151] It is highly protein bound and is excreted essentially as inactive metabolites in the urine (two thirds) and feces (one third).[151] The recommended dosage based on a few reports is 0.05 to 0.1 mg/kg/dose orally three to four times a day; the usual dose is 0.3 to 0.4 mg/kg/day divided every 8 hours, with a maximum of 0.8 mg/kg/day up to 20 mg/day.[16,97]

Summary

Hypertensive urgencies and emergencies are an underappreciated cause of morbidity and mortality in children. The intensivist needs a heightened awareness for factors that predispose children to severe hypertensive events as well as an understanding of the clinical symptoms that may reflect end-organ damage from critically high BPs.

It behooves the astute clinician to remain vigilant of extremes in BP, whether they are significantly low or high. The emphasis of didactics (e.g., Pediatric Advance Life Support and Advanced Trauma Life Support) is on the rapid recognition of sentinel signs of hypotension in children and the adverse effects of delayed therapy. Other than the clinical manifestations of increased intracranial HTN, little attention is given to hypertensive-initiated damage to the CNS, cardiovascular system, or renal system.

The appropriate evaluation of the hypertensive child includes prompt recognition of elevated BPs that may acutely compromise organ function versus BPs that afford more time for management. Understanding the conditions that commonly occur in the acute care setting will enable the practitioner to anticipate and respond carefully before organ health is threatened.

References are available online at http://www.expertconsult.com.

V

Chapter 74

Cellular Respiration

Jerry J. Zimmerman, Amélie von Saint André-von Arnim, and Jerry McLaughlin

In every one of us there is a living process of combustion going on very similar to that of a candle, and I must try to make that plain to you. For it is not merely true in a poetical sense.

Michael Faraday, *A Course of Six Lectures on the Chemical History of a Candle* (1861)

PEARLS

- Mitochondria are responsible for the generation of more than 95% of adenosine triphosphate synthesized to support aerobic respiration. Mitochondria are also involved in intracellular signaling, intracellular calcium regulation, cellular differentiation and growth, and cellular death pathways. An independent mitochondrial genome is located within the mitochondrial matrix.
- There are three paramount regulatory steps along the respiration metabolic pathways:
  1. Oxygen availability to serve as the ultimate electron acceptor.
  2. Availability of nutrient metabolism to generate reducing equivalents in the form of reduced nicotinamide adenine dinucleotide (NADH) and the reduced form of flavine dinucleotide ($FADH_2$).
  3. Overall cellular energy state defined by the ratio of adenosine triphosphate/adenosine diphosphate.
- Lactate metabolism in critical illness is complex and often does not necessarily indicate ischemic tissues. A common clinical scenario occurs during volume and vasoactive-inotropic resuscitation of patients with normal saline and epinephrine, in which a chloride load (iatrogenic hyperchloremia) and type B lactic acidosis may be interpreted as recalcitrant shock requiring further escalation of fluid and vasoactive-inotropic support. This scenario may initiate a vicious cycle and potential overresuscitation.
- If any of the five sources of hypoxemia—hypoventilation, diffusion impairment, low inspired oxygen, shunt, ventilation/perfusion mismatch—impairs adequate oxygenation of hemoglobin and limits cellular respiration, hypoxemic dysoxia results.
- Cytopathic dysoxia occurs when oxygen delivery is normal but cellular pathophysiology prevents utilization of oxygen as the terminal electron transport acceptor.

In 1920, Haldane was credited with the observation that hypoxemia not only stops the [respiration] machine, but wrecks the [respiration] machinery as well. Indeed, the priorities of pediatric advanced life support are to avoid shock and respiratory failure, and the focus of cardiopulmonary resuscitation is restoration of airway, breathing, and circulation, all targeted to maintain or reestablish oxygen delivery to tissues and cells. During critical illness, marginal oxygen delivery and/or oxygen consumption frequently manifest as the rate-limiting step for efficient energy production in the form of adenosine triphosphate (ATP). Inadequate ATP impairs the translation of cellular structure to cellular function, a defining characteristic of life.[1] A working knowledge of cellular respiration basically summarizes the key tenets of critical care medicine. This chapter reviews the metabolism of respiration, summarizes various modalities for monitoring respiration, and provides clinical correlation of alterations in respiration that are addressed by intensive care.

Metabolism of Respiration

Oxygen Chemistry

It is appropriate to initiate a discussion of respiration by describing the relevant characteristics of the rate-limiting substrate, namely molecular oxygen, that serves as the terminal electron acceptor in cellular respiration.[1] Because of the paramount role of oxygen in facilitating efficient production of ATP, oxygen has played a central role in terms of evolution of complex multicellular life.[2] In the biosphere, the concentration of oxygen is carefully regulated by the processes of photosynthesis and respiration, the former producing—and the latter consuming—atmospheric dioxygen. Premolecular oxygen appeared on Earth's surface approximately 2 billion years ago and now represents the most abundant element on Earth's crust. At its baseline triplet state, oxygen is a diradical with two unpaired electrons with parallel spin occupying the outer orbital. In its role as the ultimate electron accepter in cellular respiration, molecular oxygen undergoes a four-electron reduction to water. With the benefit of multiple redox electron exchanges, this process permits controlled release of energy from carbohydrate, fat, and protein energy substrates. Successive one-electron additions to molecular oxygen result in the production of superoxide anion, hydrogen peroxide, hydroxyl radical, and water, respectively (Figure 74-1). These partially reduced oxygen compounds are referred to as *reactive oxygen species* and identify the so-called *antagonistic pleiotropy* characteristic of oxygen.[3]

Derivation of the parent toxic reactive oxygen species, superoxide anion, occurs by multiple mechanisms, but the following four are prominent:

1. Mitochondrial electron transport bleed (approximately 1% to 2% of all electrons shuttled across mitochondrial complexes I, II, and III produce partially reduced oxygen species)[4]

2. Reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidoreductases and the related cytochrome P-450 oxidation reactions[5]
3. Xanthine oxidase during reperfusion following ischemia events[6]
4. Cyclooxygenase and lipoxygenase pathways in the metabolism of arachidonic acid[7]

Oxygen toxicity was first predicted by both Priestly and Lavoisier in 1729. It has been estimated that approximately 2 billion molecules of superoxide anion and hydrogen peroxide are produced per cell per day. An antioxidant repertoire that includes superoxide dismutase, catalase, glutathione peroxidase, uric acid, vitamin C, and vitamin E counteracts this oxidant stress to minimize a tendency toward "rust and rancidity." However, oxidant stress plays an important role in generalized aging as well as inflammation and ischemia-reperfusion pathophysiology. As Fridovich[8] has noted, "the aerobic lifestyle offers great advantages but is fraught with danger."

Nitrogen chemistry is also involved in the generation of reactive molecular species. Nitric oxide (NO) is known to be generated from at least four NO synthase isoenzymes, including constitutive, inducible, neuronal, and mitochondrial forms. Figure 74-2 depicts the reaction catalyzed by nitric oxide synthase.[9]

Production of NO is particularly prominent during periods of inflammation. At least in septic patients, intensity of inducible NO production as measured by blood or urine end catabolic products nitrate and nitrite, is directly associated with various measures of illness severity reflecting multiple organ dysfunction syndrome and death. Particularly in the setting of tissue hypoxia, NO is believed to play a role in regulation of mitochondrial respiration through nitrosyl complexes with various iron-sulfur center enzymes as well as direct competition with oxygen for binding at the heme active site of cytochrome oxidase.[10,11] Competitive inhibition of NO with oxygen at cytochrome oxidase results in decreased oxygen consumption, decreased binding affinity for oxygen, and reduced ATP production.

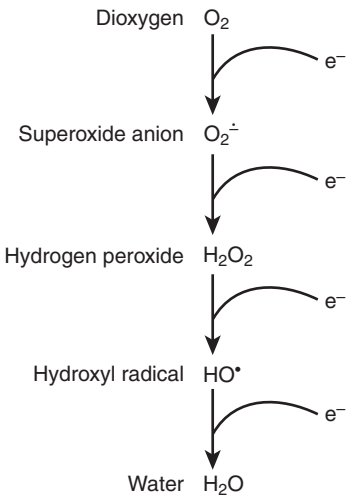

Figure 74–1. Successive one-electron reductions of molecular dioxygen to water.

Under specific conditions superoxide anion and NO can condense to form the powerful oxidant peroxynitrite with diffusion-limited kinetics: $7 \times 10^9\ M^{-1} \times sec^{-1}$.[12] Behavior of NO, superoxide anion, and peroxynitrite in clinical biochemistry has been characterized as "the good, the bad, and the ugly."[13] For example, nitrotyrosine and dityrosine represent tissue markers of peroxynitrite histopathology.[14] Peroxynitrite has been demonstrated to be involved in lipid peroxidation of cell and organelle membranes, damage to various elements of the mitochondrial electron transport chain and ATP synthase, inhibition of glyceraldehyde 3-phosphate dehydrogenase, injury of the sodium-potassium ATPase pump, disruption of plasmalemma sodium channels, production of DNA strand breaks, and activation of the poly-adenosine ribosyl phosphate system.[15] Again in reference to cellular respiration, peroxynitrite can mediate irreversible inhibition of the Krebs cycle enzyme aconitase; mitochondrial complexes 1, 2 and 3; cytochrome oxidase; ATP synthase; and creatine kinase as well as increase wasteful proton leakage. Reduced suflhydryls represent another important target of peroxynitrite oxidation, resulting in alteration of protein structure and function.[16] Peroxynitrite is known to directly alter pulmonary surfactant and injure human myocardial protein.[14,17]

Reactive oxygen and nitrogen species are also known to affect intracellular signaling through a number of redox-sensitive transcription factors, notably nuclear factor-κB (NFκB) and activator protein-1 (AP-1).[18] For example, as an aspect of the pathophysiology of gram-negative sepsis, interaction of endotoxin, toll-like receptor-4, and NADPH oxidase result in an increased flux of reactive oxygen species and subsequent activation of NFκB associated with transcription activation of a host of proinflammatory mediators.[19] In addition, peroxynitrite is known to modulate cell signaling by both phosphorylation as well as oxidation of critical protein tyrosine residues along the mitogen-activated protein kinase pathways.[20]

Mitochondria

It has been estimated that more than 1 billion years ago some aerobic bacteria invaded and subsequently colonized some form of primordial eukaryotic cells that themselves lacked the ability to use oxygen. At some point a symbiotic relationship developed between the cell and the aerobic bacteria, and this relationship has remained steadfast through evolution.[21,22] Evidence for the persistence of this endosymbiotic relationship suggesting that mitochondria have retained many aspects of their bacterial origins includes the observations that mitochondria only arise from other mitochondria; that mitochondria maintain their own genome; that the mitochondrial chromosome

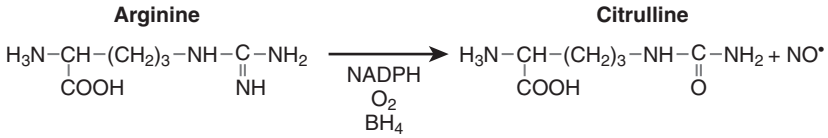

Figure 74–2. Synthesis of NO by NO synthase. *BH4,* Tetrahydrobiopterin.

is bacteria-like, circular in structure, and without associate histones; that mitochondria synthesize their own proteins; and that these mitochondrial proteins, like bacterial proteins, exhibit *N*-formyl methionine; and that antibiotics that inhibit protein synthesis in bacteria are also toxic to mitochondria.[23]

Mitochondria are responsible for the generation of more than 95% of ATP synthesized to support aerobic respiration (Figure 74-3). Enormous oxygen consumption by "power plant" mitochondria represents a double-edged sword, on the one hand permitting efficient production of ATP, but on the other hand a potential source of high quantities of reactive oxygen species. Assuming 388 L of oxygen consumed per day by a normal adult, this would require 2×10^{19} molecules of cytochrome oxidase. Considering this requirement as well as that of other members of the mitochondrial electron transport chain outlined below, the surface area of mitochondrial cristae inner membrane to scaffold this quantity of respiration elements[24] is approximately 14,000 m^2.

In addition to their role in facilitating aerobic respiration, mitochondria are also involved in intracellular signaling, intracellular calcium regulation,[25] cellular differentiation and growth, and cellular death pathways.[26,27] With respect to the latter function, the mitochondria provide close monitoring for a number of cellular "danger signals." These include loss of transmembrane potential, decreased ATP production, increased influx of reactive oxygen and reactive nitrogen species, leakage of mitochondrial proteins into the cytoplasm via mitochondrial permeability transition pores, activation of hypoxia-responsive genes, and recognition by the cell of mitochondrial proteins with signature *N*-formyl methionine.[23] Mitochondria in cells may undergo cycles of both fusion and fission.[28] If the mitochondria "senses" overwhelming cell damage as manifested by excessive reactive oxygen species, DNA damage, denatured protein, ongoing inflammation, hypoxia, or even deprivation of growth factors, the mitochondrial pathway of cellular apoptosis may be initiated.[29,30] If apoptosis is initiated by excessive reactive oxygen species, activation of the sphingomyelin/ceramide cycle precedes apoptosis.

Critical mitochondrial damage results in increased mitochondrial permeability, the mitochondrial permeability transition that results in release of proapoptotic proteins, including cytochrome c from the mitochondria into the cytoplasm. This results in activation of various caspase cascades and resultant DNAase activation and DNA dissolution.[31] Activation of the apoptotic pathway orchestrating cell death is also governed by the relative concentrations of proteins BCL-2 and BCL-X. Integrity of the mitochondrial transport chain complexes defines a fine line between maintaining mitochondrial homeostasis and efficient respiration versus excessive oxygen free radical production, mitochondrial dysfunction, and mitoptosis. This balance is maintained through multiple feedback signals related to mitochondrial proton and calcium concentrations, reactive oxygen species, overall mitochondrial redox state, mitochondrial membrane potential, and mitochondrial matrix pH, all of which affect the cascade of electron transfer along the mitochondrial transport chain.[23] It has been demonstrated that pathologic metabolic downregulation of cytochrome oxidase, such as in the setting of excessive mitochondrial production of reactive nitrogen and oxygen species, manifests as multiple organ dysfunction syndrome.[32]

Alterations in mitochondrial function in the setting of shock have been extensively scrutinized.[33-35] In addition to decreased activity of specific mitochondrial enzymes previously indicated, altered translocase activity and mitochondrial calcium transport are also coincident with actual changes in mitochondrial morphology. In sepsis, increased NO production has been associated with activation of the poly-adenosine ribosyl phosphorylase (PARP) pathway, the former associated with impaired binding of oxygen to cytochrome oxidase and the latter associated with cellular depletion of NADH.[36] In various models of multiple organ dysfunction syndrome and sepsis, mitochondrial permeability transition has been shown to result in collapse of the mitochondrial electrochemical gradient and impairment of ATP synthesis coincident with calcium influx into the mitochondria. Sepsis inflammation can induce a vicious cycle of oxidative mitochondrial damage leading to an increased flux of reactive oxygen species that further damage mitochondrial respiration components, resulting in mitochondrial glutathione depletion, enhanced mitochondrial membrane lipid peroxidation and decreased copy number, increased deletions, and decreased messenger RNA transcripts from mitochondrial DNA (Figure 74-4).[37]

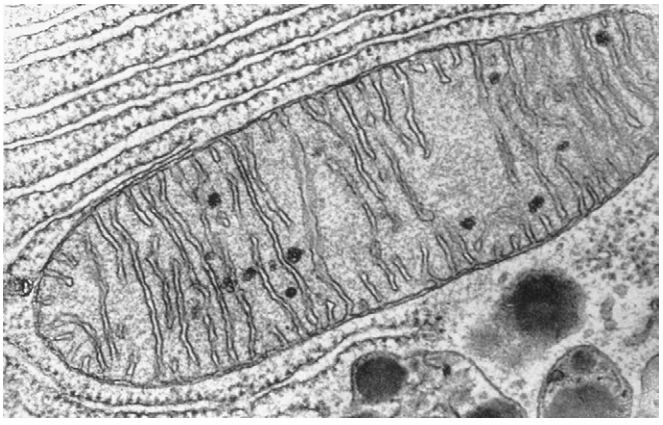

Figure 74–3. Electron micrograph of a mitochondria at the site of cellular respiration. An invaginated cristae membrane provides the scaffolding for components of the electron transport chain.

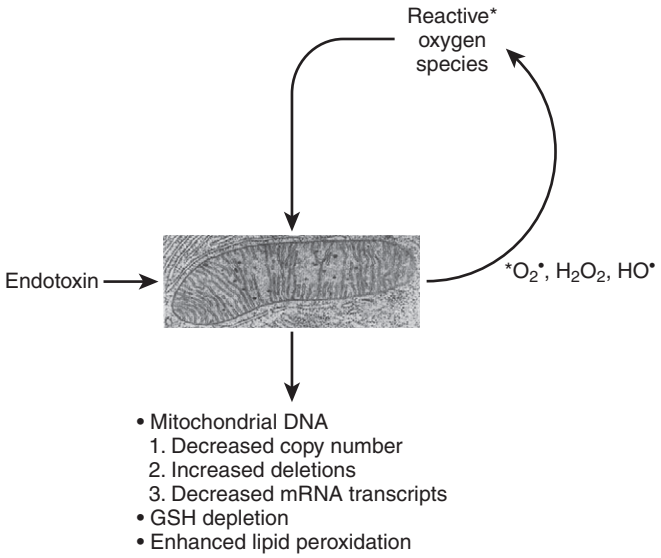

Figure 74–4. Vicious cycle mitochondrial injury in the setting of excessive reactive nitrogen/oxygen species.

The independent mitochondrial genome; located within the mitochondrial matrix, is comprised of double-stranded, circular DNA of 16.6 kb and codes for 37 genes, including proteins involved in various redox reactions, oxidative phosphorylation, ATP synthesis, and enzymes comprising the Krebs cycle, fatty acid beta-oxidation, and pyruvate oxidation.[38] Mitochondrial DNA mutations associated with the gene coding for cytochrome oxidase have been clinically linked to Leigh syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS); encephalomyopathy; lactic acidosis; and mitochondrial proliferation in muscle biopsies, the so-called *characteristic histopathology of ragged red fibers*.[21]

Adenosine Triphosphate

ATP is considered the molecular unit of intracellular energy currency. ATP derives its inherent energy secondary to anhydride bonds connecting adjacent phosphate functional groups. Hydrolysis of ATP energy generates energy for all cellular processes. In addition ATP also serves as a cofactor for signal transduction reactions using a variety of kinases as well as adenyl cyclase. Normally cellular ATP concentration is maintained in the range of 1 to 10 mmol/L, with a normal ratio of ATP/ADP of approximately 1000. Totally quantity of ATP in an adult is approximately 0.10 mol/L. Approximately 100 to 150 mol/L of ATP are required daily, which means that each ATP molecule is recycled some 1000 to 1500 times per day. Basically, the human body turns over its weight in ATP daily.[39]

Transmembrane proton flux through the mitochondrial ATPase synthase complex occurs at an estimated rate of 3×10^{21} protons per second. This corresponds to ATP reformed at a rate of 9×10^{20} molecules/sec, or approximately 65 kg ATP recycled per day in a normal resting adult (Figure 74-5).[24]

Respiration, Metabolic Pathways

Glycolysis

As previously indicated, cellular respiration allows controlled release of free energy from carbohydrate, fat, and protein energy substrate. Cellular respiration consists of three related series of biochemical reactions:

1. Degradative reactions resulting in the formation of acetyl coenzyme A and reducing equivalents
2. Metabolism of acetate to carbon dioxide in the Krebs cycle with generation of additional reducing equivalents
3. Shuttling of electrons generated from reducing equivalents along the mitochondrial electron transport chain

Acetate coupled to coenzyme A (AcCoA) is derived from carbohydrates, lipids, and proteins. Glucose is transported into cells via glucose transporter (GLUT) receptors and osmotic gradients (see Chapter 77). Ten enzymatic reactions within the cell cytoplasm define the metabolic pathway, termed *glycolysis*. These initial series of reactions ultimately generate two net molecules of ATP, two molecules of NADH, and two molecules of pyruvate.

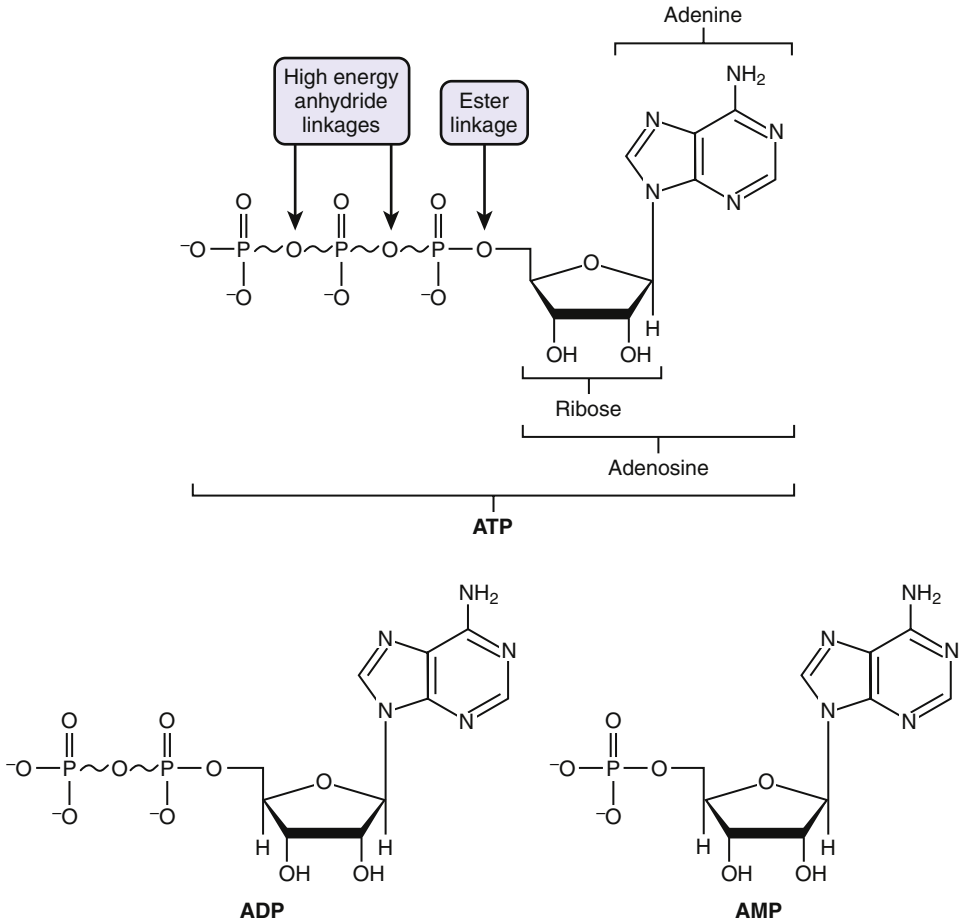

Figure 74–5. Structure of ATP. *(Modified from Baynes JW, Dominiczak MH:* Medical biochemistry, *New York, 2009, Mosby Elsevier.)*

The fates of pyruvate is multiple. Under anaerobic conditions, pyruvate may be reduced by NADH to lactate to regenerate NAD^+. Alternatively, pyruvate is shuttled to the mitochondria, where it is further metabolized to carbon dioxide (CO_2) and AcCoA. Pyruvate transamination yields alanine, whereas pyruvate carboxylase generates oxylacetate (Figure 74-6).

Catabolism of fatty acids by β-oxidation generates one molecule of AcCoA and one molecule each of $FADH_2$ and NADH for each two-carbon fatty acid fragment cycle. These reactions occur in the mitochondria after fatty acid transport by a carnitine transport system. It should be appreciated that generation of AcCoA by fatty acid β-oxidation occurs independent of pyruvate dehydrogenase that can be rate limiting for complete glucose metabolism. Particularly as an aspect of the metabolic stress response mediated by cortisol, catecholamines, and interleukins 6 and 2, protein degradation can occur with release of amino acids. All amino acids may be catabolized to either AcCoA or some Krebs cycle intermediate. Accordingly, amino acids can be mobilized for energy production as well as de novo protein synthesis. Alternatively, amino acids can undergo gluconeogenesis, a costly process that basically requires four ATP molecules plus two GTP molecules and two NADH molecules to regenerate one molecule of glucose from two molecules of pyruvate (see Chapter 77). ATP and GTP for these series of reactions are provided by β-oxidation of fatty acids.

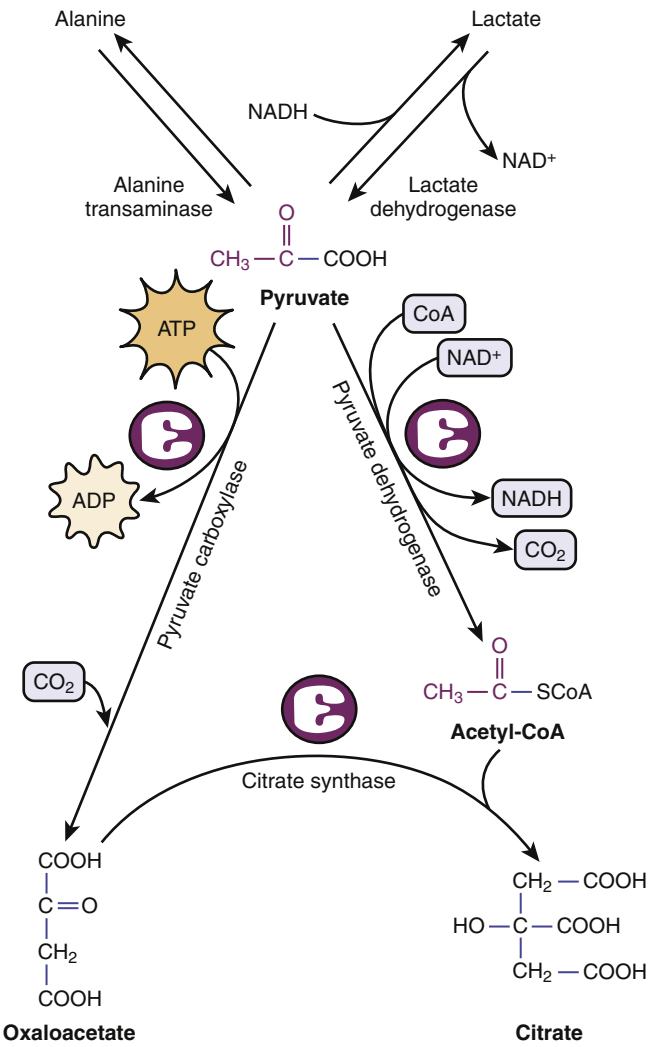

Figure 74–6. Metabolic fates of pyruvate, end product of glycolysis. *(Modified from Baynes JW, Dominiczak MH:* Medical biochemistry, *New York, 2009, Mosby Elsevier.)*

Pyruvate is metabolized in the mitochondria to AcCoA and CO_2 via pyruvate dehydrogenase, a large polyhedral protein complex with molecular weight of 10×10^6 Da. Thiamin, lipoic acid, magnesium, and coenzyme A serve as cofactors for this reaction, which represents the first irreversible step in terms of mitochondrial oxidation of pyruvate. This key reaction is regulated by a family of pyruvate dehydrogenase kinases. As noted above, AcCoA is also generated within the mitochondria by β-oxidation of fatty acids. Two molecules of AcCoA may condense to form acetyl acetate, which can subsequently be metabolized to β-hydroxy butyrate and acetone, all of which may be used as energy substrate by the heart, brain, and skeletal muscle during fasting after a depletion of glycogen stores.

Krebs Cycle

The Krebs cycle summarizes a circular series of reactions in the mitochondria to metabolize AcCoA to two molecules of CO_2 with resultant generation of one molecule of GTP, three molecules of NADH, and one molecule of $FADH_2$. GTP is equivalent to ATP in terms of energy charge. Although oxygen itself is not part of the Krebs cycle, its presence at the end of the mitochondrial electron transport chains ensures recycling of NAD^+ and FAD required in the Krebs cycle (Figure 74-7).

AcCoA, derived from glucose, fatty acids, or protein catabolism, condenses with oxaloacetate in step 1. One rotation of reactions in the mitochondria metabolizes the AcCoA to two molecules of CO_2, generates one ATP equivalent in the form of GTP, and generates reducing equivalents in the form of NADH and $FADH_2$.

Electron Transport Chain

Electrons derived from reducing equivalents NADH and $FADH_2$ are shuttled along the mitochondrial electron transport chain, ultimately reducing molecular oxygen to water. Basically, for each pair of electrons involved in one hydride equivalent, three molecules of ATP are produced. Five complexes of proteins and cytochromes comprise the mitochondrial electron transport chain and facilitate a step-down flow of $FADH_2$ and NADH reduction potential along the inner membrane of the mitochondria. These redox reaction complexes include NADH dehydrogenase–ubiquinone oxidoreductase (complex 1), succinate dehydrogenase–ubiquinone oxidoreductase (complex 2), ubiquinone–cytochrome C oxidoreductase (complex 3), cytochrome c oxidase (complex 4), and ATP synthase (complex 5). Electrons in the form of hydride ions from NADH and $FADH_2$ cascade along these protein/cytochrome complexes toward molecular oxygen. Protons generated during these reactions are pumped across the inner mitochondrial membrane matrix into the intermembrane space, generating a proton motive force. The proton electrochemical gradient across the inner mitochondrial membrane drives ATP synthesis by a reaction that has been termed *chemiosmosis*.[41] Energy for ATP synthesis arises from an influx of these protons back into the matrix, literally through the rotary motor of ATP synthase.[42]

The proton pore involves the c-ring and the a-protein. The rotary component is the coiled-coil γ-subunit, which is bound

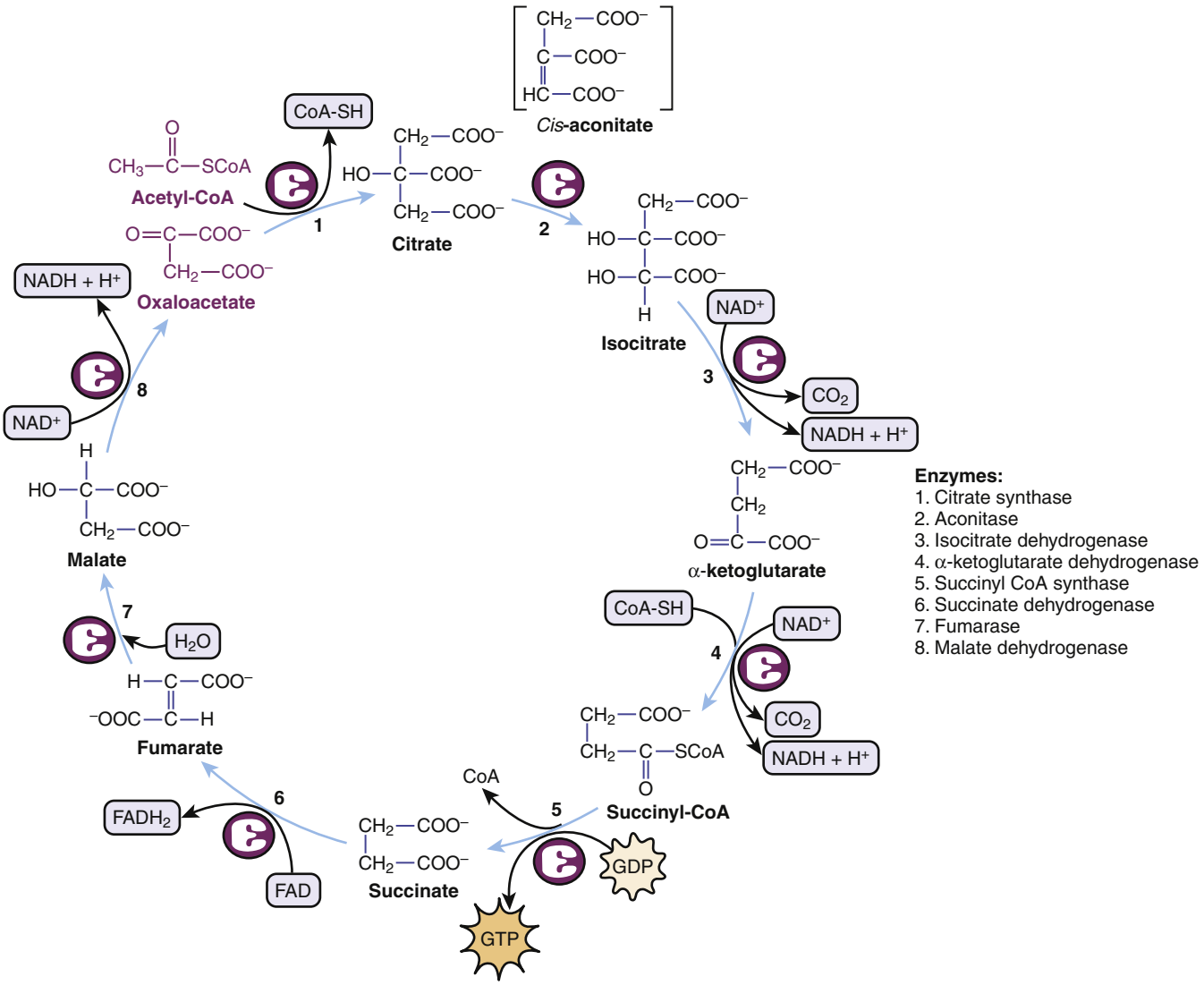

Figure 74–7. Circular series of reactions involved in the Krebs cycle. *(Modified from Baynes JW, Dominiczak MH:* Medical biochemistry, *New York, 2009, Mosby Elsevier.)*

to the ε-subunit and to the c-ring. The stationary component is the hexameric $\alpha_3\beta_3$ unit and is fixed by the δ, b, and a proteins (Figure 74-8).

Although multiple regulatory steps exist along the respiration metabolic pathways, the following three are prominent:

1. Oxygen availability to serve as the ultimate electron acceptor. This will depend on oxygen delivery to the tissue as well as regulation of oxygen binding to the heme moiety of cytochrome oxidase by NO, as previously discussed.
2. Availability of nutrient metabolism to generate reducing equivalents in the form of NADH and $FADH_2$, as previously noted. Depletion of NADH can occur in instances of severe cellular stress after activation of the PARP.
3. Overall cellular energy state defined by the ratio of ATP/ADP.

Specific adenine nucleotide translocase on the inner mitochondrial membrane as well as a voltage-dependent ion channel representing the most abundant protein of the outer mitochondrial membrane facilitate ATP transport out of the mitochondria for use as energy currency for all cellular functions.

Monitoring of Tissue Oxygenation

Blood Lactate Monitoring in Critically Ill Patients

In general, lactic acidosis occurs when there is an imbalance between production and clearance of lactate. Measurement of lactate in human blood was first described in 1843 in a lethal case of fulminant septic shock due to puerperal fever in a young woman.[43] Blood lactate monitoring is frequently performed in critically ill patients, usually with the aim of detecting tissue hypoxia[44] with resultant anaerobic hyperlactatemia, traditionally termed *type A lactic acidosis*. However, other processes not related to tissue hypoxia can also result in increased blood lactate levels,[45] such as aerobic hyperlactatemia or type B lactic acidosis that complicates clinical interpretation and therapy in cases of elevated lactate concentration. Although lactic acidosis is often associated with a high anion gap and is generally defined as a lactate level greater than 5 mmol/L and a serum pH less than 7.35, the presence of hypoalbuminemia may mask the anion gap and concomitant alkalosis may raise

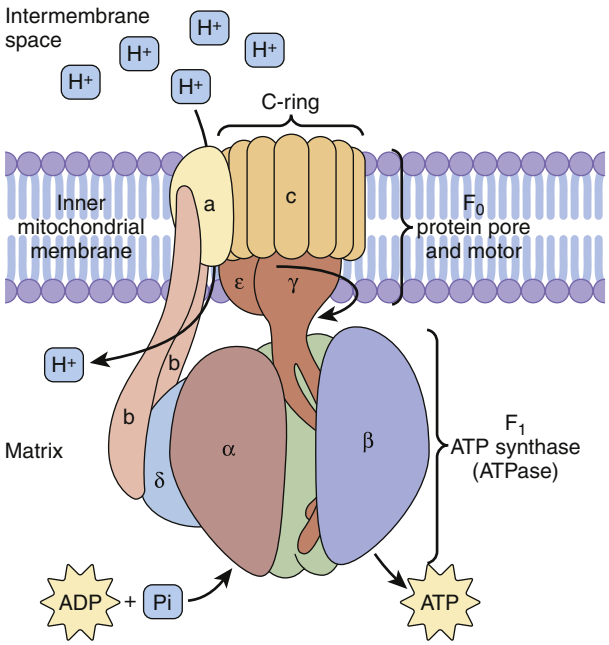

Figure 74–8. ATP synthase complex consists of a motor (proton gradient pore, F_0) and generator (ATP synthase, F_1). *(Modified from Baynes JW, Dominiczak MH:* Medical biochemistry, *New York, 2009, Mosby Elsevier.)*

the pH. As originally reported by Huckabee,[45a] normal arterial blood lactate is approximately 0.620 mmol/L and venous lactate is slightly higher at 0.997 mmol/L.

Anaerobic Hyperlactatemia

During anaerobic conditions, pyruvate derived from the conversion of glucose cannot enter the Krebs cycle via AcCoA to produce energy. Instead, pyruvate is converted into lactate, known as the *Pasteur effect*. The normal lactate/pyruvate ratio is approximately 20:1, and it rises under hypoxic conditions. The causal relationship between anaerobic hyperlactatemia and tissue hypoxemia has been confirmed by experimental[46,47] and clinical[44] studies; decreasing systemic oxygen delivery (DO_2) until oxygen demand can no longer be met and limiting oxygen consumption by DO_2 coincides with a sharp increase in lactate levels. Accordingly, in the early phase of septic shock hyperlactatemia is accompanied by oxygen supply dependency.[48] In severe sepsis or septic shock prior to resuscitation, hyperlactatemia coincides with a low central venous oxygen saturation[49] and increased lactate/pyruvate ratios,[50] whereas increases in DO_2 are associated with reductions in lactate.[49] No critical level of DO_2 or SvO_2 could be associated with hyperlactatemia. This could represent regional differences in DO_2 and demand.[51] However, improving capillary perfusion was shown to correlate with a reduction in lactate levels in patients with septic shock, independent of changes in systemic hemodynamic variables.[52] The latter observation illustrates the hypothesis that, in the absence of low systemic DO_2 relative to systemic metabolic demand, microcirculatory processes hampering oxygen use at the tissue level may raise lactate levels.

Aerobic Hyperlactatemia

Various studies demonstrate that mechanisms other than tissue hypoxia can account for hyperlactatemia, including (1) mitochondrial dysfunction[35,53,54]; (2) decreased lactate clearance in liver dysfunction,[55,56] status post liver surgery[57] and cardiac surgery,[58] as well as in sepsis,[59,60] where it was shown to predict poor outcome[61]; (3) increased aerobic glycolysis resulting in amounts of pyruvate exceeding the pyruvate dehydrogenase capacity that can be triggered by cytokine-mediated uptake of glucose[62,63] or catecholamine-stimulated increased Na-K pump activity[45,64-67]; (4) impaired activity of pyruvate dehydrogenase, essential for the conversion of pyruvate into AcCoA, that can be inhibited in sepsis,[68,69] as well as in thiamin deficiency (beriberi)[70]; (5) alkalosis[71] by increasing cellular lactate efflux due to an H^+-linked lactate carrier mechanism across the cell membrane; (6) acute lung disease[55,72]; (7) several drugs and intoxications such as epinephrine (by increased glycogenolysis, glycolysis, and stimulation of the Na-K pump),[73,74] metformin (particularly in the presence of renal insufficiency), and nucleosidic reverse transcriptase inhibitors for the treatment of HIV (by inducing mitochondrial cytopathy)[75-77]; and (8) intoxications with methanol, cyanide (by inhibition of oxidative phosphorylation),[78] or ethylene glycol (by artifactual reaction of lactate electrodes).[79]

In summary, during critical illness, the source of lactate is often assumed to be ischemic tissues that use anaerobic metabolism. This is superficially supported by lactate as an adverse prognostic marker.[80,81] However, lactate metabolism in critical illness is complex and often does not indicate ischemic tissues.[82,83] A common clinical scenario occurs during volume resuscitation of patients (iatrogenic hyperchloremia) or epinephrine infusions, in which a chloride load and type B lactic acidosis are interpreted by the body as "shock," requiring more fluid and more vasoactive-inotropic support. This scenario may initiate a vicious cycle and potential over-resuscitation.[84] It is essential to diagnose this syndrome correctly and adjust management accordingly.

Given the available evidence, patients presenting with hypotension and an elevated lactate level (>5 mmol/L) have a grave prognosis with a high mortality rate (>80%). Likewise, patients who are critically ill and do not clear lactate by 48 hours have a similarly high mortality rate.[85] There are no data currently available, however, to suggest that monitoring lactate levels beyond this time frame is prognostically useful. Early goal-directed therapy in severe sepsis is an example of outcome benefit that arguably targets the patient's primary pathophysiology rather than lactic acidosis per se.[49,86] Hence, there are no current data demonstrating that therapeutic maneuvers specifically targeted at decreasing lactate levels are beneficial. The treatment of the patient with lactic acidosis should therefore be aimed at the underlying disease and the maintenance of organ perfusion and not the lactate concentration itself. Accordingly, the routine daily measurement of serum lactate levels in critically ill patients remains controversial.

Continuous Central Venous Oxygen Saturation Monitoring

Monitoring of the mixed venous oxygen saturation (SvO_2) is used as a surrogate for quantifying the balance between systemic oxygen delivery and consumption during the treatment of critically ill patients.[87] Measurement of SvO_2 requires placement of a pulmonary artery catheter with a risk/benefit ratio that is still a matter of controversy in adult patients[88-90] and rarely performed in pediatric patients. However, measuring

central venous oxygen saturation ($ScvO_2$) only requires a central venous catheter, routinely inserted in critically ill patients, and a fiber optic catheter with a spectrophotometer for continuous $ScvO_2$ assessment. $ScvO_2$ largely reflects the degree of oxygen extraction from the brain and the upper part of the body since the catheter tip usually is located in the superior vena cava. At baseline, $ScvO_2$ is about 2% to 3% less than SvO_2 because, overall, the lower body extracts less oxygen than the upper body, resulting in a higher inferior vena cava oxygen saturation. Readings may be taken intermittently by blood sampling and co-oximetry or continuously with a fiberoptic catheter. However, beneficial effects on patient outcome to date[49] have only been demonstrated with continuous measurement of $ScvO_2$.

Low values of SvO_2 or $ScvO_2$ indicate a mismatch between oxygen delivery and tissue oxygen need.[91] Monitoring $ScvO_2$ has been successfully used as a hemodynamic goal in the management of early sepsis. Rivers et al.[49] demonstrated in a prospective randomized study in adult patients with severe sepsis and septic shock that, in addition to maintaining central venous pressure in the range of 8 to 12 mm Hg, mean arterial pressure above 65 mm Hg, and urine output higher than 0.5 mL/kg/hr, maintenance of an $ScvO_2$ above 70% resulted in an absolute reduction of mortality by 15%. Thus the guidelines of the Surviving Sepsis Campaign[92] stated that the use of SvO_2 and $ScvO_2$ is equivalent in the management of adult patients with severe sepsis and septic shock. In pediatric patients with septic shock, directing treatment to the end point of $ScvO_2$ at 70% or greater was also associated with a significant decrease in the 28-day mortality rate from 39.2% to 11.8%.[93] $ScvO_2$ goal-directed therapy resulted in more crystalloid, blood product, and inotropic support during the first 6 hours compared with the control group receiving standard resuscitation.

Continuous monitoring of SvO_2 is interesting, but clear indications for this technique in children as well as $ScvO_2$ target values remain to be determined. It has been shown that exact numeric values of SvO_2 and $ScvO_2$ saturations are not equivalent in various hemodynamic conditions.[94] Some authors have therefore argued that $ScvO_2$ cannot be used as surrogate for SvO_2 under conditions of circulatory shock.[95] However, for clinical purposes, the trends between these values were found to be reliable and clinically valuable.[96] Based on the evidence available, the primary indication for the use of central venous oximetry is as part of the early resuscitation in severe septic and septic shock patients. Further research is needed to elucidate the efficacy of venous oximetry in other patient groups as well as to assess whether an intermittent measurement using central venous blood gas analysis is as effective as continuous measurement of $ScvO_2$ using fiberoptic catheters.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a noninvasive technique for measuring brain activity. It works by detecting the changes in blood oxygenation and flow that occur in response to neural activity. When a brain area is more active, it consumes more oxygen; to meet this increased demand, blood flow increases to the active area.[97,98] Hemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated. This difference in magnetic properties leads to small differences in the MR signal of blood depending on the degree of oxygenation. Since blood oxygenation varies according to the levels of neural activity, these differences can be used to detect brain activity. This form of MRI is known as *blood oxygenation level–dependent* (BOLD) imaging, which is the most widely used method of fMRI with T2*-weighted imaging revealing changes in vascular oxygenation. A limitation is that the technique is also sensitive to changes in hemoglobin concentration that may result from alterations in vascular volume and flow as well as interconversion of oxyhemoglobin and deoxyhemoglobin. Therefore this technique provides qualitative assessment of changes in oxygenation rather than quantitative measurements. Thought to primarily reflect changes in blood flow, BOLD is widely used for functional brain mapping.[99-101] BOLD is starting to be applied to tumor studies.[102-104] BOLD is particularly responsive to oxygen manipulation accompanying hyperoxic gas breathing as a simple way to ameliorate hypoxia.[105,106] This technique may also allow direct estimates of PO_2, such as in the superior mesenteric vein or heart of children. A recent study in pediatric patients with complex congenital heart disease showed a strong correlation between oxygen saturations measured in the cardiac catheterization lab and saturations obtained noninvasively by BOLD MRI.[107] However, fMRI remains difficult to perform in critically ill unstable patients; consequently, few teams have acquired the equipment and experience necessary to apply this technique.[108]

Magnetic Resonance Spectroscopy

MRI provides anatomic images and morphometric characterization of disease, whereas magnetic resonance spectroscopy (MRS) provides noninvasive metabolite/biochemical information about tissues in vivo. MRS has been used clinically for more than 2 decades. The major applications of this advanced tool include investigation of neurologic and neurosurgical disorders, including blood vessel distribution and architecture, blood flow velocity, regional perfusion and blood volume, blood and tissue oxygenation, lactate production and intracellular pH, Krebs cycle activity, and mitochondrial oxidative phosphorylation.[109] Phosphorus-31 MRS detects compounds involved in energy metabolism such as creatine phosphate, ATP and inorganic phosphate, and certain compounds related to membrane synthesis and degradation. Proton MRS is most commonly used. Four main markers related to O_2 metabolism are studied: the peak of *N*-acetyl-aspartate (NAA), an amino acid present in neurons that reflects the status of neuronal tissue; creatine, found in glia and neurons, that serves as a point of reference because its level is believed to be stable; choline, a constitutive component of cell membranes that reflects glial proliferation or membrane breakdown[110]; and lactate, a marker of anaerobic metabolism and therefore of ischemia.[111] Elevated lactate and decreased NAA are associated with worse neurologic outcome in neonates with asphyxial injury.[112,113] Increased lactate may persist up to 1 week after asphyxial injury.[114] Compared with positron emission tomography (PET), which is frequently used to evaluate tumor hypoxia but requires injections of radioactive isotopes, multiple acquisitions, and, therefore, extended imaging times, fMRI and MRS have a number of advantages. Both MRI and MRS are currently used primarily for outcome prediction and not minute-to-minute patient management.

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) enables continuous, noninvasive bed-side monitoring of oxygenation. As with pulse oximetry, it is based on the principle that the oxygen-carrying pigments hemoglobin and cytochrome aa_3 have well-defined absorption spectra that are influenced by oxygen binding. NIRS technology thus uses a modification of the Beer-Lambert law, which describes the relationship between absorption of light and the concentration of intravascular (deoxygenated hemoglobin [Hb] and oxygenated hemoglobin [HbO_2]) and intracellular (cytochrome aa_3) chromophores. Key factors in the Beer-Lambert calculation are the absorption coefficient, tissue concentration of chromophore, distance between sensors, differential path length factor (described below), and scattering losses.[115] The distance that the light travels, known as the *optical path length,* must be determined to obtain quantitative concentration changes from the light absorption data. Path length differs due to variable tissue scattering that is reflected by the differential path length factor (DPF). The DPF is a correction factor that is multiplied by the inter-sensor distance to obtain the true path length. NIRS uses light between the 700 nm and 1000 nm wavelength. Measurement of scaled hemoglobin concentrations, reported as the tissue oxygenation index, is also available.

Clinically, NIRS is mainly accomplished by a continuous-wave spectrometer with the two sensors placed on the patient's forehead at a fixed distance that emit and detect the near-infrared light. NIRS has a greater tissue penetration than pulse oximetry and provides a global assessment of oxygenation in all vascular compartments (arterial, venous, and capillary).[116] Range of baseline cerebral oxygen saturation values is very wide. In healthy children, cerebral oxygen saturations are reported to be 68% ± 10%, whereas in children with cyanotic heart disease, baseline values range from 38% to 57%.[117] NIRS technology differs from pulse oximetry in that it does not require a pulse; therefore cerebral NIRS monitoring can be used during cardiopulmonary bypass. Perhaps the most common application of NIRS is in intraoperative neurophysiologic monitoring in children who have undergone repair of a congenital cardiac condition.[118] Therapeutic changes as a result of NIRS have lead to decreased rates of neurologic complications.[118] Also, NIRS monitoring applied in the first 48 hours after neonatal asphyxia has been shown to be useful in predicting outcome at 3 months.[119]

In addition to blood flow, evaluation of HbO_2 and Hb, NIRS can assess the cytochrome aa_3 (cyt-aa_3) redox state. cyt-aa_3 is the terminal component along the oxygen transport chain that reduces oxygen to water and remains in a reduced state during hypoxemia. The absorption spectrum of cyt-aa_3 in its reduced state shows a weak peak at 700 nm, whereas the oxygenated form does not. Therefore monitoring changes in the cyt-aa_3 redox state can provide a measure of the adequacy of oxidative metabolism. The use of NIRS in deltoid muscle during resuscitation of severe trauma patients has recently been reported.[120,121] A strong association was found between elevated serum lactate levels and an elevated cyt-aa_3 redox state during 12 hours of shock resuscitation and the development of multiorgan failure.[120] A good relationship was also shown among tissue O_2, systemic oxygen delivery, and lactate during and after resuscitation in severely injured patients during the first 24 hours.[121]

Limitations of NIRS technology include its inability to account for patients' varying ratios of brain and extracranial tissues and the fact that DPF values vary with age and pathologic state.[122,123] Icteric patients exhibit depressed regional cerebral oxygen saturation values, presumably due to absorption of light by bilirubin.[124] Ongoing blood loss also is associated with a decrease in regional cerebral oxygen saturation that may indicate that a changing hemoglobin concentration confounds cerebral oximetry measurement.[125] Furthermore, in infants the reproducibility of cerebral oxygenation measurements is poor.[126] The major limitation is that no target or critical values exist with which to compare NIRS-derived regional oxygen saturations. Poor-to-moderate correlation is seen in comparing regional cerebral oxygen saturations to global cerebral oxygenation measures, such as jugular venous saturation,[127] central venous saturation,[128,129] and invasively monitored cortical brain tissue PO_2.[130] However, NIRS measurement of continuous oxygen saturation on the brain surface could theoretically provide relative real-time alterations in brain oxygenation, which can be useful in terms of titration of therapies. A pediatric pilot study reported good agreement between NIRS and jugular venous saturations in the normal pediatric brain.[131]

Optical Spectroscopy

An extension of NIRS has been developed to allow interrogation of specific anatomic and physiologic compartments of the body. Optical spectroscopy also uses absorption of light by tissues to assess concentration of various analytes of interest. By using an entire spectral region in the visible and/or near-infrared spectral region that includes many (up to hundreds) of wavelengths of light, improved distinction between similar molecules is possible. In particular, oxygenation of myoglobin can be measured distinctly from hemoglobin, even in blood-perfused tissues. Myoglobin is an intracellular protein found in skeletal and cardiac muscle cells and is involved in the transport of oxygen from the cytoplasm to the mitochondria where oxygen is used. Because myoglobin and hemoglobin have very similar absorption spectra, it has generally been held that distinction using optical methods is not possible. Quantification of myoglobin saturation (percentage of total myoglobin bound with oxygen) directly yields intracellular PO_2 per the myoglobin oxygen dissociation curve that defines oxygen binding to myoglobin modified by temperature and pH.[132]

Advances in optical spectroscopy have made it possible to distinguish myoglobin saturation from hemoglobin saturation by using multi-wavelength spectral analysis, despite their very similar absorbance spectra. Measurements of myoglobin saturation in the presence of hemoglobin,[133-138] hemoglobin saturation in the presence of myoglobin,[139,140] and cytochrome oxidation states,[141,142] have been made from optical reflectance spectra acquired from muscle. These advances remove the ambiguity present in conventional near-infrared spectroscopic methods in which hemoglobin and myoglobin absorbances are combined.[143,144] Optical spectroscopy thus allows identification of oxygenation in anatomically and physiologically distinct tissue regions: in the vascular space (hemoglobin), at the cellular level (myoglobin), and at the mitochondrial level (cytochromes).

Direct measurement of oxygenation at the cellular level in skeletal muscle, based on distinct myoglobin saturation, has

several advantages for metabolic monitoring: it is noninvasive, it facilitates early diagnosis of shock, and it may enhance resuscitation strategies. During shock, blood and oxygen delivery are diverted to the critical organs (brain, heart, and kidneys), whereas blood flow to the physiologically "expendable" tissues (muscle and skin) is sacrificed.[145,146] Low muscle cellular oxygenation may be the "canary in the coal mine" for the presence of shock—an early, sensitive indicator of inadequate systemic perfusion. Vital signs are not accurate in early shock assessment because compensatory mechanisms often mask changes in these variables.[147] Metabolic indexes such as arterial base deficit and lactate have been found to correlate with the severity of shock.[148-150] However, since lactate levels and base deficits are metabolic responses to the presence of shock, these serum values lag changes in cellular oxygenation.

During resuscitation, the optimal therapeutic end points remain unclear.[146,151,152] Restoration of blood pressure, heart rate, and urine output alone may result in under-resuscitation because patients may remain in compensated shock after these traditional end points have been achieved.[153] Patients with occult hypoperfusion, in whom tissue acidosis persists even after resuscitation appears to have been successful, are at increased risk for multiple organ dysfunction syndrome (MODS), respiratory complications, and death.[154] Accurate assessments of cellular oxygenation are needed to refine therapy and decrease the incidence of MODS.

There is a varied and confused literature on the optical measurement of skeletal muscle oxygenation.[155-158] The problem with these attempts is that a combination of hemoglobin and myoglobin oxygen saturation was determined, with hemoglobin being the dominant signal.[143,144,159] Anything that increases the venous blood volume in the muscle (e.g., venous congestion) may be erroneously recorded as hypoxia. In addition, the intracellular oxygen tension remains unknown. Direct cellular oxygenation measurement by optical spectroscopy distinguishes myoglobin oxygen saturation from hemoglobin saturation and is thus capable of measuring intracellular tissue oxygen tension, independent of changes in blood volume.

Carbomyl Phosphate Synthase—A Marker of Mitochondrial Damage

Mitochondrial damage and dysfunction are thought to play an important role in the pathogenesis of sepsis-induced organ failure. Specific markers of mitochondrial damage in vital organs do not currently exist. Recently, carbomyl phosphate synthase (CPS)-1, a protein localized primarily in liver mitochondria, was found to be present in high concentrations in the plasma of septic humans and could serve as a novel marker of mitochondrial damage in sepsis.[160]

Clinical Correlations in Altered Cellular Respiration

Biochemical pathways and cellular energetics may seem far removed from the daily care of patients in the PICU, where discussions about the respiratory and circulatory systems seem to dominate. However, at its core, the goal of critical care medicine is to maintain and support the basic physiologic functions of the patient until their own homeostasis returns. This means the real goal is the support of cellular function, and that function requires energy derived from the metabolism of oxygen. Therefore the foundation of critical care medicine is the understanding and support of oxygen delivery and utilization.

The role of inadequate oxygen delivery in the pathogenesis of disease has been recognized for more than 80 years. In 1920, Joseph Barcroft wrote in *The Lancet* about three types of hypoxia: deficient delivery of oxygen to blood, or *hypoxic* (hypoxemic) *hypoxia*; deficient oxygen carrying capacity, or *anemic hypoxia*; and deficient circulatory delivery of oxygen, or *stagnant* (ischemic) *hypoxia*.[161] Later this century it became recognized that under certain states, even in the presence of normal or supranormal oxygen delivery, there was an apparent inability of cells to appropriately extract or utilize oxygen. This was most apparent in sepsis and certain poisonings. In 1997, Fink coined the term "cytopathic hypoxia" to describe such states.[162] In 1997, as the study of oxygen supply and utilization evolved, Robin proposed the general term "dysoxia" to describe abnormal tissue oxygen metabolism, and this is the term used in this chapter.[163] Now four classifications are recognized: hypoxemic dysoxia, anemic dysoxia, ischemic dysoxia, and cytopathic dysoxia.

Abnormal tissue oxygenation can be divided into three theoretic thresholds. In the first, cellular oxygen levels are below normal but ATP production matches ATP utilization through cellular adaptation. Cellular metabolism and mitochondrial energy production shift but aerobic metabolism is maintained. In the second level, cellular oxygen levels are so low that ATP production and utilization can only be matched through supplementary production of ATP via anaerobic metabolism. An increased supply of glucose is required, and lactate will be produced. The third level describes a state where ATP production has become oxygen limited. Neither cellular adaptation nor glycolysis is sufficient to provide adequate cellular energy. Without additional oxygen, or an increase in the cell's ability to utilize oxygen, cellular structure and function will fail. Some researchers have proposed that the third level be referred to as "dysoxia."[164] However, levels one and two represent abnormal cellular states that can generate intracellular and extracellular signals that result in altered physiologic function. Therefore "dysoxia" is used to describe any of the three states.

This section reviews examples of abnormal cellular respiration using common clinical scenarios, including hypoglycemia (substrate deficiency), the four dysoxias, and specific respiratory poisons such as cyanide, aspirin, and propofol. In addition, sepsis is used throughout as a model to demonstrate the complex interplay of oxygen delivery and altered cellular metabolism.

Substrate Deficiency (Hypoglycemia)

Hypoglycemia is probably more common in the neonatal intensive care unit (NICU) than the PICU. However, it represents the most basic form of altered energy production—inadequate energy substrate—and certainly requires recognition and therapy when it occurs (see Chapter 77). Although the clinical manifestations of acute hypoglycemia are well known to physicians, cellular hypoglycemia is a more complex problem.

As described earlier in this chapter, ATP can be produced from the metabolism of fats, proteins, and carbohydrates.

However, carbohydrates represent the dominant energy source in the regular diet of most humans, and the levels of enzymes necessary for conversion of various macronutrients into energy are skewed in favor of glucose metabolism.

There are two primary advantages of carbohydrate when compared with fat as a metabolic fuel. First, carbohydrate metabolism is the only mechanism by which cells can produce ATP in the absence of oxygen, that is, the anaerobic state. The metabolism of glucose to pyruvate yields a net of two molecules of ATP per molecule of glucose. This is obviously important to cells in crisis where oxygen delivery may be impaired. However, it is also important in the normal physiologic state for cells that have lost their mitochondria, such as red blood cells, and to cells that have high energy demands and operate under conditions of low O_2 tension even in the healthy state, such as renal tubular medullary cells. A second advantage of carbohydrate as fuel is efficiency. The ratio of ATP production to oxygen consumption is higher with glucose than with fats. Thus glucose is a more efficient fuel for ATP production yielding a 10% to 15% advantage.[165] This advantage may seem small but may become quite significant in states of high energy requirement or limited oxygen delivery such as seen in exercise or critical illness.

Glucose is important to other aspects of cellular function as well. Its participation in the pentose phosphate pathway facilitates reduction of $NADP^+$ to NADPH, a reaction product linked to many important cellular metabolic functions. It is also the source of the 5-carbon sugar ribose, which is necessary for DNA and RNA synthesis and repair.

Besides red blood cells and renal tubular cells, glucose is the preferred energy source for various other tissues in the body, including the central nervous system and the testes. Although the brain can adapt to using ketones as an energy source, this enzymatic transition takes time. Lack of immediate availability of these enzymes is readily seen in the severe central nervous system effects manifested with acute hypoglycemia. In the testes, the metabolism of glucose to lactate is necessary for healthy spermatogenesis.[166]

The Four Dysoxias

Before reviewing the various dysoxias, a brief review of DO_2 and oxygen consumption (VO_2) is in order (see Chapter 20). Oxygen delivery is defined as the product of the arterial oxygen content of the blood (CaO_2) and the cardiac output (CO) and is often indexed to the body surface area in square meters (BSA):

$$DO_2 \text{ index} = [(1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)] \times CO \times 1/BSA \quad (1)$$

Given that the amount of dissolved O_2 is so small, it is often dropped from the calculation for simplicity. Derivation of cardiac output is described elsewhere in this text (see Chapters 19 through 22).

Oxygen consumption is defined as the amount of oxygen extracted by the body from the blood and, according to the Fick principle, is calculated by the difference between the CaO_2 and the CvO_2 (the oxygen contents of arterial and mixed venous blood) multiplied by the cardiac output. It, too, is often indexed to BSA:

$$VO_2 \text{ index} \cong [1.34 \times Hb \times (SaO_2 - SvO_2)] \times CO \times 1/BSA \quad (2)$$

In the normal, healthy state DO_2 is in significant excess of VO_2. That is, the blood is carrying an excess of oxygen compared with the amount of oxygen the body needs. The ratio of consumption to delivery is called the oxygen extraction ratio (ERO_2) and is calculated as follows:

$$ERO_2 = (CaO_2 - CvO_2)/CaO_2 \cong (SaO_2 - SvO_2)/SaO_2 \quad (3)$$

Given that typical SvO_2 is approximately 65% to 75%, this ratio is typically 0.25 to 0.35. This means that delivery exceeds consumption by a factor of 2 to 3. Thus a buffer exists where decreases in cardiac output are well tolerated across a certain range. In this setting, VO_2 remains unaffected by changes in DO_2; this is accomplished by an increase in ERO_2.

There is a point, however, at which the oxygen extraction capabilities of the tissues are exceeded. At that point, VO_2 becomes dependent on DO_2. This biphasic relationship of DO_2/VO_2 is shown in Figure 74-9.

The importance of this concept cannot be overemphasized as it relates to cellular respiration. DO_2 and VO_2 can be altered in many physiologic and pathologic states. Sleep, exercise, pain, anxiety, and fever are just a few examples. Drugs, too, can have simultaneous effects on VO_2 and DO_2, such as with catecholamines and shock.[167] With certain poisons and with cytopathic dysoxia, oxygen consumption can be directly affected by the tissues' ability to extract oxygen from the blood and use it as the terminal mitochondrial electron acceptor. In these situations, tissue oxygen extraction, not DO_2, represents the limiting factor; DO_2 may be normal or even elevated.

Accordingly, a complicated interplay exists among DO_2, VO_2, and ERO_2. Although described in text and graphs in what appear to be straightforward ways—just as with preload, afterload, contractility, and stroke volume—their practical measurement remains exceedingly difficult. Bedside evaluation of DO_2 and VO_2 would be of great value to the clinician. Unfortunately, most of the methods of calculating VO_2 rely on cardiac output (via the Fick principle), which results in a situation where a single measured variable is included in two parts of a regression analysis, so-called *mathematical coupling*. This dependency leads to amplification of any error in that measurement and may result in an apparent relationship between variables that does not truly exist.[168] As in many areas

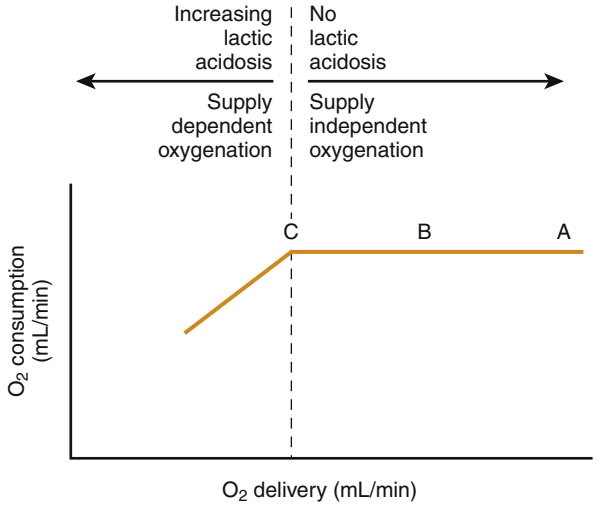

Figure 74–9. Biphasic relationship between oxygen delivery and oxygen consumption.

of critical care medicine, when something cannot be measured directly, a surrogate measure must be used.

Anemic Dysoxia

The majority of oxygen delivered to tissues is carried by hemoglobin in the red blood cells. The dissolved component of oxygen represents a very small, and usually insignificant, portion. It is therefore reasonable to postulate that in severe anemia, the decreased oxygen carrying capacity of blood may result in a severe limitation in DO_2, perhaps severe enough that VO_2 may be limited. Such limitation would represent *anemic dysoxia*.

How anemic must a child be to suffer from anemic dysoxia? A clinical scenario is instructive:

> Assuming that a normal child, approximately 1 m^2, has a VO_2 of 200 mL/min and a normal cardiac output of about 4 L/min, the formula for VO_2 (Equation 2) may be rearranged to obtain the minimum hemoglobin concentration necessary to deliver that amount of oxygen. An extreme oxygen extraction, 80%, is also assumed (this would reflect an SvO_2 of 20%!):

$$Hb = VO_2 / (1.34 \times (SaO_2 - SvO_2) \times 10 \times CO) = 5.2 \text{ g/dL}$$

This equates to a hematocrit of just over 15%. Additional manipulation of the numbers reveals that to maintain an SvO_2 in the normal range of approximately 70%, CO would have to increase by a factor of 2.7! (It should be appreciated that the increased CO itself increases VO_2.)

Oxygen content of such a patient's blood is next considered. Using the data from above and a normal PaO_2 of 90 mm Hg:

$$CaO_2 = (1.34 \times 5.2 \times 0.96) + (0.003 \times 90) = 7.0 \text{ mL/dL}$$

Notice that the dissolved portion in this patient, 0.27mL/dL, represents less than 4% of the total CaO_2. If the same patient were administered 100% FiO_2, a PaO_2 of approximately 600 mm Hg would be likely. In this case:

$$CaO_2 = (1.34 \times 5.2 \times 1.00) + (0.003 \times 600) = 8.8 \text{ mL/dL}$$

This represents an increase in CaO_2 of 22%, with the dissolved portion now representing more than 20% of the total CaO_2.

This example illustrates the need for significant tachycardia in children with severe anemia and the significant contribution of dissolved O_2 in such patients. Anemic dysoxia alone is not a common source of problems in the pediatric population. However, anemic patients are frequently encountered in the PICU, and the increased VO_2 caused by acute illness coupled with the decreased DO_2 of anemia may indeed lead to significant negative impact on cellular respiration.

Hypoxemic Dysoxia

With a normal cardiac output and a normal oxygen carrying capacity, effective oxygenation of red cell hemoglobin ensures adequate tissue delivery of oxygen. If any of the five sources of hypoxemia—hypoventilation, diffusion impairment, low inspired oxygen, shunt, ventilation/perfusion mismatch—impairs adequate oxygenation of hemoglobin and limits cellular metabolism, *hypoxemic dysoxia* results.

Respiratory diseases represent a significant portion of pediatric illness, and hypoxemia is a common finding in the PICU. In addition, such patients often have fever and increased work of breathing. Thus they exhibit increased VO_2 and diminished DO_2. This altered ratio of VO_2/DO_2 can lead to impaired cellular respiration and a shift toward anaerobic metabolism.

Another example is outlined below:

> An infant with bronchiolitis has a fever of 40° C, a pulse of 180 beats/min, and a respiratory rate of 80 breaths/min. Her hemoglobin is 10 and her oxygen saturation on arrival is 75%. Fever increases metabolism by approximately 14% per 1° C temperature increase. Work of breathing accounts for about 15% of oxygen consumption in a resting infant and can double or triple in severe states. Thus a conservative estimate of this infant's current VO_2 is:

$$\begin{aligned} VO_2 \text{ (current)} &= \text{Baseline } VO_2 + 0.42 \text{ baseline (for fever)} + \\ &\quad 0.15 \text{ baseline (for work of breathing)} \\ &= 1.57 \ VO_2 \text{ (baseline)} \end{aligned}$$

If the patient's hemoglobin oxygen saturations were normal, the 50% increase in her heart rate (assuming a normal of 120 beats/min) would just offset her increased VO_2. However, her hypoxemia causes a 25% reduction in CaO_2. A quick calculation reveals:

$$\begin{aligned} DO_2 \text{ (current)} &= 1.50 \times CO \text{ (baseline)} \times 0.75 \ CaO_2 \text{ (baseline)} \\ &= 1.12 \ DO_2 \text{ (baseline)} \end{aligned}$$

It is immediately apparent in this example that the increase in VO_2 has not been offset by the increase in DO_2. This generates a state in which the VO_2/DO_2 curve has shifted, and the threshold at which VO_2 becomes limited by DO_2 is lowered. The treatment in this case is obvious. Application of supplemental O_2 will likely alleviate her hypoxemia, and with her tachycardia, CaO_2 will return to a normal or even increased level.

As another example, children with right-to-left intracardiac shunting are frequently encountered in the PICU. These patients live in a chronic state of hypoxemia, yet grow and develop. Again, examining the equation for DO_2:

$$DO_2 \text{ index} = [(1.34 \ \mathbf{Hb} \ SaO_2) + (0.003 \ PaO_2)] \ \mathbf{CO} \ 1/\text{BSA} \quad (4)$$

To maintain adequate oxygen delivery in the face of persistent hypoxemia, these patients must increase cardiac output, hemoglobin, or both. It is worth remembering that because CaO_2 is a product of hemoglobin concentration, SaO_2, and CO, a reduction in one can be fully compensated for by an appropriate increase in the other(s). Some quick math reveals that for a patient whose arterial oxygen saturation is chronically 75%, a cumulative increase in hemoglobin and/or cardiac output of 30% is necessary to equate an SaO_2 of 100%. An increase in hemoglobin of 3 to 4 g/dL is obviously less stressful to a system than a chronic increase in CO of 1.0 to 1.5 L/min/m^2. This is especially true when one recalls that many of these patients have some element of heart failure and are not capable of long-term significant increases in cardiac output. It should also be recalled that for such patients any increase in CO results in an increase in VO_2 assuming that cytopathic dysoxia is not operative. It is obvious why these patients are so fragile. They have a limited ability to increase DO_2. Essentially, they live close to point C on the VO_2/DO_2 curve shown in Figure 74-9. Any illness or acute stressor that results in an increase in VO_2 can lead to a state at which VO_2 becomes limited by DO_2 and cellular respiration begins to suffer.

In summary, although hypoxemia is a common finding in the PICU, patients typically compensate through an increase

in cardiac output. For chronically hypoxemic patients, part of their compensation derives from elevated levels of hemoglobin. It is in those patients whose ability to increase cardiac output or whose level of VO_2 is significantly elevated that the physician must be most concerned that limited CaO_2 will cause an inability to meet VO_2 and cellular respiration will fail.

Ischemic Dysoxia

It is obvious that in tissues for which blood supply is eliminated, oxygen delivery will be eliminated and cellular energy production will fail—not only from a lack of oxygen, but also from a deficiency of substrate. This represents the most extreme form of *ischemic dysoxia*. However, this is less frequently encountered than are situations in which blood supply is merely compromised. At some point (point C on Figure 74-9), the decrease in DO_2 may fall below the level of VO_2 and cellular respiration will falter.

Ischemic dysoxia can occur on a macroscopic level, and this is how it is usually considered. A patient with severe bradycardia but normal SaO_2 suffers from global ischemic dysoxia purely as a result of inadequate cardiac output. DO_2 is severely limited and cannot meet VO_2. Anaerobic metabolism begins, and if the bradycardia is not reversed, cellular function will begin to fail. In another example, a patient develops a subdural hematoma after a fall. The increased intracranial pressure creates regional ischemia and inadequate DO_2 to that area. Draining the hematoma relieves the pressure and DO_2 returns to normal or even increased levels. There is, indeed, injury associated with the restoration of DO_2, a so-called *reperfusion injury* (see Chapter 62).

In contrast to the macroscopic examples above, ischemic dysoxia occurs much more frequently on a microscopic level. In many ways, this concept is only on the threshold of understanding. Even in good health, many areas of the body demonstrate "marginal" DO_2, with limited oxygen supply relative to metabolic needs. Classic examples include the renal medulla and corticomedullary junction and the centrilobular regions in the liver.[169-171]

In the kidney, the tubular cells of the medullary region contain a high concentration of mitochondria to provide energy for pumping ions against a strong gradient. However, the cells exist near the end of the peritubular capillaries where DO_2 is at or nearly at the limits of VO_2. In the liver the centrilobular cells lie at the end of the sinusoids, just proximal to the venous system. In addition, more than half of the liver's blood supply is provided by the portal vein with its already low oxygen tension. Once again, DO_2 hovers close to VO_2. In these examples any situation in which blood pressure or cardiac output is compromised can lead to significant insult to these areas; VO_2 simply cannot be met, cellular energy production falters, and cell functions fail. Clinically this is reflected as acute renal insufficiency due to acute tubular necrosis or hepatic dysfunction due to ischemic hepatitis—so called "shock liver."[172]

The structure of the microcirculation, a network of vessels less than 100 to 150 μm in diameter, is important when considering dysoxia. It is composed of arterioles, capillaries, and venules and represents the functional unit of the circulation, supplying tissues with oxygen and substrates and removing metabolites. It is also important to understand two aspects of the microcirculation as they relate to dysoxia. First, in the classic Krogh model of microcirculation, oxygen exchange occurs in the capillary bed. However, research reveals that a significant amount of oxygen can be lost through the arterioles.[173] This is important because it suggests that as blood enters the capillary bed, it may have already released a significant amount of oxygen to the periarteriolar tissues and may be relatively desaturated. Oxygen diffusion from the arteriole toward the capillary may or may not be able to compensate for this. This means that any state of ischemic dysoxia may be complicated by hypoxemic dysoxia at the capillary level.

The second aspect of the microcirculation to note is its overall structure. Progressively smaller vessels supply progressively larger areas of tissue. In addition, precapillary sphincters and thoroughfare channels are present. Accordingly, there exist multiple opportunities for blood to partly or entirely bypass regional capillary beds. Dysregulation of the arterioles or precapillary sphincters shunts blood directly from arteriole to venule. In sepsis, plugging of capillaries due to endothelial swelling, microscopic clots, activated white blood cells, or nondeformable red cells does the same. These scenarios all give rise to microscopic regional ischemia and potentially regional ischemic dysoxia. Much research has been devoted to the microcirculation and its role in critical illness. It is believed by many to be the pathophysiologic basis for MODS, and in sepsis its role is believed by some to be so important as to be deemed the "motor of sepsis."[174-178] Throughout the tissues there seem to be areas in the microcirculation fundamentally vulnerable to ischemic dysoxia; these areas have been termed *microvascularly weak units*.[179,180]

Cytopathic Dysoxia

The term *cytopathic hypoxia* arose just over 10 years ago to describe "diminished production of ATP despite normal (or even supranormal) PO_2 values in the vicinity of the mitochondria."[162] This term arose because of increasing evidence that in sepsis there was insufficient energy production in cells despite adequate oxygen delivery. Indeed, this does occur in sepsis, and increasing research points to it as a fundamental cause of the multiple clinical manifestations of sepsis. There are also chemicals and drugs that, despite adequate intracellular oxygen, can lead to cellular energy failure via direct functional inhibition of or damage to the mitochondria. These include cyanide, 2,4-dinitrophenol (DNP), aspirin, and propofol.

Cytopathic dysoxia during sepsis is an active area of research, and many proposed theories abound. No single pathway to cellular energy failure has proved dominant, and some proposed hypotheses have yielded conflicting results. It is beyond the scope of this chapter to review all of these in detail, but some theories bear discussion.

Inhibition of pyruvate dehydrogenase complex (PDC) has been implicated in some of the altered cellular metabolism and increased lactate production in sepsis.[181,182] Glycolysis is stimulated in many cells during sepsis. For glycolysis to be linked to oxidative phosphorylation and cellular respiration in the mitochondria, glucose must be converted first to pyruvate then irreversibly to AcCoA, which subsequently enters the mitochondria. This conversion of pyruvate to AcCoA is accomplished through the action of PDC. During sepsis, this enzyme complex is inhibited by stimulation of a PDC-kinase. The trigger for this is poorly understood. When pyruvate cannot be converted to AcCoA, energy production in the mitochondria diminishes due to a lack of substrate entering the

Krebs cycle. In addition, when pyruvate cannot be converted to AcCoA, its fate is to be converted to lactate via lactate dehydrogenase.

NO and other reactive nitrogen species (RNS) have been demonstrated in several studies to play active roles in the pathogenesis of sepsis.[183-185] As previously discussed, NO acts as a reversible inhibitor of cytochrome c oxidase. At increased concentrations, NO reacts to form $OONO^-$ (peroxynitrite), NO_2, and nitrosothiols. Increased concentrations of NO and these compounds can cause irreversible inhibition of respiratory chain components, uncoupling of oxidative phosphorylation, enhanced permeability of the mitochondrial membrane, and ultimately death of the cell.[186] In some research, the degree of mitochondrial dysfunction in sepsis was directly related to extent of NO production.[35]

A final theory of sepsis-induced mitochondrial dysfunction involves PARP.[187,188] This enzyme is involved in various aspects of cellular function, but with respect to sepsis, its most important function involves repair of single-strand breaks in DNA. During sepsis there is an increase flux of reactive oxygen and nitrogen species that mediate induce single-strand breaks in DNA. PARP is activated to repair these breaks. Activation of PARP leads to massive depletion of cellular NAD^+/NADH. Because NADH is the primary reducing equivalent transfer molecule used in cellular respiration, its depletion results in marked impairment of aerobic metabolism.

Drug Effects on Cellular Respiration

Cyanide

Cyanide ion is highly toxic via inhibition of cellular respiration. It binds to the iron atom within the heme group of cytochrome c oxidase, effectively shutting down aerobic metabolism. Rhodanese is a mitochondrial enzyme that functions to detoxify cyanide into relatively nontoxic thiocyanate. In critical care medicine, sodium nitroprusside is used as a vasodilator because of its ability to serve as an NO donor. However, on exposure to light and degradation within the body, a cyanide ion is released. Patients receiving high-dose, long-duration sodium nitroprusside infusions should be monitored for cyanide toxicity.

Aspirin

Salicylates have been used therapeutically since at least the fifth century BCE. Aspirin (acetylsalicylic acid) was synthesized in the mid-nineteenth century and has been manufactured and sold since. Toxicity to cellular respiration from aspirin overdose has been recognized for decades, but the mechanism has remained elusive. Some researchers have demonstrated an uncoupling of oxidative phosphorylation.[189] In this mechanism aspirin induces mitochondrial permeability transition (MPT). This transition allows the proton gradient established across the inner mitochondrial membrane to depolarize in a manner not linked to ATP production—hence the "uncoupling." This energy release manifests as heat. It may be part of the pathophysiology of fever in salicylate toxicity, though effects on hypothalamic function may also play a role. Recently, another mechanism of salicylate toxicity has been elucidated.[190] This research demonstrated reversible and irreversible inhibition of α-ketoglutarate dehydrogenase (AKDH) in the Krebs cycle by salicylate and acetylsalicylic acid, respectively, resulting in diminished production of NADH and failure of cellular respiration.

2,4-Dinitrophenol

DNP is a chemical compound used in the 1930s as a diet pill. Today it is rarely used as such but frequently used in research on membrane transport. Its popularity for both is due to its ability to induce depolarization of the inner membrane of the mitochondria. Just as with salicylates, this results in uncoupling of oxidative phosphorylation. Energy is released as heat rather than used for production of ATP.

Propofol

Propofol is a frequently used anesthetic in the PICU and the operating room. Although generally considered safe, there have been increasing reports of patients developing metabolic acidosis, rhabdomyolysis, refractory bradycardia and cardiac failure, renal failure, and death from propofol infusion syndrome.[191] The pathophysiology of this syndrome remains partially unexplained, but multiple studies show at least some aspects related to propofol's effects on the mitochondria.[142,192-194] Some studies demonstrate leakage of protons across the inner mitochondrial membrane similar to uncoupling of oxidative phosphorylation by DNP and aspirin. Others show inhibition of enzymes along the electron transport chain. Given that propofol infusion syndrome usually occurs in the ICU in critically ill patients, some researchers have looked at the possibility of an interaction between propofol and reactive oxygen and nitrogen species as a potential mechanism.[193] Other researchers have suggested that unrecognized mitochondrial disease may predispose patients to this syndrome, though no such association has yet been ascertained.[195] Whatever the ultimate pathway is for development of this syndrome, it almost certainly involves the mitochondria on some level. The mechanism of action of DNP, aspirin, and propofol are suggested in Figure 74-10.[40]

Complex IV with cyt-aa_3 uses four electrons from cytochrome c and eight protons from the matrix. Four protons and electrons reduce oxygen to water. Four additional protons are pumped out of the matrix.

An electrochemical gradient consisting of protons and other factors constitutes the mitochondrial membrane potential. Uncouplers transport protons into the mitochondrion, dissipating the proton gradient. DNP, aspirin, and propofol are examples of exogenous uncouplers. Endogenous uncoupling proteins in the inner mitochondrial membrane also exist and are regulated by hormones.

Sepsis and Dysoxia

Historically, sepsis is typically regarded in macroscopic dimensions. Intensivists support blood pressure, perfusion, and oxygenation because correction of these abnormalities has shown improvement in outcome. However, the cellular microscopic milieu constitutes the mechanistic focus for any macroscopic abnormalities. The microcirculation and mitochondria are at the core of organ failure and death in sepsis, although the details remain sketchy. Currently, they also remain far from therapeutic reach. Their increasingly recognized role in the pathogenesis of sepsis has led to the term *microcirculatory and mitochondrial distress syndrome* (MMDS), a term highlighting the complex interplay between circulation and cellular

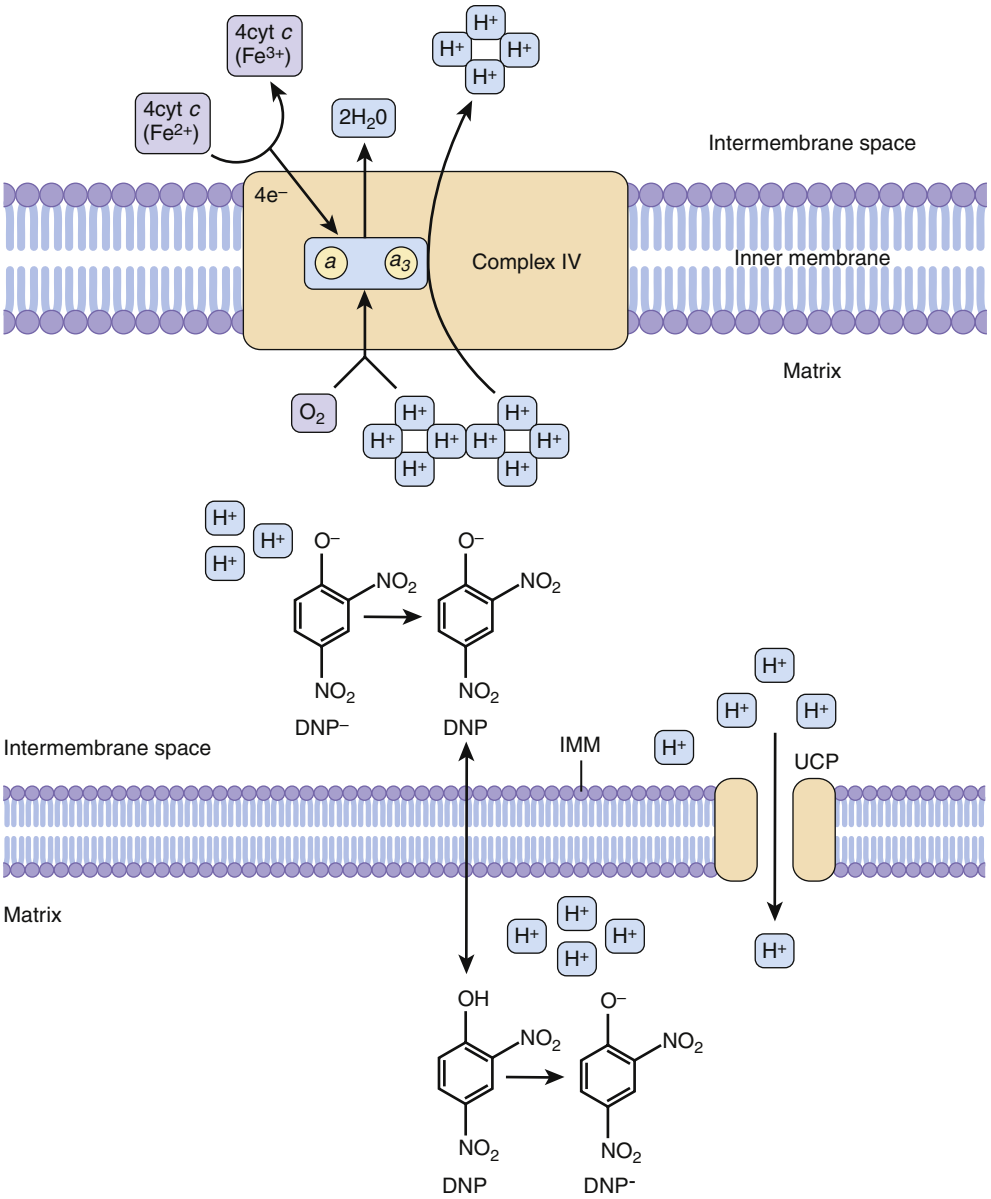

Figure 74–10. Schematic depiction of proton coupling to drive oxidative phosphorylation and decoupling activity of drugs such as DNP, aspirin, and propofol. *(Modified from Baynes JW, Dominiczak MH:* Medical biochemistry, *New York, 2009, Mosby Elsevier.)*

metabolism in sepsis.[175] Studies examining cellular energy, microcirculation, and mitochondria in sepsis have yielded conflicting results regarding the exact mechanisms and contributions each plays in sepsis pathogenesis. As with most areas in medicine, it is likely that the answer overlaps with multiple contributions, with no single element emerging as the definitive problem.

Hibernation Physiology in Sepsis

One final aspect of cellular metabolism and energetics worth mentioning is that of hibernation. Although sepsis often progresses to MODS and death, tissue examination frequently reveals little histologic evidence of cell injury and death.[196] Some research indicates a form of cellular hibernation is triggered in sepsis. Energy metabolism is altered to preserve cell life, but physiologic cell function nearly ceases. The exact mechanism is not understood, and its role in sepsis has not been extensively evaluated.[32,197] However, it does provide an explanation for extreme organ dysfunction in the absence of cell death and a platform for future study.

References are available online at http://www.expertconsult.com.

Nutrient Metabolism and Nutrition Therapy During Critical Illness

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PEARLS

- Accurate assessment of nutritional status and provision of individually tailored optimal nutrition to the critically ill child are important but elusive goals of pediatric critical care.
- Malnutrition is associated with increased physiologic instability and the need for increased quantity of care in the ICU. Careful assessment of nutritional status on admission to the PICU allows identification of at-risk or malnourished children.
- The hypermetabolic stress response places variable energy demands on the critically ill child that must be met with evidence-based strategies. The metabolic response to critical illness results in glucose and lipid intolerance and increased protein breakdown, resulting in weight reduction and loss of lean body mass.
- Supply of adequate glucose and protein does not reduce protein breakdown and nitrogen loss during the metabolic stress response. However, protein balance may be improved by increased protein synthesis in the presence of relentless protein catabolism. In starvation, protein catabolism can be reversed if adequate energy intake is provided. This characteristic differentiates starvation from a hypermetabolic state.
- Failure to accurately estimate or measure energy expenditure during critical illness results in both underfeeding and overfeeding, with significant and unintended energy imbalances over the course of illness. Indirect calorimetry targeted at high-risk patients helps prevent energy imbalances in the PICU.
- Early enteral nutrition (EN) in patients with a functioning gastrointestinal tract is desirable. It has been shown to decrease infectious episodes and decrease length of hospital stay in critically ill patients.
- The gastric route is preferred for enteral nutrition. Postpyloric (small bowel) feeding may be considered in patients at risk of aspiration or when gastric feeding has not been tolerated.
- A significant number of patients experience interruptions to EN during their PICU course. Fluid restriction, prolonged fasting for procedures, feeding tube blockage or dislocation, perceived feed intolerance (due to abdominal distension, discomfort, or high gastric residual volumes), vomiting, diarrhea, and overall failure to prioritize nutritional support in the PICU are some of the factors that make EN challenging at the bedside.
- Although widespread in its application, parenteral nutrition is associated with mechanical, infectious, and metabolic complications and hence should be used only in carefully selected patients where EN is contraindicated, not tolerated, or has failed to provide adequate nutrition.

Malnutrition is prevalent in critically ill children at the time of admission to the pediatric intensive care unit (PICU).[1,2] Further nutritional deficiencies during the course of their illness are often incurred due to the burden of illness or suboptimal nutritient intake and may result in poor outcomes. Safe provision of optimal nutrients during hospitalization is an important goal of pediatric critical care. The changing metabolic state during the course of critical ilness results in unpredictable energy demands that need to be carefully matched with evidence-based nutritional strategies. However, prediction, estimation, and measurement of true energy expenditure in PICU patients can be challenging. Failure to accurately estimate or measure energy expenditure can potentially result in unintended underfeeding or overfeeding. While underfeeding has long been recognized as a problem, a significant proportion of critically ill children are at the risk of being overfed.[3] Furthermore, there exist a myriad of barriers that impede the delivery of prescribed nutrients to the critically ill child and result in a delay or a failure to achieve the prescribed energy goal. The complexities of critical care or the nature of illness frequently conflict with nutrient provision. However, many barriers to bedside nutrient delivery may be avoidable. Examination of existing literature, audits of bedside practice, and multidisciplinary collaborations have helped identify optimal nutritional strategies, illuminated areas of practice deficiencies or knowledge gaps, and highlighted future priorities for research. There has been a resurgence in awareness and an increase in our understanding of the role of nutrition therapy during pediatric critical illness. However, the perceived benefits of novel therapies such as immunonutrition, tight glycemic control, and hormonal modulation of the stress response have not yet been realized in the general PICU population. Future studies will clarify the role of these strategies in improving patient outcomes in the PICU. Until then, careful screening for malnutrition, awareness of the metabolic state during

the course of illness, accurate assessment of energy demands with attention to energy balance, multidisciplinary efforts to overcome common barriers to nutrient intake at the bedside, and a commitment to prioritizing nutritional support during critical illness are necessary to meet nutritional goals.

Malnutrition in the Critically Ill Pediatric Patient

Critical illness increases metabolic demand on the host in the early stages of the stress response, when nutrient intake may be limited. As a result, children admitted to the PICU are at risk of deteriorating nutritional status and anthropometric changes with increased morbidity.[1] This effect is more pronounced in a subgroup of patients who are already malnourished or at risk of malnutrition on admission. The prevalence of malnutrition in children admitted to the ICU has remained largely unchanged over the last two decades. One in every four children admitted to the PICU shows signs of acute and/or chronic malnutrition on admission.[1,2] A majority of PICU patients present with conditions that impede normal growth. Nutritional status affects physiologic responses and influences outcome. Malnutrition is associated with increased physiologic instability and the need for increased quantity of care in the ICU.[4] Despite its high prevalence and consequences, medical awareness of malnutrition is lacking. The nutritional status of hospitalized patients is not routinely assessed, and only a minority of patients are referred for expert nutritional consultation or support.[5] Careful nutritional evaluation at admission to the PICU will allow identification of children at risk for further nutritional deterioration and, hence, candidates for interventions to optimize nutrient intake.

Assessment of Nutritional Status

Assessment of the nutritional status in the critically ill child is vital but often challenging. Clinicians use a combination of anthropometric and laboratory data to diagnose undernourishment. Carefully elicited past history with details of weight gain, dietary history, recent illness, and medications allows identification of risk factors for preoperative malnutrition. Weight on admission to the hospital is important and may be the only measure of the actual dry weight before capillary leak syndrome results in edema and weight gain. Unless regular and accurate weights are obtained, acute changes in nutritional status may be missed or detected late.[6] Children in the PICU are often not weighed as the procedure is deemed to be unsafe or not important. The lack of availability of reliable weight trends in PICU patients reflects the overall low priority among health care workers for nutritional assessment and, as a result, the true incidence of malnutrition in this cohort may indeed be underestimated. Physical examination should be directed toward specific signs of nutritional and metabolic deficiencies. Hair, skin, eyes, mouth, and extremities may reveal stigmata of protein-energy malnutrition or vitamin and mineral deficiencies.

A variety of other measurements including arm anthropometry (mid-upper arm circumference and triceps skin fold), body length, and body mass index have been used to monitor growth in children. In a study of infants and children admitted to the PICU, significant anthropometric abnormalities were detected by changes in mid-arm circumference and weight in correlation with energy deficits.[1] These anthropometric abnormalities accrued during the PICU admission returned to normal by 6 months after discharge. Using reproducible anthropometric measures, other investigators detected malnutrition in a majority of children on admission to their PICU.[7] Children with malnutrition had increased mortality compared with those without malnutrition.[7] On follow-up, a significant portion of children with malnutrition had further deterioration in nutritional status. Although bedside anthropometric methods are inexpensive, they are sporadically applied in hospitalized children, may be insensitive in the setting of critical illness, and are limited by significant interobserver variability. Weight changes and other anthropometric measurements in critically ill children should be interpreted in the context of edema, fluid therapy, volume overload, and diuresis. In the presence of ascites or edema, ongoing loss of lean body mass may not be evident using weight monitoring alone.

Body Composition

Body composition is emerging as a primary determinant of health and a predictor of morbidity and mortality in children. Preservation and accrual of lean body mass during illness are important predictors of clinical outcomes in patients with sepsis, cystic fibrosis, and malnutrition.[8,9] Body composition is measured by a variety of techniques including body densitometry by underwater weighing, neutron activation analysis, total-body potassium determination, bioelectrical impedance assessment (BIA), and dual-energy x-ray absorptiometry (DXA). Most of these methods are not practical for application in the clinical management of a critically ill child. DXA is a radiographic technique that can determine the composition and density of different body compartments (fat, lean tissue, fat-free mass, and bone mineral content) and their distribution in the body. DXA has been used extensively in pediatric practice for determining fat-free mass, fat mass, and lean mass, and it is recognized as a reference method for body composition research.[10] Its results correlate well with direct chemical analyses, and there is good agreement between percentage body fat estimated by hydrodensitometry and DXA.[11] However, DXA is not practical for application in the PICU. BIA, in contrast, is a bedside technique that can be applied to pediatric patients without exposure to radiation and with ease.[12,13] Electrical current is conducted by body water and is impeded by other body components. BIA estimates the volumes of body compartments, including extracellular water and total body water (TBW). TBW measures can be used to estimate lean body mass by applying age-appropriate hydration factors. BIA has not been validated in critically ill populations; hence, its use outside clinical studies is not recommended in the PICU. The ideal bedside body composition measurement technique in critically ill patients remains elusive.

Biochemical Assessment

The nutritional status can also be assessed by measuring the visceral (or constitutive) protein pool, the acute-phase protein pool, nitrogen balance, and resting energy expenditure (REE). Visceral proteins are rapid-turnover proteins produced in the liver. Low circulating levels of visceral protein are seen in the setting of malnutrition, inflammatory states, and impaired hepatic synthetic function. The reliability of serum albumin as

a marker of visceral protein status is questionable. Albumin has a large pool and a half-life of 14 to 20 days, and is not an indicator of the immediate nutritional status. Serum albumin may be affected by changes in fluid status, albumin infusion, sepsis, trauma, and liver disease, and these changes are independent of nutritional status. Prealbumin (also known as transthyretin or thyroxine-binding prealbumin) is a stable circulating glycoprotein synthesized in the liver. It binds with retinol-binding protein and is involved in the transport of thyroxine and retinol. Prealbumin, so named by its proximity to albumin on an electrophoretic strip, is readily measured in most hospitals and is a good marker for the visceral protein pool.[14,15] It has a half-life of 24 to 48 hours and reflects more acute nutritional changes. Prealbumin concentration is diminished in liver disease. Acute-phase reactant proteins are elevated proportional to the severity of injury in response to cytokines released during stress response and have been used to longitudinally monitor the inflammatory response. Serum levels of acute-phase protein are elevated in children within 12 to 24 hours after burn injury, due to hepatic reprioritization of protein synthesis.[16] When measured serially, serum prealbumin and C-reactive protein (CRP) are inversely related (i.e., serum prealbumin levels decrease and CRP levels increase, with the magnitude proportional to injury severity, and then return to normal as the acute injury response resolves). In infants after surgery, decreases in serum CRP values to less than 2 mg/dL have been associated with the return of anabolic metabolism and are followed by increases in serum prealbumin levels.[17] Proinflammatory cytokines such as interleukin 6 (IL-6) are recognized as early markers of the systemic inflammatory response syndrome (SIRS) in several disease models. Serum concentrations of IL-6 may be useful in identifying patients at risk for nutritional deterioration and to determine whether the inflammatory response is intact.

Chemistry profiles should be monitored on admission and repeated periodically. Serum electrolytes, blood urea nitrogen, glucose, coagulation profile, iron, magnesium, calcium, and phosphate levels are routinely monitored. Adequacy of cellular immunity can be estimated through the measurement of total lymphocyte count and by delayed-type hypersensitivity testing with a series of common antigens (e.g., *Candida*, *Trichophyton*, tuberculin).

Nutritional Requirements During Critical Illness

Metabolic Consequences of the Stress Response

The energy burden imposed by the metabolic response to injury, surgery, or inflammation may be proportional to the severity and duration of the stress, but cannot always be accurately estimated and varies in intensity and duration between individuals.

Importantly, nutritional support itself cannot reverse or prevent the metabolic stress response. Failure to provide optimal calories and protein during the acute stage of illness can result in an exaggeration of existing nutritional deficiencies or further exacerbate an underlying poor nutritional status. Respiratory compromise involving loss of respiratory muscle mass, cardiac dysfunction and arrhythmias involving loss of myocardial muscle tissue, and intestinal dysfunction involving loss of the gut barrier contribute to the morbidity and mortality of critical illness. In some cases, overestimation of this energy cost of metabolic stress may result in provision of energy in excess of requirement. Hence, large energy imbalances attributable to underfeeding and overfeeding in critically ill children must be avoided.[3] This requires an individualized nutritional regimen that must be tailored for each child and reviewed regularly during the course of illness. A basic understanding of the metabolic events that accompany critical illness and surgery is essential for planning appropriate nutritional support in critically ill children.

The unique hormonal and cytokine profile manifested during critical illness is characterized by an elevation in serum levels of insulin, glucagon, cortisol, catecholamines, and proinflammatory cytokines.[18] Increased serum counterregulatory hormone concentrations induce insulin and growth hormone resistance, resulting in the catabolism of endogenous stores of protein, carbohydrate, and fat to provide essential substrate intermediates and energy necessary to support maintenance energy and micronutrient needs in addition to the ongoing metabolic stress response. Figure 75-1 illustrates the basic pathways involved in the metabolic stress response.

In general, the net increase in muscle protein degradation, characteristic of the metabolic stress response, results in a large amount of free amino acids in the circulation. Free amino acids are used as the building blocks for the rapid synthesis of proteins that act as inflammatory response mediators and are used for tissue repair. Protein breakdown may continue for an extended period of time, in an attempt to channel the amino acids through the liver, wherein their carbon skeletons are used to create glucose through gluconeogenesis and for production of glucose as the preferred energy substrate for the brain, erythrocytes, and renal medulla. Reprioritization of protein during the metabolic stress results in increased synthesis of acute-phase reactant proteins such as C-reactive protein, α_1-acid glycoprotein, haptoglobin, α_1-antitrypsin, α_2-macroglobulin, ceruloplasmin, and fibrinogen. Plasma concentrations of other proteins, including transferrin and albumin, decrease with injury or sepsis. Overall intense protein catabolism outstrips anabolism with a net negative protein balance. This condition results in weight reduction and rapid loss of lean body mass. The intense catabolism seen in metabolic stress cannot be suppressed by supplying calories, and negative protein balance continues relentlessly. This is one of the principal differences between stress response and starvation. Starvation, or protein-calorie malnutrition, may be caused by socioeconomic, psychosocial, disease-related, or iatrogenic factors. The metabolic response to starvation involves decreased secretion of insulin and thyroid hormones, normal secretion of glucocorticoids and catecholamines, and decreased oxygen consumption. In starvation states, the body tries to preserve itself by using less energy for basic metabolic functions; thus, overall metabolic rate decreases. Metabolism shifts to use fat as a primary energy source, and the corresponding ketones help provide fuel for the brain and spare glucose and protein utilization. However, body tissues still must be broken down to supply amino acids for other critical functions, eventually leading to loss of lean body mass and vital organ wasting, and possibly death. Although, provision of additional proteins does not suppress protein catabolism, it may decrease the negative protein balance by increasing protein synthesis. Table 75-1 summarizes the basic differences between starvation and metabolic stress.

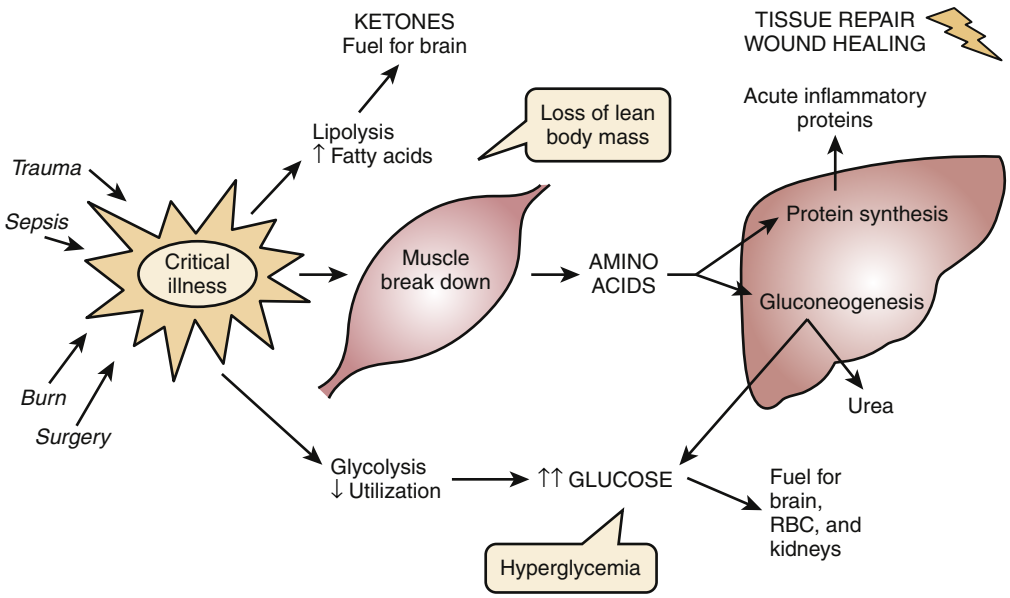

Figure 75–1. The metabolic response to stress. *(Modified from Mehta N, Jaksic T: The critically ill child. In: Duggan C, Watkins JB, Walker WA, editors:* Nutrition in pediatrics, *Hamilton, ON, 2008, BC Decker.)*

Table 75–1 Metabolic Stress vs. Starvation

	Metabolic Stress	Starvation
BMR	↑↑	↔↓
Oxygen consumption (Vo_2)	↑↑	↓
Protein catabolism	↑↑↑	↔
UUN	↑↑	↔
Weight loss	Rapid	Slow
LBM loss	Early	Late
Response to caloric intake	Protein catabolism continues	Protein catabolism halted
Insulin, cortisol, and catecholamines	↑↑	↓
Ketones	↑↑	↔
Gluconeogenesis	↑	↓

BMR, Basal metabolic rate; *UUN,* urinary urea nitrogen; *LBM,* lean body mass.

Supply of adequate nutritional intake under these circumstances is challenging, and yet recovery of critically ill patients depends on their ability to utilize energy substrates and synthesize new proteins. Carbohydrate turnover is simultaneously increased during the metabolic response, with a significant increase in glucose oxidation and gluconeogenesis. The administration of exogenous glucose does not blunt the elevated rates of gluconeogenesis, however, and net protein catabolism continues unabated.[19] A combination of dietary glucose and protein may improve protein balance during critical illness, primarily by enhancing protein synthesis. The stress response to injury stimulates lipolysis and increased rates of fatty acid oxidation.[20] Increased fat oxidation reflects the premiere role of fatty acids as an energy source during critical illness. Triglycerides in adipose tissue are then cleaved by hormone-sensitive lipase into fatty acids and glycerol. Fatty acids are oxidized in the liver for energy via the tricarboxylic acid or Krebs cycle. As seen with the other catabolic changes associated with stress response, the provision of dietary glucose does not decrease fatty acid turnover in times of illness. The increased demand for lipid use in the setting of limited lipid stores puts the metabolically stressed neonate or previously malnourished child at high risk for the development of essential fatty acid deficiency.[21,22] Preterm infants are most at risk for developing essential fatty acid deficiency after a short period of a fat-free nutritional regimen.[22,23] The beneficial effects of the acute metabolic response to illness/injury must be considered in relation to the harmful consequences of a persistently severe catabolic response. Nutritional therapy should aim to support the metabolic changes occurring during the acute catabolic stage. With resolution of a hypermetabolic stress response, an anabolic phase typically follows, with increased release of GH and IGF-1. Supply of adequate nutrition is essential for this recovery phase. In summary, the metabolic response to critical illness results in glucose and lipid intolerance and increased protein breakdown.

Underfeeding and Overfeeding in the Pediatric Intensive Care Unit

Individual assessment of energy requirements and provision of optimal nutritional support should be the standard of care. Both underfeeding and overfeeding are prevalent in the PICU, with resultant nutritional deficiencies that are associated with complications.[4,24] True energy expenditure during acute illness may not be easily predicted and several studies have documented discrepancies in measured versus equation-estimated energy expenditure.[25-27] Children with severe burn injury demonstrate extreme hypermetabolism in the early stages of injury. Standard equations have been shown to underestimate the measured REE in this population.[28] Unless increased energy requirements during the acute stage of such illnesses are accurately measured and matched by adequate intake,

cumulative energy deficits will ensue with decrease in weight, loss of critical lean body mass, and a worsening of existing malnutrition. Physicians have reported significantly escalated energy demands in a child with severe paroxysmal dysautonomia associated with ischemic brain injury. Failure to estimate this increased energy need resulted in underfeeding in this patient with severe weight loss during the course of illness in the PICU.[6] A variety of barriers, both unavoidable as well as some avoidable, exist that impede optimal nutrient delivery at the bedside and contribute to the likelihood of underfeeding in the PICU.[29,30] In the setting of fluid shifts, edema, and capillary leak in acute illness, some of these negative anthropometric outcomes may not be detected by the existing crude assessment techniques. Underfeeding during acute illness, with cumulative negative energy balance, has been associated with poor outcomes in critically ill adults.[31] However, energy imbalance in of the PICU population may also present in the form of cumulative energy excess due to unintended overfeeding. Indeed overfeeding in the PICU may be an underrecognized entity with a potential impact on patient outcomes.

Children do not predictably mount the characteristic hypermetabolic stress response as is seen in adults. The metabolic response to stress from injury, surgery, or illness is variable and the degree of hypermetabolism is unpredictable and unlikely to be sustained during a prolonged course in the PICU.[32] Critically ill children cannot be presumed to be hypermetabolic following acute illness or injury and energy expenditure may actually be decreased in some groups of patients.[33,34] While a sustained increase in metabolism has been reported for weeks after burn injury, REE peak returns to baseline within 12 hours after some surgical procedures.[35,36] Indeed children on extracorporeal life support or after surgery have failed to show any significant hypermetabolism, and measured energy expenditure is close to resting energy expenditure in these populations.[37] Critically ill children who are sedated and mechanically ventilated may have significant reduction in actual total energy expenditure, due to multiple factors. Decreased activity during illness, attenuation of insensible fluid losses in the controlled PICU environment, and transient absence of growth during the acute illness all keep total REE close to the basal rate, even in critically ill children. Historically, stress or activity correction factors have been traditionally factored into basal energy requirement estimates to adjust for the nature of illness, its severity, and the activity level of hospitalized subjects.[38,39] These patients may be at a risk of overfeeding when estimates of energy requirements are based on age-appropriate equations developed for healthy children, and especially if stress factors are incorporated in an attempt to account for the perceived hypermetabolic effects of the illness. Indirect calorimetry testing to determine the true metabolic state must be considered before incorporating stress factor correction to energy estimates in critically ill children. While the problems with underfeeding have been well documented, overfeeding too has deleterious consequences.[24,40] Overfeeding increases ventilatory work by increasing carbon dioxide production and can potentially prolong the need for mechanical ventilation. Overfeeding may also impair liver function by inducing steatosis and cholestasis, and increase the risk of infection secondary to hyperglycemia. There are no data in general pediatric populations for the role of hypocaloric feeding.[41] In general, the energy goals should be assessed and reviewed regularly in critically ill children.

Table 75–2 Recommended Energy and Protein Allowances During Critical Illness

	Age (Yr)	Energy (kcal/kg/day)	Protein (g/kg/day)
Infants	0–0.5	115	2.2
	0.5–1.0	105	2.0
Children	1–3	100	1.8
	4–6	85	1.5
	7–10	86	1.2
Males	11–14	60	1.0
	15–18	42	0.8
Females	11–14	48	1.0
	15–18	38	0.8

Data from the Food and Nutrition Board, National Academy of Science, National Research Council, ed 9, Washington, DC, 1980.

Assessing Energy Expenditure in Critically Ill Patients

Although the Food Agricultural Organization and the World Health Organization (WHO) have recommended that energy requirements and dietary recommendations be based on measurements of energy expenditure, the resources and expertise for such measurements are not easily available in all units. Current recommendations for nutritional requirements of the critically ill child are derived from limited data, based on studies in healthy children and based on limited methodologic approaches. Table 75-2 summarizes recommended energy and protein intake for critically ill children. Recommendations for pediatric nutritional requirements have traditionally focused on the supply of nutrients for growth. The components of total energy expenditure in children include (1) basal metabolic rate (BMR) 70%, (2) diet-induced thermogenesis (DIT) 10%, (3) energy expended during physical activity (PA) 20% and (4) energy expended for growth. The sum of these components determines the energy requirement for an individual. The traditional components of energy expenditure in healthy children may not apply during critical illness (see Table 75-3). Thus, prescribing optimal energy for the critically ill child requires careful review of each component of total energy expenditure.

Previous recommendations for energy requirements were based on estimates of basal metabolic rate or REE derived by either indirect calorimetry or standard equations.[34,42] Studies examining the performance of estimated energy needs in relation to measured REE in critically ill children are small-sized prospective or retrospective cohort studies. REE estimates have a large individual variability, and predictive equations are unreliable, particularly in underweight, overweight, or critically ill children.[27,43,44] Newer equations have attempted to improve the prediction of REE in children by accounting for weight-based groups or by including pubertal staging, with variable success.[44,45] These equations have not been satisfactorily validated in critically ill children.[46]

Table 75–3 Components of Energy Expenditure: Normal Health vs. Critical Illness

Component	Normal Health	Critical Illness
BMR (60%–70%)	Energy needed for maintaining vital processes of the body Measured in a recumbent position, in a thermoneutral environment after 12–18 hours fast, when the individual has awakened before starting daily activities Not practical for bedside Sleeping energy expenditure, a component of BMR was shown to be equal to REE = 0.9 Corresponds to lean body mass	Related to metabolic state May be increased in conditions such as inflammation, fever, acute or chronic disease (e.g., cardiac, pulmonary) Related to lean body mass
REE (50%–60%)	BMR + 10% Usually measured instead of BMR REE is measured at rest in a thermoneutral environment, after 8–12 hours fast and not immediately after awakening	Measured by indirect calorimetry with steady-state conditions
DIT or TEF (10%)	Reflects the amount of energy needed for food digestion, absorption, and part of synthesis	Increased energy needs following enteral feeding return to baseline approximately >4 hours of feeding
Growth (variable)	Energy for growth may be higher is healthy infants <2 years and during catch-up growth	Probably halted?
PA (variable)	Depends on age, activity level Decreased in hospitalized patients	Sedation, muscle relaxants, decreased activity
Stress	—	Variable Probably overestimated during critical illness
Total energy expenditure	REE + DIT + PA + Growth	Probably close to REE in most critically ill children Addition of stress factors may be necessary where relevant

BMR, Basal metaboic rate; *REE,* resting energy exenditure; *DIT,* diet-induced thermogenesis; *TEF,* thermic effect of food; *PA,* physical activity.

The variability of the metabolic state may be responsible for the failure of estimation equations in accurately predicting the measured REE in critically ill children. The application of stress factors might predispose some patients to the risk of overfeeding. Hence, it might be prudent to refrain from using these corrections in the absence of an accurate measurement of REE. Application of hypocaloric feeding has been recommended in critically ill adults.[47] There is not enough evidence to recommend its general use in critically ill children.

Indirect Calorimetry

Historically, indirect calorimetry (IC) has been regarded as the gold standard for accurate measurement of REE. Energy expenditure is obtained by measuring the volume of oxygen consumed (Vo_2) and the volume of CO_2 produced (Vco_2) over a period of time.[48] From this estimate the 24-hour energy intake is derived. Measurements of Vo_2 and Vco_2 are used to calculate REE using the modified Weir equation: REE = [Vo_2 (3.941) + Vco_2 (1.11)] × 1440. This technique has been validated in healthy children by using a whole-body chamber to allow 24-hour measurement. For obvious reasons, the whole-body chamber cannot be used in critically ill children.

The application of IC in different PICU populations has shown the variability in energy expended during illness. Weekes and Elia showed a relatively higher resting metabolic rate in critically ill children (37% higher than the resting metabolic rate of age-matched healthy controls).[49] However, the total energy expenditure was reduced in a group of head-injured children receiving enteral nutrition. Energy expenditure was noted to decrease over time and returned to normal after the second week of injury. In critically ill mechanically ventilated children, use of sedation and muscle paralysis decreases the component of energy requirement related to physical activity,[50] and caloric needs in the critically ill child may be lower than previously considered. IC continues to be only sporadically applied in critically ill children, despite mounting evidence of the inaccuracy of estimated basal metabolic rate using standard equations. This could potentially subject a subgroup of children in the PICU to the risk of underfeeding or overfeeding. However, IC application is not feasible in all patients due to (1) specific subject requirements, (2) device limitations, and (3) need for expertise and resources. Table 75-4 describes some of the common problems associated with IC testing in critically ill children. In the era of resource constraints, IC may be applied or targeted for certain high-risk groups in the PICU.[3] Selective application of IC may allow many units to balance the need for accurate REE measurement and limited resources (see Box 75-1 for suggested criteria for targeted IC).[51] While IC application has illuminated our understanding of energy expended during critical illness, this has yet to be translated into improving patient outcomes. Studies examining the role of simplified IC technique, its role in optimizing nutrient intake, its ability to prevent overfeeding or underfeeding in selected subjects, and the cost-benefit analyses of its application in the PICU are desirable. The effect of energy intake on outcomes needs to be examined in pediatric populations, especially in those on the extremes of body mass index (BMI).

Table 75–4 Factors Associated with Inaccurate or Unreliable Indirect Calorimetry Measurements

Error in V_{CO_2} Measurement	Limitations or Mechanical Issues with the Device	Failure to Reach Steady State
Air leak >10% around endotracheal tube	High inspired F_{IO_2} (>60%)	Recent interventions (suctioning, painful procedure)
Air leak in the circuit	Calibration issues	Fever, seizures, dysautonomia
Chest tube for pneumothorax	Moisture or obstruction due to water in the circuit	Recent change in ventilator settings
		Study period too short

Box 75–1 Suggested Criteria for Targeted Indirect Calorimetry[3,51]

Children at high risk for metabolic alterations who are suggested candidates for targeted measurement of REE in the PICU include the following:

- Underweight (BMI <5th percentile for age), at risk of overweight (BMI >85th percentile for age), or overweight (BMI >95th percentile for age)
- Children with >10% weight gain or loss during ICU stay
- Failure to consistently meet prescribed caloric goals
- Failure to wean, or need to escalate respiratory support
- Need for muscle relaxants for >7 days
- Neurologic trauma (traumatic, hypoxic, and/or ischemic) with evidence of dysautonomia
- Oncologic diagnoses (including children with stem cell or bone marrow transplant)
- Children with thermal injury
- Children requiring mechanical ventilator support for >7 days
- Children suspected to be severely hypermetabolic (status epilepticus, hyperthermia, systemic inflammatory response syndrome, dysautonomic storms, etc.) or hypometabolic (hypothermia, hypothyroidism, pentobarbital or midazolam coma, etc.)
- Any patient with ICU length of stay >4 weeks may benefit from IC to assess adequacy of nutrient intake

Another method of energy expenditure determination is based on the use of doubly labeled water; however, at this time the technique remains confined to research settings. Stable isotope technique has been available for many years and was first applied for energy expenditure measurement in humans by Schoeller and van Santen[78] in 1982. Isotope studies using doubly labeled water have since been validated and, following intense and skeptical scrutiny, have now been established as a "gold" standard for total energy expenditure estimation with widespread application.[43,74–77] In this method, stable isotopes of water (^2H_2O and $H_2{}^{18}O$) are administered orally. They mix with the body water and the ^{18}O is lost from the body as both water and CO_2, while the ^2H is lost from the body only as water. The difference in the rates of loss of the isotopes ^{18}O and ^2H from the body reflects the rate of CO_2 production, which can be used to calculate the total energy expenditure. This method has advantages in children because of its noninvasive nature. However, isotope decay is measured over two half-lives of the isotope, and hence the technique only gives an average estimate of total energy expenditure over a period of a few days. Analytical errors in the mass spectrometric estimation of isotope enrichment, isotope fractionation during CO_2 formation or vaporization of water, and the calculation of total body water or respiratory quotient are factors that might introduce errors in the estimation of total energy expenditure with this technique. If the necessary conditions are met, the doubly labeled water technique is currently the best method for estimating energy expenditure, because expired gas analysis is not required, and serial measurements of stable isotopes in urine samples provide an objective assessment of energy expenditure over a period of 4 to 21 days. However, the doubly labeled water technique for determination of energy expenditure is difficult to use in critically ill children because it requires fluid balance in the steady state. This is a major problem in the critically ill child with active capillary "leak" syndrome. Hence decreased urinary output, capillary leak syndrome, use of diuretics, or fluid overload exclude the use of this technique. The isotope costs and availability may be concerns, and the doubly labeled water technique cannot measure brief periods of peak energy expenditure.

Recently, investigators have proposed hypocaloric diets in critically ill adults.[58,66] Administration of high-calorie (glucose-load) diets during the acute phase of illness may exacerbate hyperglycemia, increase carbon dioxide generation with increased load on the respiratory system, promote hyperlipidemia resulting from increased lipogenesis, and result in a hyperosmolar state. Hypocaloric diets may have a protein-sparing effect, and have demonstrable benefits in critically ill obese patients. Overfeeding critically ill children is associated with net lipogenesis, hepatic steatosis, liver dysfunction, and increased CO_2 production and difficulty in ventilator weaning.[55] However, it is uncertain if administration of energy intake lower than the measured expenditure is appropriate for the critically ill pediatric patient.

In summary, energy expenditure must be carefully evaluated throughout the course of critical illness using measurements where available. In patients meeting the requirements for this test, IC provides an accurate measurement of REE. IC may be applied in specific patient groups targeted due to risk of metabolic instability and may help prevent unintended underfeeding and overfeeding in these patients. In the absence of measured REE, equation-estimated REE may be used. However, the uniform application of stress factors is not advisable and must only be used in individual cases after careful evaluation. Once energy needs are determined, the optimal substrate required for maintenance of energy needs is mixed fuel (glucose and fat). The proportion of each varies according to the clinical situation. See Table 75-2 for recommended macronutrient requirements for critically ill children.

Protein Requirements

Protein turnover and catabolism are increased several-fold in critically ill children. An advantage of high protein turnover is that a continuous flow of amino acids is available for the synthesis of new proteins. Specifically, this process involves a redistribution of amino acids from skeletal muscle to the liver, wound, and other tissues involved in the inflammatory response. This allows for maximal physiologic adaptability at times of injury or illness. The catabolism of muscle protein to generate glucose

and inflammatory response proteins is an excellent short-term adaptation, but it is ultimately limited because of the reduced protein reserves available in children and neonates. Although children with critical illness have increases in both whole-body protein degradation and whole-body protein synthesis, it is the former that predominates during the stress response. Children, especially preterm infants, have reduced macronutrient reserves, with less than half the protein content of adults.[52] The ill effects of negative protein balance may not be tolerated by infants and malnourished children with already decreased or depleted lean body mass reserves.

Unlike during starvation, the provision of dietary carbohydrate alone is ineffective in reducing the protein catabolism or endogenous glucose production via gluconeogenesis in the metabolically stressed state.[19] Therefore, without elimination of the inciting stress for catabolism (i.e., the critical illness or injury), the progressive breakdown of muscle mass from critical organs results in loss of diaphragmatic and intercostal muscle (leading to respiratory compromise) and the loss of cardiac muscle.[53,54] The amount of protein required to optimally enhance protein accretion is higher in critically ill than in healthy children. Infants demonstrate 25% higher protein degradation after surgery and a 100% increase in urinary nitrogen excretion with bacterial sepsis.[53,54] The provision of dietary protein sufficient to optimize protein synthesis, facilitate wound healing and the inflammatory response, and preserve skeletal muscle protein mass is the most important nutrition intervention in critically ill children. A supply of adequate proteins and energy intake improves protein balance by increasing protein synthesis, although protein breakdown is not affected. The amount of protein required to maintain a positive nitrogen balance may vary according to the severity of illness. Furthermore, the ideal amount and proportion of amino acids required during critical illness are not known. This is relevant because amino acids and other nutrients not only serve a nutritional role but also are actively involved in physiologic and pathophysiologic processes and may act as pharmacologic agents. Nitrogen balance varied in critically ill patients receiving different amounts of branched-chain amino acids in parenteral formula.[55] Sulfur amino acid metabolism in septic children is impaired, and the rates of cysteine oxidation are decreased and plasma cysteine fluxes are increased, suggesting increased protein breakdown to supply cysteine and spared cysteine catabolism by decreased rates of oxidation.[56] Further studies to determine the individual requirement of specific amino acids under catabolic conditions are necessary, particularly in view of the important functions of amino acids, not only in protein synthesis but as signaling molecules[57] and precursors for important substrates such as glutathione[58] and methyl group donors.[59] Alternatively, excessive protein administration could be deleterious, particularly in children with marginal hepatic or renal function. Neonates with higher protein intakes have been shown to develop azotemia, pyrexia, and possible long-term detrimental effects on cognitive development.[60,61] Hence further studies on specific nutritional and functional requirements of amino acids are needed.

Lipid Requirements

Nonprotein calories are commonly provided as carbohydrates (55% to 65%) and fat (35% to 45%). In the absence of adequate lipid supplementation in the diet, critically ill children, who have depleted lipid stores at baseline, are likely to suffer essential fatty acid deficiency.[67] Lipid administration is generally restricted to 30% to 40% of the total calories, and after an initial prescription of 1 g/kg/day, it may be gradually increased to 2 to 4 g/kg/day, depending on the tolerance level. Triglyceride levels should be regularly monitored for lipid tolerance. Concentrated lipid formulas (Intralipid 20%) should be used, given the limitation on fluid volume for administration of nutritional support.

Micronutrient Requirements

Micronutrients play significant physiologic roles. Beneficial effects of micronutrients such as fat-soluble vitamins (A, D, E, and K), water-soluble vitamin (C), zinc, selenium, and folic acid have been described in selected groups of patients in well-defined settings. The presumed safety of micronutrients and probably exaggerated efficacy and generalized applicability to heterogeneous populations are factors that may be responsible for the widespread prescription of these compounds.[62] Commercially available antioxidant nutrients need to be scrutinized for optimal dosage and side effects in the clinical setting where they are most likely to be beneficial. Hospitalized patients, especially those with critical illness, currently receive these additives in accordance with Food and Nutrition Board recommendations for daily allowances.

The antioxidant properties of certain micronutrients have renewed interest in their role during critical illness.[63] Vitamins C and E have important antioxidant activities. Selenium has also been shown to be a critical micronutrient with antioxidant functions in patients with thermal injury and trauma.[64] A complex system of special enzymes, their cofactors (selenium, zinc, iron, and manganese), sulfhydryl group donors (glutathione), and vitamins (E and C) form a defense system to counter the oxidant stress seen in the acute phase of injury or illness. Critically ill patients may have variable deficiencies of micronutrients in the early phase of illness. Vitamins and trace elements are redistributed from the central circulation to tissues and organs during the systemic inflammatory response syndrome (SIRS).[63] Levels of trace elements, such as iron, selenium, and zinc, and water-soluble vitamins are decreased, whereas copper and manganese levels may be increased.[65] In addition, trauma and thermal injuries are characterized by extensive losses of biologic fluids through wound exudates, drains, and hemorrhage, which cause negative micronutrient balances. The reduced stores of these enzyme cofactors, vitamins, and trace elements decrease rapidly after injury and remain at subnormal levels for weeks. Low endogenous stores of antioxidants are associated with an increase in free radical generation, augmented systemic inflammatory response, cell injury, and increased morbidity and mortality in the critically ill.[66,67]

Recently, there has been increased interest in the role of vitamin D as an antioxidant. Serum levels of vitamin D are decreased in children with severe burns.[68] Vitamin D status may be compromised for months after burn injury. Indeed, recent studies have reported the prevalence of vitamin D deficiency in the general population.[69-73] Future studies examining the associations between vitamin D deficiency and altered immunity, infectious risk, and illness severity are under way. These studies are expected to highlight the application of vitamin D replacement in deficient subjects and its role in influencing outcomes from illnesses. The concept of early

micronutrient supplementation to prevent the development of acute deficiency, to rectify the oxidant-antioxidant balance, and to reduce oxidative-mediated injuries to organs has driven recent trials in critically ill patients.[74] Antioxidant research in the critically ill has focused on copper, selenium, zinc, vitamins C and E, and the vitamin B group. Most of these studies were performed in relatively small patient populations presenting with heterogeneous diseases, such as trauma, burns, sepsis, or acute respiratory distress syndrome, however, and thus are underpowered to detect a treatment effect on clinically important outcomes. Heyland and colleagues performed a systematic review of trials supplementing critically ill patients with antioxidants, trace elements, and vitamins with an aim to improve survival.[63] They concluded that trace elements and vitamins that support antioxidant function, particularly high-dose parenteral selenium alone or in combination with other antioxidants, are reportedly safe and may be associated with a reduction in mortality in critically ill patients.

Electrolyte management in critically ill children can be complicated because of existing deficiencies, fluid shifts, increased insensible losses, drainage of bodily secretions, and renal failure. Intravenous fluids or parenteral nutrition (PN) prescriptions need to be reviewed daily in light of the basic electrolyte and blood sugar levels. In children with significant gastrointestinal fluid loss (gastric, pancreatic, small intestinal, or bile), the actual measurement of electrolytes from the drained fluid may assist in prescribing replacement fluids. Acute changes in serum electrolytes that require urgent electrolyte replacement must not be managed by changes in the PN infusion rate or composition, because this method may be imprecise and potentially dangerous. Phosphate and magnesium levels are often abnormal in critically ill children, especially in those with existing nutritional deficiencies, sepsis, or ongoing nutritional deprivation.

Enteral Nutrition in Critically Ill Children

Enteral nutrition (EN) is the preferred mode of nutrient intake in critically ill patients with a functional gastrointestinal system, due to its lower cost and complication rate when compared to parenteral nutrition (PN).[51] Early institution of EN is associated with beneficial outcomes in animal models and human studies[63] and has been increasingly implemented during critical illness, often using nutrition guidelines or protocols.[75] Early enteral nutrition has been shown to decrease infectious episodes and decrease the length of hospital stay in critically ill patients.[76] Pediatric studies have shown successful implementation of early enteral nutrition using institutional protocols.[75,77] Figure 75-2 provides an example of an approach to instituting and maintaining EN in the PICU. Although early EN has been adopted in most units, subsequent maintenance of enteral nutrient delivery remains elusive, as EN is frequently interrupted in the intensive care setting for a variety of reasons, some of which are avoidable.[30,78] Frequent interruptions in enteral nutrient delivery may affect clinical outcomes secondary to suboptimal provision of calories and reliance on PN. It has been reported that EN is interrupted in a third of patients in the PICU who were started on EN.[29] EN was frequently interrupted for avoidable reasons. Patients experiencing avoidable EN interruptions had more than a threefold increase in the use of PN and significant delay in reaching caloric goals. This collaborative study, examining bedside nutrition practice, illustrates some of the challenges to the provision of nutrition support and highlights opportunities for practice modification. Fasting for procedures and intolerance to EN were the commonest reasons for prolonged EN interruptions. Interventions aimed at optimizing EN delivery must be designed after examining existing barriers to EN and directed at high-risk individuals who are most likely to benefit from these interventions. Knowledge of existing barriers to EN, such as those identified in this study, will allow appropriate interventions to be planned. Intolerance to enteral feeds may be a limiting factor, and supplementation with parenteral nutrition (PN) in this group of patients allows earlier optimal nutritional intake. Taylor and colleagues reviewed nutritional delivery in a group of 95 children in a PICU over a 12-month period and made similar observations.[79] Children received a median of 58.8% (range 0% to 277%) of their estimated energy requirements in this investigation. Enteral feeding was interrupted on 264 occasions to allow clinical procedures. Rogers and colleagues reviewed nutritional intake in 42 patients admitted to an Australian tertiary-level PICU over 458 ICU days.[30] When actual energy intake was compared with estimated energy requirement, only 50% of patients had received their full estimated energy requirements after a median of 7 days in the ICU. Prolonged fluid resuscitation is a major factor hindering the achievement of estimated energy requirements, despite maximizing the energy content of feeds. Other contributing factors included interruption of feeds for procedures, enteral feed intolerance, and cooling. Protocols for use of transpyloric feeding tubes and changing from bolus to continuous feeds during brief periods of intolerance are strategies to achieve estimated energy requirements in this population. Box 75-2 summarizes some of the barriers to successful enteral feeding in the PICU.

The role of enteral nutrition has expanded beyond that of growth and nutritional rehabilitation. Newer components introduced in enteral feeds include l-arginine, glutamine, taurine, nucleotides, omega-3 and omega-6 fatty acids, carnitine, growth factors, probiotics, and probiotics. Disease- and health-modulating effects of these additives are becoming increasingly understood, and they may have application in the management of a subset of critically ill children with specific illnesses.

Enterally administered feeds meet nutritional requirements in critically ill children with a functional gastrointestinal system and have the advantages of cost, manageability, safety, and preservation of gastrointestinal function. Early introduction of enteral feeds in critically ill patients helps to achieve positive protein and energy balance and restores nitrogen balance during the acute hypermetabolic state of illness. Enteral nutrition elicits release of growth factors and hormones that maintain gut integrity and function.[8] Despite its perceived benefits, current practice in ICUs indicates a significant proportion of eligible patients are deprived of enteral feeds.[36] An aggressive protocol for early intragastric feeding was applied to 71 critically ill children, using full-strength enteral formula started within 12 hours of enrollment and advanced to target volumes of energy intake.[10] In this study, increases in caloric intake were well-tolerated by the children and reached predicted basal metabolic rate by day 1 and predicted REE by day 4. Children who were successfully fed had a lower mortality than those who did not respond to the early poststress intragastric feeding. The majority

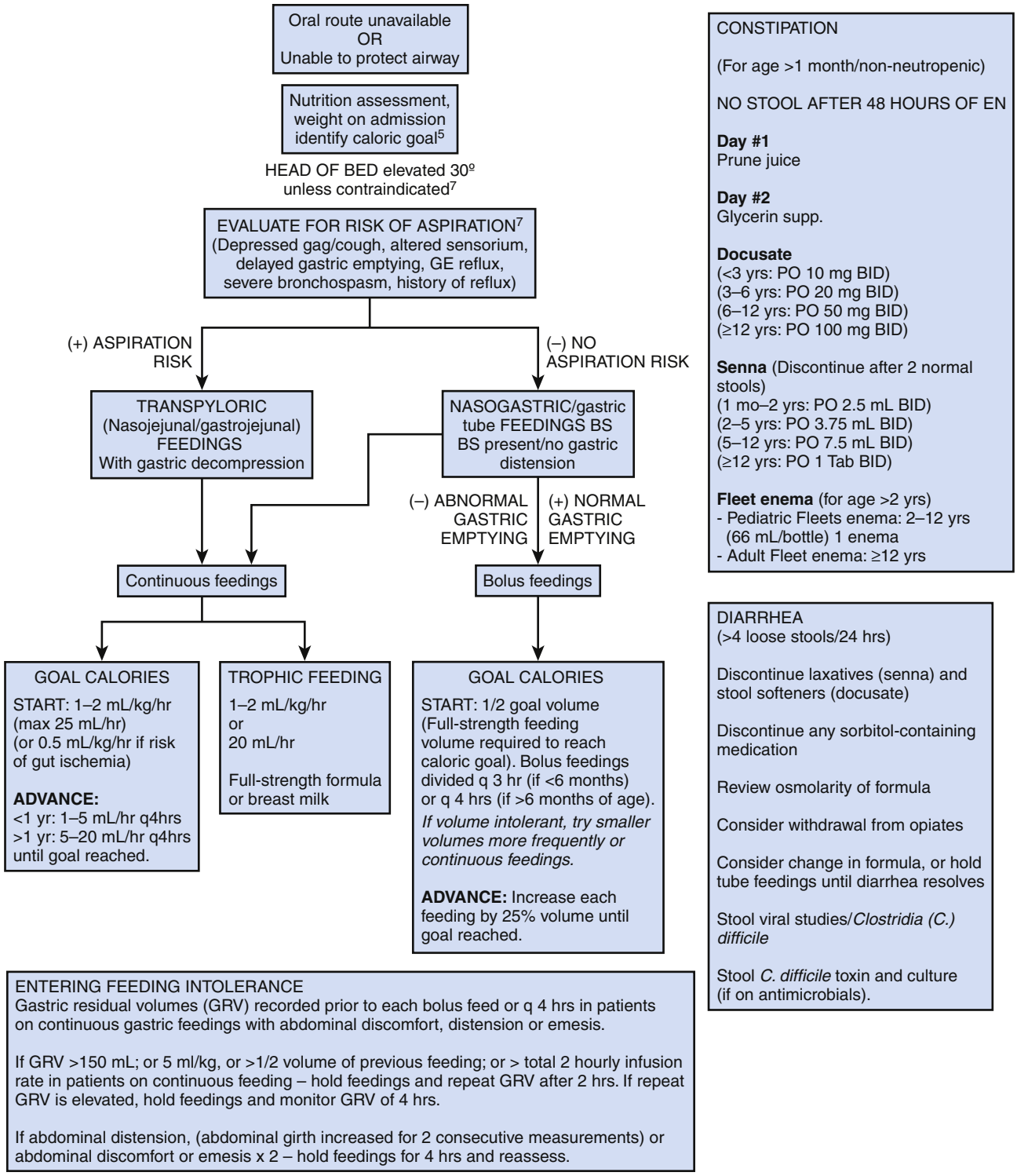

Figure 75-2. Enteral nutritional support algorithm. *(Modified from Mehta NM: Approach to enteral feeding in the PICU,* Nutr Clin Pract *24:377, 2009.)*

of children who did not respond to the early enteral feeding strategy were sicker and exhibited nonreversible septic shock and significantly lower ejection fractions on echocardiography.

Enteral feedings are indicated early in the course of critical illness if peristalsis has been established. Postpyloric feedings are recommended because of gastric distension and hypomotility. Feeds can be administered into the stomach or jejunum with the aid of feeding tubes inserted nasally or orally. Intragastric or intrajejunal feeding tube tip placement should be confirmed by radiography. Softer tubes constructed from silicone or polyurethane may be inserted using stylets at the bedside. Insertion of jejunal feeding tubes may require fluoroscopic or endoscopic guidance.

Postpyloric tubes provide the opportunity to feed a subset of children for whom intragastric feeding has not succeeded or is deemed unsafe. Postpyloric feeding is increasingly

Box 75–2 Barriers to EN Delivery in the PICU

Fasting before procedures
- Endotracheal tube–related procedures (intubation, extubation)
- Major operative procedures
- Other procedures requiring general anesthesia
- Bedside procedures requiring sedation
- Radiology suite or interventional radiology procedures

Fluid restriction

Delay in establishing enteric tube for feeding
- Delay or difficulty in enteric tube placement
- Malpositioned, obstructed, or displaced enteric tube

Gastrointestinal dysfunction
- Malabsorption, diarrhea, or severe constipation
- Ileus associated with opioid use or postoperative status

Patients at risk of aspiration of gastric contents

Holding EN for perceived intolerance
- High gastric residual volume
- Abdominal distension or discomfort
- Vomiting or diarrhea

Failure to implement evidence-based uniform algorithmic approach to EN
- Delay in initiating EN

adopted to feed children with reflux or delayed gastric emptying who are at risk for aspiration. Placement is not always successful, and a variety of novel techniques have been used to facilitate postpyloric placement. These methods rely on gravity and gut peristalsis to advance the tube tip past the pylorus. Because difficulty in tube placement can be anticipated in some patients, endoscopy or fluoroscopy guidance should be used, which avoids the rare occurrence of adverse events (such as perforation) and pancreatitis seen during blind enteral tube placement.

Surgical placement of gastrostomy or jejunostomy tubes allows long-term enteral feeding and administration of drugs in selected patients during intensive care and after discharge from the ICU. The advent of percutaneously placed gastric and jejunal tubes has minimized cost, time, and morbidity. Stoma site infection, obstruction, and tube dislodgment are common complications and must be identified and managed early. Tube tip malposition is frequently encountered with any of these devices either at placement or during the course of their use. Bedside screening methods for ascertainment of correct tip position range from auscultation during air insufflation to ultrasound-guided tip localization. However, feeds should be held when malposition of tip is suspected; when in doubt, radiographic confirmation of correct tip position should be obtained before recommencing feeds.

Immune-Enhancing Diets for the Critically Ill Child

In 1996, Bone and colleagues[80] outlined the role of the compensatory antiinflammatory response (CARS), which follows the initial proinflammatory response by the body challenged with an insult or infection. The antiinflammatory response was believed to be the second phase of a biphasic, highly coordinated inflammatory response and was aimed at keeping the proinflammatory response under control. It is clear that immunomodulation plays a significant role in the nature of response to infectious insult and impacts outcome in children with sepsis admitted to the ICU. Therapies aimed at modulating or stimulating the immune response have yet to be validated in children.

Immune-enhancing diets (IEDs) have been available for many years, and their role in the care of critically ill patients remains controversial. An increasing number of studies examining the effect of IEDs in various clinical populations and related meta-analyses continue to provide conflicting conclusions. Methodological flaws in conducting initial studies and the heterogeneous nature of the IED formulations used do not allow for dispelling current doubts regarding the safety and efficacy of these diets. The commercially available diets contain a mixture of compounds in varying doses, and the role of individual compounds is impossible to interpret. The immunomodulating effects of individual compounds are dose-dependent, and mixtures of different immunomodulating nutrients may have synergistic but also antagonistic effects. However, the compositions of the products compared in the meta-analyses are considerably different.

In a meta-analysis of randomized clinical trials examining the efficacy of enteral immunonutrients in adult patients, Heyland and colleagues selected 22 human studies, which included 2419 subjects.[81] There was no difference in mortality between the two groups, although patients who received enteral immunonutrition had a decreased incidence of nosocomial infections and decreased length of hospital stay compared with patients who received a standard enteral formula. The authors analyzed a subgroup of 13 trials involving critically ill patients. Duration of hospital stay was decreased in the experimental arm in this subgroup (treatment effect ~0.47 days; 95% confidence interval [CI] ~0.93 to ~1.01 days). When this subgroup of investigations was further subdivided into trials using experimental formulas with high arginine versus those using lower arginine content, mortality was noted to be higher in the studies using relatively lower arginine content formulas (risk ratio, 2.13; 95% CI, 1.08 to 4.21). A statistically insignificant trend toward decreased infectious complications in the high arginine group was reported. The high arginine group was associated with a shorter duration of hospitalization. This overview did not address the issue of the cost of intervention. Although an overall effect on mortality was not seen with immunonutrition intervention, some studies in the overview showed contrasting results. The study by Bower et al.[82] (n = 296) comparing IMPACT with Osmolite HN formula in critically ill adults demonstrated increased mortality (15.7%) in the immunonutrition (IMPACT) group versus the control group (8.4%). A subgroup analysis of patients designated as septic at baseline showed that mortality in the experimental arm (IMPACT) was almost three times higher (11/45 [25%]) than that in the control arm (4/45 [8.9%]).

A multicenter trial comparing enteral immunonutrition with PN conducted an interim subgroup analysis based on some reports suggestive of increased mortality in critically ill patients receiving immunonutrition.[83] Interestingly, the study was discontinued after the interim analysis. Analysis of 39 patients with sepsis or septic shock included in this interim analysis indicated mortality in the immunonutrition enteral arm (8/18 [44.4%]) was three times higher than that in the PN arm (3/21 [14.3%]).

Decreased length of hospital stay and decreased nosocomial infections in the treatment group were beneficial secondary

Table 75–5 Individual Immunonutrients and Potential Effects in Specific Critically Ill Adult Populations

Nutrient	General	Septic	Trauma	Burns	Acute Lung Injury
Arginine	No benefit	Harm	No benefit	No benefit	No benefit
Glutamine	PN beneficial (? receiving EN)	—	EN possibly beneficial	EN possibly beneficial	—
Omega-3 FFA	—	—	—	—	Beneficial
Antioxidants	Possible benefit	—	—	—	—

FFA, Free fatty acids.
Modified from Lee S, Gura KM, Kim S, et al: Current clinical applications of omega-6 and omega-3 fatty acids, *Nutr Clin Pract* 21(4):323-341, 2006.

outcomes reported by each of the three reviews/meta-analyses of studies examining the use of IEDs. In summary, no conclusive data on the beneficial effects of IEDs have been established. Proponents of immunonutrition argue that the inability to achieve goal volume of enteral feeds in most of the studies may be responsible for the lack of favorable effect on outcomes. ICU patients are heterogeneous, and the timing of intervention may be important in this subgroup of patients. The severity of illness in some patients may not be amenable to manipulation by immunonutrients, and careful selection of patients is essential to demonstrate benefit in subgroups. Future research should investigate the role of individual nutrients in select groups of patients. The novel concept of pharmaconutrition has been proposed where a disease-dedicated nutrition therapy is developed following a rigorous step-by-step procedure.[84] Nutrients are selected according to their pharmacological properties and after an in-depth evaluation of their biological interactions when mixed together. Table 75-5 summarizes a list of nutrients and their beneficial effects in specific populations in critical illness. The optimum administration schedule (i.e., dose, route, timing and duration) of the new formulae is then determined in well-conducted projective clinical trials where it is administered apart from the standard nutrition to ensure full delivery of the expected doses. Dose-response effect then identifies the essential components of immunonutrition at the correct doses. Future studies are required to prove if a critical volume must be reached in order to demonstrate a beneficial effect of these immunonutrients. There are insufficient pediatric studies evaluating the role of nutrition-based immunonutrition in critically ill children. The generalized use of immunonutrition for children in the PICU cannot be recommended.

Parenteral Nutrition

PN, or hyperalimentation, bypasses the gut, and instead utilizes intravenous administration of macronutrients and micronutrients to meet the nutritional requirements of the body, either partly (as a supplement to enteral feeds) or entirely (total PN). PN is indicated in children who are unable to tolerate enteral feeds for prolonged periods. In the setting of intact intestinal function, PN is not indicated if enteral feeds alone can maintain nutrition. Although widespread in its application, PN is associated with mechanical, infectious, and metabolic complications and hence should be used only in carefully selected patients.

Fluid and electrolyte status guides the initial PN prescription. Fluid restrictions limit the amount of calories delivered, despite use of a concentrated formula. PN should not be used for replacing ongoing losses. PN should be prescribed daily and after reviewing levels of electrolytes and blood sugar in order to allow adjustments in the macronutrient and micronutrient composition. The patient's hydration, size, age, and underlying disease dictate the amount of the fluid to be administered. Box 75-3 describes the calculations use to determine calories obtained from macronutrients in PN.

Box 75–3 Calculating Parenteral Nutrition Calories

Total carbohydrate (g): CHO/day × 3.4 kcal/g = CHO calories
1 g dextrose provides 3.4 kcal (most other CHO provide 4 kcal/g)
10% dextrose = 10 g dextrose/100 mL
Total protein (g): Protein/day × 4 kcal/g = Protein calories
1g protein provides 4 kcal
Total fat (20% lipids) (mL) × 2.0 kcal/mL = Lipid calories
(10% lipids = 1.1 kcal/mL)
Total calories = CHO + Protein + Lipid calories
Total nonprotein calories = CHO + Lipid calories

Carbohydrates

Carbohydrates are the major nonprotein source of energy. D-glucose is provided in the monohydrate form for intravenous administration and yields 3.4 kcal/g. The concentration of the dextrose solution should not exceed 10% for peripheral administration. In the setting of central venous access, a range of concentrations (5% to 40%) can be prepared. Higher glucose concentration makes the solutions hyperosmolar and may cause phlebitis or thrombosis and decrease the lifespan of the vessel when PN is administered peripherally through a vein. Blood glucose estimations must be followed carefully given the increased incidence of hyperglycemia, especially in young infants. Carbohydrate is started at 5 to 8 mg/kg/min. Gradually increasing the carbohydrate load allows an appropriate endogenous insulin response and prevents fluctuations in blood sugar. Abrupt cessation of PN may result in hypoglycemia and should be anticipated and avoided.[85] Fat is supplied as intralipid, which provides the other source of calories in PN and reduces carbon dioxide production and the water retention that is seen when carbohydrate is the sole source of calories.

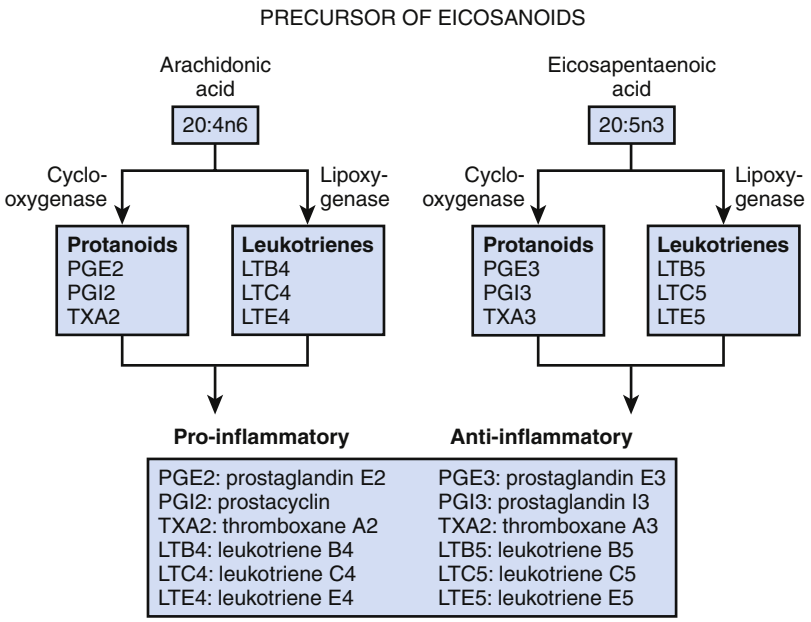

Figure 75–3. Omega-3 and omega-6 Fatty acid metabolites. *(Adapted from Lee S, Gura KM, Kim S, et al: Current clinical applications of omega-6 and omega-3 fatty acids,* Nutr Clin Pract *21[4]:323-341, 2006.)*

Amino Acids

One gram of protein yields 4 kcal. The initial recommended dosage range from 0.5 to 3 g/kg/day is based on age, disease state, and individual requirements. The usual available concentrations are between 1% and 4%, although patients with hepatic disease, renal insufficiency, and children with metabolic diseases (e.g., maple syrup urine disease) should receive appropriately modified concentrations. TrophAmine contains a higher percentage of branched-chain amino acids and a small amount of glycyl-cysteine. This solution is mainly used in the neonatal population. It is recommended and used in patients with hepatic encephalopathy and in children on long-term PN (e.g., short bowel), although data supporting this application are scarce. There is an increasing interest in the use of glutamine in PN. Glutamine, along with cysteine as glycyl-cysteine, is a precursor for glutathione, which is a major antioxidant. Glutamine is also a precursor for nucleotide synthesis, and although it is a nonessential amino acid, it can become conditionally essential, especially in catabolic states such as sepsis and trauma. Glutamine has a short shelf life. However, its applicability has been widespread. It has been introduced in PN solutions for its presumed benefits, such as restoration of protein and nitrogen balance, attenuation of gastrointestinal mucosal atrophy, and reduction of bacterial translocation and bacteremia after chemotherapy. The National Institute of Child Health and Development (NICHD) neonatal research network did not find significant differences in outcomes when a multicenter study randomized 1430 extremely low-birth-weight neonates to PN containing 20% glutamine or an isonitrogenous control. However, pediatric burn patients have been shown to have deficient peripheral glutamine production. In a double-blinded randomized control trial, glutamine-enhanced PN reduced gram-negative bacteremia in severely burned patients.[86]

Lipids

Lipids represent an integral part of PN and provide energy derived through fatty acid oxidation. Lipids are usually started at 0.5 to 1 g/kg and advanced to a maximum intake of 3 g/kg or a maximum 60% of total kilocalories. Lipid calories allow for a lower concentration of carbohydrate (lower osmolarity of PN). Lipid emulsions are available as 10% (1.1 kcal/mL) or 20% (2 kcal/mL). Intralipid prevents or treats essential fatty acid deficiency. The total lipid usually is delivered over an 18- to 24-hour period through separate tubing, using a Y-connector near the infusion site. Delivery of amino acid, glucose, and lipid (three-in-one) is no longer recommended for neonatal patients because of the risk of calcium phosphate precipitation being obscured by lipid in the preparation.

Lipids are a crucial source of nutrition in parenteral formulas. Traditionally considered a calorie-dense nutrient and a source of essential fatty acids, lipids in intravenous feeding regimens have added advantages, such as providing a more balanced energy expenditure and facilitating better respiratory function parameters. Fatty acid derivatives are major biologic modulators.[87] Figure 75-3 illustrates the basic pathways and inflammatory effects of fatty acid metabolites. The linoleic acid load, as a consequence of predominantly soy-based lipid in current formulations, results in increased arachidonic acid production and decreased production of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA).[88] Increased arachidonic acid levels may increase the proinflammatory cytokine production and activity. EPA levels may influence the production of antiinflammatory cytokines,[87] and DHA has been shown to lower blood pressure, improve endothelial function, and elevate levels of high-density and low-density lipoproteins.[89] Thus DHA and EPA, found in fish and fish oils, are essential fatty acids for humans. In an attempt to decrease the linoleic acid intake, soy-based oil has been partly replaced by medium-chain triglycerides, olive oil, or fish oil in intravenous emulsions. The metabolic roles of omega-3 polyunsaturated fatty acids are emerging. Parenteral fish oils may have immune modulatory function and have been applied for their beneficial effect in the perioperative period following major abdominal surgery.[34,86] Further research examining the efficacy and safety of different triglycerides, derived from medium-chain triglycerides, olive oil, and fish oils, will allow their application in specific disease conditions. Furthermore, in this era of nutrigenomics, the effect of fatty acids on genes

and proteins is being increasingly elucidated and will influence clinical practice. In the future, designer lipid formulations and molecules may be applied in parenteral or enteral nutrition regimens for their beneficial effects in specific disease conditions.

Electrolytes/Minerals and Trace Elements

All solutions are typically prepared with minimum acetate (i.e., all salts are added as chloride) unless prescribed otherwise. It is possible to prescribe an all-acetate solution with no chloride. Calcium and phosphorus precipitate when their concentrations exceed an allowable limit, related to the solubility index of $(Ca)_3(PO_4)_2$ and the pH of the solution. Selenium may not be routinely added to PN. A serum selenium level should be obtained if a patient requires PN for more than 30 days without enteral intake. Multivitamins and trace elements are routinely added to the PN, and recommended intakes are elucidated elsewhere.[90] Heparin usage in PN is practiced in many centers and has been shown to decrease catheter-related sepsis.[91] Heparin in concentrations of 0.5 to 1 U/mL is thought to prevent thrombosis and possibly phlebitis in peripheral lines, although there are no controlled trials showing significant benefit of heparin usage in PN.

Biochemical Monitoring

A PN profile is recommended at initiation of therapy and weekly thereafter. The profile includes serum levels of sodium, potassium, chloride, glucose, carbon dioxide, blood urine nitrogen, creatinine, albumin, magnesium, phosphate, total and direct bilirubin, and transaminases. For children requiring PN for more than 30 days, selenium, iron, zinc, copper, and carnitine levels should be checked. Daily vital statistics and routine anthropometry must be monitored to ensure adequate growth and development. Critical care units benefit from the expertise of a dedicated nutritionist, who should be consulted on a regular basis to guide optimal nutritional intake of patients.

Central venous access is required for delivery of hyperosmolar PN solutions into a large-bore vein with high-volume blood flow, to prevent thrombosis and phlebitis (see Chapter 15). The incidences of infective and life-threatening complications related to indwelling central lines have necessitated extreme caution with central PN use.[92,93] Central lines should be placed by experienced operators and line tip position confirmed by radiography before the lines are used for PN delivery. It is recommended that central line tips be positioned outside the cardiac chambers at all times. Central lines are recommended for delivery of infusates with osmolarity greater than 900 mOsm/L (10% dextrose, 2% amino acids with standard additives).

Refeeding Syndrome

Aggressive nutritional rehabilitation in malnourished patients or after prolonged starvation results in a constellation of biochemical and clinical features with cardiopulmonary complications. This well-described entity is called refeeding syndrome and is often unrecognized. Hypophosphatemia is the hallmark of refeeding syndrome, which is also associated with hypomagnesemia, hypokalemia, and fluid retention. Patients admitted to the PICU with nutritional deficiencies, those with chronic conditions causing malnutrition or those fasted for 10 to 14 days are at risk of refeeding syndrome following aggressive oral, enteral, or parenteral nourishment. Introduction of nutrition in these patients stimulates anabolism, with a switch from protein and fat catabolism to predominantly carbohydrate metabolism. Glucose becomes the primary energy source, leading to insulin release. Insulin-mediated cellular uptake of glucose causes intracelular shift of phosphate, potassium, and magnesium, thus rapidly lowering their serum levels. Insulin also causes sodium and fluid retention with rapid expansion of extracellular fluid volume. The clinical manifestations of refeeding syndrome are a result of the dyselectrolytemia and fluid overload, and involve cardiorespiratory, neuromuscular, and hematologic complications. Hypotension, respiratory failure, muscular weakness, confusion, seizures, coma ,and even death may result from refeeding syndrome.

Awareness of this syndrome, identification of at-risk patients and gradual introduction of nutrition in these individuals help prevent the refeeding syndrome. Calories may be introduced at 25% to 50% of requirement and increased 10% to 25% daily until the caloric goal is met. Careful monitoring of electrolytes and vigilance for clinical manifestations of the syndrome allow early detection of complications, and feeds are advanced in the setting of biochemical stability. Prompt correction of electrolyte abnormalities, close attention to fluid balance, and supplementation with multivitamins will help avoid the cardiorespiratory sequelae from refeeding in the critically ill child.

Nutritional Support of Obese Critically Ill Children

Overweight/obesity continues to increase in children and adolescents, and annual obesity-related hospital costs in 6- to 17-year-olds have reached $127 million per year. The severity of obesity is classified based on BMI into the following three categories: (1) overweight = BMI 25 to 30 kg/m^2, (2) obesity = BMI 30 to 40 kg/m^2, and (3) morbid obesity = BMI greater than 40 kg/m^2. Overweight children and adolescents are increasingly being diagnosed with impaired glucose tolerance and type II diabetes, and they show early signs of the insulin resistance syndrome and cardiovascular risk. Centralized distribution of body fat is associated with the risk of metabolic syndrome. Metabolic syndrome is observed in obese children and is characterized by visceral obesity, insulin resistance, and dyslipidemia. There is a high risk for type 2 diabetes and cardiovascular complications in patients with metabolic syndrome. Grossly overweight patients are prone to sleep apnea syndrome, restrictive lung disease, venous thrombosis, musculoskeletal degenerative disorders, hepatic steatosis, and metabolic disorders associated with bariatric surgery.

The metabolic response to stress in obese critically ill patients is complex, given that it occurs in a population with preexisting major metabolic and endocrine alterations. In critically ill obese patients, the pattern of substrate oxidation is mainly protein and glucose, with decreased fat oxidation.[94] The extent of protein breakdown is greater than in nonobese critically ill adults. No data on metabolic abnormalities of obese children are available. In the adult critically ill population, hypocaloric nutrition estimated for ideal weight has been recommended.[47] The limited adult literature suggests that

Box 75–4 Guidelines for Pediatric Critical Care Nutritional Support

Number	Guideline Recommendations	Grade
1A	Children admitted with critical illnesses should undergo nutrition screening to identify those with existing malnutrition and those who are nutritionally at risk.	D
1B	A formal nutrition assessment with the development of a nutrition care plan should be required, especially in children with premorbid malnutrition.	E
2A	Energy expenditure should be assessed throughout the course of illness to determine the energy needs of critically ill children. Estimates of energy expenditure using available standard equations are often unreliable.	D
2B	In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry (IC) is desirable. If IC is not feasible or available, initial energy provision may be based on published formulas or nomograms. Attention to imbalance between energy intake and expenditure will help prevent overfeeding and underfeeding in this population.	E
3	There are insufficient data to make evidence-based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based on understanding of protein metabolism and carbohydrate and lipid-handling during critical illness.	E
4A	In critically ill children with a functioning gastrointestinal tract, EN should be the preferred mode of nutrition provision, if tolerated.	C
4B	A variety of barriers to EN exist in the PICU. Clinicians must identify and prevent avoidable interruptions to EN in critically ill children.	D
4C	There are insufficient data to recommend the appropriate site (gastric vs. postpyloric/transpyloric) for enteral feeding in critically ill children. Postpyloric or transpyloric feeding may improve caloric intake compared with gastric feeds. Postpyloric feeding may be considered in children at high risk of aspiration or those who have not responded to a trial of gastric feeding.	C
5	Based on the available pediatric data, the routine use of immunonutrition or immune-enhancing diets/nutrients in critically ill children is not recommended.	D
6	A specialized nutrition support team in the PICU and aggressive feeding protocols may enhance the overall delivery of nutrition, with shorter time to goal nutrition, increased delivery of EN, and decreased use of parenteral nutrition. The effect of these strategies on patient outcomes has not been demonstrated.	E

From Mehta NM, Compher C: A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child, *J Parenter Enteral Nutr* 33(3):260-276, 2009.

protein requirements are higher in critically ill adult obese patients. It is recommended that fat be administrated sparingly, mainly to prevent essential fatty acid deficiency.[95] No data on the best nutritional support of critically ill obese children are available. Routine equations for tend to overestimate energy expenditure in obese patients. Energy requirement in this group should be guided by IC measurement of REE, where available. When REE is estimated, there is no consensus on the use of ideal body weight versus adjusted body weight. As the incidence of obesity in children admitted to the PICU is rising, future research aimed at addressing some of these knowledge gaps is desirable.

Guidelines for Pediatric Critical Care Nutrition

Due to the complexities of critical care, nutrient intake during critical illness is challenging (Box 75-4). The lack of robust evidence for many of the bedside decision-making around nutrition support in the PICU has resulted in heterogeneity in practice. Optimal nutrition support in the PICU cannot be achieved unless there is some uniformity in practice based on evidence or consensus and an attempt to systematically evaluate practice parameters for feasibility, efficacy, and impact on patient outcomes. However, the direct effect of nutritional strategies in a heterogeneous cohort of patients with varying degrees of illness severity is difficult to assess. Multiple factors influence outcome during critical illness. Due to these challenges, current literature is scarce and guidelines for pediatric critical care nutrition have been based on few good studies but mainly on smaller studies of expert opinion. In 2009, the American Society of Parenteral and Enteral Nutrition published the revised guidelines for pediatric critical care nutrition practice.[51] These guidelines were based on the best available evidence and help clarify the principles guiding nutrition therapy in the PICU population. Early enteral nutrition is recommended in critically ill children with a functional gastrointestinal tract. Careful assessment or measurement of energy expenditure with attention to unintended energy imbalance (due to underfeeding or overfeeding) seems prudent. Health care workers must work in a collaborative fashion to identify and prevent common barriers to nutrition support in the PICU. The application of indirect calorimetry and postpyloric feeding is currently limited to centers with available expertise and resources.

Conclusions

The accurate assessment of nutritional needs and the provision of individually tailored optimal nutrition support to the critically ill child are important goals of pediatric critical care. Malnutrition

and obesity are prevalent in the critical care population and have a significant influence on the outcome of critical illness. Furthermore, the hypermetabolic stress response places demands on the critically ill child that must be met with evidence-based nutrient supplementation. Intensivists must remain alert to the possibility of both underfeeding and overfeeding in order to prevent unintended cumulative energy imbalances in critically ill children. A multidisciplinary effort to overcome common barriers to nutrient delivery and the use of evidence-based algorithms will help achieve nutrition goals in the PICU.

Interest in immune-modulating effects of nutrients, micronutrient supplementation, and the role of newer sources of lipid formulations has introduced the concept of pharmaconutrients, but its benefits on outcome in the PICU have not been realized yet. Strict glycemic control is associated with a significant increase in the incidence of hypoglycemia. The feasibility of this strategy in the PICU will need to be examined in the setting of carefully designed studies. In the future, patients will benefit from individually tailored nutritional regimens suited to the type and stage of their illness. There are a number of knowledge gaps that need to be addressed by collaborative research. Until then, a multidisciplinary effort must be made to increase awareness of nutritional issues, adherence to institutional guidelines, and prioritization of nutrition support in the PICU.

References are available online at http://www.expertconsult.com.

Inborn Errors of Metabolism

Laurie Smith and Cary O. Harding

PEARLS

- Unexpected and unexplained clinical deterioration in a previously healthy infant or child is an important clue to the presence of an inborn error of metabolism (IEM).
- Loss of previously attained developmental milestones during childhood is an important clue to the presence of a neurodegenerative disorder such as lysosomal storage disease.
- Blood glucose less than 40 mg/dL is distinctly unusual after the first 24 hours of life, particularly in infants who have started feeding, and should be thoroughly investigated.
- Laboratory evaluation for inborn errors of metabolism should be undertaken in any child with a suggestive clinical history regardless of the results of newborn screening. A normal newborn screen, although perhaps reassuring, does not rule out the possibility of an IEM.
- With catastrophic illness in a previously well child without signs of any particular IEM, the "shotgun" diagnostic evaluation should minimally include plasma amino acid analysis, urine organic acid analysis by gas chromatography-mass spectrometry, and a so-called *urine metabolic screen*.

Metabolism can be defined as the sum of all biochemical processes that convert food to smaller molecules and energy for the purposes of structure and function. An inborn error of metabolism (IEM) is an inherited deficiency of any critical step in metabolism. Although genetic deficiency of catalytic enzymes in intermediary metabolic pathways is the classic paradigm for IEM, the pathophysiology of metabolic disorders may involve abnormalities of any number of cellular processes, including transmembrane transport, cell signaling, cell differentiation and development, energy production, and others. Many IEMs are individually rare, although a few, including phenylketonuria (PKU) and medium-chain acyl-coenzyme A (acyl-CoA) dehydrogenase deficiency (MCADD), a defect in fatty acid oxidation, exhibit a population incidence approaching 1:10,000 live births.[1,2] Specific IEMs may be more common in certain ethnic groups with a history of relative reproductive isolation. Collectively, the population incidence of all IEMs may approach 1:1500 live births, depending upon how broadly IEM is defined. Many IEMs are associated with catastrophic illness necessitating advanced life support. Although IEMs may present very rarely within the professional lifetime of the average medical practitioner, critically ill children with IEMs will not be uncommon visitors to the pediatric intensive care unit (ICU), especially in a tertiary care center.

The key to successful treatment of IEMs is the initial suspicion and timely diagnosis of the disorder. Certain features of the clinical history, physical signs and symptoms, and results of routine laboratory studies often suggest the possibility of IEM. Second-tier screening metabolic studies provide further evidence for the presence of a disorder. The results of routine neonatal screening studies may suggest a specific disorder prior to development of any diagnostic suspicion on the part of the clinician or even prior to the onset of symptoms in the neonate. In the case of a critically ill child with a suspected metabolic disease or with an abnormal neonatal screening test result for a specific metabolic disorder, immediate consultation with a biochemical geneticist, even if only by telephone, is paramount. The genetic consultant helps direct the diagnostic laboratory evaluation and recommends nonspecific emergency treatment, if any is warranted, prior to the availability of the definitive diagnostic studies. Communication among the intensivist, genetic consultant, and biochemical genetic diagnostic laboratory is critical to achieving the timely and correct diagnosis of IEM. A satisfactory clinical outcome for the affected child is completely dependent upon the collaborative efforts of this tripartite team approach.

Other published textbooks on the diagnosis and treatment of IEM provide an exhaustive list of known disorders.[3,4] Rather than recapitulate an encyclopedia of possible diseases, this chapter presents a diagnostic rationale based upon specific clinical symptom complexes that are likely to occur in the critically ill child. Algorithms for the differential diagnosis of specific clinical scenarios are given in support of this rationale. Symptoms often begin during early infancy in the biochemically most-severe IEMs; naturally, these IEMs with neonatal onset are the focus of our discussion in this chapter. However, "milder" or late-onset variants of virtually every IEM have been described, with onset of symptoms occurring at all ages, even during adulthood. Some IEMs uniformly present after the neonatal period; age of symptom onset (late infancy, childhood, or adulthood) often is an important clue to the specific diagnosis. The clinical presentation, diagnostic workup, and treatment of neonatal onset disorders provide a paradigm for the evaluation and management of possible IEM in a child of any age.

Pathophysiology of Inborn Errors of Metabolism

Under the classic paradigm, an IEM is associated with deficiency of a specific protein, often a catalytic enzyme, involved in a critical metabolic pathway (Figure 76-1). This deficiency leads to a block in the pathway and the accumulation of the

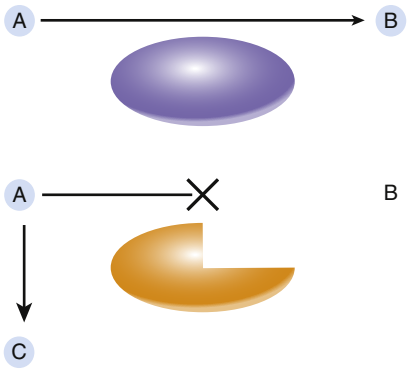

Figure 76–1. Inborn error of metabolism paradigm. Normally, in a given step of intermediate metabolism with intact enzymatic activity, the substrate A is efficiently converted to the product B. In an inborn error of metabolism, deficiency of enzyme activity may lead to excessive accumulation of the substrate; critical deficiency of the product; or production of an alternative, potentially toxic metabolite C through normally quiescent pathways.

enzyme substrate. In this model, three distinct pathogenic mechanisms are possible proximate causes of the symptoms associated with an IEM. The specific pathogenic mechanism involved in any given IEM dictates the appropriate treatment strategy. First, accumulation of the substrate may lead to toxic effects at very high levels; successful therapy requires effective elimination of the substrate or a method to block its toxic effects. An appropriate example for this mechanism is PKU, in which elevated phenylalanine levels adversely affect neuronal development, and the reduction of tissue phenylalanine content through dietary phenylalanine restriction largely prevents the major clinical features of PKU.[5] Second, deficiency of the reaction product, should it be a critically important metabolite, may lead to disease. Supplementation with the essential metabolite, if possible, may cure the disease. Biotin is a required cofactor for four distinct carboxylase enzymes. Deficiency of free biotin develops in the face of genetic biotinidase deficiency and leads to symptoms of multiple carboxylase deficiency. Supplementation with oral biotin completely prevents the clinical manifestations of biotinidase deficiency.[6] The final pathogenic mechanism involves the conversion of the enzyme substrate, through normally quiescent alternative pathways, to toxic secondary metabolites. Elimination or decreased production of these secondary metabolites may improve disease symptoms. For example, tyrosinemia type I (fumarylacetoacetate hydrolase [FAH] deficiency) is associated with recurrent attacks of abdominal pain and paresthesias reminiscent of acute intermittent porphyria. The accumulating substrate, fumarylacetoacetic acid, is converted through secondary pathways to succinylacetone, and succinylacetone in turn inhibits the heme synthetic pathway and causes porphyria-like symptoms. Pharmacologic inhibition of the tyrosine catabolic pathway proximal to the block at FAH decreases the production of fumarylacetoacetic acid and succinylacetone and alleviates the pathology associated with these toxic compounds.[7]

Inheritance of Inborn Errors of Metabolism

IEMs are heritable disorders. The majority of diseases are inherited in an autosomal-recessive pattern, yielding a 25% recurrence risk in future offspring. The gene defects associated with several IEMs are located on the X chromosome. These IEMs, such as ornithine transcarbamoylase deficiency and glycerol kinase deficiency, are inherited in an X-linked pattern. These IEMs are most severe in males, but carrier females may be symptomatic, although usually with less severe or late-onset disease as a result of skewed X-chromosome inactivation. Mutations for several mitochondrial disorders are found on mitochondrial deoxyribonucleic acid (mtDNA). Because mtDNA is exclusively passed from mothers to their offspring, these IEMs exhibit a maternal inheritance pattern but often with variable penetrance and expressivity. Prenatal diagnosis is possible for many IEMs. In addition to allowing for appropriate medical therapy, the timely diagnosis of an IEM in a sick infant or child is important for genetic counseling purposes.

BOX 76–1 Signs And Symptoms of Inborn Errors of Metabolism

Acute illness after period of normal behavior and feeding (hours to weeks)
Recurrent decompensation with fasting, intercurrent illness, or specific food ingestion
Unusual body odor
Persistent or recurrent vomiting
Failure to thrive
Apnea or tachypnea
Jaundice
Hepatomegaly or liver dysfunction
Lethargy or coma
Sepsis
Unexplained hemorrhage or strokes
Developmental delay with unknown etiology
Developmental regression
Seizures, especially if seizures are intractable
Hypotonia
Chronic movement disorder (ataxia, dystonia, choreoathetosis)
Family history of unexplained death or recurrent illness in siblings

Signs and Symptoms of Inborn Errors of Metabolism

Clinical signs and symptoms frequently associated with IEMs are listed in Box 76-1. The symptom repertoire of the critically ill infant is limited, and the clinical presentation of metabolic disorders often is nonspecific. It is for this reason that the diagnosis of an IEM may be easily missed. To maintain maximum diagnostic sensitivity for IEMs, the clinician must maintain a high level of suspicion and be willing to initiate screening metabolic laboratory studies with little provocation. As was true for appendectomies in the era prior to the advent of ultrasound-based diagnosis of appendicitis, a certain number of nondiagnostic metabolic laboratory workups in sick children must be performed to ensure ascertainment of individuals with inherited metabolic disorders. In particular, IEM should be a strong diagnostic consideration in any neonate who has become catastrophically ill following a period of normalcy. This presentation may be clinically indistinguishable from bacterial or viral sepsis, and the nonspecific supportive therapy provided to potentially septic infants (fluid and glucose administration) may alleviate the symptoms and

mask the presence of an IEM. Diagnostic metabolic laboratory studies are most likely to provide definitive information if performed on clinical samples obtained at initial presentation and before any therapy is initiated. Failure to obtain the necessary specimens at this time may miss an important diagnostic window of opportunity. Many children with IEM have been saved initially by intensive but nonspecific treatment but then suffered clinical relapse or even death in the absence of the correct diagnosis. Certainly, the possibility of an IEM should be considered in any child for whom the clinical picture suggests sepsis but the laboratory evaluation for sepsis is negative. Unfortunately, bacterial sepsis is often a complicating factor in critically ill children with IEM. For example, *Escherichia coli* infection (including pyelonephritis, bacteremia, or meningitis) is frequently detected at presentation in infants with galactosemia. The astute clinician remains ever vigilant for the signs and symptoms that may suggest an inherited metabolic disorder.

Recurrent episodes of vomiting and dehydration in response to fasting or intercurrent illness are an important clue to IEM in older infants and children. Feeding difficulties and failure to thrive are common chronic complications. Children with unexplained hypotonia, developmental delay, or movement disorder should be evaluated for possible IEM. Inherited neurodegenerative disorders, such as the lysosomal storage diseases, stereotypically cause developmental regression, specifically loss of previously attained developmental milestones. Several IEMs are associated with major physical anomalies (Table 76-1). When present, these anomalies are exceedingly valuable in suggesting a specific diagnosis and directing the diagnostic evaluation. More commonly, the child with IEM is morphologically normal, and the presenting symptoms are nonspecific. The clinician must then rely upon screening laboratory tests to evaluate the potential for IEM.

Table 76–1 Physical Anomalies Associated with Inborn Errors of Metabolism

Dysmorphic facial features	Peroxisomal disorders Glutaric aciduria type II Smith-Lemli-Opitz syndrome Menkes syndrome Lysosomal storage disorders
Structural brain anomalies	Glutaric aciduria type II (cortical cysts) Pyruvate dehydrogenase deficiency (cortical cysts, agenesis of the corpus callosum) Glycosylation disorders (cerebellar agenesis)
Macrocephaly	Glutaric aciduria type I (with subdural effusions) Canavan disease Alexander disease
Cataracts	Galactosemia Peroxisomal disorders Mitochondrial disorders Lowe syndrome
Lens dislocation	Homocystinuria Sulfite oxidase deficiency Molybdenum cofactor deficiency
Pigmentary retinopathy	Peroxisomal disorders including cherry red spots Lysosomal storage disorders Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Renal cysts	Glutaric aciduria type II, Peroxisomal disorders Mitochondrial disorders
Ambiguous genitalia	Congenital adrenal hyperplasia Smith-Lemli-Opitz syndrome
Skeletal abnormalities	Menkes disease Homocystinuria Peroxisomal disorders Lysosomal storage diseases
Hair or skin abnormalities	Menkes disease Holocarboxylase synthetase deficiency Biotinidase deficiency Argininosuccinic aciduria Phenylketonuria

Laboratory Evaluation of Suspected Inborn Errors of Metabolism

Abnormal results of routine laboratory studies may provide clues to the presence and type of IEM (Table 76-2). Highly informative but sometimes subtle laboratory abnormalities are often overlooked, especially in a busy ICU or hospital ward. For instance, a clinically relevant newborn screening result may have been sent to the primary care provider or birth hospital but not efficiently communicated to the ICU, in a different hospital, to which the now critically ill infant has been admitted. It is imperative to verify the infant's screening results with the primary care provider or newborn screening laboratory (Box 76-2). Calculation of the anion gap, another example of a routine and highly informative result, is key to the differential diagnosis of metabolic acidosis. The absence of urine ketones in hypoglycemic children older than 2 weeks strongly suggests impaired ketogenesis as a consequence of either hyperinsulinism or fatty acid oxidation disorder. On the other hand, fatty acid oxidation and ketogenesis are incompletely developed in neonates. The presence of ketones in the urine of infants younger than 2 weeks is very unusual even during fasting or hypoglycemia and suggests the presence of an unusual keto acid, such as those excreted in maple syrup disease or the organic acidemias. Keto acids, organic acids, and sugars such as galactose or fructose increase urine specific gravity. Urine specific gravity greater than 1.020 in any neonate or in a well-hydrated older child suggests the unexpected presence of an osmotically active substance. Routine urinalysis at many hospitals may not include use of the Clinitest to detect reducing substances. Urine Chemstrips utilize a colorimetric glucose oxidase-based method to specifically detect glucose. This test does not react with any other sugar (galactose or fructose). However, some bedside glucose monitoring systems do react with galactose or fructose; inappropriately elevated capillary blood "glucose" accompanied by a normal venous glucose as measured by chemistry analyzer suggests the presence of a sugar other than glucose in the blood. A comatose infant with a blood urea nitrogen (BUN) level below the limits of detection may have an inherited defect in the urea cycle. Blood ammonia measurement is crucial to confirming that suspicion. Failure to check the blood ammonia level has caused missed diagnoses, failure to appropriately treat hyperammonemia, and further morbidity and mortality in comatose infants with urea cycle disorders

Table 76–2 Initial Laboratory Evaluation of Suspected Inborn Errors of Metabolism

Laboratory Test	Abnormality	Disorder
Complete blood count	Neutropenia Macrocytic anemia Pancytopenia	Organic acidemias Glycogenosis type 1b Cobalamin processing defects Congenital lactic acidoses
Serum electrolytes	Metabolic acidosis	Glycogenoses Organic acidemias FAO disorders MSUD Congenital lactic acidoses
Blood gas	Metabolic acidosis Metabolic alkalosis	Same as above Urea cycle disorders
BUN	Low or undetectable BUN (with hyperammonemia)	Urea cycle disorders
Transaminases (ALT, AST)	Liver dysfunction	Galactosemia Fructosemia Tyrosinemia α1-antitrypsin deficiency FAO disorders Organic acidemias Congenital lactic acidoses Congenital disorders of glycosylation
Total and direct bilirubin	Hyperbilirubinemia	Galactosemia Fructosemia Tyrosinemia α1-antitrypsin deficiency Congenital lactic acidoses
Serum uric acid	Hyperuricemia	Glycogenoses Purine disorders
Blood ammonia	Hyperammonemia	Urea cycle disorders FAO disorders Organic acidemias
Blood lactate	Lactic acidemia	Congenital lactic acidoses Glycogenoses Fructosemia Gluconeogenesis disorders
Urinalysis Odor Color pH Specific gravity Ketones Reducing substances	Unusual odor Inappropriately high specific gravity due to metabolites Ketosis Positive reducing substances	PKU, MSUD, organic acidemias Organic acidemias, galactosemia, fructosemia MSUD, organic acidemias Galactosemia, fructosemia

BUN, Blood urea nitrogen; *FAO,* fatty acid oxidation; *MSUD,* maple syrup urine disease.

or organic acidemias. Finally, bacterial sepsis and meningitis are more common causes of severe lethargy and coma in infants than is IEM, but bacterial infection may also be a complicating feature in severely ill infants with IEM. Infants with galactosemia, for example, are particularly prone to pyelonephritis, bacteremia, sepsis, or meningitis, often with *E. coli*, as noted above. Antibiotic therapy without diagnosis and specific treatment of the underlying disorder may be useful in the short term but does not mitigate long-term IEM-specific effects.

Box 76–2 Screening Metabolic Laboratory Studies for Children with Suspected Inborn Errors of Metabolism

- Plasma amino acid analysis
  Minimum 2 mL blood in a heparin tube
- Urine organic acid analysis
- Urine metabolic screen
  Minimum 10 mL urine

Suspicion of an IEM based upon clinical and routine laboratory findings should initiate specialized biochemical testing (Table 76–3). In the case of severely ill infants or when the clinical suspicion of IEM is very high, consultation with a biochemical geneticist, even if only by phone, is strongly advised to help direct the laboratory investigation and initial therapy. When the clinical presentation is nonspecific, that is, catastrophic illness in a previously well child without signs of any particular IEM, the "shotgun" diagnostic evaluation should minimally include plasma amino acid analysis, urine organic acid analysis by gas chromatography-mass spectrometry, and a so-called *urine metabolic screen*. The battery of qualitative assays included in a urine metabolic screen differs among laboratories, and the ordering clinician should be aware of which tests and disorders are included in the repertoire of the diagnostic laboratory chosen. Furthermore, although diagnostic laboratories in the United States must meet Clinical Laboratory Improvement Amendments requirements and often are accredited by the College of American Pathologists, the testing methodologies used, the quality of diagnostic testing for IEM, and more problematically, the availability of laboratory-associated consultants with experience in the diagnosis and treatment of IEM vary widely among laboratories. Although the ability of clinicians to direct clinical specimens toward specific diagnostic laboratories may be inhibited by contractual arrangements between the hospital and large referral laboratories, the critically ill patient is best served by diagnostic evaluation carried out in a timely manner by an experienced biochemical genetics laboratory, with laboratory staff available by phone for expert consultation on interpretation of test results.

The specific clinical presentation or specific screening laboratory findings may direct the intensivist or biochemical geneticist to order other more specialized metabolic tests (see Table 76-3). These analyses may provide diagnostic confirmation for specific disorders and supportive evidence alone for others. For several IEMs, confirmation of diagnosis may require enzyme activity analysis in tissue (red blood cells, lymphocytes, cultured skin fibroblasts, liver, or skeletal muscle depending upon the specific disorder in question) or molecular DNA testing for a specific gene defect. In general, these tertiary tests, which are often difficult, labor-intensive, and expensive, should be ordered following consultation with a biochemical geneticist. In some instances, confirmatory diagnostic biochemical or molecular tests are available only through specialized research laboratories.

Table 76–3 Biochemical Genetic Laboratory Studies

Specimen	Test	Disorder
Blood	Plasma amino acid analysis	Aminoacidopathies
	Plasma carnitine	Organic acidemias FAO disorders
	Plasma acylcarnitine profile	Organic acidemias FAO disorders
	Serum transferrin electrophoresis	Congenital disorders of glycosylation
Urine	Metabolic screen	
	Ketones	Organic acidemias
	Reducing substances	Galactosemia, fructosemia
	Ferric chloride	PKU
	Dinitrophenylhydrazine	PKU, MSUD
	2,4-nitrosonaphthol	Tyrosinemia
	Cyanide-nitroprusside	Sulfur-containing amino acids
	Mucopolysaccharide screen	Mucopolysaccharidoses
	Qualitative amino acid chromatography	Multiple amino aciduria s
	Organic acid analysis	Organic acidemias FAO disorders
	Acylglycine profile	Organic acidemias FAO disorders
	Quantitative mucopolysaccharide measurement and electrophoresis	Mucopolysaccharidoses
	Qualitative sulfites (Sulfitest) or quantitative sulfocysteine	Sulfite oxidase deficiency Molybdenum cofactor deficiency
	Quantitative succinylacetone	Tyrosinemia type 1
	Quantitative purines	Purine synthesis disorders

PKU, Phenylketonuria; *FAO,* fatty acid oxygenation; *MSUD,* maple syrup urine disease.

Postmortem Evaluation of a Child with Suspected Inborn Errors of Metabolism

Some IEMs, particularly those exacerbated by fasting, may present as sudden infant death. For many IEMs, acute metabolic compensation may be rapid and lethal despite intensive medical intervention. The time after clinical presentation but prior to death may be insufficient to execute an adequate metabolic evaluation. Disease diagnosis is still possible postmortem and is important for fully understanding the cause of death and determining recurrence risk in the family. A protocol for postmortem evaluation of an infant or child with suspected IEM is given in Box 76-3. Many of the biochemical genetic analyses recommended for acutely ill children are still valid on postmortem specimens. Valuable information may be learned from amino acid, carnitine, and acylcarnitine analyses in blood and from metabolic screening and organic acid analysis in urine. However, collection of blood and urine

Box 76–3 Postmortem Biochemical Genetic Evaluation

To be performed on any deceased infant <1 year of age for whom the cause of death is not apparent or any child with suspected IEM.

Analyses are most reliable if obtained within 6 hours after death.

1. Contact newborn screening laboratory for results of neonatal screening.
2. Obtain a 3-mm punch biopsy of skin or Achilles tendon for fibroblast culture.
   - A. Prepare skin with chlorhexidine (Hibiclens) or alcohol. Do not use Betadine because it may inhibit fibroblast growth.
   - B. Use sterile technique.
   - C. Store biopsy specimen in sterile RPMI culture media (if available) at room temperature. May be stored in sterile nonbacteriostatic saline for up to 24 hours prior to culture if culture media is not readily available.
   - D. Send to cytogenetics or biochemical genetics laboratory for culture, possible enzyme analyses, and frozen storage.
3. Collect blood via cardiac puncture (~5 mL per tube).
   - A. One red-top tube at room temperature. Collect and store serum at 70° C.
     - i. Comprehensive metabolic panel (potassium, lipids, uric acid may not be accurate postmortem)
     - ii. If hypoglycemic, insulin, growth hormone, and cortisol levels
   - B. One green-top (sodium heparin) tube at room temperature. Collect and store plasma at 70° C.
     - i. Plasma amino acid analysis
     - ii. Plasma carnitine levels
     - iii. Plasma acylcarnitine profile
   - C. One green-top (sodium heparin) tube at room temperature for cytogenetic (karyotype) analysis.
   - D. If storage disorder suspected, one green-top tube (sodium heparin) at 48° C (wet ice) for leukocyte isolation and diagnostic enzyme analyses.
   - E. One lavender-topp (EDTA) tube at room temperature for CBC.
   - F. One yellow-top (ACD) tube for DNA isolation and possible mutation analysis.
   - G. If infant is <1 year old, spot whole blood onto newborn screening filter paper card for repeat screen.
   - H. Blood lactate and ammonia may not be accurate postmortem.
4. Collect urine (10–20 mL) by suprapubic tap or by swabbing the bladder interior with cotton swab.
   - A. Urinalysis
   - B. Urine reducing substances
   - C. Urine metabolic screen
   - D. Urine organic acid analysis
   - E. If storage disorder suspected, quantitative urine mucopolysaccharide and oligosaccharide analysis
5. If urine is unobtainable, organic acid analysis may be performed on vitreous humor collected by needle aspiration from an eye. Freeze vitreous humor at –70° C.
6. If blood is unobtainable, collect bile (2–3 mL) via puncture of the gallbladder for acylcarnitine profile. Store at –20° C.
7. Collect several biopsies (2 g each) from skeletal muscle, cardiac muscle, kidney, and liver.
   - A. For routine histology, biopsies should be submitted fresh to the pathology laboratory.
   - B. For enzyme analyses, biopsies should be wrapped in aluminum foil, placed in a labeled small specimen container, and immediately frozen in liquid nitrogen. Store at –70° C.

Modified from Steiner RD, Cederbaum SD: Laboratory evaluation of urea cycle disorders. *J Pediatr* 138 (Suppl 1):S21-29, 2001.

may not be possible postmortem, especially if the autopsy is performed many hours after death. In these instances, metabolic testing may be obtained on alternative specimens such as vitreous humor or bile. In the event that screening biochemical studies suggest a specific diagnosis, disease confirmation by enzyme analysis in tissue is highly desirable. Many enzymes can be assayed in cultured fibroblasts; viable fibroblasts may be cultured from skin or Achilles tendon samples obtained as late as 24 hours after death. Biopsies of other organs may be necessary for analysis of certain other enzymes. Muscle, liver, and kidney specimens may be obtained postmortem for enzymatic analysis, but most enzymatic activities in solid organs deteriorate rapidly following death. Collection of specimens as soon as possible after death is critical for valid enzyme analyses.

Emergency Treatment of Children with Suspected Inborn Errors of Metabolism

Laboratory investigation of suspected IEM may require several days to complete, given that the biochemical genetics laboratory may be physically remote from the treating hospital and many of the tests involve complex specimen preparation and analysis. A general approach to the emergency treatment of children with suspected IEM, while awaiting diagnostic studies, is given in Table 76-4. For many IEMs associated with acute catastrophic illness, elimination of the offending metabolite is the key to therapy. Immediate cessation of oral feedings, to stop protein or fat intake, will begin to limit toxin production in disorders of amino acid or fatty acid metabolism. Adequate energy intake as carbohydrate must be supplied, usually parenterally, until a specific diagnosis and definitive treatment plan are available. Dextrose infusion at a high rate suppresses catabolism and reduces the consumption of endogenous protein or fatty acid stores. In extremely recalcitrant cases, insulin infusion drives anabolism and further decreases toxin production. Acute metabolic decompensation in some IEMs (e.g., maple syrup disease) is associated with mild peripheral insulin resistance. Insulin administration (often as little as 0.01 to 0.05 units/kg/hour given by continuous intravenous [IV] infusion or subcutaneous bolus injection) overcomes this resistance and has an immediate impact upon metabolic control. Some clinicians also use anabolic agents such as growth hormone or testosterone to acutely suppress protein and fat catabolism. In certain types of congenital lactic acidosis, particularly defects of pyruvate metabolism, carbohydrate infusion worsens lactic acidosis. Replacement of some carbohydrate with fat as an intralipid infusion may partly reduce blood lactate levels, but infants with this degree of sensitivity to glucose infusion often are difficult to treat and suffer high mortality. Severe hyperammonemia that does not respond to dietary protein restriction and dextrose infusion must be treated by hemodialysis. Ammonia clearance with exchange transfusion or peritoneal dialysis is insufficient to adequately decrease blood ammonia levels. If the results of specialized biochemical genetic diagnostic tests are expected within 2 to 3 days, then parenteral dextrose infusion alone should be adequate to maintain nutrition until a more definitive treatment plan is available. Beyond 3 days, developing essential amino acid and fatty acid deficiencies may induce catabolism of endogenous protein and fat. To prevent this occurrence, enteral or parenteral nutrition with minimal amounts of protein (0.5 g/kg body weight/day) and lipid (20% of total energy intake) should be considered. Empiric administration of cofactors such as the B vitamins is not harmful and may improve metabolite clearance, particularly in disorders caused by deficiency of enzymes that require specific cofactors. Carnitine is required for transport of long-chain fatty acids across the mitochondrial membrane and serves a secondary role in the disposal of excess and potentially toxic acyl-CoA species. Secondary carnitine deficiency is commonly associated with acute metabolic decompensation in organic acidemias and fatty acid oxidation defects. L-Carnitine administration prevents secondary carnitine deficiency and may improve clearance of toxic metabolites; it is lifesaving in specific inherited dilated cardiomyopathies.

Table 76–4 Emergency Treatment of Suspected Inborn Error of Metabolism

Goal	Action
Suppress toxic metabolite production	Discontinue oral feedings
Correct fluid imbalance and electrolyte abnormalities	Appropriate IV fluid management
Correct hypoglycemia	IV dextrose-containing fluid infusion
Correct metabolic acidosis	Intravenous hydration if pH >7.2 Add IV bicarbonate if pH <7.2 Sodium bicarbonate (1 mEq/mL solution), 1 mEq/kg IV push at <1 mEq/min May repeat ×3 until pH >7.2; maximum dose 7 mEq/kg/24 hr
Correct hyperammonemia	Suppress protein catabolism Hemodialysis
Treat infection	Appropriate infectious disease laboratory evaluation and antibiotic therapy
Suppress protein and lipid catabolism	Infuse D_{10}1/2NS at 1.5-2 × maintenance rate Add insulin infusion if hyperglycemic If severe, unrelenting acidosis, consider growth hormone or testosterone therapy to promote anabolism
Empiric cofactor administration	L-carnitine, 25-50 mg/kg/every 6 hours IV if organic acidemia suspected or cardiomyopathy present B vitamin complex, 100 mg each vitamin every day Vitamin B_{12}, 1 mg IM × 1 if macrocytic anemia
Maintain nutritional status (if without enteral feeds ×2 days and without diagnosis of a specific IEM)	Enteral feeds or parenteral hyperalimentation to include: Protein, 0.5 gm/kg/day only Lipid, 20% of total energy intake Carbohydrate to provide at least the minimum necessary energy intake

Classification of Inborn Errors of Metabolism by Clinical Presentation

As mentioned previously, the clinical presentation of IEM in neonates provides a paradigm for the suspicion and evaluation of potential IEM at all ages. The classification outlined

Table 76–5 Features of Group 1 Inborn Errors of Metabolism

Clinical Features	Laboratory Findings	Possible Diagnoses	Specialized Diagnostic Tests
Hepatosplenomegaly Coarse facies Macroglossia Fetal hydrops Macular cherry red spots Bone changes Hypotonia or hypertonia Chronic rhinorrhea Failure to thrive	Liver dysfunction No acidosis Normal ammonia Normal glucose	Neonatal onset: GM1 gangliosidosis Icell disease Sialidosis Galactosialidosis Niemann-Pick type A MPS VII CDG Later onset Tay-Sachs disease Krabbe disease Other MPS syndromes Niemann-Pick B or C	Urine mucopolysaccharides Urine oligosaccharides Serum transferrin electrophoresis Enzyme analysis in serum, lymphocytes or fibroblasts
Hepatomegaly Dysmorphic facies Severe hypotonia Large anterior fontanelle Seizures Epiphyseal calcific stippling on radiograph	Liver dysfunction No acidosis Normal ammonia Normal glucose Adrenal insufficiency	Peroxisomal disorders: Zellweger syndrome Neonatal adrenoleukodystrophy Others	Plasma very long chain fatty acid analysis Functional and genetic analysis of fibroblasts

MPS, Mucopolysaccharidosis; *MPS VII*, Sly syndrome; *CDG*, congenital disorders of glycosylation.

here is adapted and expanded to include late-onset disorders from a neonatal IEM classification system first described by Jean-Marie Saudubray and colleagues.[4,8]

IEMs can be classified into one of three groups by pathogenic mechanism. In group 1 IEMs, the production or catabolism of complex molecules is disturbed. The lysosomal storage and peroxisomal disorders are included in this group. The symptoms of these disorders include permanent and progressive somatic and neurologic abnormalities that develop in utero, are often clinically apparent at birth, and are unaffected by food intake. This group is often distinguished by the presence of somatic abnormalities such as dysmorphic features or hepatosplenomegaly. Typical clinical features, potential neonatal and late-onset diagnoses, and confirmatory diagnostic tests are listed in Table 76-5.

In group 2 IEMs, the symptoms are caused by defects in the production or utilization of energy. This group includes the congenital lactic acidoses, glycogenoses, gluconeogenic defects, and fatty acid oxidation disorders. In group 3 IEMs, clinical symptoms are caused by progressive intoxication in a previously well infant because of accumulation of toxic metabolites proximal to a metabolic block. Often, neonatal onset IEM in groups 2 and 3 can be distinguished by the time of clinical onset relative to birth. The symptoms of a block in energy production or utilization (group 2) may present within hours after birth, whereas symptoms of intoxication (group 3) develop over the first week of life with increasing food intake and accumulation of toxic metabolites. However, variants of many of these disorders may not become clinically apparent for several months or even years after birth.

Group 2 Inborn Errors of Metabolism

Systemic or tissue-specific impaired energy production from food substrates is the unifying feature of disorders classified in group 2. Generalized profound neurologic dysfunction, including severe central hypotonia, coma, and seizures, sometimes with peripheral spasticity or abnormal movements, typifies the clinical presentation. Children with these disorders present with similar clinical phenotypes but are easily separated into four subgroups (A through D) based upon associated results of routine laboratory studies (Table 76-6). Severe refractory generalized motor seizures, often beginning within the first hours after birth, sometimes even prenatally, are the hallmark of subgroup A. Routine laboratory studies (glucose, blood pH, electrolytes, ammonia) are generally normal unless the infant is near extremis, and secondary metabolic abnormalities are present. Several inherited disorders are associated with this phenotype; diagnostic differentiation depends upon clinical evaluation by an experienced pediatric neurologist or geneticist and the judicious use of specialized diagnostic laboratory tests.

The amino acid glycine is an abundant neurotransmitter within the central nervous system (CNS). Inherited deficiency of the glycine cleavage system, which removes glycine from its receptor in the neuronal synapse, causes severe unrelenting generalized seizures and profound developmental arrest. The only ubiquitous laboratory finding is an elevated cerebrospinal fluid (CSF/plasma glycine ratio).[9] Sulfite oxidase deficiency, either as a primary genetic defect or secondary to generalized deficiency of its molybdenum-containing cofactor, is another rare but important cause of neonatal-onset seizures. Recently, infantile-onset pyridoxine-dependent or folinic acid-dependent seizure disorders have both been found to be caused by recessively inherited deficiency of α-aminoadipic semialdehyde (α-AASA) dehydrogenase, an intermediate enzyme in the metabolism of the amino acid lysine.[10] Consequently, all neonates with refractory seizures should be screened for these treatable disorders either through measurement of α-AASA in urine or sequencing of the ALDH7A1 (antiquitin) gene. Profound neurologic dysfunction with seizures is one of many possible clinical presentations of infants with peroxisomal or respiratory chain disorders. Some subtypes of a still expanding list of congenital disorders of glycosylation present with seizures,[11] as do disorders of sterol production such as Smith-Lemli-Opitz syndrome,[12] but these diagnoses are often associated with stereotypic dysmorphic features and anomalies. Finally, disorders of neurotransmitter synthesis should be

Table 76–6 Features of Group 2 Inborn Errors of Metabolism

Clinical Features	Associated Laboratory Findings	Possible Diagnoses	Specialized Diagnostic Testing
SUBGROUP A			
Profound neurologic dysfunction Severe hypotonia Seizures	No acidosis Normal ammonia Normal glucose	Nonketotic hyperglycinemia Sulfite oxidase or molybdenum cofactor deficiency Pyridoxine- or folinic acid-responsive seizures Peroxisomal disorders Respiratory chain disorders CDG Cholesterol synthesis defects Neurotransmitter synthesis defects	Plasma and CSF amino acid analysis Urine sulfocysteine Urine oxypurines Urine α-aminoadipic semialdehyde *ALDH7A1* gene sequencing Plasma very long chain fatty acid analysis Blood and CSF lactate Plasma acylcarnitine Urine organic acids Serum transferrin electrophoresis Plasma sterols CSF neurotransmitters
SUBGROUP B			
Neurologic dysfunction Hypotonia Seizures With severe acidosis ± Liver dysfunction ± Dilated cardiomyopathy	Severe acidosis Lactic acidosis ± Ketosis ± Hypoglycemia ± Anemia	Congenital lactic acidoses Pyruvate dehydrogenase Pyruvate carboxylase Respiratory chain disorders	Blood and CSF lactate Plasma and CSF amino acid analysis Urine organic acids Diagnostic muscle biopsy to include histology, enzyme analysis
SUBGROUP C			
Neurologic dysfunction Vomiting Dehydration Hypotonia Coma ± Hepatomegaly, liver dysfunction ± Dilated cardiomyopathy Triggered by fasting or intercurrent illness	Hypoglycemia No ketones in urine Acidosis ± Hyperammonemia ± Lactic acidosis	Fatty acid oxidation defects: MCAD LCHAD VLCAD CPT II CAT MACD Ketogenesis defects: HMG-CoA lyase MCKAT SCOT	Urine organic acids Plasma carnitine Plasma acylcarnitine profile Diagnostic fasting study Fatty acid oxidation studies in cultured skin fibroblasts Gene-specific mutation analysis
SUBGROUP D			
Neurologic dysfunction triggered by short fast Hepatomegaly	Severe fasting hypoglycemia Lactic acidosis Normal ammonia ± Ketosis ± Hyperuricemia ± Hypophosphatemia	Glycogen storage: Glycogenosis 1 Glycogenosis 3 Fructose 1,6-bisphosphatase deficiency	Diagnostic fasting study Enzyme studies in liver Gene-specific mutation analysis

CDG, Congenital disorders of glycosylation; *MCAD*, medium chain acyl-CoA dehydrogenase; *LCHAD*, long chain 3-hydroxyacyl-CoA dehydrogenase; *VLCAD*, very long chain acyl-CoA dehydrogenase; *CPT II*, carnitine palmitoyltransferase II; *CAT*, carnitine acylcarnitine translocase; *MACD*, multiple acyl-CoA dehydrogenase deficiency (also known as glutaric aciduria type 2); *HMG-CoA lyase*, 3-hydroxy-3-methylglutaryl-CoA lyase; *MCKAT*, medium chain ketoacyl-CoA thiolase; *SCOT*, succinyl-CoA oxaloacetate transferase.

considered in any infant with idiopathic seizures and neurologic dysfunction, especially if a movement disorder, most commonly dystonia, is also present. Abnormal CSF neurotransmitter levels (5-methyltetrahydrofolate, 5-hydroxyindoleacetic acid, homovanillic acid, 3-methyl-DOPA) are the only associated laboratory diagnostic clue in this latter category of disease.

Severe persistent lactic acidosis is the hallmark of the disorders in subgroup B of early-onset energy deficiency diseases. The presence of metabolic acidosis with an elevated anion gap suggests the possibility of lactic acidosis (subgroup B) or an organic acidemia (see group 3, intoxication types); these are differentiated by measurement of blood lactate and urine organic acid analysis. Blood lactate is most reliably measured on arterial blood or a free-flowing sample drawn from an indwelling central venous catheter. Artifactual elevation of lactate in peripheral venous blood samples is nearly ubiquitous and should be confirmed by lactate measurement in a more appropriate sample. Secondary lactic acidosis resulting from asphyxia, poor tissue perfusion, or tissue necrosis is much more common and may be difficult to differentiate from the congenital lactic acidoses. Occult cardiac disease, intracranial hemorrhage, or bowel necrosis must be considered and ruled out in infants with severe lactic acidosis. Congenital lactic acidosis generally persists despite adequate life support measures, including fluid resuscitation and ventilatory assistance. In certain enzyme deficiencies, the blood lactate level may further increase with IV dextrose infusion. Simultaneous measurements of blood and CSF lactate and amino acids are useful for differentiating primary from secondary lactic acidoses. In congenital lactic acidosis, the CSF lactate level often is higher than the blood lactate level, while the CNS is relatively protected from systemic acidosis in secondary lactic acidemias. The

blood pyruvate level is elevated in some congenital lactic acidoses such as pyruvate dehydrogenase deficiency. However, accurate measurement of blood pyruvate is difficult and fraught with false-positive elevations. Elevated plasma alanine (which is measured as part of a plasma amino acid analysis) is a more stable and reliable indicator of pyruvic acidosis, as alanine and pyruvate are in equilibrium. Enzymatic analysis in cultured skin fibroblasts or mitochondria isolated from a fresh muscle biopsy often is necessary to confirm a specific enzyme deficiency.

Children with subgroup C defects present with hypoketotic hypoglycemia, triggered by fasting, metabolic stress, or intercurrent illness. In these disorders, utilization of fatty acids as fuel is impaired. The most common of the fatty acid oxidation defects is MCADD, which occurs in up to 1:10,000 white births. Although fatty acid oxidation and ketogenesis defects may present in the newborn period, particularly in the setting of delayed maternal milk production for exclusively breastfed infants, the first clinically significant episode may not occur for weeks to months or even years after birth. With extended fasting or intercurrent illness where metabolic demand exceeds available energy supply, severe lethargy acutely develops and then progresses to coma. Recurrent vomiting and consequent dehydration may be associated. Sudden infant death after an overnight fast is an all-too-frequent initial presentation in up to one third of infants with fatty acid oxidation defects. Infants who survive may suffer recurrent episodes of fasting or illness-induced coma, leading to progressive CNS damage and permanent disability. Metabolic acidosis (resulting from accumulation of partially oxidized fatty acids or secondary lactic acidosis), hyperammonemia, hepatomegaly and liver dysfunction, and hypertrophic cardiomyopathy may occur during acute metabolic decompensation episodes. Liver histology is typified by severe steatosis. Chronically affected children may exhibit recurrent vomiting, failure to thrive, developmental delay, and muscular hypotonia. Certain disorders that affect oxidation of long-chain fatty acids are frequently associated with recurrent rhabdomyolysis and myoglobinuria (long-chain 3-hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency, trifunctional protein deficiency, very-long-chain acyl-CoA dehydrogenase [VLCAD] deficiency, or carnitine-palmitoyl transferase [CPT]-II deficiency) or pigmentary retinopathy and slowly progressive vision loss (LCHAD or trifunctional protein deficiency). Mothers of infants with fatty acid oxidation disorders (particularly LCHAD or trifunctional protein deficiency) may present with acute liver dysfunction during pregnancy with an affected fetus. This may manifest as acute fatty liver of pregnancy or maternal HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. In the affected infant, hypoglycemia (serum glucose <40 mg/dL) with inappropriately low or absent ketone production during a symptomatic episode is the key laboratory finding that leads to suspicion of a disorder in this subgroup. Differentiation of the specific defects requires analysis of urine organic acids and plasma acylcarnitine species. Between episodes, when the child is clinically well, the urine organic acid profile may be completely normal. Acylcarnitine profiles are more consistently abnormal, but both tests, if normal initially, should be repeated on samples obtained during a symptomatic period to absolutely rule out the possibility of a fatty acid oxidation defect. Carnitine is required for normal fatty acid oxidation; long-chain fatty acids are activated to fatty acyl-CoA, then esterified to carnitine by CPT-I on the outer mitochondrial membrane. These acylcarnitine esters are then transported into mitochondria to complete the oxidation process. In fatty acid oxidation defects, the metabolic block leads to accumulation of the fatty acyl-CoA substrate specific to the deficient enzyme; these species appear in blood as acylcarnitine esters. Analysis of plasma acylcarnitine profiles by tandem mass spectrometry often suggests a specific enzyme deficiency in children with suspected fatty acid oxidation disorders.[13] Diagnostic confirmation may require enzyme analysis in liver tissue or radiometric evaluation of fatty acid oxidation in cultured skin fibroblasts. For certain defects, molecular DNA analysis is clinically available. Two disorders, namely, MCADD[14] and LCHAD deficiency,[15] are associated with relatively common disease-causing mutations. Treatment of all disorders in this subgroup is based upon the provision of adequate nonfat calories and prevention of fasting. Generous IV glucose infusion is lifesaving and essential during acute episodes of metabolic decompensation. Chronic dietary therapy is tailored to the specific enzyme deficiency involved. Many practitioners prescribe carnitine supplementation, initially intravenously during an acute episode and later orally, but the efficacy of this intervention has not been formally investigated in any controlled clinical trial, and its use in disorders of long-chain fatty acid oxidation remains controversial.

Hypoglycemia following a short fast of only 4 to 6 hours is highly suggestive of a glycogen storage disease or a disorder of gluconeogenesis such as fructose 1,6-bisphosphatase deficiency. These disorders of energy deficiency are classified in subgroup D. These infants appear healthy while fed but quickly become obtunded and hypotonic with fasting hypoglycemia. Hepatomegaly is a prominent physical feature. During acute hypoglycemia, other biochemical derangements, including lactic acidosis, hypophosphatemia, hyperuricemia, and hypertriglyceridemia, are frequently present. Confirmation of the diagnosis may require a provocative fast under controlled conditions with continuous monitoring and, sometimes, measurement of glycogen content or enzymatic analysis on a liver biopsy specimen. Molecular DNA analyses are increasingly available for a less invasive approach to diagnostic confirmation in this class of diseases.

Group 3 Inborn Errors of Metabolism

Infants with group 3 IEMs display symptoms and a progressive clinical course suggestive of intoxication. In these infants, who appear completely healthy at birth and for the first few days of life, neurologic dysfunction appears as toxic metabolites accumulate with increasing food intake. Initial symptoms may include vomiting and lethargy that progress, perhaps over only a few hours, to complete coma or shock. This specific clinical presentation in particular suggests the possibility of bacterial or viral sepsis; evaluation for infectious disease is entirely appropriate. However, the clinician must remain alert to the possibility of an underlying IEM in a previously healthy infant suffering catastrophic illness within the first days of life. Group 3 IEMs can be subdivided into four subgroups (A through D) based upon specific clinical and laboratory findings (Table 76-7).

Maple syrup urine disease (MSUD), or branched-chain keto acid dehydrogenase (BCKD) deficiency, affects the catabolism of the branched-chain amino acids leucine, isoleucine, and valine and is the only disorder in subgroup A. Affected

Table 76–7 Features of Group 3 Inborn Errors of Metabolism

Clinical Features	Associated Laboratory Findings	Possible Diagnoses	Specialized Diagnostic Studies
Subgroup A			
Neurologic deterioration Coma Abnormal movements Hypertonia Sweet odor	Mild acidosis Normal lactate ± Ketonuria Normal ammonia + urine DNPH test	Maple syrup disease (branched-chain keto acid dehydrogenase deficiency)	Plasma amino acid analysis Urine organic acid analysis
Subgroup B			
Neurologic deterioration Coma Dehydration	Severe acidosis Severe ketonuria ± Hyperammonemia ± Lactic acidosis ± Hypoglycemia ± Neutropenia Negative urine DNPH test	Organic acidemias: Propionic acidemia Methylmalonic acidemia Isovaleric acidemia MCD deficiency Others	Urine organic acid analysis Plasma carnitine levels Plasma acylcarnitine profile Urine acylglycine profile Molecular DNA analysis
Subgroup C			
Neurologic deterioration Coma Seizures Hypotonia ± Liver dysfunction	Severe hyperammonemia No acidosis + Alkalosis Low BUN Normal glucose Normal lactate	Urea cycle disorders (CPS, OTC, ASS, ASL deficiencies) Triple H syndrome (hyperornithinemia-hyperammonemia-homocitrullinuria)	Plasma amino acid analysis Urine organic acid analysis Urine orotic acid Enzyme studies in liver or fibroblasts Molecular DNA analysis
Subgroup D			
Neurologic deterioration Hepatomegaly Liver dysfunction Cholestatic jaundice	Direct hyperbilirubinemia ± Hypoglycemia ± Acidosis ± Lactic acidosis ± Ketosis	Galactosemia Fructosemia Tyrosinemia type 1 Neonatal hemochromatosis Respiratory chain disorders	Urine reducing substances Plasma amino acid analysis Urine organic acid analysis Urine succinylacetone Enzyme studies Molecular DNA analysis

ASL, Argininosuccinate lyase; *ASS*, argininosuccinate synthetase; *BUN*, blood urea nitrogen; *CPS*, carbamyl phosphate synthetase; *DNPH*, dinitrophenylhydrazine; *MCD*, multiple carboxylase deficiency; *OTC*, ornithine transcarbamoylase.

infants present with coma; abnormal body movements including seizures; and, in contrast to many IEMs, hypertonia and opisthotonus. A severe burst-suppression pattern is the typical EEG abnormality. A sweet body odor, concentrated particularly in urine and cerumen, is often present. Mothers with previously affected children can often diagnose MSUD in a new infant by the presence of this odor. Routine laboratory studies may document mild metabolic acidosis and mild ketosis, but normal lactate and ammonia. The branched-chain keto acids that accumulate in MSUD react only slightly with the urine dipstick test for ketones but readily form a flocculent white precipitate with 2,4-dinitrophenylhydrazine (DNPH) in a urine metabolic screen. The presence and specific identities of branched-chain keto acids in urine are confirmed by urine organic acid analysis. Plasma amino acid analysis reveals tremendous elevation of leucine with lesser accumulations of valine and isoleucine. The neurologic symptoms associated with MSUD result entirely from leucine intoxication. Valine and isoleucine, which do not cross the blood-brain barrier as readily as leucine, seem to contribute little to the neurologic phenotype. Reduction of leucine levels in the body is the goal of MSUD treatment.[16] Emergency therapy during the initial clinical episode includes dietary protein restriction and IV infusion of dextrose-containing fluids. Hyponatremia is a common associated feature; IV hydration with hypotonic fluids easily exacerbates this problem. Additionally, leucine accumulates in CSF and brain and is strongly osmotically active. Rapid IV infusion of hypotonic solutions in several instances has led to acute cerebral edema and death. Dextrose solutions containing a minimum of 0.45% saline (one-half normal saline) are essential, but 10% dextrose with normal saline is preferred if the serum sodium concentration is greater than 135 mEq/L. With administration of IV dextrose, mild hyperglycemia secondary to insulin resistance may occur; inclusion of regular insulin (often only 0.05 units/kg body weight/hour) by either IV infusion or subcutaneous injection promotes anabolism, suppresses endogenous protein catabolism, and accelerates leucine clearance. The vitamin thiamine is a cofactor for BCKD; some individuals with BCKD deficiency (usually with a late rather than neonatal presentation) may respond clinically to thiamine supplementation. Oral thiamine (100 mg/day) is often given empirically to determine whether there is any effect on leucine levels. Once the diagnosis of MSUD is confirmed by plasma amino acid analysis, enteral feedings with a medical food that is free of branched-chain amino acids should be initiated, even if the infant is comatose and nasogastric feedings are necessary. Parenteral hydration should continue until results of urine ketone and DNPH tests are negative and full enteral feeds are reestablished. On this regimen, plasma valine and isoleucine levels plummet rapidly, but several days may be required before plasma leucine normalizes. The valine and isoleucine deficiencies that frequently develop on this regimen stimulate endogenous protein catabolism, which impairs reduction of blood leucine, prolongs neurologic impairment, and chronically may be associated with symptoms of protein insufficiency (hair loss, skin breakdown,

growth failure). Therefore valine and isoleucine supplementation (50 to 100 mg/kg/day) is required. Chronic lifelong therapy involves dietary protein restriction and provision of sufficient energy and amino acids in a leucine-free synthetic medical food. Despite this, infants who suffered prolonged severe leucinosis as neonates often exhibit significant developmental disability. Early diagnosis and appropriate therapy critically enhance neurodevelopmental outcome.

Severe ketoacidosis is the hallmark of IEMs in subgroup B, the organic acidemias. Methylmalonic, propionic, and isovaleric acidemias are the most common disorders in this subgroup. Infants with organic acidemia present with catastrophic episodes of vomiting, dehydration, and coma. Hypoglycemia, lactic acidosis, hyperammonemia, neutropenia, or pancytopenia may be associated findings depending upon the specific IEM. The urine dipstick test for ketones is strongly positive, but in contrast to MSUD, little precipitate forms following the addition of DNPH reagent to the urine. Identification of the specific offending organic acid is accomplished by urine organic acid analysis using gas chromatography-mass spectrometry. Diagnostic confirmation may require enzymatic analysis in tissues such as leukocytes, liver, or cultured skin fibroblasts. Molecular DNA analysis is increasingly available as a diagnostic modality as well. Cessation of protein intake, vigorous rehydration with dextrose-containing fluid, and management of acidosis with sodium bicarbonate infusion are the mainstays of emergency management. In severely acidotic patients, especially with associated hyperammonemia, hemodialysis may be useful for quickly removing both ammonia and the offending organic acid with the goal of minimizing CNS damage. IV infusion of L-carnitine (100 to 300 mg/kg/day) assists with the removal of the offending organic acid and prevents secondary carnitine deficiency. Oral L-glycine supplementation has a similar role in certain IEMs, most notably isovaleric acidemia. Chronic therapy is tailored to the specific enzyme deficiency but often involves dietary protein restriction and provision of a synthetic medical food supplying sufficient energy and amino acids. Recurrent episodes of life-threatening ketoacidosis and coma, generally triggered by fasting or intercurrent illness, are often the greatest long-term clinical difficulties.

Advancing dietary protein intake and normal protein catabolism during the first few days of life lead to severe hyperammonemia in infants with urea cycle and allied disorders (subgroup C). The clinical presentation is nonspecific, with progressive vomiting and neurologic dysfunction. Routine laboratory studies are generally deceptively normal, although the BUN often is below the limits of detection in infants who are unable to synthesize urea. No acidosis is present unless the infant is apneic or hypoperfused and secondary lactic acidosis has developed. Most severely hyperammonemic infants demonstrate respiratory alkalosis secondary to Kussmaul-like hyperventilation triggered by cerebral edema. Detection of hyperammonemia is the critical diagnostic key. The blood ammonia level must be measured in any child with acute-onset obtundation without a clear etiology such as trauma. Determination of the specific IEM involved requires analysis of blood amino acids and urine organic acids. Diagnostic confirmation is now often accomplished through molecular DNA analysis of specific genes involved in the urea cycle, but in rare instances, enzyme analysis in liver or for a few defects in cultured skin fibroblasts may yet be necessary if molecular testing is inconclusive. Provision of nonprotein energy and suppression of protein catabolism through IV dextrose infusion are essential, as in the organic acidemias, but emergency hemodialysis to rapidly decrease blood ammonia is absolutely required if any possibility of favorable neurodevelopmental outcome is to be preserved. Ammonia clearance by exchange transfusion or peritoneal dialysis is insufficient to accomplish this goal. Even with prompt hemodialysis, the metabolic derangement in some infants is so severe that little sustained decrease in blood ammonia is observed. Despite aggressive therapy, neonatal-onset urea cycle disorders are frequently lethal. The few infants exposed to hyperammonemia for a prolonged period who, because of extraordinary life-support efforts, survive are often profoundly neurologically impaired. On the other hand, clinical outcome is favorable in cases where blood ammonia levels rapidly correct on hemodialysis. This dichotomy in outcome presents a considerable dilemma to the intensivist faced with these critical treatment decisions. In practice, hemodialysis should be attempted as soon as possible after the discovery of hyperammonemia unless clinical signs of severe permanent CNS damage are already present. Disorder-specific therapy should continue for infants whose blood ammonia levels immediately normalize with hemodialysis. Aggressive life support measures should be limited for those infants with recalcitrant hyperammonemia. Following dialysis, generous IV hydration and provision of nonprotein calories should continue. The amino acid arginine, normally synthesized through the urea cycle, becomes an essential amino acid that must be provided exogenously in urea cycle disorders. L-Arginine hydrochloride is available for IV administration as 10% solution and should be added to the IV fluid bag to give 0.66 g arginine HCl/m^2/day (6 mL/kg/day in infants). The ammonia scavenging agents sodium phenylacetate and sodium benzoate are available as a combined IV solution (Ammonul, Ucyclyd Pharma). Administration of this solution dramatically improves ammonia clearance and is indicated for the acute management of the proximal urea cycle disorders, but it is associated with severe adverse effects including metabolic acidosis and erosive gastritis if administered inappropriately. Ammonul should be used only in consultation with a provider experienced with its administration and with careful monitoring. Long-term therapy is based upon dietary protein restriction and oral L-arginine or L-citrulline supplementation. Oral administration of sodium benzoate or sodium phenylbutyrate (Buphenyl, Ucyclyd) as ammonia scavengers is often prescribed. Episodes of fasting- or illness-induced hyperammonemic coma frequently recur. Management of recurrent hyperammonemia in a patient known to have a urea cycle disorder is similar to that outlined earlier but can be tailored to the specific defect. Liver transplantation is a viable treatment option for individuals suffering recurrent hyperammonemia and chronic clinical and developmental difficulties despite adequate nutritional and medical therapy.

Hepatomegaly, liver dysfunction, and cholestatic jaundice in association with neurologic deterioration are the central presenting features of IEM in subgroup D. For all of these disorders, the accumulating toxin is particularly damaging to hepatocellular function. Hypoglycemia, acidosis, and mild ketosis may be present. Bacterial infection, particularly urinary tract infection, bacteremia, or meningitis, often caused by *E. coli* or other gram-negative enteral flora, is a frequent occurrence in infants with galactosemia. The specific diagnosis is suggested by the clinical scenario and by the results of

screening laboratory studies. Infants with this clinical presentation who are breastfed or receiving cow's milk-based infant formula are at risk for symptoms of galactosemia, given that lactose (milk sugar) is a disaccharide of galactose and glucose. Infants receiving exclusively soy milk-based formula ingest little galactose. The predominant dietary carbohydrates in soy formula are fructose and glucose, so infants fed soy formula who have this clinical presentation are likely to have fructosemia rather than galactosemia. More typically, infants with fructosemia present clinically after the introduction of fruit to their diet. In either galactosemia or fructosemia, reducing sugars are detected in urine following ingestion of the offending sugar by the urine reducing substance test (Clinitest). Plasma tyrosine level is elevated, urine organic acid analysis displays metabolites from the tyrosine pathway, and succinylacetone is detected in the urine of children with tyrosinemia type I (fumarylacetoacetate hydrolase deficiency). Neonatal hemochromatosis can be diagnosed only on liver biopsy by staining for iron. Diagnostic confirmation differs for each disorder but may include further metabolite analyses, enzymatic analysis in tissue, or molecular DNA testing. Initial therapy is nonspecific: cessation of enteral feeding and IV infusion of dextrose-containing fluid. Once the exact diagnosis is known, a specific therapy plan can be developed. For the carbohydrate disorders, the offending sugar must be reduced or eliminated from the diet. Galactosemic infants are fed soy-milk based formulas only. After weaning, ingestion of dairy products, including baked goods prepared with dairy products, is strictly avoided. Similarly, fructosemic individuals must strenuously avoid any fructose-containing foods. In prior eras, cirrhosis and liver failure were the inevitable outcomes in children with tyrosinemia type I unless they received a liver transplant. Effective therapy that prevents liver degeneration in tyrosinemia has now been developed. The oral drug 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione (NTBC) blocks tyrosine metabolism upstream from FAH and prevents accumulation of the intermediate metabolites that are toxic to hepatocytes.[17] This medication was highly successful in preventing cirrhosis in two separate clinical trials and has been approved by the United States Food and Drug Administration for general use. The long-term efficacy of NTBC therapy, particularly with regard to the incidence of hepatic adenoma, a common complication of tyrosinemia I, has yet to be proven.[18]

Summary

Most IEMs with symptom onset in the neonatal period emerge as one of the clinical presentations described. As mentioned previously, many of these IEMs have milder or late-onset forms that present with identical symptoms as described, but months or years after birth and often following the stress of fasting or intercurrent illness. These clinical scenarios provide a framework for the recognition, initial evaluation, and emergency treatment of infants with IEM. The remainder of this chapter focuses upon the differential diagnosis of select clinical situations encountered in the pediatric intensive care unit.

Metabolic Acidosis

The key to the differential diagnosis of metabolic acidosis is calculating the serum anion gap ($Na^+ - [Cl^- + HCO_3^-]$). This calculation, normally 10 to 15 mmol/L, represents the unmeasured negative ions, predominantly albumin, in blood. Normal anion gap acidosis (low serum HCO_3 but normal anion gap) is caused by excess bicarbonate loss from either the gut (diarrhea) or kidney (renal tubular acidosis). An elevated or so-called *positive anion gap* suggests the presence of another unmeasured anion. Incidentally, a low serum anion gap may be seen in extreme hypoalbuminemia, as occurs in nephrotic syndrome (see Chapters 68 and 71).

The differential diagnosis of positive anion gap metabolic acidosis in children is similar to that of adults (e.g., using a favorite mnemonic, such as MUDPILES or KETONES), but with the addition of another class of acidoses, the IEMs. Poisoning with methanol, ethanol, paraldehyde, isoniazid, or salicylates can be readily ruled out by history or drug screen. Uremia is also easily discovered by laboratory evaluation. The most common etiologies of a positive anion gap acidosis in children are ketosis, lactic acidosis, or a combination of the two. Extreme dehydration can cause both ketosis and lactic acidosis; these abnormalities are readily corrected with vigorous parenteral rehydration with dextrose-containing fluids. Persistent lactic acidosis suggests ongoing tissue damage from hypoxemia, hypoperfusion, or, more rarely, an inborn error of mitochondrial metabolism. It should be remembered that several organic acids, such as propionic and methylmalonic acids, react with the urinary ketones dipstick. These pathologic organic acids can be differentiated only from the more typical ketones, 3-hydroxybutyric and acetoacetic acids, by urine organic acid analysis. Severe positive anion gap metabolic acidosis that cannot be easily explained by the clinical context, especially if it occurs recurrently or is recalcitrant to parenteral fluid therapy, suggests an inborn error of organic acid metabolism and should be evaluated with a battery of screening metabolic studies, including plasma amino acid analysis, urine organic acid analysis, and urine qualitative metabolic screen.

Hypoglycemia

Hypoglycemia can be defined as a blood glucose concentration less than 40 mg/dL.[19] Low blood glucose may be present within the first few hours after birth, especially in preterm or low-birth-weight infants, but the capacity for effective gluconeogenesis and fatty acid oxidation is induced within the first day after birth. Therefore blood glucose less than 40 mg/dL is distinctly unusual after the first 24 hours of life, particularly in infants who have started feeding, and should be thoroughly investigated (Fig. 76-2). A review of hypoglycemia in infants and children along with a useful diagnostic algorithm have been published.[20] A detailed medical history and careful physical examination are essential to discovering the cause of hypoglycemia. The timing of hypoglycemia relative to feeding is a critical item of historical information. Persistent or postprandial hypoglycemia suggests hyperinsulinism. Hypoglycemia after a short fast (3 to 6 hours) along with permanent hepatomegaly suggests a glycogen storage disorder. Hypoglycemia following a longer fast (8 to 12 hours) suggests a defect in gluconeogenesis or a problem with utilization of fatty acids. The presence of ketones in urine (as measured qualitatively by urine dipstick) or in serum (quantitative measurement of 3-hydroxybutyrate or acetoacetate) is an important clue to the etiology of hypoglycemia. Ketosis during hypoglycemia demonstrates that insulin secretion is appropriately suppressed and that fatty acid mobilization and oxidation are

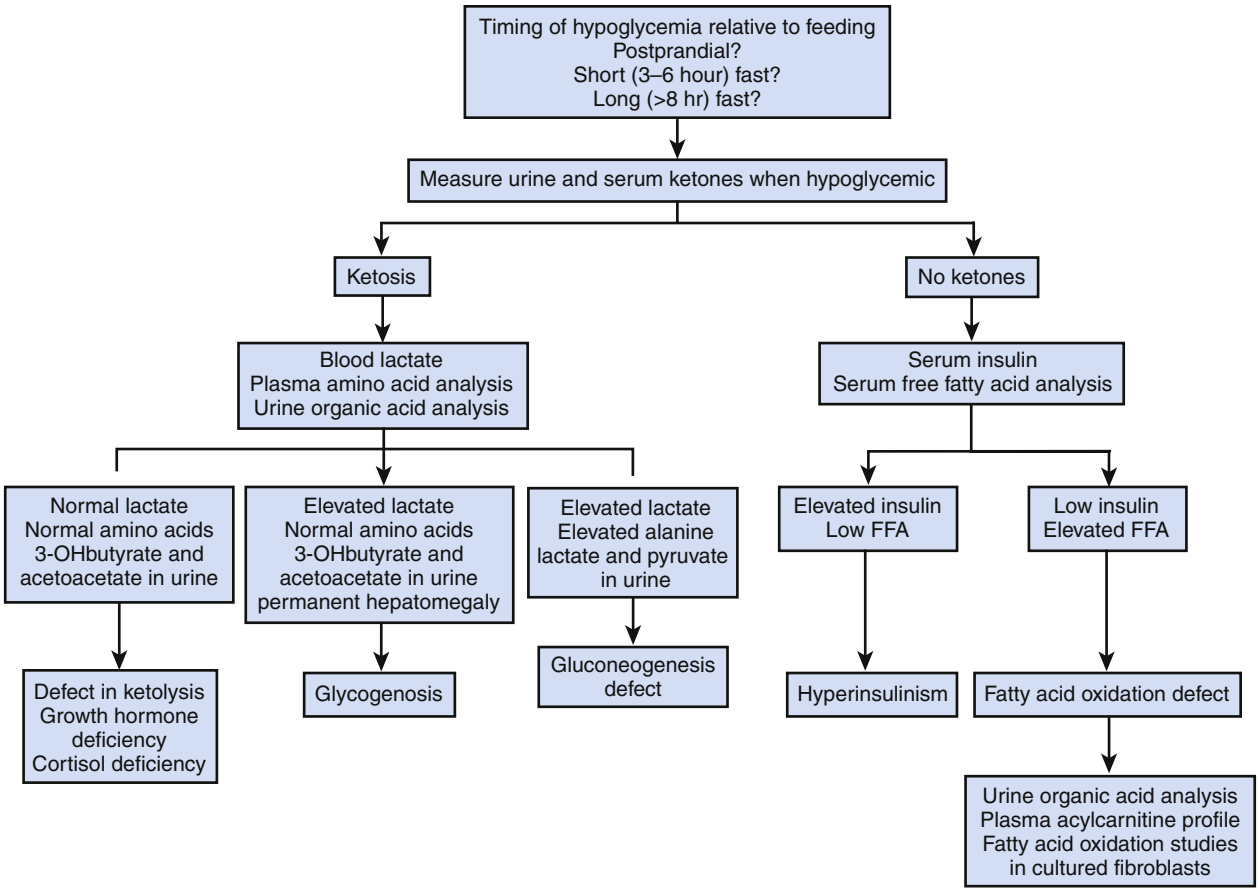

Figure 76–2. Algorithm for evaluation of hypoglycemia in children. *FFA,* Free fatty acid.

intact. Glycogen storage disorders, gluconeogenic defects, and defects of ketone utilization all are associated with ketosis. The absence of ketogenesis during hypoglycemia suggests that either insulin levels are inappropriately elevated or fatty acid oxidation is blocked. An important caveat to this rule is that infants younger than approximately 1 week cannot normally produce enough ketones during fasting to trigger a positive urine dipstick test for ketones. The absence of urine ketones in an infant younger than 1 week does not contribute to the differential diagnosis of hypoglycemia. On the other hand, serum ketones increase with fasting even in neonates, and this test provides a valuable result in the investigation of hypoglycemia. In hypoketotic hypoglycemia, measurement of total serum free fatty acids provides further useful diagnostic information. During fasting, insulin secretion normally is suppressed, free fatty acids are mobilized into circulation from peripheral adipose tissues, and ketones are produced by oxidation of fatty acids in liver. A low serum total free fatty acid level during hypoketotic hypoglycemia strongly suggests inappropriate insulin secretion, even if insulin levels do not appear to be dramatically elevated. Hypoketotic hypoglycemia in association with elevated serum total free fatty acids suggests a defect in fatty acid oxidation.

The importance of treating hypoglycemia cannot be overemphasized as affected individuals are at high risk for seizures and permanent brain damage.[21] After appropriate diagnostic studies are obtained, hypoglycemia should be treated with IV glucose administration at the rate of normal hepatic glucose production, approximately 10 mg glucose/kg body weight per minute or 150 mL/kg per day of a 10% solution until the underlying disorder is identified and more appropriate therapies can be initiated.

Hypoketotic hypoglycemia with low serum total free fatty acids suggests hyperinsulinism. Hyperinsulinism presenting in the newborn period may be caused by intrauterine exposure to elevated glucose levels (maternal diabetes mellitus), familial hyperinsulinemic hypoglycemia (defect in the sulfonylurea receptor), or hyperammonemia/hyperinsulinism syndrome (abnormality in regulation of insulin secretion secondary to mutation in glutamate dehydrogenase). Infants with hyperinsulinism often are obese and require glucose infusions greater than 10 mg/kg/min to maintain normoglycemia. Glucagon administration (0.03 mg/kg, up to 1 mg total dose) reverses hypoglycemia in hyperinsulinism. Oral diazoxide has not been shown to be efficacious in most neonatal cases; however, it can be effective in normalizing blood glucose levels in patients who have infantile forms of hyperinsulinism, including hyperammonemia/hyperinsulinism syndrome.[22] This usually is given at doses of 5 to 10 mg/kg/day divided into three doses. When initially administered, it is given along with glucose and glucagon. The efficacy of diazoxide is defined by demonstrating normal preprandial and postprandial glucose concentrations after overnight fasting and after having stopped IV glucose and any other medications for 5 consecutive days.

Hypoketotic hypoglycemia with elevated serum total free fatty acids, usually occurring following an extended fast (8 to 12 hours) or in association with an intercurrent illness, suggests a defect in fatty acid oxidation. The clinical presentation

of fatty acid oxidation disorders has been described. Although inherited deficiency of at least nine different enzymatic steps in the mitochondrial β-oxidation pathway has been described, the clinical presentation of infants and children with these diseases is stereotypically similar and can be differentiated only by appropriate metabolic testing. In all cases, vigorous hydration with dextrose-containing parenteral fluids is lifesaving. Fasting avoidance is key to long-term treatment and prevention of hypoglycemic episodes.

Infants and children with glycogen storage disorders present with hypoglycemia and permanent hepatomegaly. Hypoglycemia in these disorders is poorly responsive to glucagon administration. Enzymatic defects affecting glycogen synthesis, including glycogen synthase deficiency (GSD-0), as well as defects in glycogen breakdown, such as debranching enzyme deficiency (GSD-III), result in hypoglycemia. Glycogen synthase deficiency usually presents as severe morning hypoglycemia with hyperketonemia and low lactic acid and alanine. Debranching enzyme deficiency results in hypoglycemia secondary to limitation of glucose release from the outer branches of the glycogen molecule. Ketosis is present in GSD-III as the body attempts to generate fuel by increased fatty acid oxidation. Furthermore, the gluconeogenesis pathway is intact; thus hypoglycemia is much milder. In glucose 6-phosphatase deficiency (GSD-1a) and glucose 6-phosphate translocase deficiency (GSD-1b), hypoglycemia usually is apparent 2.5 to 3 hours postprandially as these disorders not only affect glucose release from glycogen but also disrupt gluconeogenesis. Individuals with these disorders have lactic acidosis, ketosis, and hyperuricemia in addition to hepatomegaly.

Hypoglycemia following a longer fast (8 to 12 hours) suggests a defect in gluconeogenesis, ketogenesis, ketolysis, or fatty acid oxidation. Fructose 1,6-bisphosphatase, a disorder of gluconeogenesis, presents as fasting hypoglycemia but also with metabolic decompensation following fructose ingestion. Ketonemia and lactic acidemia are major features, in addition to the hypoglycemia. The ketone synthesis defects that present with fasting hypoketotic hypoglycemia include 3-hydroxy-3-methylglutaryl-CoA synthase deficiency and 3-hydroxy-3-methylglutaryl CoA lyase deficiency. These patients have hypoglycemia in combination with normal blood lactate but no ketonuria. Infants with 3-hydroxy-3-methylglutaryl CoA lyase deficiency also are hyperammonemic. Defects in succinyl-CoA oxoacid transferase and methylacetoacetyl-CoA thiolase represent ketolysis defects. Although the consistent biochemical abnormality is severe ketoacidosis, hypoglycemia also can be seen. Blood lactic acid and ammonia concentrations usually are normal.

Cardiomyopathy and Inborn Errors of Metabolism

Cardiomyopathies, as a rule, are rare. Studies undertaken by the Pediatric Cardiomyopathy Registry have determined that the overall annual incidence is 11.8 per 1 million patient-years and that the incidence was higher in children younger than 1 year than in those between 1 and 18 years old.[23] In this regional study, 40% of cases were hypertrophic cardiomyopathies, 49% of cases were dilated cardiomyopathies, 3% of cases were restrictive or other types, and 8% were unspecified. Further study revealed that of cases of hypertrophic cardiomyopathy, 16% had an identifiable IEM as the underlying cause. These causes included disorders of glycogen metabolism (5%), mucopolysaccharide metabolism (4%), oxidative phosphorylation (5%), and fatty acid metabolism (2%). In the cases of dilated cardiomyopathy, 5% were found to be of a metabolic etiology with disorders of glycogen metabolism (1%), mucopolysaccharide metabolism (2%), and oxidative phosphorylation (2%) as the recognizable underlying cause. Thus it is important to consider IEM in the differential diagnosis of any child with dilated or hypertrophic cardiomyopathy. Because the prevalence of underlying metabolic disorders is so high, some authors have recommended that all children with cardiomyopathy undergo metabolic screening, including blood lactate, plasma amino acid analysis, urine organic acid analysis, urine metabolic screening (particularly for the detection of excessive urinary mucopolysaccharides), plasma carnitine levels, and plasma acylcarnitine profile (Box 76-4).[24] Additionally, serum creatine kinase (CK) should be measured to exclude muscular dystrophy.

Box 76–4 Screening Laboratory Studies for Evaluation of Cardiomyopathy

Blood lactate
Serum creatine kinase
Plasma amino acid analysis
Urine organic acid analysis
Urine metabolic screening
Plasma carnitine levels
Plasma acylcarnitine profile

Autosomal dominant hypertrophic cardiomyopathy has an incidence of 1:500 but demonstrates extremely variable penetrance. Mutations in genes encoding structural sarcomeric proteins are frequent causes of dominant hypertrophic cardiomyopathy. More than 140 mutations in 15 different genes have been identified.[25]

Cardiomyopathy may be a complicating feature of several IEMs (Table 76-8), but with a few exceptions, other associated symptoms or physical examination findings at the time of presentation point toward the appropriate diagnosis. Very broadly, the pathogenesis of cardiomyopathy in IEMs is either myocardial energy deficiency, as occurs in the dilated cardiomyopathy associated with several organic acidemias, or excessive storage of complex molecules in the heart, as occurs in the hypertrophic cardiomyopathy of mucopolysaccharidoses such as Hurler syndrome. Cardiomyopathy occurs as the sole initial clinical manifestation in a relatively restricted list of metabolic diseases, including autosomal recessively inherited deficiency of the cellular carnitine transporter, fatty acid oxidation disorders, glycogenosis types II and IX, and disorders of oxidative phosphorylation. The carnitine transporter defect is caused by deficiency of the sodium-dependent transporter OCTN2, which is responsible for transporting carnitine from the circulation into tissues including cardiac and skeletal muscle.[26] Dilated cardiomyopathy with symptoms of heart failure generally presents within the first years of life and is associated with severely low plasma total carnitine levels. Cardiac function improves dramatically after carnitine supplementation, and cardiomyopathy rarely recurs if carnitine is continued.

Hypertrophic cardiomyopathy resulting from myocardial steatosis may be an isolated presenting feature in several disorders of fatty acid oxidation, particularly those affecting

Table 76–8 Cardiomyopathy and Inborn Errors of Metabolism

Cardiomyopathy as the sole or key presenting feature	Carnitine transport defect
	Fatty acid oxidation defects including: VLCAD deficiency Mitochondrial trifunctional protein deficiency Carnitine palmitoyltransferase deficiency
	Glycogen storage disease type II (Pompe disease)
	Glycogen storage disease type IX (phosphorylase b kinase deficiency)
	Disorders of oxidative phosphorylation (mitochondrial myopathy)
Cardiomyopathy as a secondary feature	Organic acidemias, including: Propionic acidemia Methylmalonic acidemia 3-methylglutaconic aciduria D-2-hydroxyglutaric aciduria Biotinidase deficiency
	Glycogen storage disease type III
	Glycogen storage disease type IV
	Mucopolysaccharidoses
	Congenital disorders of glycosylation
	Congenital myotonic dystrophy
	Congenital muscular dystrophies

VLCAD, Very long chain acyl-CoA dehydrogenase.

long-chain fatty acid metabolism such as VLCAD or mitochondrial trifunctional protein deficiencies. Saudubray et al.[27] examined a series of 109 patients with fatty acid oxidation defects and found that cardiac involvement, including hypertrophic cardiomyopathy or arrhythmia, was apparent at presentation in 51% of cases. Fatty acid oxidation disorders are most reliably detected by analysis of plasma acylcarnitine profiles by tandem mass spectrometry. Long-chain fatty acids are activated to CoA derivatives and then esterified to carnitine prior to transport into mitochondria for β-oxidation. In fatty acid oxidation disorders, especially during acute metabolic decompensation, acylcarnitine species accumulate in plasma and provide a diagnostic profile that is specific to a given enzyme deficiency. Confirmation of the diagnosis may require enzymatic analysis in cultured fibroblasts or mutation analysis. Once the diagnosis of a long-chain fatty acid oxidation disorder has been established, restriction of dietary long-chain fat intake and provision of medium-chain triglyceride oil as an alternative fuel source for the myocardium often reverses cardiomyopathy. Cardiac support measures, including extracorporeal membrane oxygenation, may be necessary for as long as 1 to 2 weeks after presentation before heart function improves.

Glycogen storage disease type II (acid α-glucosidase deficiency; Pompe disease) is a disorder of lysosomal glycogen accumulation that frequently presents as hypertrophic cardiomyopathy, yielding the classic "boot-shaped" radiographic appearance of the cardiac silhouette. Skeletal myopathy manifesting as severe hypotonia may complicate the presentation. Confirmation of the diagnosis requires measurement of enzyme activity in skeletal or cardiac muscle or cultured fibroblasts. In the past, treatment has only been supportive, but enzyme replacement therapy is now available. IV infusion of recombinant acid a-glucosidase every other week has led to improved cardiac function, neuromuscular development, and survival in infants with Pompe disease.[28] However, antibody formation against the drug in some infants, with subsequently decreased treatment effectiveness, remains a clinical problem.

Myocardial function is highly dependent upon mitochondrial oxidative phosphorylation; up to 30% of the total myocardial volume is composed of mitochondria.[29] Dilated or hypertrophic cardiomyopathy is a frequent presenting feature in infants with severe defects of mitochondrial oxidative phosphorylation. Skeletal muscle myopathy, liver dysfunction, renal tubulopathy, bone marrow failure, or CNS abnormalities may occur. Chronic lactic acidosis, if present, is an important indicator of mitochondrial dysfunction. Screening metabolic laboratory studies demonstrate nonspecific abnormalities associated with chronic lactic acidosis. Definitive diagnosis requires histologic evaluation of skeletal muscle and measurement of respiratory chain enzyme activities. Isolated deficiency of cytochrome c oxidase (COX or complex IV) and reduced nicotinamide adenine dinucleotide (NADH)-ubiquinone oxidoreductase (complex I) of the mitochondrial respiratory chain are the most common oxidative phosphorylation defects presenting with cardiomyopathy. Although some protein subunits of complexes I and IV are encoded by mtDNA, most infant-onset isolated complex deficiencies probably are the result of autosomal-recessively inherited deficiency of nuclear-encoded respiratory chain subunits or of chaperone proteins that ensure proper assembly of functional complexes. For instance, hypertrophic cardiomyopathy caused by functional COX deficiency has been associated with mutations in nuclear COX subunit genes[30,31] or nuclear genes for COX associated-proteins SCO1 and SCO2.[32]

Cardiomyopathy may be seen in several other IEMs, but in these disorders, other physical or biochemical features are generally apparent at initial clinical presentation. For instance, dilated cardiomyopathy may complicate propionic acidemia during acute metabolic decompensation, but features of severe metabolic acidosis, vomiting, dehydration, coma, and possibly hyperammonemia are part of the initial clinical presentation.

Metabolic Myopathies and Rhabdomyolysis

Rhabdomyolysis is a clinical syndrome resulting from skeletal muscle injury and release of potentially toxic substances into the circulatory system. Acute onset of severe muscle pain associated with increased serum CK levels is the hallmark of the disorder. In extreme cases, massive myoglobinuria may cause acute renal insufficiency. Although trauma and direct muscle injury are by far the most common causes of rhabdomyolysis, inborn errors of muscle metabolism should be considered in the differential diagnosis of rhabdomyolysis occurring at any age. In the absence of a history of trauma, the differential diagnosis of acute rhabdomyolysis should include drug or toxin exposure, muscle hypoxia (often associated with seizures), temperature alterations, inflammatory diseases, and IEMs. Because muscle contraction depends upon adenosine triphosphate (ATP) generated by the mitochondrial electron

transport chain, it follows that any process that impairs muscle ATP synthesis or which results in energy expenditure that surpasses ATP production could lead to rhabdomyolysis. The clinical history should lead toward the appropriate diagnosis. A family history that includes rhabdomyolysis or a history in which more than one episode of exercise-induced rhabdomyolysis has been observed should induce suspicion of a metabolic disorder. Along with muscular dystrophy and endocrine etiologies (hypothyroidism, hyperthyroidism, diabetic ketoacidosis, pheochromocytoma), glycolytic defects, fatty acid oxidation disorders, purine biosynthetic disorders, and disorders of mitochondrial oxidative phosphorylation should be considered if historical elements do not direct toward the more common etiologies. As described previously, the fatty acid oxidation disorders can be detected by urine organic acid analysis and plasma acylcarnitine profile. Chronic lactic acidosis may be a clue to a disorder of oxidative phosphorylation. Measurement of blood lactate level before and after an exercise treadmill protocol may help detect a respiratory chain defect if the postexercise lactate level is severely elevated. Definitive diagnosis of a mitochondrial disorder requires histologic and enzymatic analysis of a fresh muscle biopsy. The glycolytic defects of phosphofructokinase and phosphoglycerate mutase deficiencies along with myophosphorylase deficiency (glycogen storage disease type V or McArdle disease) cause severe recurrent rhabdomyolysis; their detection requires enzymatic analysis of muscle tissue. Likewise, myoadenylate deaminase deficiency, a defect in purine catabolism, and CPT-II deficiency are also diagnosed by measurement of the enzyme activities in muscle.

Neonatal Screening for Inborn Errors of Metabolism

Newborn screening for IEMs was first introduced in the 1960s, with screening for phenylketonuria. Technological advances, most significantly the introduction of tandem mass spectrometry to mass screening, have greatly increased the number of disorders that can be identified by analysis of a dried blood spot on a filter paper card.[33] An expert review conducted by the American College of Medical Genetics led to the recommendation that 29 core conditions, including several aminoacidopathies, fatty acid oxidation defects, and organic acidurias detectable by tandem mass spectrometry, should be included in the panel of disorders screened.[34] As of 2009, all states in the United States and most of Europe have now adopted this recommendation. The cost versus benefits of expanded screening, whether to include specific very rare or poorly treatable disorders in the screening panel, and the availability of adequate follow-up resources continue to be debated, but a general consensus has emerged that expanded newborn screening is an effective tool for identifying IEMs early in life, allowing for the initiation of therapy, often before the infant becomes symptomatic, and for preventing morbidity and mortality associated with IEMs.[35] It must be remembered, however, that newborn screening is just that—a screen, and both false-positive and false-negative results are possible. Thus the astute clinician must remain cognizant of the fact that in an ill infant, a normal newborn screen is reassuring but should not be taken as absolute proof-positive that an IEM identifiable on newborn screen is not present. Appropriate screening laboratory evaluation and emergency treatment should be instituted if clinical signs and symptoms of an IEM are present in a sick child.

Conclusion

Inborn errors of metabolism are individually rare but collectively will make not-infrequent appearances in a busy pediatric ICU. The signs and symptoms of IEMs may be nonspecific and often overlap extensively with more common disorders. When clinical suspicion of an IEM arises, screening biochemical genetic laboratory studies must be ordered. Further confirmatory testing often is necessary if screening laboratory tests point toward a specific disease. Confirmatory testing and disease-specific therapy should be instituted following consultation with a biochemical genetics specialist. If detected and treated early, the clinical outcome for many IEMs can be favorable.

References are available online at http://www.expertconsult.com.

Common Endocrinopathies in the Pediatric Intensive Care Unit

Kalia P. Ulate and Jerry J. Zimmerman

PEARLS

- During stress, the endocrine system interacts synergistically with the neurogenic and inflammatory systems to mediate classic "fight or flight" responses.
- Cortisol, produced in the adrenal zona fasciculata, is a key mediator in directing the compensatory antiinflammatory response syndrome by modulating the transcription of thousands of genes, perhaps 20% of the entire genome.
- Critical illness–related corticosteroid insufficiency represents the most common cause of secondary adrenal failure seen in the intensive care unit. Critical illness–related corticosteroid insufficiency reflects a dynamic, typically reversible situation that is thought to result from both decreased cortisol production as well as tissue resistance to cortisol.
- Critical illness hyperglycemia is the result of inflammation-mediated increased endogenous glucose production and decreased utilization resulting from insulin resistance.
- Although the evidence regarding glycemic control and its benefits is controversial, it is difficult to ignore the convincing association that exists between hyperglycemia and morbidity and mortality, as well as the results of initial trials reporting a significant decrease in mortality when critically ill adult and pediatric patients were maintained in a euglycemic state.
- It is crucial that "critical" blood and urine samples be obtained prior to treating hypoglycemia unless one can be absolutely certain of the etiology of the hypoglycemia.
- Sick euthyroid syndrome, common among critically ill patients, is characterized by a rapid decrease in triiodotyrosine and a variable increase in reverse triiodotyrosine that appears to be proportional to the intensity of illness severity and concentration of TNF-α.

Functional Elements of the Stress Response

The stress response involves an integrated interaction between neurogenic, endocrine, and inflammatory systems, as indicated in Figure 77-1.[1-5]

Appendix materials for this chapter are available online at http://www.expertconsult.com.

A variety of afferent stimuli that include pain, sight, hearing, smell, pressure changes, chemical alterations, vascular stress receptors, as well as overt inflammation lead to two primary efferent responses: (1) increased sympathetic (and parasympathetic) nervous system activity, and (2) increased release of hypothalamus and pituitary hormones (counter-regulatory response). Catecholamine release inhibits insulin release and action and stimulates synthesis of glucagon, adrenocorticotropic hormone (ACTH), and antidiuretic hormone (ADH). Hypothalamic production of ADH facilitates water retention at the renal distal collecting tubule. Direct neuronal innervation of the kidney and changes in osmolality sensed at the juxtaglomerular apparatus result in activation of the renin-angiotensin-aldosterone axis, ultimately increasing systemic vascular resistance and facilitating sodium retention at the renal distal convoluted tubule, as indicated in Figure 77-2.

Hypothalamic-Pituitary-Adrenal Axis

Stressful stimuli lead to activation of the supraoptic and paraventricular nuclei of the hypothalamus, causing the release of ADH and corticotropic-releasing hormone, respectively.[3-5] Corticotropic-releasing hormone is transported via hypophysial portal capillaries to the anterior pituitary, facilitating the production of pro-opiomelanocortin, a 239 amino acid peptide that includes primary protein sequences for ACTH, β-lipotropin, β-endorphin, and melanocyte-stimulating hormone. ACTH is transported by the blood to the zona fasciculata of the adrenal gland, where it stimulates the de novo synthesis of cortisol. A schematic overview of the regulation of cortisol synthesis and secretion is provided in Appendix Figure 77-A (see http://www.expertconsult.com).[6]

Primary activation of the hypothalamic-pituitary-adrenal (HPA) axis in the intensive care unit (ICU) largely reflects the intensity of the systemic inflammatory response syndrome. Interleukin (IL)-6 has been shown to mediate lipopolysaccharide-induced ACTH secretion during infection and inflammation.[7]

IL-1 and IL-2 also stimulate cortisol production,[8,9] whereas tumor necrosis factor-α (TNF-α), macrophage inhibitory protein, and corticostatin (a peptide defensin with anti-ACTH activity) are believed to inhibit it. A general overview of

classic endocrinologic pathways affecting cortisol production is shown in Figure 77-3.

Cortisol Biochemistry

The starting point in all steroid hormone synthesis is the conversion of cholesterol into pregnenolone, which represents the rate-limiting step in cortisol production. It requires both mobilization of cholesterol from storage depots and its transfer to cytochrome P-450 located on the inner mitochondrial membrane that catalyzes side chain cleavage. Pregnenolone is then converted to 17-hydroxyprogesterone, and through the enzyme 21-β hydroxylase, it then is converted to 11-deoxycortisol. This process leads to a final key step in cortisol synthesis, the conversion of 11-deoxycortisol to cortisol by the enzyme 11-β hydroxylase, another specific cytochrome P-450 isoenzyme. Generation of a unique hydroxyl group at carbon 11 is essential for both the antiinflammatory and glucose homeostasis functions of cortisol. In addition, cortisol exhibits weak mineralocorticoid activity equivalent to approximately 1% that of aldosterone. A schematic overview of the biosynthesis of adrenal cortical hormones is summarized in Appendix Figure 77-B.[10]

A diurnal rhythm of cortisol production is noted among healthy individuals, with peak cortisol production typically between the hours of 8 and 9 AM and a nadir of cortisol production typically around midnight mediated by negative feedback mechanisms of the HPA axis. These regulatory mechanisms and diurnal variation are overridden during stress and critical illness because of the continued stimulus of ACTH secretion. Consequently a marked increase in cortisol levels is seen in critically ill patients with normal adrenal function. The physiologic adrenal production of cortisol is approximately 9 mg/m^2/day. Stress production of cortisol may reach 200 to 300 mg/day, resulting in a plasma total cortisol level occasionally exceeding 60 μg/dL. The mean and range of plasma cortisol concentrations as a function of age have been reported for normal children and may be found in Appendix Table 77-A.[11]

Although the plasma half-life for cortisol ranges from 80 to 115 minutes, biologic duration of action of cortisol is approximately 8 hours. Cortisol is catabolized by reduction of the steroid nucleus C4-C5 double bond, by reduction of the C3 ketone to a hydroxyl, by oxidation of the C11 hydroxyl group, or conjugation of the C11 hydroxyl group with either sulfate or glucuronic acid.

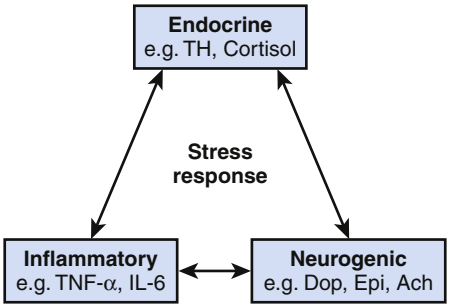

Figure 77–1. Neurogenic-endocrine-inflammation response to stress. *Ach,* Acetylcholine; *Dop,* dopamine; *Epi,* epinephrine; *IL-6*, interleukin-6; *TH,* thyroid hormone; *TNF-α*, tumor necrosis factor-α.

Actions of Cortisol

Cortisol is transported from the adrenal gland to various tissues via cortisol-binding globulins, namely transcortin, and albumin. Transcortin has a high affinity for cortisol but a low carrying capacity. The opposite is true for albumin.[12]

Cortisol diffuses through the plasma membrane by binding to the glucocorticoid receptor that is flanked by heat shock proteins (70, 90, and 56) for transport to the cell nucleus, where cortisol binds to glucocorticoid responsive elements. Once in the nucleus, cortisol modulates the transcription of thousands of genes, perhaps 20% of the entire genome.[13,14] Although the majority of corticosteroid action is related to changes in gene transcription, corticosteroids also decrease the stability of messenger ribonucleic acids, ultimately decreasing protein synthesis, including a number of inflammatory proteins.[13]

Cortisol affects three general areas of physiology, namely inflammation, hemodynamics, and metabolism.

Inflammation

Much critical illness is thought to be a product of a disturbance of the balance between systemic inflammatory responses (SIRS) versus compensatory anti-inflammatory responses.[15-17] Cortisol concentration is locally increased at sites of inflammation through degradation of transcortin by neutrophil elastase and by local up-regulation of 11 β-hydroxy steroid dehydrogenase, which converts cortisone to cortisol.

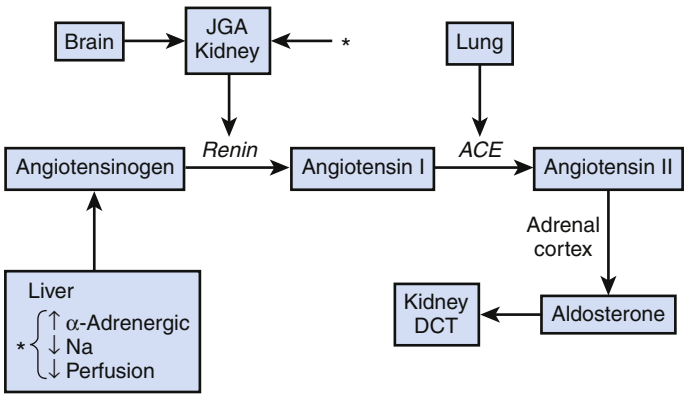

Figure 77–2. Renin-angiotensin-aldosterone axis. *ACE,* Angiotensin converting enzyme; *JGA,* juxtaglomerular apparatus.

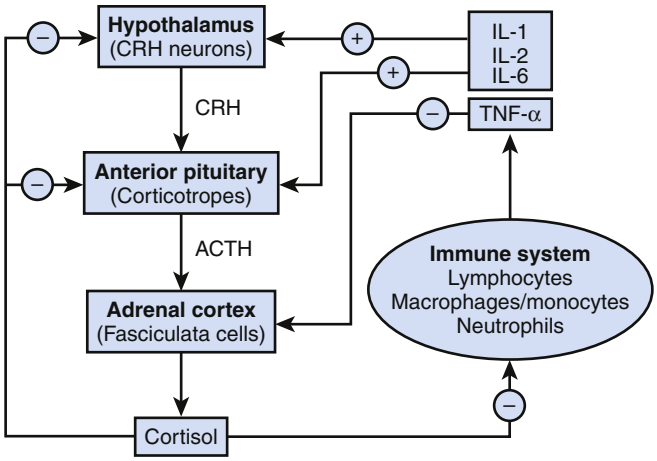

Figure 77–3. Signaling along the hypothalamic-pituitary-adrenal (HPA) axis. (+) Indicates stimulatory signaling and (–) indicates inhibitory signaling. In general, proinflammatory cytokines stimulate the HPA axis at the level of the hypothalamus and pituitary. It should be noted that TNF-α also inhibits cortisol production at the adrenal. Cortisol provides negative feedback relative to its own production, including its antiinflammatory action of inhibition of proinflammatory cytokines synthesis.

Cortisol plays a key antiinflammatory role. It inhibits the internalization of nuclear factor κB (NFκB) into the nucleus by increasing the synthesis of IkB, which traps NFκB in the cytoplasm and thus effectively thwarts the up-regulation and synthesis of a variety of proinflammatory genes and mediators. Similarly, cortisol blocks intranuclear NFκB binding to appropriate deoxyribonucleic acid promoter regions (Figure 77-4). Cortisol exhibits similar activity with nuclear transcription factor activator protein-1.

Furthermore, cortisol increases the production of annexin, which inhibits phospholipase A_2, resulting in an inhibition of both cyclooxygenase and lipoxygenase pathways and associated modulation of the synthesis of a variety of inflammatory lipids. In addition, cortisol decreases both B-cell and T-cell proliferation, increases apoptosis of both cell types, and inhibits inflammatory cell degranulation.

Less well recognized antiinflammatory effects of cortisol include the augmentation of macrophage inhibitory factor, activation of antiinflammatory acute phase proteins including IL-1 receptor antagonist, inhibition of inflammatory cell chemotaxis, down-regulation of adhesion molecules, and the inhibition of neutrophil adhesion and respiratory burst.

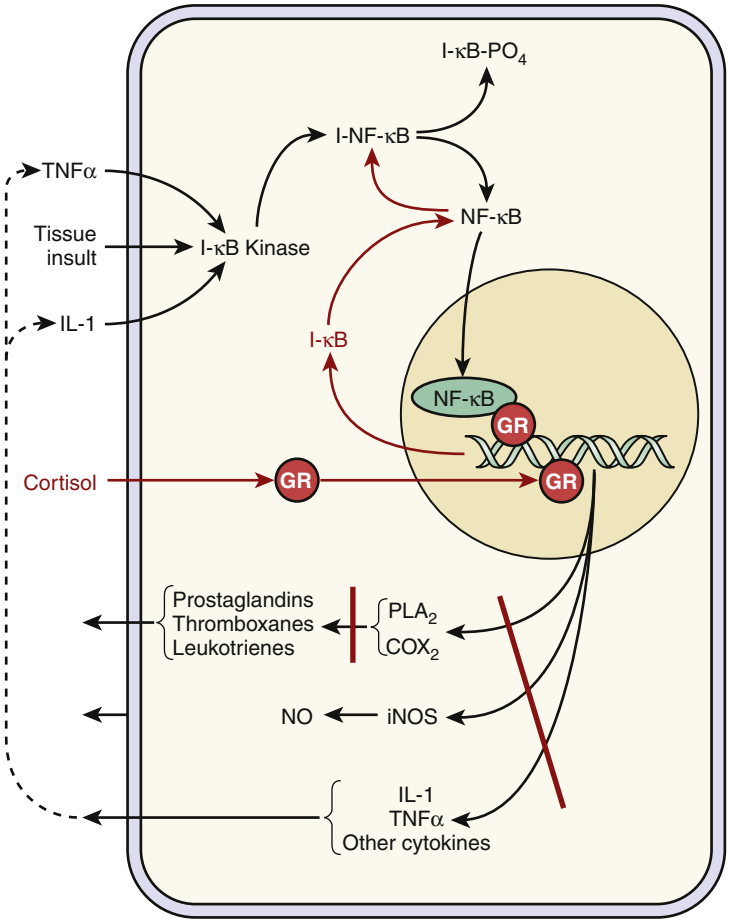

Figure 77–4. Antiinflammatory actions of cortisol. Cortisol facilitates the production of the inhibitor of NFκB (I-κB), which binds to NFκB and prevents it from entering the nucleus and activating target genes. Activated glucocorticoid receptor (GR) also interferes with NFκB binding to its response elements in deoxyribonucleic acid, thus preventing the induction of phospholipase A_2, cyclooxygenase 2 (COX2), and inducible nitric oxide synthase (iNOS). By blocking further production of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-1, cortisol disrupts the positive feedback cycle involving these cytokines. *NO,* Nitric oxide. *(Modified from Goodman HM:* Basic medical endocrinology, *Boston, 2009, Elsevier, p 80.)*

Hemodynamics

Cortisol augments cardiac contractility, maintains vascular tone by inhibition of inducible nitric oxide (NO) synthase, ensures endothelial integrity, up-regulates vasoactive receptors, and increases catecholamine synthesis. These effects allow the maintenance of normal hemodynamics and are particularly important in the setting of sepsis, where proinflammatory cytokines mediate increased NO production, compromised endothelial integrity, systemic vasoplegia, and cytopathic dysoxia.

Metabolism

Cortisol promotes energy substrate mobilization through proteolysis, lipolysis, and gluconeogenesis. It exerts permissive actions on glucagon and is antagonistic to insulin. SIRS-activated and cortisol-facilitated lean muscle catabolism provides substrate for hepatic gluconeogenesis and synthesis of acute-phase reactants to cope with the adversity of critical illness but may be inexorably linked to significant corticosteroid adverse effects that may be life-threatening in the ICU. Increased cortisol concentration during stress represents a key mediator in hyperglycemia of critical illness, which will be discussed later. A schematic diagram of the effects of cortisol on metabolism is displayed in Figure 77-5.[10]

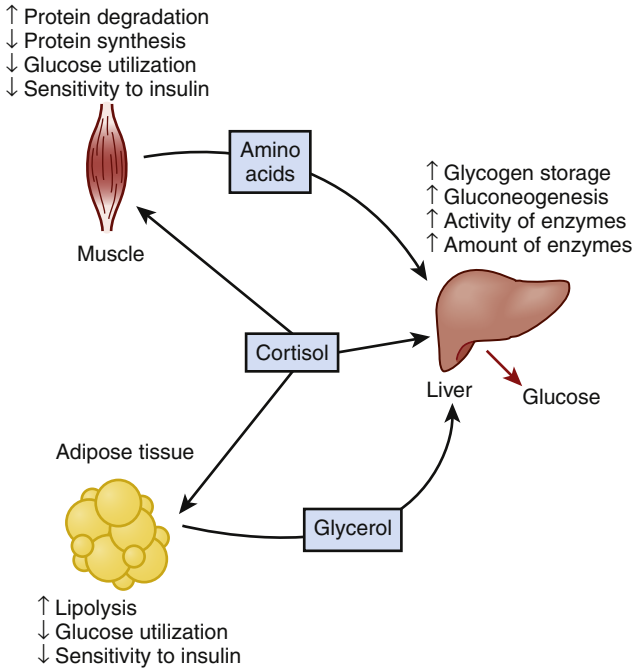

Figure 77–5. Schematic overview of metabolic actions of cortisol. *(Modified from Goodman HM:* Basic medical endocrinology, *Boston, 2009, Elsevier, p 76.)*

Assessing Adequacy of the Cortisol Stress Response

Historically, adrenal function during critical illness has been ascertained by random baseline plasma cortisol concentrations or by calculating the difference between a corticotropin-stimulated plasma cortisol concentration minus a baseline cortisol concentration. In the latter case a so-called δ value less than 9 μg/dL is considered evidence of inadequate adrenal reserve.[18] Depending on the cutoff value chosen (10, 15, 18, 20, or 25 μg/dL), critically ill patients may demonstrate a range of adrenal insufficiency occurrence when random baseline total plasma cortisol concentrations are evaluated.[19] Examples of cortisol testing are illustrated in Figure 77-6.

A normal total circulating cortisol concentration is typically in the range of 5 to 10 μg/dL. Patients with true adrenal insufficiency demonstrate concentrations below 5 μg/dL that do not increase with corticotropin or ACTH adrenal stimulation. In the setting of severe stress such as trauma, burns, or sepsis, a normal person typically increases circulating total cortisol twofold to fivefold, generally in the range of 25 to 50 μg/dL. Similarly, a normal person with adequate adrenal reserve will increase circulating total cortisol by at least 9 μg/dL following an exogenous dose of corticotropin. Traditionally, corticotropin stimulation testing has used a corticotropin dose of 250 μg or, alternatively, 145 μg/m^2 for children. It has been argued that such a pharmacologic dose of corticotropin may result in a nonsensitive stimulation test, and accordingly, a dose of 1 μg of corticotropin has been suggested.[20] However, the latter approach has not been scrutinized as rigorously as the higher dose. For example, more than 50% of a healthy adult cohort demonstrated a δ cortisol concentration less than 9 μg/dL with the low-dose corticotropin stimulation test.[21] A detailed evaluation of critically ill adults with sepsis indicated that patients with a high baseline plasma cortisol concentration but a δ

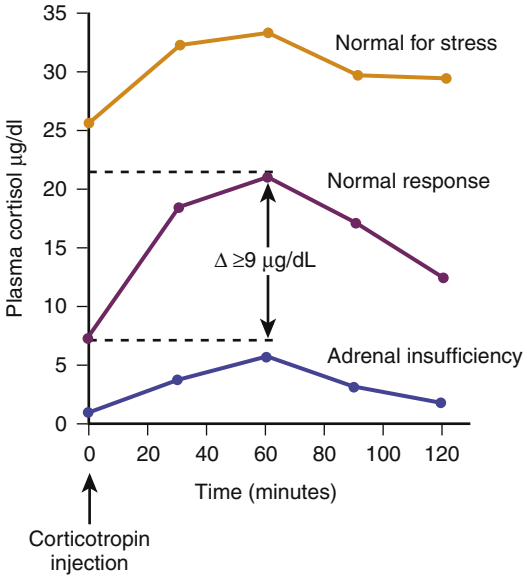

Figure 77–6. Cortisol testing in the pediatric intensive care unit. Normal serum total cortisol typically ranges from 5 to 10 μg/dL. Following intravenous corticotropin administration of 145 μg/m^2 (maximum 250 μg), cortisol concentrations between ~15 and 20 μg/dL are generally considered an appropriate response, which is a change from baseline of at least 9 μg/dL. Levels below 5 μg/dL are diagnostic of absolute adrenal insufficiency. Baseline cortisol concentration during severe stress should generally increase to levels exceeding 25 μg/dL.

cortisol concentration <9 μg/dL exhibited the highest risk for hemodynamic instability and mortality. In fact, a subsequent interventional trial of cortisol was designed based on these findings.[22]

Although the overnight metyrapone test is not generally applicable to critically ill patients, it has been used as a

gold standard in an attempt to identify a population with an apparent inadequate adrenal response to the stress of critical illness. Metyrapone administration will result in an increased ACTH and buildup of the cortisol precursor 11-β deoxycortisol. Among adult patients with severe sepsis, approximately 60% exhibited an abnormal cortisol stress response per the overnight metyrapone test. Best predictors of this situation included a baseline total cortisol concentration of ≤10 μg/dL, a δ cortisol concentration ≤9 μg/dL, or a free cortisol concentration <2 μg/dL.[18]

Free Cortisol

Although most cortisol is bound to transcortin or serum albumin, the free fraction comprising 10% to 15% of the total is actually responsible for the protean effects of cortisol. Accordingly, it has been suggested that perhaps free cortisol rather than total cortisol might be more reliable in terms of identifying a population that would most benefit from cortisol replacement therapy.[23] For most critically ill patients, cortisol-binding globulin is typically decreased and the percentage of cortisol as the free fraction is increased. Moreover, with corticotropin adrenal stimulation, the increase in the free cortisol concentration is greater than the increase in the total cortisol concentration.[24,25] Assessing total cortisol concentrations may be especially problematic in critically ill patients with low albumin concentrations.[23] Multiple limitations of corticotropin stimulation testing to assess total cortisol concentrations during critical illness have been summarized.[26] Free cortisol concentrations may be assessed in urine as well as in saliva,[27] but blood contamination of either specimen may limit this approach in the pediatric ICU (PICU). Recently it has been demonstrated that free cortisol concentrations may be determined among critically ill children in real time utilizing temperature-controlled centrifugal ultrafiltration and immunochemiluminescence assay.[28] However, what constitutes an adequate free cortisol response among critically ill patients, again with the intent of identifying a population who might benefit from cortisol supplementation, has not been ascertained.

Adrenal Insufficiency in the Intensive Care Unit

Adrenal insufficiency may be classified under two major categories: primary, where direct malformation or destruction of the adrenal glands occur, and secondary, where typically loss of HPA axis integrity occurs. The latter situation is most often encountered among critically ill patients.

Primary Adrenal Insufficiency

Thomas Addison first described primary adrenal insufficiency in his treatise, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules" in a manuscript published in London in 1855.[29] Addison's disease is more typically encountered in adult patients and is included in a group of disorders termed autoimmune adrenalitis.[30,31] Signs and symptoms of Addisonian crisis include intercurrent illness with a history of chronic weight loss and anorexia, dizziness, lethargy, and chronic pigmentation. Symptoms more likely to be associated with admission to the ICU include sudden hypovolemic shock, hyperkalemia, vomiting, diarrhea, abdominal pain, and coma. Other causes of primary adrenal failure include congenital adrenal hyperplasia, with approximately 95% of such cases secondary to 21 hydroxylase (CYP 21) deficiency. In this category, the next most common congenital inborn error of metabolism is 11 hydroxylase deficiency.[32] Primary congenital adrenal failure also can occur among infants with adrenoleukodystrophy associated with a metabolic defect in metabolism of very long chain fatty acids. Other causes of congenital adrenal failure include Wolman disease and familial unresponsiveness to ACTH.[33]

Because of its precarious circulation associated with a subcapsular arteriolar plexus, the adrenal glands are subject to hemorrhage and infarction, particularly in the setting of septic shock—the so-called *Waterhouse-Friderichsen syndrome*—initially described as adrenal apoplexy.[34,35] As indicated in Figure 77-7, a variety of drugs are known to inhibit various metabolic steps along the cortisol synthetic pathway.[6]

Prominent among these inhibitors of cortisol synthesis is etomidate, because it is increasingly being utilized as a sedative for endotracheal intubation to facilitate mechanical ventilation. In one study evaluating patients in an emergency department, more than 50% exhibited a δ cortisol concentration less than 9 μg/dL during a corticotropin stimulation test following etomidate sedation for endotracheal intubation.[36] Multiple other investigations report similar findings. In an observational cohort study of 60 children with meningococcal severe sepsis, it was noted that a single bolus of etomidate was associated with impaired adrenal function, specifically 11 β-hydroxylase activity.[37] Similarly, an important risk factor for adrenal insufficiency among adult ICU patients requiring mechanical ventilation was use of etomidate for sedation.[38] Some experts have advised eliminating the use of etomidate entirely from the ICU[39,40] because it may be an independent risk factor for mortality associated with acute adrenal insufficiency.

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency in the PICU can be seen with pituitary disorders in which inadequate ACTH is produced in response to stress. Probably the most common example would be children undergoing surgical resection of a craniopharyngioma. In addition, long-term corticosteroid administration (e.g., among patients with recalcitrant asthma patients with oncologic or rheumatologic diagnoses, or transplantation patients) results in suppression of ACTH release, occasionally with resultant adrenal atrophy.

Probably the most common cause of secondary adrenal failure seen in the ICU is so-called *critical illness–related corticosteroid insufficiency* (CIRCI).[41] A seemingly inadequate adrenal response relative to the degree of stress characterizes CIRCI, which represents a dynamic, typically reversible situation that is thought to be a result of both decreased cortisol production as well as tissue resistance to cortisol. This resistance to cortisol may result from depletion of corticosteroid-binding globulins, activation of 11β-hydroxyl steroid dehydrogenase and other catabolic reactions, decreased glucocorticoid receptor density and activity, and elevated antiglucocorticoid compounds and receptors.[42-45] Currently CIRCI is thought to be best diagnosed by δ cortisol (following corticotropin stimulation) less than 9 μg/dL or a random total cortisol concentration of less than 10 μg/dL.[18,41]

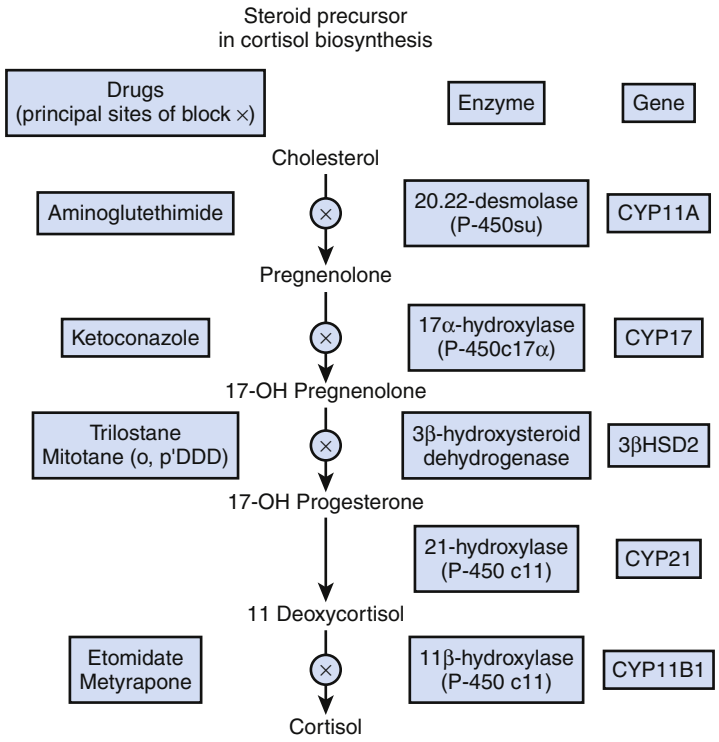

Figure 77–7. Inhibitors of cortisol synthesis. *(Modified from Belchetz P, Hammond P:* Diabetes and endocrinology, *London, 2003, Mosby Elsevier, p 286.)*

Multiple pediatric observational studies, most related to sepsis, have correlated random, baseline serum cortisol concentrations with various outcomes.[37,46-49] In summary, these studies indicated a loss of ACTH-cortisol circadian rhythm among children with sepsis. As critical illness severity increased (e.g., sepsis → septic shock → death from sepsis), proinflammatory mediators such as IL-6 and TNF-α, as well as ACTH, increased while cortisol concentrations decreased. Both serum cortisol and ACTH concentrations correlated with illness severity per pediatric risk of mortality and organ dysfunction scores, lactate, and C-reactive protein. Three pediatric observational studies also have examined corticotropin stimulation testing among children with severe sepsis.[50-52] These studies in general demonstrated that, like adults, an inadequate adrenal reserve is common among children with sepsis. For children with inadequate adrenal reserve, illness severity is increased, as is the requirement for vasoactive-inotropic resuscitation. Such children also more frequently demonstrate vasoactive-inotropic resistance shock and multiple organ dysfunction syndrome. Chronic illness, the degree of organ dysfunction at presentation, and an inadequate adrenal reserve (δ cortisol concentration <9 μg/dL) predicted risk of mortality.

Cortisol Replacement Studies

Adult Investigations

Most clinical investigations related to cortisol replacement therapy in the ICU have focused on patients with septic shock and unstable hemodynamic status despite both fluid and vasoactive-inotropic support. Several investigations examining high doses of methylprednisolone in the 1970s and 1980s found no benefit in terms of reduced mortality but increased risk of significant adverse effects. Subsequently, the notion of relative adrenal insufficiency or CIRCI emerged as a concept. Multiple investigations utilizing hydrocortisone instead of methylprednisolone administered at low stress doses consistently demonstrated hastened resolution from septic shock, and some investigations also reported reduced mortality with this alternative approach. A key hydrocortisone interventional trial was conducted among 19 adult ICUs in France.[53] In this investigation, 229 of 300 adult patients with septic shock (74%) demonstrated a δ cortisol concentration less than 9 μg/dL in a standard corticotropin adrenal stimulation test. Among this predefined group treatment, both low-dose hydrocortisone as well as fludrocortisones resulted in faster resolution of septic shock and reduced mortality. However, a follow-up trial, Corticosteroid Therapy of Septic Shock (CORTICUS, ClinicalTrials.gov number NCT00147004), which involved 499 adult patients with severe sepsis, did not confirm these findings. This investigation concluded that hydrocortisone did not improve survival among adults with septic shock but did hasten reversal of shock among patients in whom shock was reversed.[54]

Pediatric Investigations

Interventional clinical trials examining adjunctive corticosteroids for pediatric sepsis are sparse. Data regarding corticosteroid administration for pediatric Dengue fever are conflicting, and a Cochrane systematic review on this subject concluded no benefit from adjunctive corticosteroids for pediatric Dengue shock, summarizing four trials that enrolled a total of 284 subjects.[55] A retrospective descriptive investigation querying the Pediatric Health Information System concluded no benefit of adjunctive corticosteroids for pediatric sepsis, but this investigation was hampered by lack of illness severity data.[56] Subsequently a similar retrospective descriptive cohort study has been reported utilizing the database generated during the

Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective (RESOLVE, F1K-MC-EVBP) trial of activated protein C for pediatric severe sepsis.[57] Among a cohort of 477 children with severe sepsis, baseline characteristics did not differ among children who did or did not receive corticosteroids. In particular, their mean pediatric risk of mortality III score and number of dysfunctional organs were similar. Indications for corticosteroid prescription (mostly hydrocortisone) were primarily therapeutic to address shock (89%). The 28-day mortality rate from all causes among children receiving and not receiving corticosteroids was 15% and 19%, respectively ($P = .30$). Similarly, no difference in mean days of vasoactive-inotropic infusion or mean days of mechanical ventilator support was found.

Current Guidelines for Corticosteroid Prescription in the Pediatric Intensive Care Unit

Septic Shock

The American College of Critical Care Medicine has provided updated recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients.[41] Based on expert summary of six randomized controlled trials including a meta-analysis, they concluded that adults with recalcitrant septic shock may benefit from moderate doses of hydrocortisone (200 to 300 mg/day or a similar total daily dose administered by continuous intravenous infusion). Higher doses of corticosteroid equivalents appear to be associated with an increased incidence of adverse events.[41] Similarly updated clinical practice guidelines for hemodynamic support of children with septic shock recommend (albeit with no level I evidence) hydrocortisone replacement therapy if a child is at risk for adrenal insufficiency or HPA axis failure, for example, children with purpura fulminans, congenital adrenal hyperplasia, prior recent steroid exposure, and those who remain in shock despite high-dose vasoactive-inotropic and fluid resuscitation.[58]

Bronchopulmonary Dysplasia

Corticosteroids, typically dexamethasone, also have been utilized to decrease lung inflammation and the risk of subsequent bronchopulmonary dysplasia. In this setting a higher corticosteroid dose was associated with increased risk of neurodevelopmental impairment. Some authors have concluded that corticosteroids should not be administered to neonates with a low risk for bronchopulmonary dysplasia because there appears to be no "safe" window for corticosteroid administration among extremely low birth weight infants.[59]

Neonatal Hypotension

Hydrocortisone is also commonly used to treat hypotension among neonates. However, this practice may be associated with a higher incidence of intraventricular hemorrhage, periventricular leukomalacia, and death.[60] A meta-analysis demonstrated that hydrocortisone increases blood pressure and reduces vasoactive-inotropic requirements among hypotensive preterm neonates. However, the actual long-term clinical benefits of this practice remain unclear.[61] Long-term sequelae of hydrocortisone administered to hypotensive neonates are yet to be fully elucidated. Similarly, corticosteroids have been used to improve hemodynamic stability following neonatal/pediatric cardiac surgery. Variable practice precludes generalizations regarding the long-term benefits of this intervention.[62-64]

Acute Lung Injury/Acute Respiratory Distress Syndrome

Five randomized studies enrolling more than 500 adults have evaluated the role of corticosteroid treatment among patients with acute lung injury and acute respiratory distress syndrome (ARDS). These interventional trials consistently reported that corticosteroid treatment was associated with significant improvement in Pao_2/fraction of inspired oxygen (Fio_2) ratio, reduction in markers of systemic inflammation, duration of mechanical ventilation, and length of ICU stay. It has been recommended that moderate-dose corticosteroids be considered in the management strategy of adults with early severe ARDS and before day 14 in patients with unresolving ARDS.[41] Both methylprednisolone and hydrocortisone also have been used in this regard. Best available evidence suggests optimal initial administration of methylprednisolone as a continuous infusion with a total dose of 1 mg/kg/day.[41] Similar data are not currently available regarding children with acute lung injury/ARDS.

Postextubation Stridor

A Cochrane systematic review of 11 trials examining corticosteroids for the prevention and treatment of postextubation stridor in neonates, children, and adults (summarizing 2301 subjects) concluded that the prescription of corticosteroids to prevent or treat stridor after extubation has not been proven to be effective overall for neonates or children. However, this intervention merits further study, particularly for patients at high risk of having the extubation procedure fail. Studies of high-risk adults found multiple doses of corticosteroids initiated 12 to 24 hours before extubation to be helpful.[65]

Corticosteroid Adverse Effects

Relative to the relative balance of SIRS versus compensatory antiinflammatory response syndrome, excessive steroid administration has been associated with increased risk for hospital-acquired infection among adult patients with septic shock,[54] among children receiving hydrocortisone following surgery for congenital heart disease,[66] and among adults with trauma treated with corticosteroids.[67,68] Subjects enrolled in the CORTICUS trial who received hydrocortisone also exhibited a higher risk of both sepsis and septic shock.[54]

Dissolution of lean body mass mediated by both endogenous and exogenous corticosteroid administration is common in stress states. Although this response may be beneficial in the short term as previously noted, prolonged steroid-mediated muscle catabolism can be associated with prolonged ICU weakness and hyperglycemia. An overview of corticosteroid-mediated proteolysis is displayed in Figure 77-8.[69]

Prolonged ICU weakness has been associated with prolonged neuromuscular weakness and the need for continued mechanical ventilation even in the setting of resolved lung

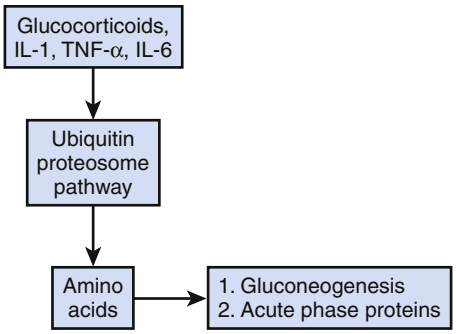

Figure 77–8. Proteolysis in catabolic states. Glucocorticoids, tumor necrosis factor-α, interleukin-1, and interleukin-6 stimulate the ubiquitin proteosome pathway, which causes proteolysis and amino acid release that are used as precursors of gluconeogenesis or in the synthesis of acute phase reactant proteins. *IL,* Interleukin; *TNF,* tumor necrosis factor.

disease,[70-73] whereas hyperglycemia has been associated with a variety of adverse events in the PICU, as detailed in the section of this chapter in which hyperglycemia is discussed. Additional important clinical consequences of protein catabolism that may be exaggerated by exogenous corticosteroid administration include impaired wound healing, hypoalbuminemia, disordered coagulation, and impaired gut function with bacterial translocation.[74]

In the CORTICUS trial,[54] transient hypernatremia also was noted among patients receiving hydrocortisone. Although gastrointestinal hemorrhage represented an important adverse effect in previous clinical trials examining the potential utility of high-dose methylprednisolone as adjunctive therapy in patients with sepsis, this adverse effect has not been problematic in later investigations utilizing low-dose hydrocortisone.

Long-term exposure to excessive corticosteroids results in Cushing's syndrome. In the absence of obvious exogenous steroid administration, Cushing's syndrome is diagnosed as a high 24-hour urine-free cortisol concentration that is not suppressed by administration of dexamethasone. Clinical characteristics of Cushing syndrome include hypertension, hypokalemic alkalosis, proximal myopathy, hyperglycemia, osteoporosis, opportunistic infections, psychiatric problems, and central obesity with characteristic striae.

Alterations of Glucose Homeostasis

Normal Glycemic Regulation

Euglycemia occurs when the rate of glucose utilization parallels the rate of glucose production or absorption. Following a glucose load, the body assumes an absorptive state, and its metabolic profile is primarily regulated by insulin. Insulin binds to a tyrosine kinase receptor on cell membranes and triggers a complex series of events that lead to insulin receptor substrate binding, recognition of the activated insulin receptor substrate by intracellular signal transducing proteins, and activation of postreceptor signaling pathways. This action activates phosphatidylinositol-3 kinase and nuclear gene expression modulating proteins. These in turn stimulate glycogen synthesis and inhibit glycogenolysis in liver and muscle, increase glucose uptake by increasing glucose transporter (GLUT)-4 on the cellular membrane, and downregulate the expression of phosphoenolpyruvate carboxykinase (PEPCK) and inhibits fructose 1,6 biphosphatase, the key rate-limiting steps of hepatic gluconeogenesis (Figure 77-9). Insulin also exerts lipogenic and antilipolytic effects.

During the fasting or postabsorptive state, glucagon is secreted. Glucagon opposes the effects of insulin on enzymes involved in glycogen mobilization and storage, thereby increasing glycogenolysis and decreasing glycogen synthesis, increasing gluconeogenesis through upregulation of PEPCK gene expression, and increasing ketogenesis. This oppositional action of glucagon toward insulin is shared by cortisol, epinephrine, and growth hormone and are all grouped together as counter-regulatory hormones.

Hormone release in response to serum glucose is regulated by the hypothalamus. It modulates autonomic efferent activity through signals received from peripheral (gustatory, intestinal, and hepatic) and central glucoreceptors. A glycemic rise activates the parasympathetic system and suppresses the sympathetic system, increasing insulin secretion through vagopancreatic stimulation. A drop in blood glucose produces the opposite response, thereby inhibiting insulin secretion and increasing counter-regulatory hormone secretion.[75] Euglycemia is maintained not only by a carefully orchestrated and dynamic combination of neuroendocrine mechanisms but also by hepatic autoregulation,[76] in which the liver controls hepatic glucose output in response to circulating glucose concentration.[77]

Glucose Uptake and Metabolism

Glucose enters the cell through GLUT-4 in insulin-dependent tissues (i.e., adipose tissue and cardiac and skeletal muscle) and through GLUT-1, GLUT-2, and GLUT-3 in non–insulin-dependent tissues. GLUT-1 and GLUT-3 have a high affinity for glucose and ensure its entry even during episodes of relative hypoglycemia. GLUT-1 and GLUT-3 are present in the brain, nerves, kidneys, and red blood cells. GLUT-2 is a low-affinity transporter present in the liver that captures excess glucose primarily for storage and ensures bidirectional flow for glucose output from the liver. Once glucose enters the cell, it is either stored as glycogen or metabolized for energy production or lipid synthesis.

Hyperglycemia

The American Diabetes Association defines hyperglycemia as a fasting glucose level more than 125 mg/dL. As many as 86% of patients admitted into a PICU were found to exhibit hyperglycemia at some point during their stay.[78] Once thought to simply represent an alteration of carbohydrate metabolism in response to severe stress,[79] hyperglycemia in critically ill adults and children has more recently received greater attention because of its association with increased morbidity and mortality.[80-84]

Etiology of Critical Illness Hyperglycemia

During the acute stages of illness there is an increase in glucagon, cortisol, growth hormone (GH), and catecholamine secretion. The resultant increase in gluconeogenesis and glycogenolysis raises serum glucose to levels that would, under physiologic circumstances, be enough to cause a decreased secretion of counter-regulatory hormones and an increase in

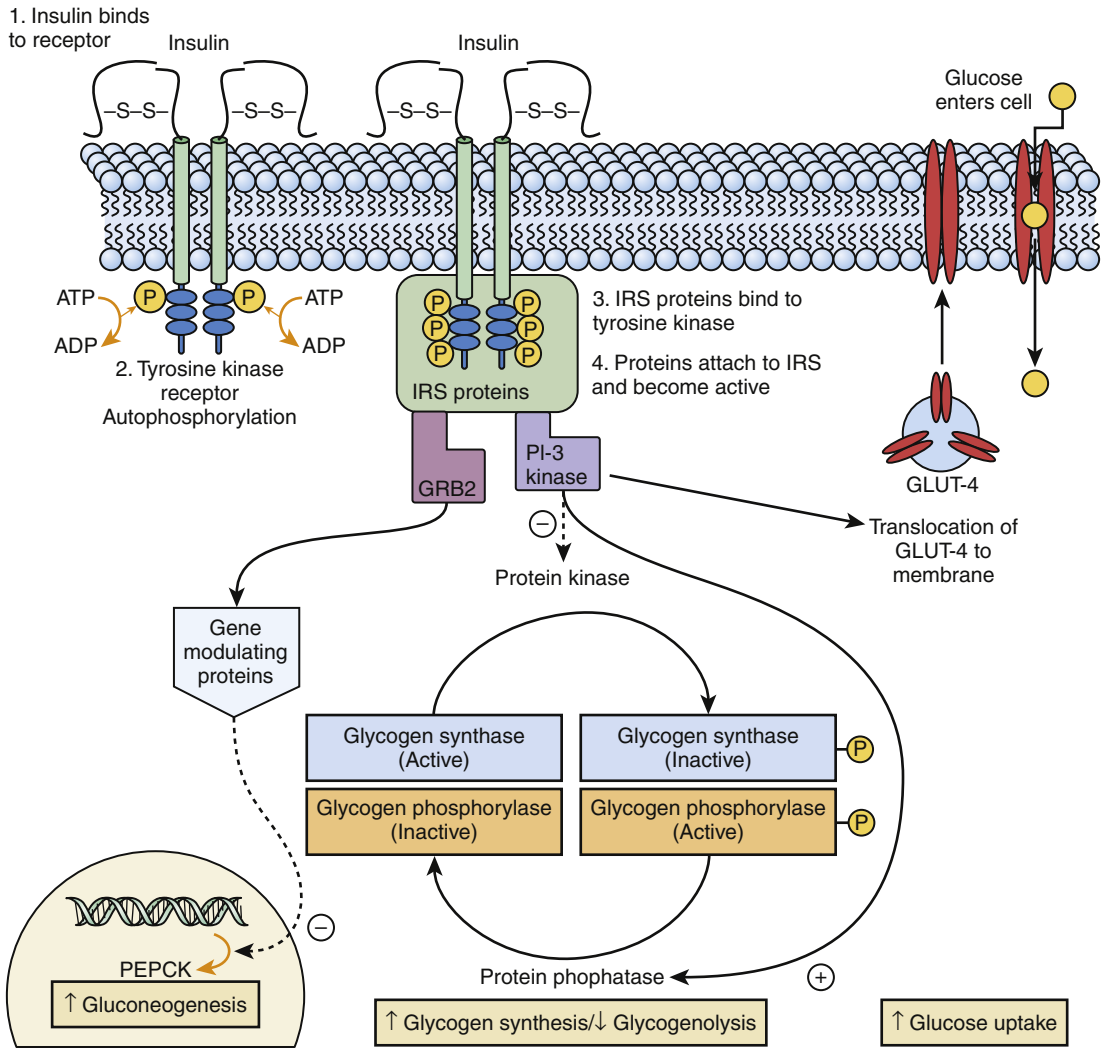

Figure 77–9. Insulin receptor signaling pathways. After insulin attaches to the receptor, it activates tyrosine kinase activity, causing it to autophosphorylate. Insulin receptor substrate (IRS) protein binds to the now active tyrosine kinase receptor. IRS then serves as a loading dock for several different proteins. Growth factor receptor-bound protein 2 (GRB2) is one of the proteins involved in signal transduction and will activate gene modulating proteins that inhibit phosphoenolpyruvate carboxykinase (PEPCK) expression in the nucleus, thereby decreasing gluconeogenesis. Phosphatidylinositol-3 kinase also becomes active after attaching to IRS and leads to inhibition of protein kinases and stimulation of protein phosphatases; this results in increased glycogen synthesis and decreased glycogenolysis. Phosphatidylinositol-3 kinase also leads to translocation of glucose transporter 4 (GLUT-4) to the membrane, therefore increasing glucose uptake.

insulin secretion. In critical illness, however, hyperglycemia is accompanied by persistently elevated levels of proinflammatory cytokines and stress hormones. Normal-to-high insulin levels fail to normalize blood glucose, which reflects insulin resistance. Recent evidence suggests that pediatric patients with cardiovascular and respiratory failure have an absolute rather than a relative insulin deficiency.[85] However, it is still unknown whether this deficiency is the result of a primary pancreatic β cell dysfunction in this subset of patients or β cell exhaustion resulting from severe insulin resistance.[86]

Critically ill patients may demonstrate hepatic and peripheral insulin resistance. In hepatic insulin resistance, high insulin levels fail to inhibit PEPCK expression, and gluconeogenesis continues in the presence of hyperglycemia. The mechanism by which insulin fails to dominantly inhibit PEPCK expression is not known. Although the mechanisms leading to peripheral insulin resistance in critically ill patients are not yet completely elucidated, evidence indicates that the defect lies primarily in the insulin-mediated glycogen synthesis pathway in skeletal muscle[87] and not in glucose oxidation.[88] Increased levels of counter-regulatory hormones, catecholamines, and inflammatory cytokines, particularly TNF-α, IL-1, and IL-6, have all been linked to the occurrence of insulin resistance.[89,90] TNF-α leads to decreased glycogen synthesis and glucose uptake by muscle cells in vitro by impairing insulin postreceptor signaling pathways.[89] Additionally, TNF-α induces peripheral resistance to GH,[91] leading to decreased insulin-like growth factor-1 levels and reduced inhibition of GH secretion through negative feedback, therefore markedly increasing the release of GH during acute stress. The combination of insulin resistance with high circulating levels of counter-regulatory hormones mediates a catabolic state previously discussed. Concomitant lipolysis causes an increase in free fatty acids (FFAs) that further exacerbates insulin resistance[92,93] by altering postreceptor signaling pathways and aggravates the inflammatory response.[94]

In summary, critical illness hyperglycemia is the result of inflammation-mediated increased endogenous glucose production and decreased utilization resulting from insulin resistance. Conditions that are unique to each patient, such as underlying comorbidities (e.g., hepatic dysfunction, obesity, and pre-existing insulin resistance), exogenous administration of glucose through the oral or parenteral route in the form of nutrition or dextrose diluted drugs, dialysate that contains dextrose, and exogenous corticosteroid and catecholamine administration also play an important role in the development of hyperglycemia in critically ill children.

Hyperglycemia and Outcomes

The association between hyperglycemia and adverse outcome measures has been well documented in adults admitted to ICUs.[81,95] More recently, the link between hyperglycemia and increased morbidity and mortality in critically ill children has been the target of investigation. Hyperglycemia has been associated with increased mortality in a variety of pediatric populations including children and neonates with respiratory failure,[96] congenital cardiac defects (following surgery),[97,98] septic shock,[99,100] severe burn injuries,[101] necrotizing enterocolitis,[102] and traumatic brain injuries and general critical illness.[78,103,104] The intensity and duration of hyperglycemia[78,97,98,104] and glucose variability[104,105] have all been found to be associated with poor outcomes among critically ill children, including increased rates of renal failure, liver dysfunction, adverse central nervous system events (e.g., hemorrhage, strokes, and seizures) and hospital-acquired infections.

Hyperglycemia Pathogenesis

The association between hyperglycemia and organ dysfunction or death might be as simple as the relationship between a surrogate marker of severity of illness or stress and the expected outcome. However, clinical and laboratory evidence suggests that hyperglycemia is more than an epiphenomenon.[106] Studies have shown that hyperglycemia adversely modulates both endogenous and pharmacologically induced cardioprotective signal transduction pathways,[107] increases myocardial infarction size, impairs endothelial function, and adversely affects coronary microcirculatory regulation.[108] Hyperglycemia also has been shown to increase systemic vascular resistance, decrease stroke volume, impair cardiac output in rats,[109] and promote cardiomyocyte damage and apoptosis.[110,111] In addition, hyperglycemia has been shown to contribute to renal mesangial cell apoptosis,[112] increase the risk of infection,[113,114] and worsen cerebral injury by adversely affecting the blood-brain barrier and augmenting ischemic injury.[115,116] Despite peripheral insulin resistance, stress increases whole body glucose uptake, which occurs at the expense of non–insulin-dependent tissues, especially those involved in the immune response.[117] Cytokines have been shown to up-regulate the expression of GLUT-1 and GLUT-3,[118,119] placing non–insulin-dependent tissues at risk for direct glucose toxicity in the presence of elevated plasma glucose levels.

Normally a small amount of superoxide is generated from the mitochondrial electron transport chain that is then cleared by manganese superoxide dismutase. In the presence of a cellular glucose overload, the rate of production of superoxide exceeds the enzyme's capacity to clear it. Superoxide then interacts with NO within the mitochondria to produce peroxynitrite. Production of peroxynitrite is further increased in critical illness because of increased NO availability resulting from a cytokine-induced activation of inducible NO synthase. Peroxynitrite has been shown to induce apoptosis in rodent cardiomyocytes,[120] thymocytes,[121] renal cells,[122] and neurons.[123] Furthermore, its production in the endothelium rapidly consumes NO and leads to endothelial dysfunction.[124]

Hyperglycemia has important effects on the immune system as well. It facilitates activation of NFκB, which governs inflammatory gene expression.[125] The effect hyperglycemia has on neutrophil chemotaxis, phagocytosis, and reactive oxygen species generation is controversial.[113] Hyperglycemia may hinder migration of neutrophils and macrophages to an infectious focus because of decreased microvasculature dilation and decreased blood flow to the area as a result of an impaired NO response to bradykinin. Additionally, by causing an increased expression of adhesion molecules on the endothelium, hyperglycemia decreases the number of free leukocytes available for migration.[126] Hyperglycemia also can impair complement fixation by IgG, and by attaching to the active site of C3, it can disenable complement binding to the microbial surface for opsonization.[113]

Management of Critical Illness Hyperglycemia

Clinical Trials

An initial landmark trial of intensive insulin therapy (IIT) was conducted in an adult surgical ICU.[83] Patients were randomly assigned to an IIT group to maintain blood glucose levels between 80 and 110 mg/dL or to a conventional treatment group in which administration of insulin was begun if glucose levels exceeded 215 mg/dL, and insulin was then titrated to maintain glucose levels between 180 and 200 mg/dL. A total of 1548 patients were enrolled in this study. IIT resulted in a decrease in the ICU death rate from 8.0% to 4.6% ($P < .04$), resulting in a 42% drop in ICU mortality and a 34% drop in overall in-hospital mortality. A reduction occurred in the incidence of bloodstream infections, acute renal failure requiring dialysis or hemofiltration, median number of red blood cell transfusions, critical illness polyneuropathy, and duration of mechanical ventilation and ICU length of stay in the IIT group.

A similar trial was subsequently conducted in the medical ICU of the same institution enrolling adult patients who were predicted to require at least 3 days of intensive care.[95] A total of 1200 patients were enrolled and randomized to IIT or conventional therapy in the same manner as the previous trial. Only 767 patients remained in the ICU for at least 3 days. In the intention to treat analysis, IIT did not significantly reduce in-hospital mortality. In fact, mortality was increased in patients in the IIT group who had an ICU length of stay of less than 3 days. However, in the patients who remained in the ICU for 3 or more days, in-hospital mortality was reduced from 52.5% to 43.0% ($P = .009$). Morbidity also was reduced in the IIT group, reflected as a reduction in newly acquired kidney injury, earlier weaning from mechanical ventilation, and shorter ICU and hospital lengths of stay. Hypoglycemia occurred more frequently in the IIT group and was identified as an independent risk factor for death by logistic regression analysis.

Subsequent studies have yielded conflicting results. A multicenter randomized trial, Volume Substitution and Insulin

Therapy in Severe Sepsis (VISEP), that examined the effect of insulin therapy in severe sepsis was terminated early after the first safety analysis because of a significantly increased number of hypoglycemic events in the IIT group compared with the conventional insulin therapy group.[127] No difference in morbidity or mortality was found between the IIT and conventional therapy groups. Another recent large randomized multicenter trial examined the effects of IIT on outcomes of 6104 critically ill adult patients admitted to surgical or medical ICUs.[127a] Only patients thought to require at least 3 days of intensive care were enrolled in the study. IIT (glycemic target: 81 to 108 mg/dL), was not associated with a significantly different ICU or hospital length of stay, duration of mechanical ventilation, need for renal replacement therapy, incidence of infection, rate of red blood cell transfusion, or new single or multiple organ failures when compared with a conventional treatment group (glycemic target <180 mg/dL). In addition, IIT was not only associated with a higher incidence of hypoglycemia but also with a higher mortality than was conventional glycemic control.

To date two meta-analyses have been published evaluating the effects of glycemic control on outcomes in critically ill adults.[128,129] In the first study, strict glycemic control did not confer any survival benefit over conventional therapy and placed patients at a significantly higher risk of hypoglycemia. The subsequent meta-analysis reported similar results but differed in that IIT was associated with decreased mortality in critically ill adult surgical patients. In this study, the incidence of hypoglycemia also was found to be higher among patients in the ITT group and did not vary by type of ICU or insulin dose.

Few similar pediatric studies have been published. In a neonatal multicenter trial, very low birth weight infants were randomly assigned to an early insulin group and a control group.[130] Patients in the early insulin group were assigned a fixed insulin dose with additional dextrose to maintain euglycemia from 24 hours from birth until 7 days of age. Patients in the control group only received additional glucose or insulin in the setting of hypoglycemia or hyperglycemia, respectively. Although hyperglycemia and weight loss during the first week was significantly less frequent in the early insulin therapy group, mortality at 28 days was significantly higher in this group than in the control group. Hypoglycemia was significantly more frequent in the early insulin therapy group compared with the control group (29% vs. 17%). This trial was prematurely stopped because of increased mortality rates and increased incidence of intraventricular hemorrhages and brain parenchymal lesions in the insulin therapy group.

Most recently a randomized control trial studied the effect of strict glycemic control on outcomes of critically ill children.[131] Seven hundred patients were randomly assigned to IIT and control groups. Patients assigned to the IIT group were targeted to maintain blood glucose levels at age-adjusted fasting normoglycemic levels. Patients in the control group were treated with insulin if blood glucose level exceeded 214 mg/dL on two occasions and was then targeted to maintain glucose levels between 180 mg/dL and 214 mg/dL. Patients in the IIT group had significantly lower mean glucose concentrations and a higher incidence of hypoglycemia (25% in the IIT group vs 1% in conventional group; $P < .0001$). When compared with the control group, patients in the IIT group had shorter lengths of ICU and hospital stay and an attenuated inflammatory response, as per reduction in C-reactive protein levels. Mortality was significantly lower in the IIT group (3%) compared with the control group (6%).

Although intensive glycemic control has become ubiquitous to many adult ICUs and recommendations to implement glycemic control in this setting have been issued by the American Diabetes Association and American Association of Clinical Endocrinologists,[132] currently insufficient evidence exists to adopt glycemic control as the standard of care for critically ill children, and accordingly at this time no professional organizations have issued position statements regarding glycemic control for critically ill children.

The Ideal Glycemic Target

As glycemic control strategies are permeating into pediatric intensive care practice, the ideal glycemic target for our patients is still subject to debate. However, it is very likely that the same glycemic control targets used for critically ill adult patients might not be appropriate for the entire pediatric age spectrum. One must take into consideration that strict glycemic control trials have been set to maintain normal fasting glucose levels for patients, or, as in the most recent pediatric trial, to maintain levels within age-adjusted fasting normoglycemic ranges. However, most patients in the critical care setting are not truly fasting. Patients generally receive some form of nutrition through intravenous or parenteral routes. A fasting glucose level therefore may not be the ideal target for these patients, especially when one considers the increased incidence of hypoglycemia seen in the IIT groups of the existing pediatric trials of glycemic control. Hypoglycemia can have serious repercussions, particularly in the developing brain,[133,134] and it has been associated with increased morbidity and mortality in pediatric patients.[104] Observational studies suggest that glycemic ranges not strictly in the euglycemic range may accrue a mortality benefit[135] and be associated with a lower incidence of hypoglycemia.[136]

Recently, a protocolized approach to identify and manage hyperglycemia in critically ill patients was successfully and safely implemented in a PICU and in pediatric postoperative cardiothoracic surgery patients, in which a glycemic target of 80 to 140 mg/dL was safely maintained.[137,138] However, because the protocol was applied to all patients in that unit, it is unknown whether any benefit was obtained from maintenance in this range. To date no pediatric randomized controlled trials have been performed to examine the potential benefit of a more permissive target.

Summary

Hyperglycemia is common in PICUs and is a result of a combination of insulin resistance, conditions that are unique to each patient, and iatrogenic effects from various therapies. Although the evidence on glycemic control and its benefits is controversial, it is difficult to ignore the convincing association that exists between hyperglycemia and mortality and the results of initial trials reporting a significant decrease in mortality when a euglycemic state was maintained for critically ill adult and pediatric patients. Studies that refute this evidence have demonstrated an increased incidence of hypoglycemia in their study patients, which makes it difficult to discern whether glycemic control has not led to improved outcomes or whether its benefit is obscured by the deleterious effects of hypoglycemia. The practice of glycemic control in pediatrics behooves further study. Large pediatric randomized control trials need to be performed

to confirm a benefit from ITT and to refine its practice so that children may reap the potential benefits of strict glycemic control without being placed at increased risk of harm.

Hypoglycemia

Definition

The definition of hypoglycemia has been controversial. Historically its diagnosis was made upon satisfaction of the Whipple's triad, which includes presence of clinical manifestations of hypoglycemia, a low blood glucose concentration coincident with the timing of the manifestations, and the resolution of the signs and symptoms when normoglycemia is reestablished. The triad dates back to the 1930s, when in the absence of current imaging and laboratory diagnostic techniques, criteria were developed to minimize unwarranted surgical intervention for insulinoma. These criteria have fallen out of surgical favor and instead are now applied as the classic definition of symptomatic hypoglycemia and are used by many practitioners to guide therapy for hypoglycemia. This triad, although very helpful in other clinical settings, is of little value in the ICU, where the signs and symptoms of hypoglycemia may not be evident in patients who often are sedated and undergoing neuromuscular blockade.

Although the determination of which glucose levels represent hypoglycemia is controversial, a glucose level less than 40 mg/dL is generally accepted to be in the hypoglycemic range. However, this concentration is well below the level at which counter-regulatory responses occur. As plasma glucose levels reach 80 to 85 mg/dL, insulin secretion decreases, and as levels approximate 65 mg/dL, glucagon, epinephrine, cortisol, and growth hormone are released.[139] In addition, a decrease in mental efficiency may be seen when levels fall below 50 to 60 mg/dL.[140] Because a delay in the recognition and management of hypoglycemia may lead to long-term neurologic sequelae,[141] it is important to make a distinction between the laboratory diagnosis of hypoglycemia (<40 to 50 mg/dL) and an interventional threshold at which therapies to raise serum glucose will be applied. Setting the interventional threshold at a level similar to that which elicits counter-regulatory responses seems appropriate, and as such, treatment should be offered for hypoglycemia when levels fall below 60 mg/dL to prevent complications, especially in young children. An even higher interventional threshold (<70 mg/dL) is warranted for children who are at increased risk of hypoglycemia.

Pathogenesis

Imaging studies of infants who sustained neonatal hypoglycemic brain injury display diffuse cortical and subcortical white matter damage that is most prominent in the parietal and occipital lobes. This pattern differs from the neuroimaging features of other neonatal insults, including hypoxic-ischemic encephalopathy.[142] Interestingly this pattern does not resemble the glucose uptake pattern of neonatal brains by positron emission tomography,[143] which may indicate that neuronal damage is not simply due to cerebral deprivation of its primary substrate for energy production. Evidence indicates that hypoglycemia activates receptors for excitatory amino acids within the brain and causes cell depolarization, with subsequent cellular edema and apoptosis.[144] Slow correction of hypoglycemic coma[145] and induced hypothermia prior to glucose reperfusion[146] were shown to be protective in animal models by reducing reperfusion-associated superoxide production and by decreasing cerebral metabolism. Thus neuronal injury might occur not only during the hypoglycemic event but during glucose reperfusion, which triggers neuronal death. Studies of its kind have not been performed in humans and likely would be impractical, yet we should consider careful correction of hypoglycemia to avoid large, sudden swings in blood glucose levels because glucose variability has also been associated with mortality in critically ill patients.[146a]

Clinical Manifestations

Diaphoresis, tremor, tachycardia, anxiety, weakness, hunger, nausea, and vomiting are all autonomic manifestations caused by an adrenergic stress response that occurs with a rapid decline in blood glucose levels. Other symptoms that are associated with hypoglycemia are a result of a deficiency of the brain's primary energy substrate and as such are known as neuroglycopenic symptoms. These symptoms include headache, visual disturbances, lethargy, restlessness, irritability, dysarthria, confusion, somnolence, stupor, coma, hypothermia, seizures, and motor and sensory disturbances. The glycemic ranges at which these symptoms manifest vary, and in many cases they may be asymptomatic or masked by sedatives and muscle relaxants.

Fasting Adaptation

Consumption of glucose is largely dependent on the brain-to-body ratio. This phenomenon explains the reduced fasting tolerance of infants whose glucose utilization rate (approximately 6 mg/kg/min) is much greater than that of older children and adults (1 to 2 mg/kg/min). This reality places younger patients at increased risk of hypoglycemia. In addition, their ability to maintain euglycemia through glycogenolysis and gluconeogenesis is reduced because glycogen stores and muscle bulk are small, thus having a smaller pool of available gluconeogenic substrates. Fasting tolerance increases rapidly in the first days of life. Neonates may fast up to 18 hours after 1 week of age. By 1 year a 24-hour fast is tolerated, and by 5 years a child may fast for up to 36 hours without experiencing hypoglycemia.[147]

Understanding fasting physiology is crucial to the logic and methodologic approach that is required for diagnosing the etiology of hypoglycemia. Normally in the postabsorptive state, metabolism is governed primarily by counter-regulatory hormones. In the first 4 hours of a fast in infants or in the first 8 hours in older children, glucagon is released and euglycemia is maintained primarily by glycogenolysis. Following glycogen store depletion, gluconeogenesis gains importance in the maintenance of normal glucose levels (Figure 77-10).

Muscle provides amino acids, particularly alanine and glutamine as gluconeogenic substrates. Glycerol 3-phosphate derived from triglyceride hydrolysis is also a gluconeogenic precursor. Fatty acids resulting from triglyceride hydrolysis are transported to the liver where they are oxidized to generate acetyl coenzyme A and ketones. The latter may then be used as alternative fuel by skeletal and cardiac muscle to help ensure availability of glucose to the brain and to erythrocytes that are strictly dependent on glucose for energy production. The brain also may utilize ketones as an alternative fuel source, but it does so only during a prolonged fast.

Hypoglycemia that occurs early during fasting should be a clue regarding a hormonal imbalance or a primary disorder of glycogenolysis. Disorders of gluconeogenesis will not manifest

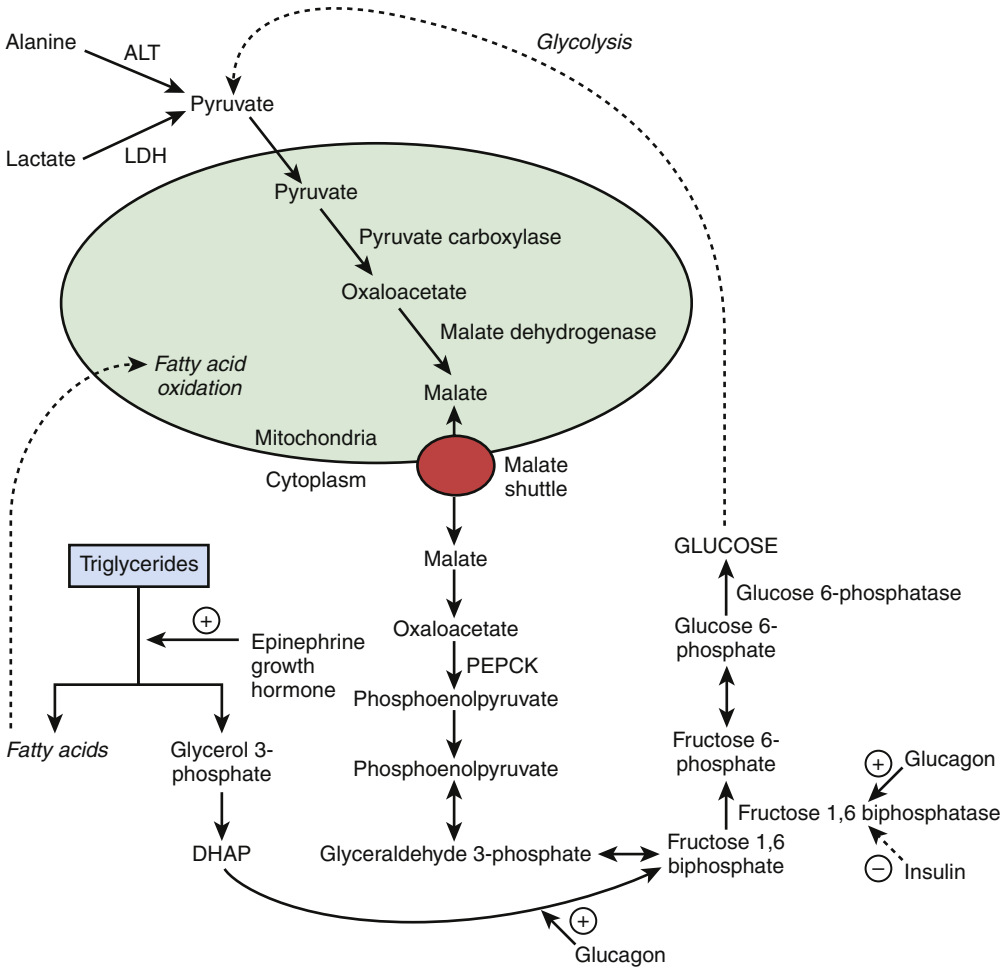

Figure 77–10. Schematic overview of gluconeogenesis. Pyruvate is generated from glycolysis, lactate, or alanine through pyruvate kinase, lactate dehydrogenase (LDH), and alanine-amino transferase (ALT), respectively. Pyruvate enters the mitochondria freely and is converted into oxaloacetate, which is then converted into malate in order to enter the malate shuttle and cross the mitochondrial membrane into the cytoplasm, where it is again converted into oxaloacetate and through phosphoenolpyruvate carboxykinase (PEPCK) is converted into phosphoenolpyruvate that goes through the series of enzymatic-driven reactions depicted and is finally converted into glucose. Note that one of the rate-limiting steps of gluconeogenesis is the conversion of fructose biphosphate into fructose 6-phosphate and is regulated by the actions of glucagon (stimulates) and insulin (inhibits) on fructose 1,6 biphosphatase. Triglycerides also contribute to gluconeogenesis by their breakdown into fatty acids and glycerol 3-phophate, which is then transformed into dihydroacetone phosphate and then into fructose 1,6 biphosphate to follow the rest of the gluconeogenic pathway and result in the generation of glucose.

after an early fast. They become apparent only after glycogen stores have been depleted; hence typically they present later in infancy once feeding intervals become increasingly prolonged. The same is true for fatty oxidation disorders. These disorders generally require a more prolonged fast to manifest, nearing 12 to 18 hours in infants and 18 to 24 hours in older children.

Diagnostic Approach

The history at presentation and the timing of hypoglycemia in relation to the last meal help differentiate disorders of glycogenolysis that present in the immediate postprandial period from disorders of gluconeogenesis, fatty acid oxidation defects, and hormonal imbalances that have a later onset. Physical examination also may suggest the diagnosis. Large-for-gestational-age neonates suggest hyperinsulinism. Midline defects, microphallus, and optic nerve atrophy are suggestive of hypopituitarism. Some glycogen storage disorders are associated with marked hepatomegaly. Ambiguous genitalia in an infant or hyperpigmentation in an older child suggest adrenal insufficiency. Abnormal neuromuscular signs may indicate adrenal leukodystrophy or a fatty acid oxidation defect. However, although a thorough history and physical aid in the diagnosis, physical examination findings often are absent or subtle, and even when they are present and clearly suggestive of a diagnosis, confirmatory laboratory testing is necessary. Therefore it is crucial that "critical" blood and urine samples be obtained prior to treating hypoglycemia unless one can be absolutely certain of the etiology of the hypoglycemia. If the etiology is uncertain, these samples must be obtained and tests performed as outlined in Figure 77-11.

This testing is the most valuable step in the evaluation of the hypoglycemic child. It will quickly point toward a particular pathway of glucose homeostasis that is dysfunctional, help guide further work-up, and may eliminate the need to do a formal diagnostic fast study with its inherent risks. One of the most important differentiations to be made in the work-up of a hypoglycemic child is whether hypoglycemia is accompanied by acidosis.

In an intact gluconeogenic pathway, all gluconeogenic substrates must be exhausted prior to the onset of hypoglycemia;

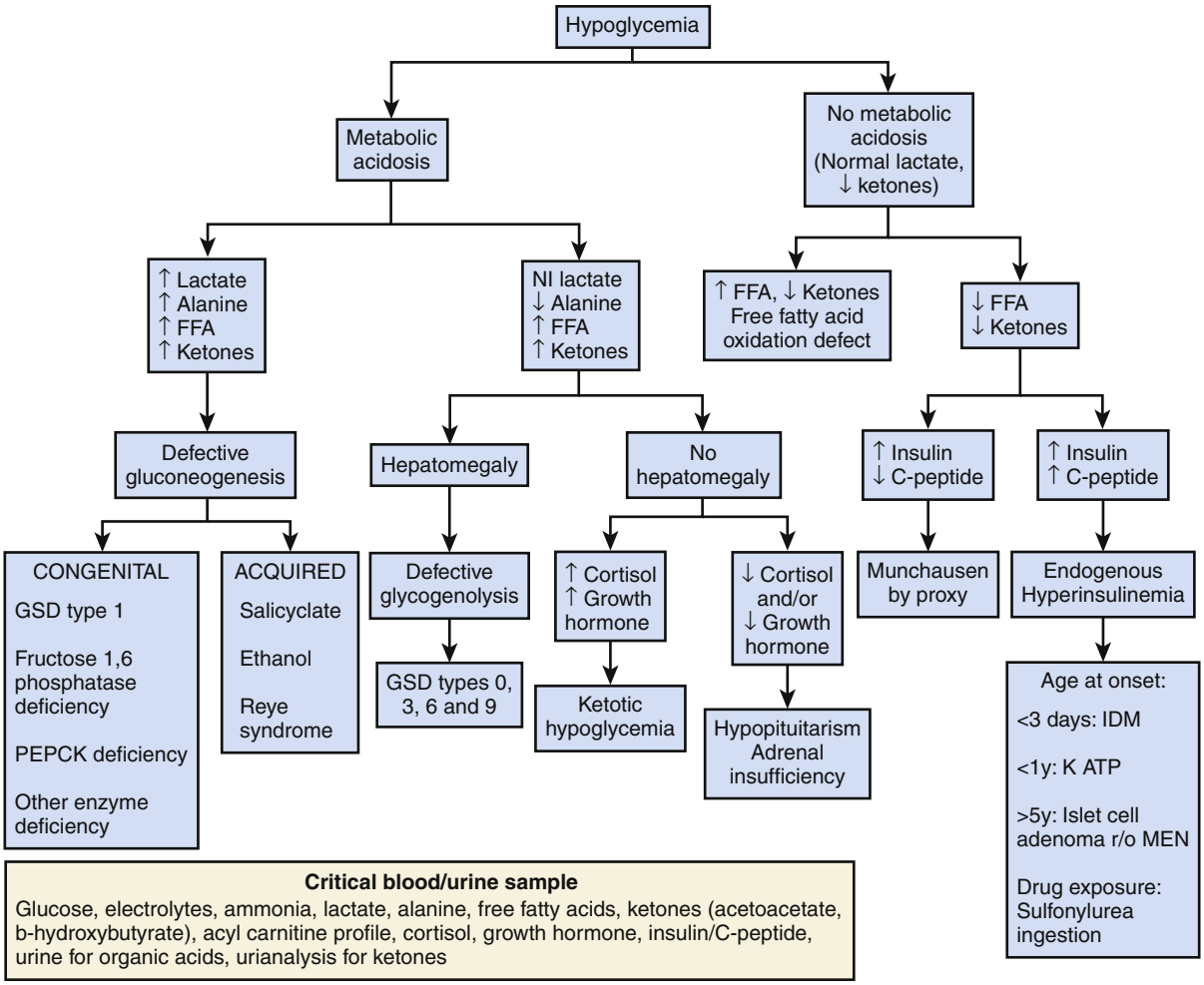

Figure 77–11. Algorithmic approach to hypoglycemia. *FFA,* Free fatty acids; *GSD,* glycogen storage disease; IDM, infant of diabetic mother; *MEN,* multiple endocrine neoplasia; *PEPCK,* phosphoenolpyruvate carboxykinase; K_{ATP}, potassium adenosine triphosphate channel hyperinsulinism, persistent hyperinsulinemic hypoglycemia of infancy.

therefore, lactic acid should not be elevated. The presence of lactic acidosis suggests a defect of gluconeogenesis if no other causes for increased lactic acid, such as shock, are present. On the other hand, the presence of ketoacidosis with a normal lactate points toward a defect of glycogenolysis, ketotic hypoglycemia, or a hormonal deficiency. In these conditions lactate and alanine are low, reflecting normal gluconeogenesis. As the body turns to fat as the primary source of substrate for energy production, increased ketone production occurs. A rise in free fatty acids without an associated elevation in serum ketones during a hypoglycemic event points toward a fatty acid oxidation defect. Decreased FFAs strongly suggests endogenous or exogenous hyperinsulinism because of the antilypolytic effect of insulin.

Defects of Gluconeogenesis

Deficiencies of pyruvate carboxylase, PEPCK, and fructose 1,6 biphosphatase are two of the major enzymatic defects responsible for inadequate gluconeogenesis. Glucose 6-phosphate deficiency (glycogen storage disease [GSD] type 1) is a combined defect of gluconeogenesis and glycogenolysis, because this enzyme is the common final step of both processes. Although most disorders of gluconeogenesis typically manifest after a 4- to 8-hour fast, GSD type 1 presents after an extremely brief postprandial period because of the combined gluconeogenic and glycogenolytic impairment. Its clinical presentation is that of severe hypoglycemia, hepatomegaly, hyperlipidemia, hyperuricemia, and hyperketonemia. Inadequate availability of gluconeogenic substrate and inability to utilize these substrates appropriately are seen with inborn errors of metabolism such as hereditary fructose intolerance (fructose 1-phosphate aldolase deficiency) and galactosemia (see Chapter 76). Gluconeogenesis also may be impaired by drugs such as alcohol[148] and aspirin[149] and may be associated with profound hypoglycemia.

Defective Glycogen Storage and Mobilization

GSDs are, for the most part, defects not in the storage of glucose in the form of glycogen but rather in the "un-storage" of glucose from glycogen. Only glycogen storage disease 0 (glycogen synthase deficiency) represents a defect of glycogen synthesis, and it is rare. Other disorders that are classified as GSDs reflect defects of glycogen breakdown. With the exception of GSD type 1, all other GSDs are associated with minimal to no hypoglycemia because gluconeogenesis usually can maintain normoglycemia in these patients. GSD types III (glycogen debranching enzyme), VI (hepatic glycogen phosphorylase),

and IX (phosphorylase kinase deficiency) are associated with mild hypoglycemia and usually present with associated liver enlargement.

Ketotic Hypoglycemia

In a normal person who is allowed to fast long enough hypoglycemia will develop along with increased ketones. Similar symptomatology develops in patients with this diagnosis, but typically after a short fast, in some cases as short as a few hours. Metabolic pathways are generally intact. Ketotic hypoglycemia is rare before the age of 6 months, subsides before puberty, and is common in children with a low body mass index.[150] It is generally considered a benign condition because sequelae are rare. A lower substrate pool due to decreased muscle mass,[150] insufficient ketone body use, and unrecognized hepatic glycogen synthase deficiency[151] have all been proposed causes, although the definite etiology remains unclear. The low alanine levels during fasting suggest that a limited gluconeogenic supply could be responsible, although some investigators propose that ketotic hypoglycemia represents the end of the Gaussian curve for normal fasting tolerance.[152]

Hormonal Deficiencies

Deficiencies in any of the counter-regulatory hormones can lead to hypoglycemia. Hypopituitarism with isolated GH deficiency and panhypopituitarism with decreased ACTH release typically present during infancy. The latter usually occurs in association with an intercurrent illness that unmasks an impaired cortisol response to stress. Adrenal insufficiency from other causes should be considered in the differential diagnosis of a critically ill child with hypoglycemia because, as previously discussed, multiple factors place such patients at increased risk for CIRCI. Measurement of hormonal levels during the hypoglycemic event will demonstrate inappropriately normal or low levels of these hormones.

Fatty Acid Oxidation Disorders

An increase in FFAs without increased ketonemia suggests a dysfunction in the oxidation of FFAs and conversion into ketones, either as a problem related to transport of these acids into the mitochondria or because of a metabolic defect in the β-oxidative process (see Chapter 74). These problems generally manifest after a 12-hour fast or after a shorter fast if it is associated with an intercurrent illness that places the patient in a catabolic state. Patients may present with encephalopathy and increased ammonia levels, and if it is unrecognized, the condition may be fatal. Fatty acid oxidation defects may be diagnosed by analysis of an acylcarnitine profile and urine for organic acids and by genomic profiling. Carnitine transport deficiency may present with cardiomyopathy, and carnitine supplementation may be life saving.[153] Treatment includes avoidance of fasting and quick reversal of hypoglycemia. Of note, valproic acid may interfere with fatty acid oxidation and mimic these disorders, leading some experts to recommend carnitine supplementation in infants treated with this anticonvulsant agent.[154]

Hyperinsulinism

An elevated insulin level in the presence of hypoglycemia is an inappropriate response to fasting and is diagnostic of hyperinsulinism. The high insulin levels cause an inhibition of gluconeogenesis and lipolysis. Therefore these patients have normal lactate and low FFA and ketone levels in their serum. Measurement of C-peptide differentiates between exogenous hyperinsulinism as seen in Munchausen by proxy and endogenous hyperinsulinism. When endogenous hyperinsulinism presents in the first 3 days of life, it is generally explained by persistently elevated insulin secretion in the neonate after being accustomed to a hyperglycemic environment in utero, as is the case among infants of diabetic mothers or among infants subject to perinatal stress. More than 90% of patients in whom hyperinsulinism persists have K_{ATP} channel hyperinsulinism, formerly known as persistent hyperinsulinemic hypoglycemia of infancy. Potassium flow through this channel regulates insulin secretion. When glucose enters the β cell and undergoes glycolysis, the generation of ATP causes closure of the K_{ATP} channel and stops potassium efflux from the cell. This phenomenon generates a positive membrane potential, and cell depolarization occurs, which in turn causes calcium channels to open, and insulin granules are released. When intracellular glucose levels are low, ATP is decreased and K_{ATP} channels open, allowing potassium to leave the cell and maintain a negative potential, causing closure of calcium channels and inhibiting glucose release. Genetic mutations that cause loss of function of the K_{ATP} channel cause it to remain closed and allow for a constant positive membrane potential and persistent insulin release despite low glucose levels and decreased ATP production[155] as schematically depicted in Appendix Figure 77-C.

Different modes of inheritance exist, with autosomal recessive inheritance operative in the most severe form. Other modes of inheritance are another homozygous form with a single recessive paternal gene mutation with loss of the normal maternal allele (focal adenomatosis), and a milder autosomal dominant form. Treatment consists of diazoxide, but it may be ineffective. Octreotide is an alternative. If hypoglycemia persists despite medical management, pancreatectomy may be necessary.

When hyperinsulinism presents after infancy, insulinoma and multiple endocrine neoplasia enter into the differential diagnosis. Sulfonylurea, quinine, and pentamidine also may augment insulin secretion and mediate hypoglycemia in cases of intentional or accidental ingestion. A detailed history about medications in the home must be obtained in all patients presenting with hypoglycemia.

Hypoglycemia and Critical Illness

Hypoglycemia has been observed in association with a variety of diagnoses, including sepsis,[156] congestive heart failure,[157] renal failure,[158] liver failure,[159] and pancreatitis,[160] and it has been associated with increased mortality among critically ill children.[136,161] Critically ill patients are at risk of hypoglycemia, not only because of their underlying illness but because of factors unique to their hospitalization, such as muscular atrophy from prolonged immobilization and gluconeogenic substrate depletion, undernutrition often resulting from the limitation of caloric intake because of fluid restriction, increased glucose consumption, adrenal insufficiency, loss of intravenous access or inadvertent disconnection of infusion lines, or iatrogenic factors related to drugs and therapies, including the practice of strict glycemic control.

Hypoglycemia Treatment

After obtaining the "critical" blood/urine samples, the administration of 2 mL/kg of 10% dextrose water solution is indicated for patients with hypoglycemia. An intravenous maintenance

fluid regimen should be initiated to provide a glucose infusion rate of 8 mg/kg/min. Serum glucose should be rechecked 15 minutes after the initial bolus, and if hypoglycemia persists, a repeat bolus of 5 mL/kg of 10% dextrose water and an increase in the glucose infusion rate by 50% is recommended. If the amount of fluid to be administered in order to maintain a glucose infusion rate that will maintain blood glucose levels at greater than 70 mg/dL is excessive, a fluid with a higher dextrose concentration should be used to prevent fluid overload. Glucagon (0.03 mg/kg) can reverse hypoglycemia in patients with adequate glycogen stores and normal glycogenolytic pathways. Definitive treatment will depend on the underlying etiology. Avoidance of long fasts for patients with fatty acid oxidation defects, appropriate supplementation for patients with hormonal deficiencies, and continuous gavage feedings for patients with severe fasting intolerance may be needed.

Summary

Hypoglycemia is a manifestation of iatrogenesis, intentional or accidental drug ingestion or administration, or the manifestation of an underlying disorder. All critically ill patients with hypoglycemia should raise a high index of suspicion because many defects that cause hypoglycemia remain silent until an intercurrent illness or stress overwhelm the compensatory capacity of the individual. Unless certitude of the etiology of the hypoglycemia exists prior to therapy, a "critical" blood/urine sample should be obtained whenever possible prior to correction of the hypoglycemia to guide diagnosis and further management. Prompt recognition and treatment are necessary to prevent neurologic injury. A multidisciplinary approach is often necessary.

Alterations of Thyroid Hormone in Critical Illness

Classic Thyroid Endocrinology

Thyroid-stimulating hormone (TSH), which is derived from the anterior pituitary, is a pleiotropic hormone that affects basically all aspects of thyroid hormone synthesis. TSH action within the thyroid follicular cells facilitates the sodium iodide symporter, resulting in iodide trapping in the thyroid gland; it increases the synthesis of thyroglobulin (the site of tyrosine residues destined for derivation of thyroid hormones) and activates thyroid peroxidase, resulting in so-called *organification* or iodination and coupling of tyrosine residues. It is important to note that autoantibodies may bind to TSH receptors and stimulate a response similar to TSH, resulting in a hyperthyroid state.

Thyroid Hormone Biochemistry

An overview of thyroid hormone biosynthesis and secretion is provided in Figure 77-12.[10] In this schematic diagram, iodide is transported into the thyroid follicular cell

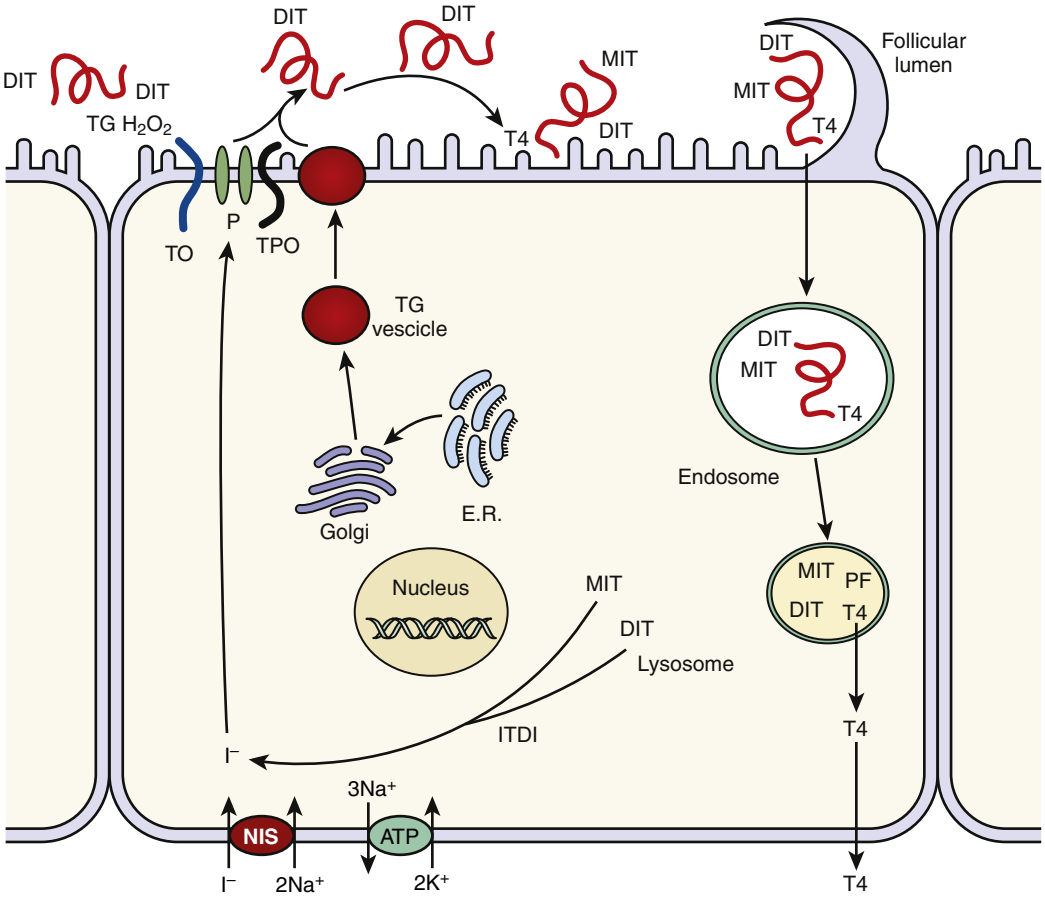

Figure 77–12. Thyroid hormone biosynthesis and secretion. *(Adapted from Goodman HM:* Basic medical endocrinology, *Boston, 2009, Elsevier, p 45.)*

by the action of the sodium-iodide symporter. Subsequently this iodide diffuses passively through the iodide channel, termed pendrin. Thyroglobulin (TG) is synthesized within the rough endoplasmic reticulum and subsequently is packaged by the Golgi apparatus into TG secretory vesicles that are released into the follicular cell lumen. Thyroid oxidase produces hydrogen peroxide that is subsequently utilized by thyroid peroxidase to oxidize iodide to iodine. Iodine then reacts with the tyrosine residues within TG to produce monoiodotyrosine and diiodotyrosine residues within the TG peptide.

Thyroid peroxidase also catalyzes coupling of adjacent iodotyrosines to form thyroxin (T4), as well as lesser amounts of triiodothyronine. Secretion of T4 from the thyroid follicular cell begins with TG phagocytosis and formation of TG endosomes that then fuse with lysosomes containing proteolytic enzymes capable of digesting TG into peptide fragments, as well as monoiodotyrosine, diiodotyrosine, and tT4. T4 is released from the cell at the basal membrane, and both monoiodotyrosine and diiodotyrosine are deiodinated by iodotyrosine deiodinase and recycled.

T4 is transported to peripheral tissues via the transport hormones T4-binding globulin, transthyretin, and albumin. Because all of the T4 transport proteins are of at least moderate size, T4 is not filtered by the kidney. In peripheral tissues, T4 is metabolized to triiodotyrosine (T3) and reverse T3 (rT3) by the action of various isoforms of iodotyrosine deiodinases. Transcription and translation of this enzyme is highly dependent upon cytokine stimulation. If monodeiodination occurs on the outer tyrosine ring the product is T3, and if the monodeiodination occurs on the inner tyrosine ring the resultant product is rT3 (Figure 77-3).[10]

In peripheral tissues, T3 binds to thyroid hormone receptors that can bind to specific nucleotides sequences termed *thyroid responsive elements* within promoter regions of genes that they regulate, whether or not the thyroid hormone is present. The presence or absence of T3 on the thyroid receptor dictates a corepressor or coactivator activity.[162]

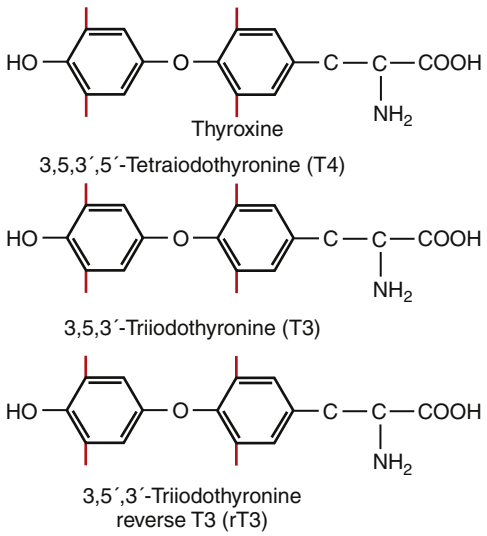

Figure 77–13. Thyroid hormone chemical structures. *(Adapted from Goodman HM:* Basic medical endocrinology, *Boston, 2009, Elsevier, p 40.)*

Thyroid Hormone Actions

Box 77-1 summarizes the effects of thyroid hormone on metabolism.[163]

Thyroid hormone significantly affects skeletal and central nervous system growth and maturation. Unrecognized hypothyroidism in infancy results in marked physical, motor, and mental delay, termed *cretinism*. Hemodynamically, thyroid hormone is known to increase β-adrenergic receptor density and activity, as well as up-regulation for genes encoding calcium channels (ryanodine receptor) and sodium potassium adenosine triphosphatase. In a general way, thyroid hormone provides gain control for carbohydrate and lipid metabolism and significantly accelerates both protein synthesis and degradation. Through its effects on uncoupling of ATP production, thyroid hormone can significantly affect oxidative metabolism as well as heat production.

Hyperthyroidism

Manifestations of thyrotoxicosis reflect increased thyroid hormone concentration. Box 77-2 summarizes signs and symptoms characteristic of thyrotoxicosis.

Grave's disease is probably the best known example of hyperthyroidism and classically is associated with a diffusely enlarged thyroid gland (goiter), exophthalmos, and cardiac palpitations. Pathophysiology of Grave's disease involves thyroid-stimulating autoantibodies that bind to TSH receptors. Hypertrophy and hyperplasia of the thyroid accompanying Grave's disease is typically associated with lymphocytic infiltration.[164] Grave's disease typically occurs in adults and chronically is associated with nervousness, fatigue, tremor, heat intolerance, and weight loss.[165] Hyperthyroidism also may occur via increased production of TSH resulting from a pituitary adenoma. Painful thyroiditis (de Quervain thyroiditis) can occur following a viral illness and may be

Box 77–1 Thyroid Effects on Metabolism

1. Increased oxygen consumption
2. Enhanced thermogenesis
3. Accelerated amino acid and lipid metabolism
4. Facilitated and water and ion transport
5. Enhanced tissue growth and development
6. Altered cortisol and insulin catabolism
7. Modulated growth hormone and parathormone activity
8. Enhanced respiratory response to hypoxia and hypercarbia
9. Increased β-adrenergic receptor affinity and responsiveness to catecholamines

Box 77–2 Signs and Symptoms of Thyrotoxicosis

1. Hyperactivity, tremor, agitation, hyperreflexia
2. Sinus tachycardia, palpitations, arrhythmias, systolic hypertension, heart failure
3. Perspiration
4. Abdominal pain, diarrhea
5. Bulging eyes (exophthalmos)
6. Thirst
7. Proximal myopathy
8. Apathy, stupor, coma

associated with hyperthyroidism.[166] A more likely presentation of hyperthyroidism in a teenager is likely to be caused by Hashimoto's thyroiditis. Amiodarone can be associated with either hyperthyroidism or hypothyroidism because its chemical structure is similar toT4.[167] Neonatal thyrotoxicosis is similar to Grave's disease and involves transplacental passage of TSH-like autoantibodies from the mother to the fetus. Thyrotoxicosis is more common among patients with Down syndrome, diabetes mellitus, and McCune-Albright syndrome.

Patients admitted to the ICU with hyperthyroidism typically will exhibit either sinus tachycardia or supraventricular tachycardia, nausea, vomiting and diarrhea, and weakness, as well as confusion, delirium, or even coma. Classic findings of a diffusely enlarged thyroid with a overlying bruit or murmur may not be present.

Thyroid storm is the most severe manifestation of hyperthyroidism. It is an exaggerated state of thyrotoxicosis that generally follows an acute stressor, is of sudden onset, and may progress to extreme hyperthermia, cardiovascular collapse, coma, and, if left untreated, to death. Treatment of thyroid storm involves a four-pronged approach: (1) provide supportive measures such as antipyretics, anxiolytics, and volume resuscitation as needed; (2) block T3 activity in peripheral tissues by utilizing thionamides, iopanoic acid, or β-adrenergic blockage with an esmolol infusion and subsequently with propranolol (1 to 2 mg/kg/day) and corticosteroids; (3) control thyroid gland production of T4 utilizing thionamides such as propylthiouracil (20 mg/kg/day in four divided doses) or methimazole, which interfere with thyroid peroxidase iodination (iodide administration in large doses to exceed 0.1 mg/kg/day [Lugol solution 5 to 10 drops orally every 8 hours] interferes with the transport of iodide in the thyroid and thyroid hormone release); and (4) identify and treat identifiable precipitating antecedents. With adequate management, clinical improvement is seen within 24 hours. In severe cases of recalcitrant thyroid storm, plasmapheresis with charcoal hemoperfusion has been used to reduce circulating T4. Occasionally, subtotal thyroidectomy may be required for chronic thyrotoxicosis. Anticipated postsurgical complications in such patients include recurrent laryngeal nerve damage, hypocalcemia with tetany secondary to inadvertent parathyroid gland resection, and hypothyroidism.

Hypothyroidism

The most common cause of hypothyroidism is iodine deficiency, which affects approximately 800 million people worldwide. The signs and symptoms of congenital hypothyroidism include prolonged neonatal jaundice, coarse features, protruding tongue, apathy, poor feeding, umbilical hernia, and eventual mental retardation. For this reason, unrecognized neonatal hypothyroidism is of particular concern. Patients with Down syndrome are especially at risk of the development of hypothyroidism. Thus hypothyroidism should be suspected in children with trisomy 21 with unstable hemodynamics following cardiovascular surgery. True hypothyroidism resulting from thyroid gland failure or maldevelopment will manifest with an elevated TSH concentration, although this response may be blunted in the ICU by malnutrition, dopamine, and corticosteroids. Levothyroxine constitutes the primary treatment for hypothyroidism.

Sick Euthyroid Syndrome in Critical Illness

The sick euthyroid syndrome occurs in the setting of illness, malnutrition, and surgery including pediatric cardiac surgery patients.[168,169] The syndrome is characterized by a rapid decrease in T3 and variable increase in rT3 that appears to be proportional to the intensity of illness severity and concentration of TNF-α. In addition, a decline in various thyroid hormone–binding proteins is evident. Conversion of T4 to T3 is suppressed as a result of decreased 5′-deiodinase activity. Because of decreased thyroid-releasing hormone gene expression in the hypothalamus, thyroid-releasing hormone is decreased with a resultant reduced TSH messenger ribonucleic acid. Laboratory finding characteristics of sick euthyroid syndrome are summarized in Table 77-1.[170]

The significance of sick euthyroid syndrome in critical illness remains controversial. Evidence indicating overt pathology in this setting is sparse. Some persons argue that this scenario reflects an effort of the body to conserve energy expenditure during stress. Thyroid hormone alterations characteristic of sick euthyroid syndrome would also be expected to modulate protein catabolism.[171] Sick euthyroid syndrome should be differentiated from true hypothyroidism. The latter can occur occasionally among patients to whom dopamine and high-dose corticosteroids are administered, both as a result of inhibition of TSH. Various drug effects on thyroid hormone metabolism are summarized in Table 77-2.

Table 77–1 Sick Euthyroid Syndrome Laboratory Data

Variable	Value
Free T4	Normal
T4 →T3 conversion	Decreased
T3	Markedly decreased
rT3	Variable
TSH	Normal

rT3, Reverse triiodotyrosine; *T3,* triiodotyrosine; *T4,* thyroxin; *TSH,* thyroid-stimulating hormone.

Table 77–2 Effects of Various Drugs on Thyroid Hormone Metabolism

Drug	Effect
Dopamine	Blunts TSH response to TRH
Corticosteroids	Suppresses basal and TRH-stimulated TSH release
Iodinated contrast agents	Decreases hepatic conversion of T4 to T3
Amiodarone	Decreases hepatic conversion of T4 to T3, and decreases servo feedback T3 binding at the pituitary
Phenytoin	Enhances T4 to T3 conversion (low free T4 and low total T4)

T3, Triiodotyrosine; *T4,* thyroxin; *TRH,* thyroid-releasing hormone; *TSH,* thyroid-stimulating hormone.

Thyroid Hormone Supplementation in the Pediatric Intensive Care Unit

Patients with true hypothyroidism should receive replacement T4. Treatment of patients with sick euthyroid syndrome is more controversial. Although the basis for the observation is not clear, adult investigators have previously demonstrated that low serum T3 levels represent the single most significant predictor of cardiovascular mortality and mortality resulting from all causes among adults with heart disease.[172] Triiodothyronine replacement in adults with impaired left ventricular function resulted in improved left ventricular function, as well as restored cardiomyocyte gene expression to euthyroid levels.[173] Among adult patients with heart failure, infusion of T3 for 72 hours resulted in normalization of serum T3 levels with concomitant improvement in stroke volume as well as left ventricular end-diastolic volume compared with pretreatment levels.[174] Such findings have stimulated interest in thyroid hormone pathophysiology among children with cardiovascular disease. Thyroid function, as well as clinical outcomes, were assessed serially among children undergoing cardiac bypass surgery. All subjects demonstrated defined nonthyroidal illness syndrome characterized by reduced TSH, total T3, free T3 index, and T3 uptake. These changes were correlated with prolonged need for mechanical ventilation, degree of organ dysfunction, and vasoactive-inotropic scores.[175]

One interventional trial has reported the effect of T3 supplementation among children undergoing cardiovascular surgery. In this investigation, replacement dosing of T3 following cardiopulmonary bypass resulted in increases in plasma T3 concomitant with measures of improved myocardial performance, particularly among children exhibiting low postoperative cardiac output.[176] Currently other interventional studies assessing the potential benefits of T3 supplementation during and following pediatric cardiac surgery are in progress (e.g., a study of Triostat among infants during heart surgery: ClinicalTrials.gov:NCT00027417).

References are available online at http://www.expertconsult.com.

V

Chapter 78

Diabetic Ketoacidosis

Catherine Pihoker, Ildiko H. Koves, and Nicole S. Glaser

PEARLS

- Diabetic ketoacidosis (DKA) results either from absolute insulin deficiency or from relative insulin deficiency in the setting of high levels of counter-regulatory hormones stimulated by infection or other illness.
- DKA is characterized by hyperglycemia, ketosis, and acidosis.
- Treatment of pediatric DKA involves insulin administration and intravenous fluid administration to correct dehydration, and replacement of electrolyte deficits.
- Cerebral edema is the most frequent serious complication of DKA in children and is the most frequent cause of morbidity and mortality resulting from DKA.
- See Box 78-1 for more information about DKA treatment in children and adolescents.

Etiology, Definition, and Presentation

Diabetic ketoacidosis (DKA) occurs when serum insulin concentrations are very low in relation to concentrations of glucagon and other counterregulatory hormones (epinephrine, norepinephrine, cortisol, and growth hormone). This situation occurs most commonly in new onset of type 1 diabetes and in patients with known diabetes during infections or other illnesses, or with insulin omission (see the following section). In the setting of low insulin concentrations in relation to counterregulatory hormone concentrations, the normal physiological mechanisms responsible for maintaining adequate fuel supply during fasting and physiological stress are exaggerated, resulting in hyperglycemia, ketosis, and acidosis. A diagnosis of DKA can be made when the serum glucose concentration is greater than 200 mg/dL (>11 mmol/L) and venous pH is less than 7.30 (or the serum bicarbonate concentration is less than 15 mmol/L) in the presence of elevated urine or serum ketone concentrations.

In a child with new onset of type 1 diabetes, declining insulin production results from autoimmune destruction of pancreatic beta cells. The concentration of insulin is decreased relative to glucagon causing excess hepatic glucose production and decreased peripheral glucose uptake in muscle and adipose tissue.[1,2] When the serum glucose concentration rises above approximately 180 to 200 mg/dL, the renal threshold for glucose reabsorption is exceeded causing glycosuria, which leads to osmotic diuresis and compensatory polydipsia. Low insulin concentrations also stimulate the release of free fatty acids (FFA) from adipose tissue to fuel ketogenesis.[3] This, in combination with activation of the hepatic β-oxidative enzyme sequence resulting from relative excess of glucagon in relation to insulin, results in markedly increased hepatic ketone production.[2-4]

Progressive dehydration and increasing acidosis eventually stimulate additional release of the counterregulatory ("stress") hormones, cortisol, catecholamines, and growth hormone, which accelerate hepatic glucose output and ketone production.[5,6] Infection or other illness or injury can likewise contribute to this process by stimulating release of counterregulatory hormones. Elevated cortisol concentrations augment FFA release from adipose tissue and decrease peripheral glucose uptake. Increased epinephrine concentrations directly increase glycogenolysis and stimulate release of gluconeogenic precursors from muscle.[7,8] Both epinephrine and norepinephrine also stimulate lipolysis and β-oxidation of FFAs.[9,10] Catecholamines may also directly inhibit insulin secretion, thereby accelerating DKA in those with endogenous insulin capacity, such as a new diagnosis of type 1 diabetes or those with type 2 diabetes.[11,12] Growth hormone also decreases peripheral glucose uptake, and enhances ketone production by increasing FFA release.[13] Elevated concentrations of counterregulatory hormones thus result in increased acidosis, hyperglycemia, and dehydration. This in turn stimulates further counterregulatory hormone release thereby creating a "vicious cycle" resulting in rapid worsening of DKA (Figure 78-1).

During DKA, intestinal ileus results from potassium depletion, acidosis, and diminished splanchnic perfusion, causing abdominal pain and vomiting and thereby limiting fluid intake. Progressive dehydration eventually leads to diminished tissue perfusion sufficient to cause accumulation of lactic acid, enhancing acidosis.[14] In addition, poor perfusion may result in diminished renal function, limiting the capacity for clearance of glucose and ketones. Ongoing osmotic diuresis and ketonuria in the setting of acidosis also results in urinary losses of electrolytes (potassium, sodium, chloride, calcium, phosphate, and magnesium).

Classical symptoms of DKA include polyuria, polydipsia, polyphagia, weight loss, abdominal pain, nausea, and vomiting. Abdominal tenderness, absence of bowel sounds and guarding are frequent and may even mimic an acute abdomen.[15] Tachycardia and signs of hypoperfusion, such as delayed capillary refill time and cool extremities, are also common as well as dry mucous membranes, absence of tears, and poor skin turgor. Despite substantial volume depletion, however, hypotension

Box 78–1 DKA Treatment in Children and Adolescents

Fluids

- Most children require an initial fluid bolus of 10 mL/kg of isotonic fluids (0.9% saline or lactated Ringer's). Additional fluid boluses may be administered if necessary to restore perfusion.
- Subsequent fluid administration should replace the remaining fluid deficit (typically ~70–90 mL/Kg) plus maintenance fluids over 36–48 hours using 0.45%–0.9% saline. 0.9% saline may be used initially with a transition to 0.45% saline after several hours.

Insulin

- After initial fluid bolus(es), begin insulin administration at 0.1 U/kg/hr.
- An initial insulin bolus dosage is not necessary.
- Insulin should be administered 0.1 U/kg/hr until ketoacidosis resolves (pH >7.30, HCO_3 >15, normalization of anion gap).
- To prevent hypoglycemia, glucose-containing intravenous fluids should be used after the plasma glucose concentration declines below ~250–300 mg/dL.

Potassium and other electrolyte replacement

- Potassium replacement is required, and should begin immediately in patients with hypokalemia. Potassium replacement should begin concurrent with insulin treatment in all others. For patients with hyperkalemia, potassium replacement should be based on the serum potassium measurements and given only after adequate renal function is verified.
- Potassium administration should begin at 40 mEq/L of intravenous fluids (excluding rare patients with significant hyperkalemia). Subsequent potassium administration should be adjusted according to serum potassium concentrations.
- Calcium, magnesium, and phosphate concentrations should be monitored during therapy. Phosphate concentrations typically decrease during treatment and replacement of phosphate by using potassium phosphate in combination with potassium chloride can be considered. Replacement of calcium and magnesium is rarely required.

Correction of Acidosis

- Bicarbonate treatment should not be used routinely.
- In rare circumstances (symptomatic hyperkalemia, cardiovascular instability caused by severe acidosis), bicarbonate treatment should be considered.

Monitoring

- Vital signs should be measured hourly.
- Continuous cardiac monitoring is recommended.
- Fluid intake and output should be recorded hourly.
- Blood glucose concentrations should be measured hourly. Electrolytes, serum urea nitrogen, creatinine, venous pH, and P_{CO_2} should be measured every 2–4 hours. Calcium, magnesium, and phosphate should be monitored approximately every 6 hours. More frequent electrolyte measurements may be necessary in patients with abnormal or rapidly changing electrolyte concentrations.
- Mental status should be assessed hourly. More frequent assessment may be necessary for patients with headache or other symptoms or signs of cerebral edema.

Modified from Glaser NS: Pediatric diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Clin North Am* 52:1611-1635, 2005.

is unusual in children with DKA and occasional children may present with hypertension. Kussmaul breathing and tachypnea are the result of metabolic acidosis and respiratory compensatory mechanisms. Fruity breath odor (acetone) may be present. Hypothermia has also been described.[16]

Although hyperglycemia is part of the definition of DKA, in rare cases, the serum glucose concentration may be nearly normal, so called "euglycemic DKA." This situation has been reported most frequently in pregnant women.[17-19] Normal glucose concentrations or even hypoglycemia despite ketosis may also occur in children with known diabetes who administer insulin to treat DKA prior to arrival in the emergency department. In general, however, the persistence and severity of hyperglycemia reflects the severity of dehydration. In the absence of preexisting renal disease or unusually high carbohydrate intake just before presentation, blood glucose concentrations in excess of 500 to 600 mg/dl imply that dehydration is of sufficient severity to diminish the glomerular filtration rate and thereby diminish the capacity for renal clearance of excess glucose.[20]

Concentrations of ketone bodies (beta-hydroxybutyrate [βOHB] and acetoacetate [AcAc]) are elevated in DKA resulting in acidosis. Hyperchloremic acidosis frequently coexists with increased anion-gap acidosis, and the anion gap reflects the combination of these processes.[21] The ratio of βOHB:AcAc (typically 1:1 in the normal state) is increased during DKA and may be as high as 10:1.[22] During treatment, this ratio returns to normal. The nitroprusside reaction used to test urine ketone concentrations detects only AcAc and not βOHB. As a result, nitroprusside urine testing cannot be relied on to determine DKA severity or treatment response. Bedside blood ketone meters provide a rapid means for measuring βOHB, and may be useful in place of or in addition to urine testing particularly in patients with anuria or oligoria who produce insufficient amounts of urine for ketone testing.[23] Blood ketone measurements are also useful for determining the timing of transition from intravenous to subcutaneous insulin administration. Urine ketones may be present even when blood ketones have normalized as a result of urine stagnating in the bladder.

Hyperglycemia results in fluid shifts from the extravascular to the intravascular space and a decrease in the serum sodium concentration. This decrease can be calculated as an approximately 1.6 mEq/L decrease in sodium concentration for every 100 mg/dl increase in serum glucose higher than 100 mg/dl or $Na_{corrected} = Na_{actual} + (\text{glucose in mmol/L} - 5.5 \text{ mmol/L})$}.[24,25] Hyperlipidemia may also contribute to a decrease in measured serum sodium concentrations.[26] Typically, serum

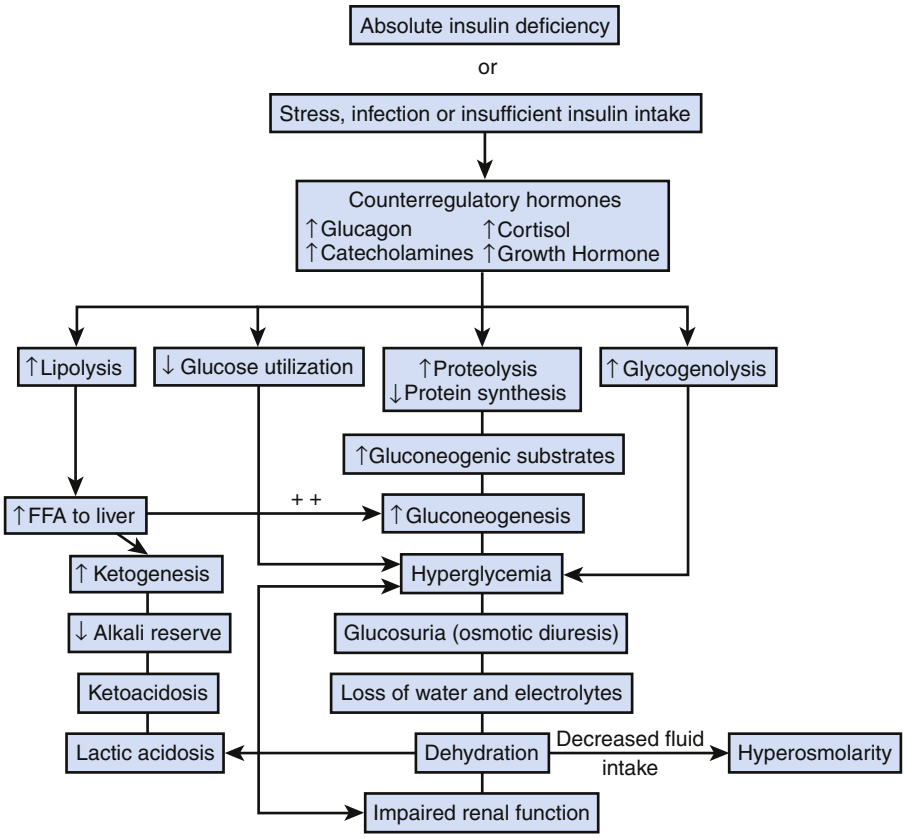

Figure 78–1. Pathophysiology of DKA. *(From Wolfsdorf J, Glaser N, Sperling MA: Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association,* Diabetes Care *29[5]:1150-1159, 2006.)*

potassium at presentation is in the high-normal range as a result of redistribution of potassium ions from the intracellular to the extracellular space. Several processes are responsible for intracellular potassium depletion including direct effects of low insulin concentrations, intracellular protein and phosphate depletion, and buffering of hydrogen ions in the intracellular compartment.[27] Intracellular potassium stores may be profoundly depleted and the serum potassium concentration typically declines rapidly with insulin treatment. Serum phosphate concentrations similarly decrease during treatment.

Leukocytosis is frequent in children with DKA, likely resulting from elevated concentrations of catecholamines and proinflammatory cytokines. In children, new onset of type 1 diabetes or insulin omission are far more common causes of DKA than infection. [28] Therefore, an elevated or left-shifted white blood cell count need not prompt a search for an infectious process in the absence of fever or other symptoms or signs of infection. However, in the presence of fever, careful history, physical examination, and laboratory evaluation to assess for infection is prudent.

Epidemiology

Frequency of Diabetic Ketoacidosis at Diagnosis

The frequency of DKA at diagnosis varies widely by geographic region, with an overall estimated frequency of approximately 20% to 67%. In the population-based US study, SEARCH for Diabetes in Youth, data were collected from self-reported health questionnaires and medical record review. In this study, 25.5% of children and adolescents presented at onset of diabetes in DKA.[29] A similar frequency was observed in Germany, with 26.3% of children under the age of 15 presenting in DKA at diagnosis of diabetes. In a collaborative study from Germany and Austria, the Diabetes Patienten Verlausdokumentation (an electronic documentation system for children with diabetes), the frequency of DKA at presentation was 21.1%.[30] Younger age (<5 years) and female sex were associated with higher likelihood of presenting in DKA.[31,32] A delay in diagnosis is associated with a higher likelihood of DKA, and two factors contributing to this are patient age and provider experience. Regions with a higher prevalence of type 1 diabetes generally have a lower frequency of DKA,[33] attributed to heightened awareness in providers and thus earlier detection. The non-specific nature of individual symptoms, such as polyuria, tachypnea, and altered mental status, may cause such symptoms to be misconstrued as urinary tract infection, pneumonia, or meningitis, respectively.[34] Mallare et al.[35] reported a frequency of DKA of 33% in children and adolescents at the initial visit, and almost double (59%) in those in whom the diagnosis of diabetes was missed at the initial visit. The diagnosis of diabetes was more likely to be missed in very young children (34% of children ≤5 years of age compared to 8.5% in those greater than 10 years of age),[35] particularly when these very young children are evaluated by family practitioners rather than pediatricians.[36]

Frequency of Diabetic Ketoacidosis in Children and Adolescents After Diagnosis

Although there are several population-based studies reporting the frequency of DKA at presentation, fewer data are available describing the incidence of DKA in children and adolescents with established diabetes. Reported frequencies range from 1 to 10 per 100 patient years.[37] In the Diabetes Control and Complications Trial, the incidence of DKA in adolescents treated with intensive management regimens was 2.8 per 100 patient-years, significantly lower than the incidence in those treated conventionally (4.7 per 100 patient years). Although this is an older study, it was a time and resource-intensive study, and represents a more idealized situation than often encountered in the overall pediatric diabetes population.[38] In a more recent study from the Barbara Davis Center for Childhood Diabetes in Denver, Colorado, the overall incidence of DKA was 8 per 100 person-years. In that study, factors associated with higher incidence included older age, higher HbA1C (relative risk [RR] of 1.68 per 1% increase in HbA1C in younger children, RR of 1.43 in older children), higher reported insulin dose, DSM4 psychiatric diagnoses, and "underinsurance" reflecting lower socioeconomic status.[39] DKA is also observed more often in children and adolescents on continuous subcutaneous insulin infusion therapy (CSII) than on subcutaneous injections, particularly in the first year of initiation of CSII.[40] However, lower rates of DKA are achievable for those on CSII with adequate training and resources.

Over the past two decades T2DM has been occurring with increasing frequency in older children and adolescents. Certain racial/ethnic groups in the United States are disproportionately affected including Native Americans, Hispanics, and African Americans. DKA can be the clinical presentation for T2DM in youth estimated at 5% to 10%.[41] Youth with T2DM may also present with hyperglycemic hyperosmolar state (HHS), also referred to hyperosmotic hyperglycemic non-ketotic coma (HHNK, described more fully in the following section).

Morbidity and Mortality Associated with Diabetic Ketoacidosis

Mortality in children presenting with DKA is approximately 0.25% to 0.30%.[37] Most of the mortality in DKA occurs in children with cerebral edema, accounting for 57% to 87% of deaths. Neurologic sequelae of DKA are described in the section on DKA-associated complications. Other causes of morbidity and mortality include sepsis and secondary infection, electrolyte abnormalities (e.g., hypokalemia), arrhythmias, rhabdomyolysis, thrombosis, pneumomediastinum, subcutaneous emphysema, and pulmonary edema.

Management Guidelines

Fluids

Restoration of adequate peripheral perfusion and hemodynamic stability with bolus administration of intravenous fluids (0.9% saline or other isotonic fluids) should begin as soon as possible. Typical patients require an initial fluid bolus of 10 ml/kg that may be repeated if ongoing hemodynamic instability is present. Studies have shown that clinical assessments of dehydration severity in children with DKA tend to be inaccurate (Figure 78-2).[42] The average degree of dehydration for most patients is approximately 7% to 9% of body weight and this figure should be used as a basis for determining the total volume of fluids to be replaced.[42,43] The estimated fluid deficit, along with maintenance fluid requirements, should be replaced over 36 to 48 hours using 0.45% to 0.90% saline, generally initially with 0.9% saline, then transitioning to 0.45% saline after several hours assuming serum Na is not falling. Replacement of ongoing urinary fluid losses is usually unnecessary because osmotic diuresis typically resolves rapidly after beginning insulin infusion. However, in circumstances of persistently high urine output, or profuse vomiting or diarrhea, replacement of ongoing losses may be considered.

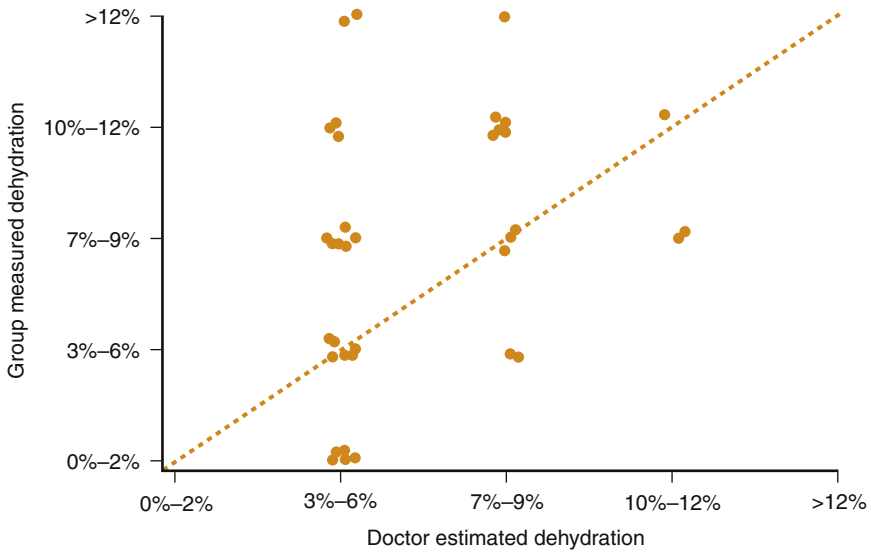

Figure 78–2. Estimated versus measured dehydration in children with DKA. *(From Koves IH, Neutze J, Donath S, et al: The accuracy of clinical assessment of dehydration during diabetic ketoacidosis in childhood,* Diabetes Care *27[10]:2485-2487, 2004.)*

Insulin

Insulin should be administered intravenously at a rate of 0.1 units/kg/hour. Insulin administration results in resolution of acidosis and hyperglycemia via suppression of ketogenesis, and hepatic glucose output and promotion of peripheral glucose uptake. An initial bolus or loading dose of insulin is not recommended. Maximal suppression of ketogenesis is achieved rapidly with an insulin infusion (0.1 unit/kg/hour).[44,45] Even in the absence of insulin administration, the serum glucose concentration usually decreases substantially with initial rehydration, reflecting improvements in renal perfusion and decreased counter-regulatory hormone concentrations.[14] This decline in glucose concentration during the initial period of rehydration should not be interpreted as indicating excessive insulin administration.

Serum glucose concentrations typically normalize before ketosis and acidosis resolve. To continue insulin administration at dosages sufficient to allow resolution of ketosis, dextrose should be added to the intravenous fluids. Transition to dextrose-containing fluids should occur when the serum glucose concentrations decline below approximately 250 mg/dl. The "two-bag system" for dextrose administration allows a rapid response to changes in serum glucose concentration and is cost-effective.[46] Two bags of intravenous fluids with identical electrolyte content, but varying dextrose content (0% and 10%) are administered simultaneously with the relative rates of administration frequently adjusted to increase or decrease the dextrose concentration while maintaining a constant overall rate of administration of fluid and electrolytes.

Electrolytes

Serum potassium concentration often declines rapidly during treatment and potassium replacement is mandatory. Typical patients require potassium administration at concentrations of 30-40 mEq (occasionally up to 80 mEq) per liter of intravenous fluids. Potassium chloride may be used alone or in combination with other potassium salts (potassium phosphate or potassium acetate), permitting lower chloride administration. Adequacy of renal function should be considered before administration of potassium.

Phosphate replacement in children with DKA is controversial. Theoretically, low 2,3-diphosphoglycerate levels in red blood cells may occur in association with hypophosphatemia leading to decreased tissue oxygen delivery.[47,48] However, clinical relevancy of this supposition has not been demonstrated. Although the risk of hypocalcemia during DKA treatment is increased with phosphate replacement, symptomatic hypocalcemia is very uncommon when phosphate is administered slowly and in the more modest concentrations recommended in most DKA treatment protocols.[49,50] Severe hypophosphatemia during DKA has been shown to be associated with rhabdomyolysis and hemolytic anemia, suggesting that monitoring of serum phosphate concentrations is necessary and treatment of severe hypophosphatemia is essential.[51,52]

Hypomagnesemia and hypocalcemia may also occur during DKA treatment but are generally mild, rarely requiring treatment. Monitoring of serum calcium and magnesium concentrations, however, is recommended.

Correction of Acidosis

Routine bicarbonate administration is contraindicated in children with DKA as acidosis generally corrects rapidly with insulin and fluid administration, and hemodynamic instability resulting from acidosis is rare. However bicarbonate administration is associated with several possible adverse effects including an increase in the risk of hypokalemia and a theoretical increase in tissue hypoxia resulting from a leftward shift in the hemoglobin-oxygen dissociation curve.[47,53] Paradoxical acidosis of the cerebrospinal fluid has also been documented with bicarbonate administration, likely resulting from diminished respiratory drive and a rise in the partial pressure of CO_2, which readily crosses the blood-brain barrier augmenting CSF acidosis.[54,55] Bicarbonate administration has also been associated with an increased risk of DKA-related cerebral edema.[56] In very rare circumstances (severe hemodynamic instability not responding to standard measures or potentially life threatening hyperkalemia), bicarbonate administration may be considered.

Monitoring

Intensive monitoring is essential for children with DKA and most should be treated in a pediatric intensive care unit (PICU) or other unit with similar capacities.[57,58] Blood glucose concentrations are typically measured hourly and electrolyte concentrations every 2 to 4 hours. Determinations of serum pH (every 2 to 4 hours) are helpful, particularly because serum bicarbonate concentrations may not increase during the first several hours. Venous blood gas samples generally are sufficient and arterial samples are rarely needed. Failure of acidosis to improve during treatment should prompt evaluation of the adequacy of insulin infusion, fluid balance, presence of non-anion gap hyperchloremic acidosis and a search for other causes such as renal failure, sepsis, or even appendicitis.

All fluid intake and output should be accurately recorded. Consideration of fluids and other management that may have occurred prior to admission to a PICU is important. Vital signs and mental status should be monitored hourly. One study showed a high frequency of prolonged QT interval corrected for heart rate in children with DKA and arrhythmias have been described in rare cases.[59] Therefore, cardiac monitoring is recommended.

Diabetic Ketoacidosis–Associated Complications

Cerebral Edema

Cerebral edema (CE) has been recognized as a complication of diabetes mellitus in children since 1936. It is essentially a clinical diagnosis, based on deterioration of mental state during resuscitation for DKA. Signs and symptoms that should prompt consideration of CE include inappropriate slowing of heart rate, hypertension, severe headache, recurrence of vomiting, irritability, lethargy, or other mental status changes.[60] Some patients progress to coma, respiratory arrest, and cerebral herniation. Most episodes of CE occur several hours after initiation of DKA treatment; however, 5% to 20% of cases occur at the time of presentation, before the initiation of therapy. Cerebral edema remains the leading cause of death

and morbidity in children with type 1 diabetes mellitus. The frequency of CE associated with DKA remains unchanged despite clinical efforts to the contrary.[32]

Reported mortality from CE varies widely and is in part dependent on the criteria used to define CE. Rates as high as 50% to 90% have been reported, but more recent studies[56,61] report lower rates of 21% to 24%. Overall, the incidence of CE is approximately 0.7% to 0.9% within DKA presentations. In other words, approximately 1 in 400 children with DKA die as a result of CE. Morbidity is significant; in particular, debilitating neurologic sequelae occur in 21% to 26% of children with DKA-related CE.[56, 61] Although frank CE is uncommon, there are substantial data to suggest that sub-clinical or asymptomatic CE occurs in many children with DKA, perhaps even in the majority. Limited data suggest that subtle brain injury may also be associated with DKA, even in the absence of clinically apparent CE.[62]

The pathophysiology of CE remains enigmatic. Several causative theories have been proposed for the occurrence of CE during DKA. Idiogenic, osmotically active substances that regulate cell volume have been thought to play a role in causing DKA-related CE. Taurine (2-aminoethane sulfonic acid), in particular, is thought to mediate a critical role in neuroosmoregulation during DKA.[63] Alternatively, cerebral hypoperfusion (caused by volume depletion) before DKA treatment and the effects of reperfusion during DKA therapy have been hypothesized to result in CE and cerebral injury.[64,65] Direct effects of ketone bodies and inflammatory cytokines on blood-brain barrier function have also been hypothesized to play a role.[66,67] To date, however, the precise pathophysiology of CE remains unresolved and multiple factors may be involved.

Epidemiological studies of risk factors for CE show that children with higher initial blood urea nitrogen concentrations, lower initial PCO_2 concentrations and greater acidosis at the time of presentation of DKA seem to be at greatest risk for CE.[56,65,68,69] A blunted rise in measured serum sodium concentration during DKA treatment has also been associated with increased risk of CE as has treatment with bicarbonate.[56] Early administration of insulin (within the first hour) was also associated with increased CE risk in one study.[68] Studies evaluating the impact of variations in fluid administration protocols on risk of CE have yielded conflicting results. As yet, there is no clear association between any aspect of fluid treatment and increased risk of CE.

After the diagnosis of CE is made, treatment is a matter of urgency and should not be delayed while awaiting imaging studies or further testing. Intravenous mannitol (0.25-1 g/kg) should be administered immediately. Recent reports suggest the use of 3% saline in boluses or as a continuous infusion for treatment of CE, but data demonstrating beneficial effects are limited to case reports.[70,71] Ongoing intensive care unit monitoring is essential. Pulmonary support by means of endotracheal intubation is likely to be required because of severe alterations in mental status, impaired airway reflexes, and altered respiratory drive. Therapeutic hyperventilation in intubated patients, however, has been associated with poorer outcomes.[72] Therefore, decreasing P_{CO_2} below the patient's own compensation for metabolic acidosis should be avoided in children with DKA except where absolutely necessary to treat impending cerebral herniation. A reasonable approach would be to initially maintain the patient's current P_{CO_2} level and then gradually allow the P_{CO_2} to increase as acidosis corrects. If the patient's respiratory drive remains intact, utilization of support rather than mandatory ventilation modes, permits the patient to determine rate and depth of breathing. Central nervous system imaging in patients with suspected CE is recommended to exclude other etiologies of altered mental status such as central nervous system thromboses or infarction.

Neuropsychologic Sequelae

Adverse neurodevelopmental outcomes in children with diabetes have in large part been attributed to recurrent hypoglycemia, and this area has been extensively investigated. More recently, hyperglycemia and hyperglycemic extremes such as occur with DKA have been attracting increasing attention and interest for resultant potential neuropsychological sequelae. Short-term effects on neurocognitive performance involving complex skills, such as inhibiting an overlearned response and learning of complex novel information have been described.[73] Long-term deficits in memory have been found to be associated with DKA.[62] Rapid and significant variability in blood glucose levels may have further impact, particularly on the developing brain and may be more neurotoxic than sustained hyperglycemia.[74]

Thrombotic Complications

Thrombotic complications are common in children with DKA and central venous catheters are particularly prone to thrombosis.[75,76] Cerebral thromboses and pulmonary emboli have also been described. Hyperosmolarity may result in direct osmotic disruption of endothelial cells leading to release of tissue thromboplastins.[77] Higher levels of vasopressin stimulated by hypertonicity and decreased vascular volume may also contribute to enhanced coagulation.[78] Prophylaxis with low dose heparin should be considered for children with central venous lines.

Other Complications

Rhabdomyolysis[79,80] is potentially life threatening. It is characterized by elevated serum creatine kinase, lactate dehydrogenase, and amino alanine transferase concentrations due to muscle injury. Rhabdomyolysis may result in renal failure, compartment syndrome, severe hyperkalemia and other electrolyte disorders leading to arrhythmias. Hyperosmolarity has been thought to be one causative factor and the risk is higher in children who have DKA complicated by features of HHS.[79]

Acute pancreatitis has been described in case reports of both children and adults with DKA, but occurs rarely. Far more frequent are benign elevations in serum amylase and/or lipase occurring in 24% to 40% of children with DKA. These elevated pancreatic enzyme concentrations typically normalize rapidly with DKA treatment and are not associated with clinical features of pancreatitis.[81]

Although neurological deterioration in children with DKA is most frequently caused by cerebral edema, cerebral infarctions with and without hemorrhage and cerebral thromboses have also been described.[82] Other rare complication of DKA in children include pulmonary edema,[83] cardiac arrhythmias,[84] renal failure,[85] intestinal necrosis,[86-88] and rhinocerebral mucormycosis.[89,90]

Hyperglycemic Hyperosmolar Syndrome

HHS is characterized by extreme elevations in serum glucose (>600 mg/dL) and hyperosmolarity (serum osm >330 mOsm/kg) in the absence of significant ketosis or acidosis

(urine ketone concentration <1.5 mmol/L and serum bicarbonate >15 mEq/L). Although HHS is defined as a condition separate from DKA, 30% of cases occur in combination with substantial ketosis and acidosis meeting criteria for both HHS and DKA. Until recently, HHS was thought to occur infrequently in pediatrics. A recent increase in case reports of HHS in children suggest that the frequency may be increasing.[91,92] As in adults, HHS in children has a relatively high mortality of 10% to 35%.[93,94] The majority of HHS reports in children include acanthosis nigricans, obesity, African-American race, and family history of type 2 diabetes. Most cases of HHS are the initial presentation of diabetes, and most of these youth will subsequently have a clinical diagnosis of type 2 diabetes.

Occurrence of HHS during DKA poses challenges in terms of recognition and treatment. Generally, dehydration is more profound than the clinical assessment would suggest, reflecting difficulties in clinical evaluation due to obesity and relative preservation of intravascular volume because of hyperosmolarity. Electrolyte losses similarly exceed those of DKA as a result of more prolonged osmotic diuresis. Patients who meet criteria for both DKA and HHS require more prolonged and aggressive fluid and electrolyte replacement therapy than typical children with DKA. Replacement of ongoing urinary losses may be necessary. Frequent reassessment of circulatory status and fluid balance is critical. A high frequency of thromboses has been described in children with HHS as well as rhabdomyolysis and a malignant hyperthermia-like syndrome.[95,96] Cerebral edema appears to be a rare complication of HHS, with only one case reported.[97]

Health Care Costs Associated with Diabetic Ketoacidosis

Health care costs for DKA vary by geographic regions in the United States, and comparing costs is often complicated by variations in health care systems, methods of reporting costs (e.g., hospital costs versus payer costs), and contractual arrangements. One strategy to decrease the frequency of DKA is to promote awareness in the general population, in communities, and among providers. A successful campaign to heighten awareness of signs and symptoms of DKA took place in Parma, Italy. In the Parma campaign, simple messages regarding signs and symptoms of diabetes were provided to practitioners and schools, and free access to care arranged. Compared with neighboring regions where the frequency of DKA at the time of diagnosis was quite high at 78%, the Parma region observed a very low frequency of 12.5% during the 8 years of the campaign. Of note, the campaign was relatively inexpensive, the costs $23,000 for the 8 years of the campaign.[33]

Another more targeted strategy is linked to recognition of diabetes risk. In children enrolled in prevention studies, which are mostly siblings of probands with type 1 diabetes, the frequency of DKA is far less than that of the general population; less than 4% for those participating in the Diabetes and Prevention Trial-1 presented in DKA, and 63.3% were asymptomatic.[98] For children and adolescents with diagnosed diabetes, multidisciplinary and intensive team management approaches have been shown to decrease the frequency of DKA. Unfortunately, obtaining sufficient reimbursement for intensive case management in the United States has been challenging, despite demonstrated savings to the health care system. In a relatively small study, the costs for emergency and hospital visits for those not involved in intervention more than exceeded (125%) the costs of intensive case management.[99] This included only hospital charges and did not include additional societal costs, such as missed days of work and school, patient and family worry and anxiety, and impact of recurrent DKA, possible cerebral edema, and poor diabetes control on long-term health. In a larger, longer study of multisystemic home-based psychotherapy for adolescents with poorly controlled diabetes, admissions for DKA were reduced by almost half compared with the control group over a 2-year period, resulting in a estimated cost savings of $23,886 to 72,226 (range reflecting hospital costs and third party costs, respectively).[100] These examples emphasize the need for preventative rather than crisis-based approaches to the pediatric diabetes population.

Very young children with diabetes remain the most likely to present in DKA with CE, and comprise the age group with the most rapid rise in incidence of diabetes. Taken together, these data suggest that there are very important opportunities for prevention strategies in this age group. Major efforts are needed to address health care disparities overall in children with diabetes, and prevention of DKA is no exception.

References are available online at http://www.expertconsult.com.

Structure and Function of Hematopoietic Organs

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PEARLS

- Hematologic intervention is one of most frequent therapeutic modalities in the intensive care unit setting.
- The blood system is frequently affected by severe illnesses, and its failure contributes to morbidity and mortality.
- Normal ranges for blood cell numbers or function depend on the age of the patient.
- The degree of hematopoiesis in a given bone varies with age and must be considered for successful bone marrow aspiration or biopsy.
- For major invasive procedures such as surgery or placement of arterial lines or endotracheal, platelet count should be maintained at 50,000/μL.

The hematopoietic system responds quickly to changes in oxygen tension, bleeding, or infection. When stressed, as in a very ill child, hematopoiesis and blood cell function may be insufficient. The extensive use of red blood cell (RBC) or platelet transfusions, and antimicrobials support the importance of the blood system as a vital organ affected in the pediatric intensive care unit setting. This chapter reviews the anatomy and physiology of the hematopoietic system to provide a basis for understanding the repercussions of primary hematological abnormalities, as well as hematopoietic manifestations of nonhematological diseases. Aspects that are of practical importance to the intensivist are emphasized. The structure and function of the coagulation system are discussed in Chapters 81 and 82 and that of the immune system (particularly B and T lymphocytes and macrophages) in Chapter 90.

Structure and Function of the Bone Marrow

During embryogenesis and fetal development, hematopoiesis shifts from the yolk sac to the liver and, after the twentieth week of gestation, to the bone marrow.[1] Although hepatic erythropoiesis may persist for several weeks after birth, in the term infant hematopoiesis takes place almost entirely in the bone marrow. A defining feature of hematopoietic stem cells is their ability to home to the bone marrow. This homing occurs via chemoattractants such as stromal cell-derived factor-1 and its cognate chemokine receptor on the stem cell, as well as interaction between a variety of stem cell adhesion molecules and their ligands on stroma and endothelial cells. The hematopoietic stem cell may be identified by the presence of cell surface markers, such as CD34 or by properties to exclude Hoeschst dye 33342, via a multidrug transporter.[2]

Grossly, two types of bone marrow can be recognized in normal individuals: yellow marrow, so called because of the predominance of fat cells, and red marrow, in which blood cells predominate. White marrow, consisting predominantly of stromal cells and intercellular matrix, may result from atrophy or starvation. Red marrow proportionately is a much greater component of body weight and volume in the infant than in the adult (Figure 79-1).[3] Early in life, it is contained in the medullary cavities of the long bones, which gradually fill with fat such that by late puberty, the adult distribution of hematopoiesis (sternum, pelvis, vertebrae, cranium, ribs, epiphyses of long bones) is achieved. That the degree of hematopoiesis in a given bone may vary with age is an important consideration in selecting a site for bone marrow aspiration or biopsy; for example, although the anterior and posterior iliac crests can be used at any age, the tibia can be used only until the age of 2 years. In disease states characterized by excessive destruction of blood cells, such as some severe hemolytic anemias, hematopoiesis may increase twofold to eightfold. Active sites of hematopoiesis may expand, and extramedullary hematopoiesis may be found, particularly in the liver and spleen.

Microscopically, the marrow is a network of vascular channels (sinuses) separating islands of fat, hematopoietic cells, and rare osteoblasts and osteoclasts (which are important for bone remodeling).[4,5] The vasculature and cells are joined by a reticulin (fiber) network or scaffolding. By light microscopy, bone marrow aspirate specimens demonstrate hematopoietic elements; however, a bone marrow biopsy provides a more accurate measure of cellularity. Reticulin can be seen by light microscopy when special histochemical stains are used.

The blood vessels that feed the marrow are branches of those that feed the surrounding bone.[6] Large central arteries run longitudinally within the marrow and send radial branches that penetrate the endosteum and form capillaries in the Haversian and Volkmann's canals of the bony cortex.[7] These capillary systems drain into the bone marrow sinuses, which in turn drain into a central sinus or vein. Because the marrow circulation interconnects with the general circulation

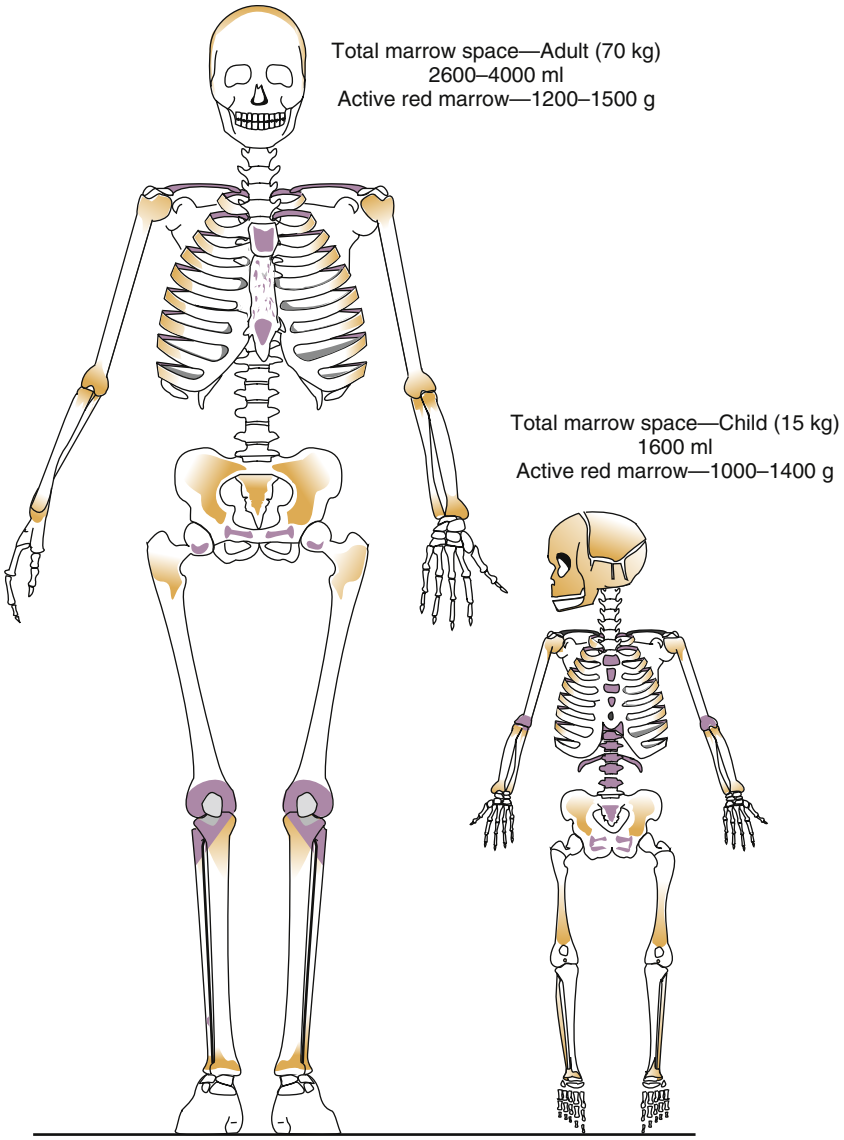

Figure 79–1. Comparison of active red marrow–bearing areas in the child and the adult. Note the almost identical amount of active red marrow in the child and adult despite a fivefold discrepancy in body weight. *(Modified from MacFarlane RC, Robb-Smith AHT:* Functions of the blood, *Oxford, 1961, Blackwell.)*

in this fashion, fluids and medication injected in bone marrow are absorbed as rapidly as through intravenous routes. Unlike peripheral veins, intramedullary vessels supported by their bony shell do not collapse in shock; therefore, intraosseous (either tibial or iliac crest) infusion is appropriate when standard intravenous access is not available.[8] It is also noteworthy that the interconnection between the marrow and general circulation provides the mechanism by which bone marrow may embolize to the lung after osseous trauma or fracture. This has not been demonstrated to be of clinical significance in the case of intraosseous infusion.[9]

The concept of the stem cell has expanded recently,[10] and its ex vivo manipulation has raised much interest by a wide group of physicians and scientists studying nonhematologic systems. One essential feature of the stem cell is its plasticity.[11] Provocative studies have shown that stem cells isolated from the bone marrow can be driven to differentiate to muscle, liver, cardiac, or neuronal tissue. This raises the possibility that the marrow may be a convenient and ethically less challenging source of stem cells for stem cell engineering and tissue replacement. Although the clinical applications to nonhematologic tissues remain distant, the use of hematopoietic stem cells to replace a diseased marrow is a common practice (i.e., stem cell transplantation). Alternative sources of hematopoietic stem cells have been found peripheral blood following growth factor–induced mobilization or from placental cord blood.

Hematopoiesis

Cells within the hematopoietic island include the RBCs, granulocytes (neutrophils, eosinophils, basophils), monocytes and macrophages, platelets, lymphocytes, and their precursors. The earliest precursors, or stem cells, are thought to look like small lymphocytes and are not usually distinguishable from them by microscopy. Their existence was best confirmed by in vitro culture assays in which nucleated cells from bone marrow aspirate specimens plated onto tissue culture dishes layered with methylcellulose generate colonies (aggregates

of cells) of one or more lineages. Now, immunophenotyping provides rapid identification of cell lineage and stage of development.[12] The first morphologically identifiable precursor cells are the proerythroblast, myeloblast, monoblast, megakaryoblast, and lymphoblast. These committed precursors and their terminally differentiated counterparts sit within the hematopoietic islands. Megakaryocytes (which make up <1% of hematopoietic cells) generally are located next to marrow sinusoids and shed platelets (fragments of megakaryocyte cytoplasm) directly into the lumen. Erythroblasts also are produced near the walls of the vascular sinuses in clusters with macrophages called erythroblast islets. As the erythroblasts develop, they extrude their nuclei, which are phagocytosed by the macrophages. In contrast, granulocytes (most numerous of the hematopoietic cells), monocytes, and lymphocytes are produced throughout the marrow away from vascular sinuses. The mature white blood cells (WBCs) are motile and migrate to the sinuses.

Within the peripheral circulation, the number of cells of each type is maintained in a narrow range in the normal individual. Adults and post-pubertal adolescents have approximately 5000 granulocytes, 2000 lymphocytes, 500 monocytes, 5×10^6 RBCs, and 150,000 to 300,000 platelets per microliter of whole blood. Age-dependent values for younger children are shown in Table 79-1.[13] To a lesser extent, values also are a function of race and sex, so that African Americans (especially males) normally may have granulocyte counts less than 1500/μL. Normative values for Latinos are less clear, but have been reported to be closer to those of Caucasians.[14] As summarized elsewhere, under normal conditions the rate of production of each cell type equals the rate of destruction. Because the life span of mature RBCs in adults is 100 to 120 days, 5×10^4 RBCs/μL are produced daily. The average platelet life span is 7 to 10 days so that approximately 2×10^4 platelets/μL are produced daily. With less than a 12-hour life span, granulocytes production occurs at a rate of 10^4 cells/μL. The very slow rate of production of lymphocytes reflects their long life span, measured in years.

The mechanisms that regulate this steady state are incompletely understood. However, evidence strongly suggests the existence of a pluripotent stem cell that is capable of self-renewal, from which progenitor cells committed to hematopoiesis (RBCs, granulocytes, megakaryocytes, and monocytes) and to lymphopoiesis develop (Figure 79-2).[13] The "trilineage myeloid" stem cell has been designated *colony forming unit-stem* (CFU-S) on the basis of bone marrow culture assays and experiments in which the spleens of lethally irradiated mice infused with donor marrow cells are found to contain colonies each consisting of precursors of RBCs, granulocytes, monocytes, and megakaryocytes.[16] The existence of CFU-S in human beings is further deduced from chromosomal studies in myeloproliferative disorders. Lymphoid development appears to arise from a separate progenitor. Although the CFU-S is found predominantly in the bone marrow, there probably are small numbers of circulating pluripotent stem cells because marrow of lethally irradiated animals can be reconstituted by using peripheral blood.[3]

The numbers of committed progenitor cells that differentiate in any time period is dependent on feedback from humoral regulators that are produced within the marrow microenvironment and by extramedullary sources, including T cells, macrophages, endothelial cells, and fibroblasts. These hematopoietic growth factors are cytokines, known by a variety of names. Many of the cytokines have overlapping functions.

Table 79–1 Normal Values for Hematology

Age	Hemoglobin (g %)	Hematocrit (%)	Mean corpuscular volume (fl)	MCHC (g/%RBC)	Reticulocytes (%)	WBC/μL × 100 range (avg)	% Neutrophils	Platelet (10^3/μL)
28-week gestation	14.5	45	120	31	5–10	—	—	275 ± 60
32-week gestation	15.0	47	118	32	3–10	—	—	290 ± 70
1 day*	16.8–21.2	57–68	110–128	29.7–33.5	1.8–4.6	7–35 (18)	45–85	310 ± 68
1 week*	15.0–19.6	46–62	107–129	30.4–33.6	0.1–0.9	4–20 (10)	30–50	
1 month*	11.1–14.3	31–41	93–109	33.3–36.5	0.1–1.7	6–18 (10)	30–50	
3-5 months	10.4–12.2	33	80–96	31.8–36.2	0.4–1.0	6–17 (10)	30–50	300 ± 50
6-11 months	11.8	35	77	33	0.7–2.3	6–16 (10)	30–50	
1 year	11.2	35	78	32	0.6–1.7	6–15 (10)	30–50	
2-10 years	12.8	37	80	34	0.5–1.0	7–13 (9)	35–60	
11-15 years	13.4	39	82	34	0.5–1.0	5–12 (8.5)	40–60	
Adult								300 ± 50
Male	16.0 ± 2.0	47 ± 7	91	34	0.8–2.5	4.3–10 (7)	25–62	
Female	14.0 ± 2.0	42 ± 5	(82–101)	(31.5–36)	0.8–4.1			

Absolute eosinophil count: average 250/μL (100–600/μL).
*Under 1 month of age, capillary hemoglobin exceeds venous hemoglobin: 1 hour, 3.6 g difference; 5 days, 2.2 g difference; 3 weeks, 1.1 g difference.
MCHC, Mean corpuscular hemoglobin count.
Data from Guest GM, Brown EW: Erythrocytes and hemoglobin of the blood in infancy and childhood. III. Factors in variability, statistical studies, *Am J Dis Child* 93:486, 1957; Matoth Y, et al: Postnatal changes in some red cell parameters, *Acta Paediatr Scand* 60:317, 1971; Wintrobe MN: *Clinical hematology,* ed 7, Philadelphia, 1974, Lea & Febiger; Mauer AM: *Pediatric hematology,* New York, 1961, McGraw-Hill; Oski FA, Naiman JL: *Hematologic problems in the newborn infant,* Philadelphia, 1972, WB Saunders; and Nathan D, Oski F: *Hematology of infancy and childhood,* Philadelphia, 1981, WB Saunders.

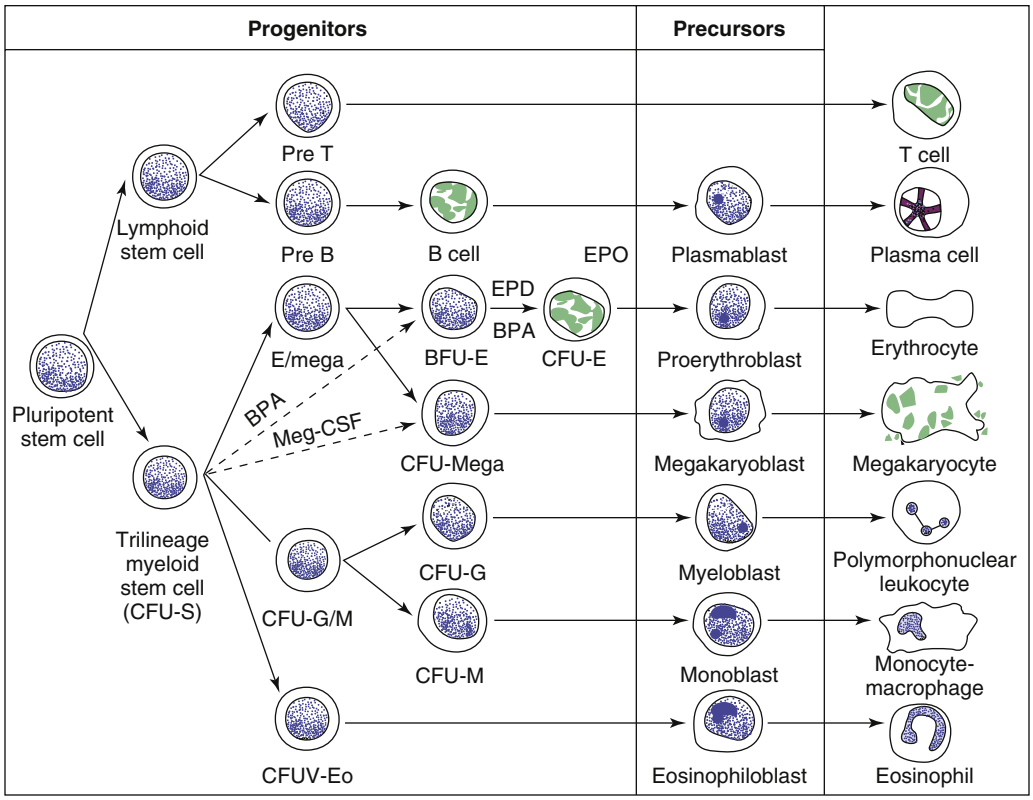

Figure 79–2. A schematic outline of the progenitor basis of hematopoiesis. Not shown in this outline is the process of self-renewal of fractions of the progenitor cell populations, particularly the immature progenitors. Also not shown is the progressive amplification of progenitors and precursors as they mature and differentiate. The bipotential erythroid-megakaryocyte progenitor shown in this drawing has been demonstrated in the mouse, but not definitively in humans. *Dotted arrows* indicate an alternative scheme. *(Modified from Nathan DG: Introduction: hematologic diseases. In Wyngaarden JB, Smith JH, editors:* Cecil's textbook of medicine, *Philadelphia, 1988, WB Saunders.)*

However, gene targeting in the mouse ("knockout mouse") of cytokines or their receptors has identified the essential nonredundant functions for several hematopoietic growth factors. Mice deficient in erythropoietin (Epo), thrombopoietin (Tpo), and granulocyte colony-stimulating factor (G-CSF) suffer from severe anemia, thrombocytopenia, or neutropenia, respectively.

Although the list of cytokines and small molecules that regulate hematopoiesis continues to grow, clinical application has been chiefly limited to Epo and G-CSF. Chemical modification of Epo and G-CSF has resulted in two longer-acting forms, darbepoetin alpha, and pegfilgrastim, respectively. Their primary advantage is longer half-lives. Recently, two platelet-stimulating agents, romiplostim and eltrombopag, have been Food and Drug Administration–approved for use in adults with chronic immune thrombocytopenic purpura (ITP).[15] Characteristics of specific hematopoietic growth factors, discussed in the following sections, are summarized in Table 79-2.

Table 79–2 Recombinant Hematopoietic Growth Factors

CSF	Target	Clinically Available
SCF	HSC, mast cells	No
IL-3	HSC	No
Epo	Erythroid progenitors	Yes
G-CSF	Granulocytes and their precursors	Yes
GM-CSF	Phagocytes and their precursors, dendritic cells	Yes
M-CSF	Monocytes and their precursors	No
Tpo*	Megakaryocytes	Yes*
IL-11	Megakaryocytes	Yes

Epo, Erythropoietin; *G-CSF,* granulocyte colony-stimulating factor; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *HSC,* hematopoietic stem cells; *IL,* interleukin; *M-CSF,* macrophage colony-stimulating factor; *SCF,* stem cell factor; *Tpo,* thrombopoietin.
*Thrombopoietin-like peptides have been approved.

Erythropoiesis

On its way toward RBC maturation (see Figure 79-2), the CFU-S sequentially differentiates into burst-forming units-erythroid (BFU-E) and colony forming units-erythroid (CFU-E), which are identifiable experimentally on the basis of growth characteristics in culture. These phases of development, which involve amplification of cell number, are extensively reviewed elsewhere.[16] As noted earlier, the proerythroblast is the earliest morphologically identifiable precursor and presumably is the successor to the CFU-E. The subsequent sequence of RBC production normally takes 3 to 4 days in the marrow and involves multiple cell divisions with increasing differentiation, characterized chiefly by globin messenger RNA, cytoplasmic synthesis of hemoglobin, and

ultimately extrusion of the RBC nucleus. The enucleated cell is large and, because it contains residual RNA, stains deeply by the Wright-Giemsa technique (i.e., polychromatophilic macrocyte). Normally at this stage the erythrocyte is released into the circulation where it can be demonstrated as a reticulocyte. In newborns younger that 1 week of age, reticulocytes in the blood can comprise more than 5% of the total RBCs. At any older age, the normal reticulocyte count is less than 2%. From this uncorrected reticulocyte count, the absolute reticulocyte count can be calculated by multiplying by the RBC count. The normal absolute reticulocyte count would be 0.02 to 5×10^6 RBC/μL. Alternatively, a corrected reticulocyte is used: multiplying the reticulocyte percentage by the observed hematocrit divided by the normal hematocrit. If the corrected reticulocyte count is less than 1%, one must suspect bone marrow failure or insufficiency. Because the reticulocytes lose their RNA within 24 to 30 hours, their quantitation provides a rough estimate of the rate of erythropoiesis during the past 24 hours. This can be more accurately measured by ferrokinetic studies, which are not readily available. The proportion of erythroid precursors in a bone marrow aspirate also provides a more convenient estimate of total erythropoiesis that is valid if a cellular specimen is obtained and if granulopoiesis is normal. In the older child or adult, erythroid precursors normally are one third as plentiful as myeloid precursors (i.e., the myeloid/erythroid ratio is about 3:1). Approximately 10% of erythroid precursors do not produce circulating RBCs (ineffective erythropoiesis).

Maturation of RBC precursors is regulated by a number of humoral and nutritional factors. Epo appears to act predominantly by increasing proliferation of CFU-E (see Table 79-2 and Figure 79-2). Its production is stimulated by hypoxemia or acute hemorrhage. During fetal development, it is mainly produced in the liver, but this site shifts later to the juxtamedullary region in the kidneys. Humoral factors less well characterized than Epo that are derived from multiple sources (spleen cells, peripheral blood monocytes, and mononuclear bone marrow cells) appear to act at an earlier stage of differentiation to amplify the number of progenitors committed to Epo responsiveness. Among these are burst-promoting activity, which enhances production and proliferation of BFU-E. Within the marrow, normal RBC maturation requires both folate and vitamin B_{12}; a deficiency of either results in abnormal nucleic acid synthesis and the production of an abnormal precursor, the megaloblast. Iron is required for hemoglobin synthesis, and deficiency results in poorly hemoglobinized small (hypochromic, microcytic) RBCs.

Once in the peripheral blood, the life span of the normal RBC in the adult or older child is 100 to 120 days. In the term newborn the RBC life span is about 60 days, which grows progressively shorter with increasing prematurity.[14] Presumably these differences in age-dependent RBC longevity reflect differences in membrane stability and oxidative metabolism. Removal of RBCs from the circulation is not a random process. Senescent RBCs are removed selectively from the circulation by the macrophages of the reticuloendothelial system. Although this is primarily a function of the spleen (see the following section), asplenic patients with normal RBCs accomplish this process in the liver and other sites and do not exhibit an increased RBC life span. In subjects with hemolytic anemias who undergo therapeutic splenectomy, the red cell life span increases, but not to normal levels.

The primary function of the circulating RBC is to carry O_2 from the lungs to the tissues. Hemoglobin (Hb) must be packaged within the RBC membrane to prolong its plasma half-life. Interference with the reversible binding of O_2 by Hb can occur by several mechanisms, including (1) methemoglobinemia, the inability to maintain ionic iron within the Hb molecule in the reduced state; (2) the presence of abnormal hemoglobins, among which are the methemoglobins which have an abnormal affinity for O_2; (3) age- or disease-related differences in the percentage of structurally normal HbF, which has a high affinity for oxygen; and (4) changes in the microenvironment that alter the intracellular concentration of 2,3-diphosphoglycerate (2,3-DPG).[17] The oxyhemoglobin interaction also is complicated by the Bohr effect (at a lower pH, Hb binding of O_2 with less affinity) independent of 2,3-DPG concentration. Patients with severe acidosis have low concentrations of 2,3-DPG, which results in an oxygen dissociation curve that shifts to the left. However, the in vivo curve may be normally placed because the Bohr effect counterbalances the reduction in red cell 2,3-DPG. If metabolic acidosis is rapidly corrected, the prompt rise in blood pH is reflected in a proportional increase in oxygen affinity (the Bohr effect). However, there is a lag of several hours before the red cell 2,3-DPG increases to normal. During this time, there is a shift to the left in both the in vivo and the in vitro O_2 dissociation curves. This phenomenon may compromise tissue oxygenation in patients who have diminished cardiovascular reserves.

Premature infants with respiratory failure may have a left-shifted O_2 affinity curve both because of the high levels of HbF and because of an acidosis-induced decrease in 2,3-DPG levels. Exchange transfusions with fresh adult blood have been found to reduce mortality, perhaps by providing blood with "normal" O_2 affinity.[18] Other reasons for impaired O_2 delivery are decreased RBC mass (anemia, which leads to a compensatory increase in 2,3-DPG) and decreased blood flow, either because of vascular anatomical abnormalities or because of increased blood viscosity (e.g., in sickle cell disease). In addition to Hb-bound O_2, the oxygen dissolved in plasma (which normally amounts to less than 2% of the total oxygen carried in the blood) increases linearly with increases in PO_2. For this reason, very anemic patients, although they have insufficient Hb with which to carry O_2, benefit from administration of O_2. Extensive research into the design of artificial blood has focused both on "red blood" (repackaged Hb from senescent RBCs or of Hb produced with genetic engineering) and "white blood" or perfluorocarbons (emulsions that dissolve large amounts of O_2), but their use is still limited and investigational. For now, RBC transfusions ameliorate anemia acutely, otherwise Epo may be used to elevate Hb over several weeks. Although antibody-mediated Epo-associated pure red cell aplasia is infrequent,[19] familiarity with possible Epo toxicity should accompany its use.

Granulopoiesis

As shown in Figure 79-2, in addition to BFU-E, CFU-S also gives rise to several other distinct cell populations. The best characterized of these are the CFU-GM (which in turn generate both CFU-G [granulocyte colony-forming units] and CFU-M [monocyte-macrophage colony-forming units]) and the CFU-Eos (eosinophil colony-forming units). As with the

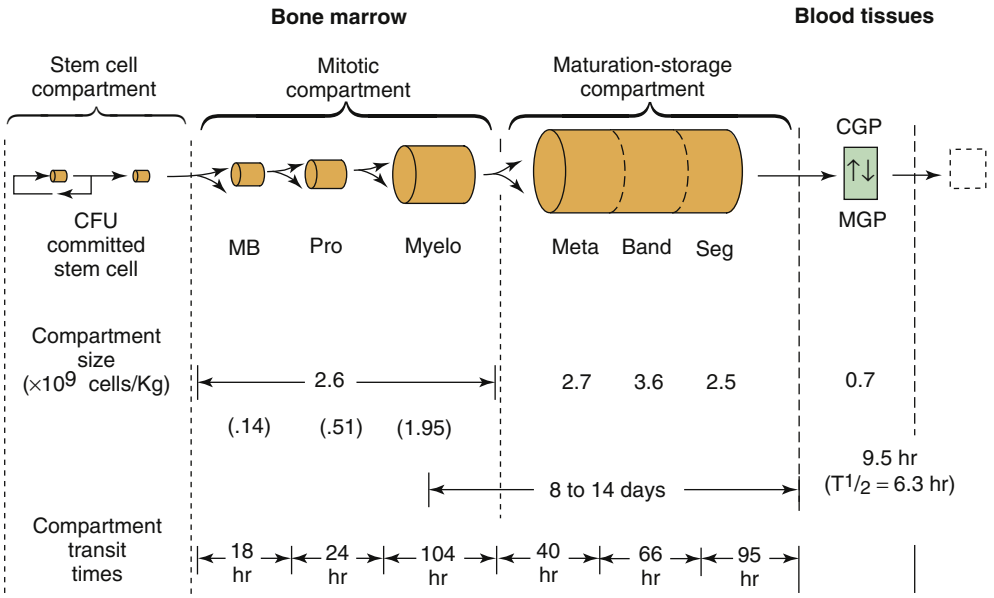

Figure 79–3. Model of the production and kinetics of neutrophils in humans. The marrow and blood compartments have been drawn to show their relative sizes. The compartment transit times, as derived from $DF^{32}P$ studies are shown on the next to last line. Values derived from tritiated thymidine studies are shown on the last line. *(Modified from Wintrobe MN et al:* Clinical hematology, *ed 8, Philadelphia, 1981, Lea & Febiger.)*

CFU-E, these are not morphologically recognizable and probably masquerade in the bone marrow as small lymphocytes. They are identified on the basis of growth characteristics in in vitro bone marrow culture assays.

Subsequent stages of granulocytic (neutrophilic, eosinophilic, and basophilic) and monocytic differentiation can be visualized by routine histochemical stains of bone marrow aspirates.[20] In the neutrophilic polymorphonuclear (PMN) series, the transition from myeloblast to mature PMN involves an overall decrease in cell size; coarsening, indentation, and ultimately separation of nuclear chromatin, with loss of nuclear chromatin, with loss of nucleoli; and replacement of azurophilic granules (whose contents include myeloperoxidase [MPO]), prominent in promyelocytes, by the specific granules (containing a number of secretory factors important for neutrophil function, but not MPO) in mature PMNs. Other structural changes during the course of PMN maturation include the disappearance of certain surface antigens, which can be identified by specific monoclonal antibodies and the appearance of receptor sites for complement (C3) and for the Fc portion of the immunoglobulin molecule. These stages in development are accompanied by functional changes, including increases in cell motility, responsiveness to chemoattractants, deformability, and phagocytic capabilities.

Parallel morphologic and functional changes occur with eosinophilic granulocyte differentiation. It is noteworthy that the peroxidase in eosinophil granules is different from that in neutrophils or monocytes, so that congenital deficiencies of myeloperoxidase in the latter cells leave eosinophil function intact. The blood basophil (which histologically is similar to the tissue mast cell) also is presumed to arise in the bone marrow from the CFU-GM (also known as *granulocyte macrophage progenitor cell*). In contrast to the CFU-Eos, there is no evidence as yet for a separate basophil CFU. DNA labeling studies have demonstrated the kinetics of neutrophil development within the bone marrow. As shown in Figure 79-3 there is a mitotic pool (myeloblast and myelocyte) that allows for amplification of cell number, and a storage or reserve pool (metamyelocyte and PMN) that in older children and adults contains roughly 100 times the number of granulocytes normally found in the peripheral blood.[21] This reserve is mobilized and leads to mature neutrophilia at times of stress (e.g., sepsis, exercise, tachycardia, and pregnancy) or on administration of pharmacological doses of corticosteroids or exposure to endotoxin. In neonates, the storage pool is only two to three times the circulating pool of PMNs and can be depleted, for example, by overwhelming sepsis.[22] Sepsis-related neutropenia may be due to apoptosis of neutrophils and their progenitors as well as a block in their maturation.[23] Thus, sepsis results in both neutropenia and neutrophilia.

Eosinophilic granulocytes also have mitotic and storage pools in the marrow that are about 300 times that seen in the periphery. After less than a week, they are released from the marrow in response to hypoxia and eosinophilic factors (e.g., heparin, histamine). In contrast to their effects on neutrophils, corticosteroids and epinephrine block mobilization of eosinophils from the marrow. The effect of epinephrine can be blocked by propranolol, suggesting mediation by β-adrenergic receptors. Little is known about basophil development in the bone marrow. Monocyte development, which, as previously suggested, is closely related to myelopoiesis, is also poorly understood. However, there does not appear to be a storage pool.

The mature neutrophil escapes from the marrow into the circulation by migration through reversible gaps between the endothelial cells lining the sinuses and capillaries. Factors known to influence this process include chemoattractants, such as products of the serum complement system. Those factors noted previously that mobilize the storage pool may cause an egress of less mature granulocytes with a resultant "shift to the left" in the peripheral blood. Once in the periphery, approximately half of the polymorphs adhere to the endothelium of blood vessels as the marginating pool while the other half actually circulate. Stress and epinephrine release the

marginating cells and therefore double the absolute granulocyte count. Eosinophils have a similar arrangement of circulating and marginating cells, whereas the marginating pool of monocytes is three times that of the circulating pool.

The life span of the neutrophil once in the periphery is 6 to 12 hours and can be less in the presence of inflammation, fever, or infection. Neutrophils are irreversibly removed from the circulation into the liver, lungs, bowel, or bladder, back to the bone marrow, or to sites of infection where they contribute to the acute inflammatory response. Their extravascular half-life also is on the order of hours. Although the circulating half-life of eosinophils is comparable with that of neutrophils, eosinophils can persist in the tissues for many days. Under pathological conditions, eosinophils may cycle back and forth between the tissues and circulation. Monocytes also have a circulating half-life measured in hours. Once in the tissues, however, they can persist for months or years and undergo the histological (larger), biochemical (increased lysozymes and ectozymes), and functional (enhanced endocytosis) changes associated with tissue macrophages. The precise changes depend on the organ of residence; for example, in the liver they are identified as Kupffer cells and in the lung as alveolar macrophages.

The CSFs that regulate myelopoiesis are diverse, and their biological specificities may overlap.[24] Cytokines such as interleukin (IL)-1, tumor necrosis factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), and G-CSF expand the PMN precursor compartment and mobilize them by promoting their diapedesis from the marrow and from vascular endothelium. Endotoxin promotes the host inflammatory response by stimulating endothelial cells, macrophages, and fibroblasts to produce cytokines.

Both GM-CSF and G-CSF prime PMNs for enhanced phagocytosis and superoxide production in vitro, modulate cell surface expression of adhesion receptors, inhibit apoptosis, and promote antibody-dependent cellular cytotoxicity. However, GM-CSF inhibits chemotaxis, whereas G-CSF promotes it. G-CSF acts only on the granulocytic lineage. GM-CSF affects macrophages and eosinophils, which accounts for its side effects of eosinophilia and, at high doses, capillary leak syndrome. Because of stickiness and margination along vascular endothelium, a transient drop in O_2 saturation may occur within minutes after administration. GM-CSF can result in transient fever. Bone pain may occur with administration of either drug, if marrow production is high. WBCs must be monitored, and the drug typically is discontinued when the absolute neutrophil count exceeds 1500 to 10,000/μL. When it is discontinued, the number of circulating PMNs decreases. Multiple trials have demonstrated the efficacy of growth factors in decreasing the time interval of profound neutropenia or length of antibiotic coverage and hospitalization; their use has not changed overall survival. Clinical uses of G-CSF and GM-CSF are given in Table 79-3. Although nonhematopoietic tumor cell lines can display receptors for GM-CSF or G-CSF, administration of these drugs has not led to an appreciated increase in relapse or progressive disease. There has been some concern over erythroid stimulating agents in stimulating cancer growth.[25] Although these agents can be given to patients with myeloid leukemias or myelodysplastic syndromes without adverse effects, caution should be exercised.

As in the case of RBC and platelet development, normal myelopoiesis also requires the presence of vitamin and mineral growth factors. One hallmark of megaloblastic anemia (vitamin B_{12} and folate deficiencies) is the hypersegmented PMN. The hypochromic microcytic anemia of copper deficiency is characteristically associated with neutropenia. Among the non-lymphoid WBCs, clinical sequelae of quantitative or qualitative deficiencies of neutrophils have been particularly well studied. Systemic or mucocutaneous bacterial infections (gram-positive and gram-negative organisms) are frequent. They occur with an incidence that increases with the degree and duration of neutropenia and in the presence of indwelling catheters, intravascular lines, and endotracheal tubes.

Recommendations for prevention of infections in neutropenia include strict handwashing, changing sites of percutaneous lines as often as every 48 hours, and use of recombinant CSFs in limited situations (as noted previously). The use of prophylactic antibiotics and reverse isolation is controversial, and will vary among centers and divisions within centers. In addition to clearing bacteria and fungi, monocytes secrete a variety of inflammatory cytokines.

Table 79–3 Comparison of GM-CSF and G-CSF

Factor	Additional Uses	Starting Dose
G-CSF	Chemotherapy-induced suppression, severe congenital neutropenia, peripheral stem cell harvest, drug-induced neutropenia	5 μg/kg/d SQ or IV
GM-CSF	Autologous BMT, enhanced antigen presentation, drug-induced neutropenia	250 $\mu g/m^2$/d SQ or IV

BMT, Bone marrow transplantation.

Megakaryocyte and Platelet Production

The CFU-S gives rise to a committed megakaryocyte progenitor, the CFU-Mega (see Figure 79-2) identifiable in in vitro clonogenic assays and by the presence of platelet glycoprotein surface antigens. Unlike RBC and granulocyte differentiation in which cell division keeps up with mitosis, the next phase of development of megakaryocytes is characterized by endoreduplication, a process of mitosis without cell division that leads to increased DNA content up to a ploidy of 32N (where 2N is a diploid cell). With increasing ploidy comes increased cell volume, degree of nuclear lobulation, and granules containing factors that influence platelet function. A system of "demarcation membranes" identified by electron microscopy separates the megakaryocyte cytoplasm into several thousand anucleate platelets, which are shed into the lumens of the marrow sinusoids. The entire process takes about 5 days. Although megakaryocytes can be visualized on bone marrow aspirates and biopsy specimens, their quantitation by these techniques is approximate and correlates only loosely with platelet production. Factors controlling platelet shedding have not been studied extensively. With exceptions, however, large platelets or megathrombocytes (increased mean platelet volume) are seen in thrombocytopenia caused by increased platelet destruction. Normal platelet volume occurs more frequently in thrombocytopenia resulting from decreased platelet production.

Some platelets go directly from the marrow to the blood, where they remain; others go temporarily to the spleen, which possibly contributes to their further maturation. Normally one third of the total body platelet mass is sequestered there, although the number can go as high as 90% in pathological states. Once in the peripheral blood, platelets have a life span of about 10 days. Chromium studies, useful to assess platelet life span, have severe limitations in estimating the extent of organ-specific uptake of platelets and response to splenectomy.

Tpo is the critical growth factor for the production of platelets.[26] Whereas IL-3, GM-CSF, Epo, IL-11, and IL-6 stimulate CFU-Mega growth in vitro, none of these factors has proved to be highly effective in increasing platelet counts in clinical trials. Clinical trials are beginning in pediatrics and these agents may be available on a compassionate basis for older children. Thrombopoietin potently stimulates the expression of CFU-Mega and megakaryocytes, resulting in an increased platelet mass. Because knockout mice have been created that lack the gene for the thrombopoietin receptor but still produce some platelets, other cytokines must contribute to platelet production. These factors, such as IL-3 and IL-11, most likely synergize with thrombopoietin. Whether Epo itself has thrombopoietic activity is controversial. Although iron deficiency anemia is often associated with thrombocytosis, increases in Epo may not be the immediate mechanism, and not all disease states associated with elevated Epo levels are characterized by increased platelet number. As with the other cell lines, megakaryopoiesis is also dependent on vitamins; severe megaloblastic anemia may be associated with thrombopenia and bizarre platelet and megakaryocyte morphology.

Spontaneous bleeding is unlikely unless there are fewer than 20,000 normally functioning platelets/μL. However, for major invasive procedures such as surgery or placement of arterial lines or endotracheal tubes, the platelet count should be maintained at a level more than 50,000/μL or even 100,000/μL. The minimum platelet count for performing a spinal tap is less clear, but most clinicians would ask that the platelet count be at least 30,000/μL. Other indications for platelet transfusions are discussed in Chapter 73. In the rare patient with idiopathic thrombocytopenic purpura and intracranial hemorrhage, optimum control of bleeding requires cooperation between neurosurgery, general surgery, hematology, and intensive care clinicians and some combination of splenectomy, high-dose gamma globulin, steroid therapy, and platelet transfusions.

Lymphopoiesis

The bone marrow and thymus are the primary lymphoid organs, the site of lymphocyte production. The secondary lymphoid organs, to which the B and T cells migrate, include the spleen, lymph nodes, and gut-associated lymphoid tissue (tonsils, appendix, and Peyer's patches of the small intestine).

The Spleen

The spleen is enclosed in a thick, fibromuscular capsule. Numerous trabeculae spring from the capsule to divide the interior pulp into lobules, within which is a scaffolding of reticular cells and fibers. Unlike the thymus, the spleen has a hilum through which the splenic artery and its branches enter and then branch further to course along the trabeculae. Collaterals from the gastric artery enter through the splenic capsule so that splenic artery ligation does not result in infarction. The branches of the splenic artery pass into the parenchyma to form central arteries that are surrounded for much of their length by a dense sheath of T lymphocytes and macrophages. Lymphoid follicles, some with germinal centers containing B cells from the bone narrow (as noted previously), are also present in the periarterial lymphatic sheath. Together the B cell– and T cell–dependent areas comprise the white pulp of the spleen. The rest of the splenic parenchyma is the red pulp. It contains radial branches of the central arteries that carry hemoconcentrated blood (plasma is skimmed off and runs in other arterial branches), well-defined endothelial lined venous sinuses that ultimately drain into the splenic vein, and an anatomically separate reticulin network, the splenic vein, which function as endothelial lined blood vessels. Most of the circulation runs from the arterial system into the cords and then into the venous system, probably by squeezing through gaps in the endothelium. After the neonatal period, a marginal zone of the red pulp that abuts the white pulp becomes more prominent. It contains antigen-processing macrophages that are needed for B-cell function. It is believed to be the initial site of interactions between antigen and lymphocytes. Small numbers of efferent lymphatic vessels lie at the proximal end of the central arteries and leave the spleen through the trabeculae.

Normally the spleen is found in the left-upper quadrant of the abdomen. Its weight increases linearly with body weight until puberty, after which it shrinks somewhat. A spleen tip is palpable in 10% of normal children. On the basis of data from splenectomy cases, small accessory spleens occur in almost 20% of individuals. Generally they are located near the hilum of the main spleen, with which they share their vascular supply.

The spleen has many functions. The red pulp filters damaged and old RBCs from the systemic circulation by several mechanisms. (1) The cells are distorted and disrupt as they pass through the small lumens of the arterial capillaries or between the endothelial cells of the sinuses: in particular, cells with HbS undergo increased sickling, and cells with abnormalities of glycolytic metabolism or senescent cells become increasingly fragile in the face of decreased O_2 tension with lactic acidosis and decreased adenosine triphosphate production. (2) Cells are entrapped in the viscous blood within the fine mesh reticulin. (3) Cells undergo antibody-mediated (especially immunoglobulin G) hemolysis or phagocytosis, as seen in some autoimmune hemolytic anemias. Damaged cells or their debris produced by any of these mechanisms are removed by macrophages of the red pulp or may escape back into the circulation. Rigid inclusions such as Howell-Jolly bodies may be pitted without destroying the parent RBC on passage through the sinus endothelium. Therefore the presence of even small numbers of Howell-Jolly bodies is a subtle indicator of impaired splenic function except in the term and especially in the premature neonate, where they also are seen and thought to be a normal developmental stage.

As mentioned earlier, the spleen also is a temporary reservoir for platelets and to a small extent for WBCs. Thus after splenectomy there is a usually transient thrombocytosis that resolves within 3 to 6 months. In children it does not appear to carry a predisposition to thrombosis even with platelet counts as high as 10^9/μL. In the presence of antiplatelet or anti-WBC

antibody (some synthesized by the spleen) and in hypersplenism without antibody, the spleen may also function as a filter and result in thrombopenia and neutropenia, which may be reversible by surgical or pharmacological (steroids, high-dose gammaglobulin) splenectomy (see section on platelet production).

The spleen, predominantly the white pulp and marginal zone, also plays a number of roles in host defense, elegantly and elaborately discussed elsewhere.[8,15] In short, splenectomy has been associated with an increased incidence of serious infections with encapsulated bacteria, intraerythrocytic parasites, and possibly leukemia in patients who have splenectomy as part of the management of Hodgkin disease. Most clinicians recommend use of *Haemophilus influenzae* type b, meningococcal, and pneumococcal vaccines 1 to 2 weeks before splenectomy (in previously unimmunized individuals), with boosters against pneumococcal disease every 5 to 10 years, and prophylactic antibiotics for variable times, but at least through adolescence. Although it is not a site of hematopoiesis beyond fetal life under normal conditions, in certain disease states the spleen can reactivate its hematopoietic potential. These states include some congenital hemolytic anemias and acquired diseases, such as myeloid metaplasia. All are associated with splenomegaly and usually with hepatomegaly, signifying a more general expansion of hematopoiesis. The liver can fulfill some of these functions so that in functionally or literally asplenic patients RBC life span, for example, is not increased. However, the liver is less effective at other functions, including pitting and host defense.

Lymph Nodes

Like most of the rest of the lymphoreticular system, lymph nodes are surrounded by capsules and have architecturally distinct cortices and medullary zones, functionally distinct B cell– and T cell–dependent areas, and macrophages—all compartmentalized by a reticular meshwork. Many of the small lymphocytes, especially the T cells, continually are recycled through the systemic circulation by the thoracic duct. They function primarily as a site of interaction between the immune system and invading antigens. Mediastinal lymph node enlargement as a result of invasion by lymphoid or nonlymphoid tumors or from endogenous antigenic stimulation may compromise the airway and present anesthetic risks.

References are available online at http://www.expertconsult.com.

Thrombosis in Pediatric Intensive Care

John Roy and Paul Monagle

PEARLS

- Vascular access devices are the most common cause of thromboembolic disease in children, and every attempt should be made to limit their use based on real clinical need.
- Thrombophilia is rarely the major cause of thrombosis in critically ill children, and multiple tests to identify thrombophilic states are rarely useful to patient management.
- For reasons that remain uncertain, heparin-induced thrombocytopenia is rarely seen in children.
- Care must be taken in the diagnosis of thrombosis in children, as assumptions made in adult diagnostic strategies may not be true in children.
- Unfractionated heparin is the most useful anticoagulant in critically ill children; however, dosing errors are common, and pediatric intensive care units should spend considerable resources on training and systems to ensure safe management of heparin.

Dramatic improvements in pediatric intensive care have led to the improved survival of critically ill children, and to the emergence of previously rare complications. In order to achieve this improved survival, there has been a dramatic increase in the invasiveness of supportive care. The use of central venous access, invasive arterial monitoring, and circulatory support including ventricular assist devices (VAD) and extracorporeal membrane oxygenation (ECMO), as well as processes such as hemofiltration and hemodialysis that are performed through large-bore vascular access devices, increases the likelihood of vascular endothelial damage or direct vascular obstruction. These insults to the vascular system are often combined with prolonged hypotension, systemic inflammatory states, and infection, all of which may alter endothelial and vascular responsiveness. Finally, there are a multitude of drugs and fluids administered during the periods of critical illness, which can impact directly on plasma proteins and endothelial function, or which may lead to dilution of critical plasma proteins involved in the coagulation system. Not surprisingly, therefore, thromboembolism is an increasingly common problem faced in the pediatric intensive care setting, and contributes significantly to morbidity and mortality.

This chapter describes key issues related to thrombosis in the pediatric intensive care unit. Developmental hemostasis is a crucial concept both to the understanding of the etiology of thrombosis in children, and to the application of diagnostic and therapeutic strategies. The etiology, epidemiology, clinical features, diagnosis, and management of the major types of thrombosis encountered in children in the intensive care unit (ICU) will be discussed. However, thrombosis of the central nervous system (CNS), including arterial ischemic stroke and cerebral sinovenous thrombosis are beyond the scope of this chapter (see Chapter 63). As in many areas of pediatrics, high-level evidence is often lacking; however, best-available evidence will be drawn upon where possible. Extrapolation from adult studies resulting in suboptimal treatment outcomes in children highlights the need for pediatric-specific trials and guidelines.

Developmental Hemostasis

The hemostatic system is a dynamic, evolving entity that not only likely affects the frequency and natural history of thromboembolic disease in children, but also the response to therapeutic agents.[1-5] The concept of developmental hemostasis was first coined in the late 1980s and is now uniformly accepted. Not only are the plasma levels of many individual coagulation proteins different in pediatric patients from adults, but the global functioning of the coagulation system appears to be quite different. In additional to quantitative differences, there is evidence (mostly from animal models) of qualitative differences in many coagulation proteins, especially in neonates.[6,7] Finally, again from animal models, data would support significant differences in the antithrombotic properties of the blood vessel wall, with altered concentrations of active glycosaminoglycans.[8,9] Although ongoing research in this area is desperately needed, current knowledge regarding the differences between adults and children in plasma proteins most likely to impact on anticoagulation therapy is as follows.

Plasma concentrations of antithrombin (AT) are physiologically low at birth (~0.50 U/mL) and do not increase to adult values until 3 months of age. Sick premature neonates frequently have plasma levels of AT of less than 0.30 U/mL. Fetal reference ranges are now available and show that AT levels range from 0.20 U/mL to 0.37 U/mL at gestational ages of

19 to 38 weeks. This likely has a profound effect on the action of heparin, whose antithrombotic activity is dependent on catalysis of AT to inactivate specific coagulation enzymes, in particular thrombin. Some studies suggest children in pediatric intensive care units have markedly reduced AT levels compared to age-matched controls, potentially further enhancing this effect (Figure 80-1). The capacity of plasmas from neonates to generate thrombin is both delayed and decreased compared to adults, and is similar to plasma from adults receiving therapeutic amounts of heparin.[10] Following infancy, the capacity of plasmas to generate thrombin increases but remains approximately 25% less than for adults throughout childhood.[11] Both an increased sensitivity and an increased resistance to unfractionated heparin's anticoagulant activities have been reported in vitro in plasma from neonates. Increased sensitivity to unfractionated heparin is observed in systems based on assays dependent on thrombin generation (e.g., activated partial thromboplastin time [APTT]). The in vitro effects of unfractionated heparin (0.25 U/mL), on neonates, children, and adults were compared recently, and thrombin generation was delayed and reduced in children compared to adults, and virtually absent in neonates.[12] Resistance to unfractionated heparin is observed in systems based on assays that measure the inhibition of exogenously added Factor Xa or thrombin and that are dependent on plasma concentrations of AT.

In vitro, thrombin generation is similar in adults and children at the same concentration of low-molecular-weight heparin (LMWH). However, at 0.25 U/mL LMWH, thrombin generation was delayed and reduced by approximately half in newborns compared to adults. These differences were matched by reductions in rates of prothrombin consumption.[12]

The vitamin K–dependent clotting factors are the most extensively studied group of factors in infants. Physiologically low levels of clotting factors (II, VII, IX, and X) were measured in infants who received vitamin K prophylaxis at birth. The levels of the vitamin K–dependent factors and the contact factors (Factors XI and XII, prekallikrein, and high-molecular-weight kininogen) gradually increase to values approaching adult levels by 6 months of life. For children receiving vitamin K antagonists, the capacity of their plasmas to generate thrombin is delayed and decreased by 25% compared to plasmas from adults with similar INRs.[13]

Whether the overall activity of the protein C/protein S system varies with age is unknown. However, at birth, plasma concentrations of protein C are very low, and they remain decreased during the first 6 months of life. Although total amounts of protein S are decreased at birth, functional activity is similar to that in the adult because protein S is completely present in the free, active form because of the absence of C4-binding protein.[14,15] Furthermore, the interaction of protein S with activated protein C in newborn plasma may be regulated by the increased levels of α_2-macroglobulin. Plasma concentrations of thrombomodulin are increased in early childhood and decrease to adult values by late teenage years. However, the influence of age on endothelial cell expression of thrombomodulin has not been determined.[16]

Total tissue factor pathway inhibitor (TFPI) levels in newborns are reported as being similar to levels in older children or adults. Free TFPI is reported as being significantly lower in newborns.[17]

Despite the changes in individual protein levels and in global tests of coagulation, the hemostatic system in neonates and children does not seem disadvantageous compared to the "normal" coagulation system as measured in adults. There is no data to support either an increased bleeding or thrombotic risk during infancy and childhood for any given stimulus and on the contrary, one could argue that the hemostatic system in neonates and children is protective against bleeding and thrombotic complications compared to adults. This is despite the fact that when considering individual proteins, many proteins exist at levels during stages of infancy that would be associated with disease in adults. There clearly remains much to be learned about the evolution of the coagulation system with age, and this is an area in which there is much ongoing active research. As a better understanding of the neonatal and child coagulation system is achieved over coming years, thinking may change regarding many aspects of thrombosis development and management in this patient population.

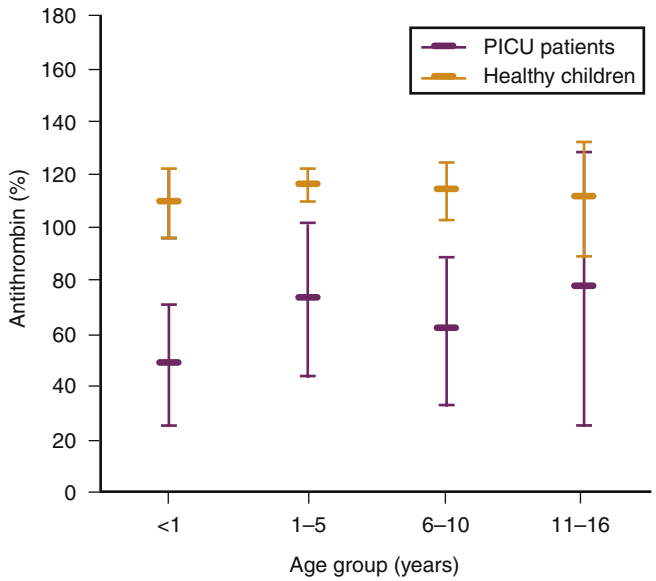

Figure 80–1. Antithrombin levels by age group in samples obtained from children in a pediatric intensive care unit (PICU) compared to age-matched controls. Note the reduction in antithrombin levels in sick children. *(Courtesy P. Monagle.)*

Etiology and Epidemiology

While there has been much published recently on a variety of factors that may contribute to the etiology of thrombosis, perhaps the most useful concept for the clinician to understand remains Virchow's triad[18]. Virchow's triad recognizes that three factors are involved in the development of thrombosis, those being the blood vessel wall, the blood constituents, and blood flow[19] (Figure 80-2). Patients in the pediatric ICU (PICU) often demonstrate abnormalities in one, two, or all of these factors, and in the consideration of each patient, it is important to determine which of these abnormalities may be predominant, as this can be a useful guide to therapy. For example, in a patient with a cardiac lesion, either primary or postsurgical, where there is extremely poor blood flow in one part of the cardiovascular system, the optimal management is to improve the blood flow. While anticoagulation may well have an important role, progressively increasing the intensity of anticoagulation will significantly increase the risk of bleeding and yet may not substantially further reduce the risk of thrombosis, which is being driven

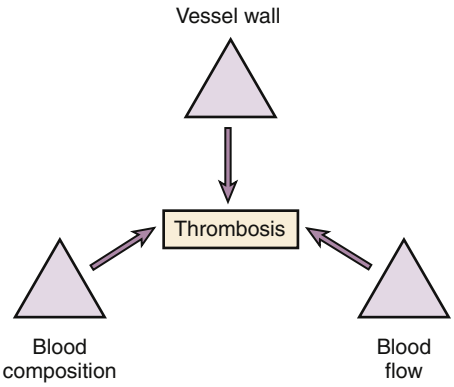

Figure 80–2. Virchow's triad, highlighting the importance of each factor in contributing to thrombosis formation.

primarily by flow. Alternatively, patients with disseminated intravascular coagulation (DIC) have a marked perturbation of function of the vascular endothelium (blood vessel wall) and anticoagulation alone is unlikely to prevent thrombotic complications, which will only be avoided by treatment of the primary illness and subsequent resolution of the DIC.

Combinations of these factors are important in many instances. For example, central venous access is a common precipitant of thrombosis most commonly through interruption to flow (especially in small infants where the catheter-to-vein diameter ratio is close to 1:1), and through disruption of the vessel wall at the insertion site. However, thrombosis is seen more commonly when there is an additional abnormality in the blood constituents as well, for example in protein-losing states like nephrotic syndrome or enteropathy, or through inflammatory or septic conditions, or via drugs such as oral contraceptives. Additional scenarios that reduce blood flow further, such as hypotension, may also increase the risk of thrombosis. Consideration of the etiological factors in this way often enables clinicians to make some attempt at risk stratification and to modify care to reduce some of the multifactorial drivers of thrombosis on an individual basis, even though there may not be clear numerical data from large studies on the actual level of risk.

Table 80-1 summarizes the epidemiology and known risk factors for most etiologies of common non-CNS thrombosis seen in critically ill children. The most important risk factors for thrombosis in the pediatric intensive care unit remain the presence of vascular access devices and recent cardiac surgery. Two additional risk factors worth discussing, although they are not often particularly relevant in children are thrombophilias and heparin-induced thrombocytopenia.

Central Venous Access Devices

The most common risk factor for venous thrombosis in children appears to be the presence of a central venous catheter (CVC) although most children have several concomitant risk factors.[20]

Over 50% of venous thromboembolisms in children occur in the upper venous system secondary to the use of central venous catheters (CVCs). Three types of CVC-related thrombosis are described in the literature: clots at the tips of CVCs that impair infusion or withdrawal of blood; fibrin sleeves that are not adherent to vessel walls but may occlude CVCs; and CVC-related thrombi that adhere to vessel walls, with partial or complete obstruction of vessels where the CVC is located. This discussion refers to this third type of thrombosis only; that is, obstructive CVC-related thrombosis. There are a number of mechanisms that may be contributory to the development of CVC-related thrombosis, including damage to the vessel wall by the CVC or by substances infused through the CVC (total parenteral nutrition [TPN], chemotherapy), disrupted blood flow due to the presence of the CVC, and thrombogenic catheter materials. Use of CVCs occurs most commonly in children who require short-term intensive care, hemodialysis, or long-term supportive care (TPN or chemotherapy).[21]

The incidence of CVC-related thrombosis reported in the literature varies, reflecting differences in underlying conditions, diagnostic tests, and index of suspicion. For example, the incidence of CVC-related thrombosis in children receiving long-term TPN varies from 1% based on clinical diagnosis,[22] to 35% based on ventilation-perfusion scans or echocardiography, to 75% based on venography.[23] In a prospective cohort, 18% of children in an intensive care setting with CVCs in place for at least 48 hours developed CVC-related thrombosis.[24] The recently completed Prophylactic Antithrombin Replacement Therapy in Kids with ALL Treated with L-Asparaginase (PAARKA) study reported a venographically proven CVC-related thrombosis incidence of 37% among asymptomatic children with acute lymphocytic leukemia receiving L-asparaginase therapy,[25] In many patient populations, the incidence is not accurately known.

Arterial Access

The most common type of arterial thrombosis in children occurs as a result of placement of arterial catheters. Non–catheter-related arterial thrombosis may be congenital (familial hyperlipidemia and hyperhomocysteinemia) or acquired (Takayasu arteritis, Kawasaki disease, congenital heart disease, and arterial thrombosis in transplanted organs). There are, in general, three types of arterial catheterizations that are used in children that may result in arterial thrombosis: umbilical arterial catheterization in neonates (will not be discussed in this chapter), cardiac catheterization, and peripheral catheterization. Arterial occlusion causes tissue ischemia resulting in tissue necrosis if the vascular occlusion persists. Organ and tissue damage at remote sites may result from embolic events occurring due to fragmentation of the original thrombus.

Often, in the PICU, short-term femoral artery access will be required, or emergency femoral artery puncture will be performed, or alternatively, the femoral artery will be inadvertently accessed during attempts at femoral venous access. In terms of understanding the implications of this, one can only really extrapolate from the cardiac catheterization literature, recognizing that diagnostic and therapeutic cardiac catheterization via the femoral artery have some significant differences in terms of thrombosis risk.

Adverse events occurring as a result of femoral artery puncture include arterial spasm and arterial thrombosis. Clinically, vascular spasm and thrombosis are indistinguishable in the initial phases of presentation with the following symptoms: decreased or absent pulses, pale or mottled limb, and decreased capillary refill. Arterial spasm usually resolves within a few hours in the absence of therapy while arterial thrombosis usually requires therapy. The incidence of femoral artery thrombosis following cardiac catheterization without thromboprophylaxis is approximately 40%. The incidence is inversely proportional to patient age and weight, with infants

Table 80–1 Summary of the Epidemiology, Clinical Features, Diagnosis, and Complications of the Most Common Types of Non-CNS Thromboembolism in Children

	Type/Location	Age/Sex	Incidence	Underlying Illness or Risk Factors	Clinical Features	Diagnosis	Complications
Spontaneous VTE	Lower limb	M = F Teenagers	1.2 per 10,000 hospital admissions		Leg, inguinal, or abdominal pain Leg swelling or discoloration	Doppler US	Immediate: PE Cardiac extension Chylothorax SVC syndrome Long-term: Recurrent VTE PPS
	Axillary	M = F Teenagers	Very rare	Mass lesion Thoracic inlet obstruction New sport involving arms	Arm swelling, pain, and discoloration	Doppler US	
CVAD-related VTE	Line tip thrombosis	Higher in neonates		Cancer, sepsis, trauma, surgery, immobility, long-term lines, congenital heart disease, burns, cardiac catheterization	Inability to flush or draw from line	Linogram Echocardiogram if tip in RA	Variceal hemorrhage
	Fibrin sleeve				Asymptomatic	Linogram, venography	
	CVAD-related DVT Iliofemoral, IVC, jugular, subclavian		Catheter material		Asymptomatic Limb or facial swelling, pain, discoloration SVC syndrome, chylothorax	Doppler US for neck, limb, and abdominal TE Venography (radiograph, CT, or MR) for intrathoracic TE	
PE			Up to 30% children with CVC-related DVT	CVAD-related DVT RA thrombus, cancer, CHD, cardiomyopathy, burns, sepsis, trauma, nephrotic syndrome, APLA, transplantation	Asymptomatic (up to 50%) Tachycardia Chest pain Respiratory distress Increased oxygen requirements Acute right heart failure Collapse Sudden death	V/Q scan Pulmonary angiography Plain radiography, CT, MR ECG Autopsy most common diagnostic test in children	Death Pulmonary hypertension and heart failure Recurrence
Arterial TE	Peripheral arterial catheter Radial artery, occasionally foot arteries			Peripheral arterial catheter	Acute limb ischemia: blanching, pallor, diminished pulses/CR Loss of patency	Doppler US	Ischemia (hand)
	UAC Celiac, mesenteric, renal, and lower limb arteries			Umbilical arterial catheter	Loss of patency Lower limb ischemia NEC/organ ischemia	Doppler US Contrast angiography	Organ Ischemia NEC Lower limb TE CNS TE (via PFO)
	Cardiac catheter Femoral artery	Increased in younger children	Up to 10%	Repeated manipulations, balloon dilatations, raised hematocrit	Limb ischemia	Doppler US	Reduced limb growth Claudication Loss of future access

	Congenital and acquired arterial disease Coronary, cerebral, peripheral arterial disease	Rare		Hyperlipidemia, homocysteinuria, acquired arteritis (Takayasu, Kawasaki)	Xanthomata Features of vasculitis or underlying disease	Echocardiography Doppler US Angiography	Myocardial infarction Stroke
	Cardiac valve				Murmur, valvular dysfunction	Echocardiography Angiography, CT, MR	Stroke Limb TE PE
	Cardiac shunt including Fontan		19% post-Fontan patients	Mechanical heart valves Shunts including Fontan	Acute loss of pulmonary blood flow		
Renal vein thrombosis	Neonates: Unilateral, 70% Bilateral, 30%	M = 64%		Asphyxia, polycythemia and dehydration, sepsis, cyanotic CHD, infant of diabetic mother	Flank mass Hematuria, Proteinuria Thrombocytopenia Renal failure	Doppler US (CT, MRI)	Adrenal hemorrhage Renal failure Hypertension
	Older children			Nephrotic syndrome, burns, SLE, transplant	Diarrhea and vomiting Dehydration, hypovolemia		
Portal vein thrombosis				Neonates: UVC Children: Liver transplant, abdominal sepsis, splenectomy, sickle cell disease, APLA Up to 50% idiopathic	Acute abdomen Portal hypertension- GI bleeding, splenomegaly	Doppler US MRI/MRA CT	Death Portal hypertension and variceal hemorrhage
Hepatic artery thrombosis					Asymptomatic	Pulsed Doppler + real time US Angiography CT/MRI	
Renal artery thrombosis					Anuria, renal failure Other signs of acute rejection	Doppler US	

APLA, Antiphospholipid antibody; *CHD,* congenital heart disease; *CNS,* central nervous system; *CR,* capillary return; *CT,* computed tomography; *CVAD,* central venous access device; *CVC,* central venous catheter; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *F,* female; *IVC,* inferior vena cava; *M,* male; *MR[I/A],* magnetic resonance [imaging/angiography]; *NEC,* necrotizing enterocolitis; *PE,* pulmonary embolus; *PFO,* patent foramen ovale; *PPS,* postphlebotic syndrome; *RA*, right atrium; *SLE,* systemic lupus erythematosus; *SVC,* superior vena cava; *TE,* thromboembolism; *UAC,* umbilical arterial catheter; *UVC,* umbilical venous catheter; *US,* ultrasound; *V/Q,* ventilation/perfusion; *VTE,* venous thromboembolism.

at highest risk.[26] The frequency of femoral artery thrombosis in PICUs is unclear. Similarly with peripheral arterial catherization, the mechanism of injury is endothelial damage and blood vessel occlusion. The exact frequency of peripheral arterial occlusion in the PICU remains unknown.

Cardiac Surgery

Children with congenital heart disease constitute a major proportion of children seen in tertiary hospitals with thrombosis. Recent data shows that almost 50% of infants less than 6 months old and 30% of older children who suffer venous thromboembolic disease have underlying cardiac disorders. Similarly, almost 70% of infants (less than 6 months) and 30% of children who suffer arterial thrombosis have underlying cardiac defects. In addition, the majority of children receiving primary anticoagulant prophylaxis are being treated for complex congenital heart disease or severe acquired cardiac illness.[26] Presumably, the mechanisms underlying this increased risk of thrombosis are alterations to blood flow (for example, following Fontan surgery, where venous return is driving the pulmonary blood flow), and disturbances of the vascular endothelium related to intravascular sutures or vascular manipulation. Whether a postsurgical inflammatory state induces changes in the blood constituents that predispose to thrombosis is also unknown. Two classic examples of cardiac surgery-related thrombosis are the Blalock Taussig (BT) shunt, and the Fontan procedure.

The natural history of BT shunts has been assessed using angiography. Godart et al.[27] assessed BT shunt growth and development of stenosis and distortion in 78 patients at a mean follow-up time of 51 months. They found that growth of the pulmonary arteries occurred but did not exceed the normal growth of the pulmonary arterial tree. However, a shunt procedure could cause distortion and stenosis of the pulmonary artery that might have important implications for future corrective surgical intervention. Risk factors for patency and stenosis include the age of the patient and graft size.[28,29]

The incidence of thrombotic occlusion of BT shunts in the literature ranges from 1% to 17%.[28-42] This risk might be increased in children having first-stage Norwood surgery, as these children are small and unstable and often have labile blood pressures as well.

There have been a number of recent reviews regarding anticoagulation after Fontan surgery.[43,44] The Fontan procedure, or a modified version, is the definitive palliative surgical treatment for most congenital univentricular heart lesions. Thrombosis remains a major cause of early and late morbidity and mortality. Reported incidences of venous thrombosis and stroke ranged from 3% to 16% and 3% to 19%, respectively, in retrospective cohort studies where thrombosis was the primary outcome, and from 1% to 7% in retrospective studies assessing multiple outcomes. Thrombosis may occur anytime following Fontan procedures, but often presents months to years later. No predisposing factors have been identified with certainty, although this may be due to inadequate power and the retrospective nature of the studies.

Thrombophilia

Congenital thrombophilia is usually defined as having the following features: (1) positive family history, (2) early age of onset of thromboembolism, (3) recurrent disease, and (4) multiple or unusual thrombosis locations. Clinically, the most significant inherited prothrombotic conditions are deficiencies of antithrombin (AT), protein C (PC), and protein S (PS), because of the large increase in relative risk these deficiencies confer. Activated protein C resistance/factor V Leiden (FV-R506Q) and prothrombin G20210A (IIG20210A) polymorphism, while having less impact on individual risk, are significant because of their frequencies in certain populations. A large number of other candidate genes have been proposed as risk factors for congenital thrombophilia.[45] However, most of these candidates have not undergone careful segregation or population studies to define their pathogenic role. In fact, some of the seemingly obvious candidates such as abnormalities in fibrinolysis do not appear to confer thrombotic risk.[46] These latter studies are, however, hampered by the low prevalence of most of these inherited abnormalities in the general population.

Recent reports demonstrate an increased risk for thrombosis in families with a second genetic abnormality.[47] Most reports have described a combination of FV-R506Q with abnormalities of PC, PS, or AT. These findings begin to shed light on the marked variability in clinical expression of these syndromes. The effect of more severe deficiencies has long been evident from the severely affected neonates with homozygous PC and PS deficiency. Apart from the well-defined homozygous cases, the risk and severity of thrombosis appear to vary with the type and number of underlying genetic abnormalities.[47-50]

The role of these congenital prothrombotic states in childhood thrombosis remains controversial. Despite recent meta-analysis suggesting that thrombophilia is a significant risk factor in childhood thrombosis, there are serious limitations to the published literature on which these meta-analyses are based. [51]

The reported incidence of congenital prothrombotic disorders in children with venous thrombosis varies from less than 1% to over 60%.[48-50,52-84] If one considers the deficiencies of AT, PC, and PS in addition to the Factor V Leiden and prothrombin gene mutations, large family studies found negligible rates of thrombosis in children less than 15 years.[85] A number of cohort studies have failed to identify AT deficiency in children with both arterial and venous thrombosis.[70,71,75,76] Those studies that reported higher frequencies of AT deficiency did not distinguish between acquired and inherited deficiency.[57] In children with cancer and venous thrombosis, the reported incidences of thrombophilias are 3%.[75,86] The variability in incidence reported in all these studies reflects small sample sizes, variability in study design, differing definitions of prothrombotic disorders, and different patient selection criteria.[87] A prospective study of an unselected cohort of children with venous thrombosis found that with the exception of teenagers with spontaneous thrombosis, inherited thrombophilic markers did not contribute significantly to the pathogenesis of venous thrombosis in children.[88]

Screening for congenital prothrombotic disorders in children with venous thrombosis is of unproven benefit, regardless of the presence or absence of acquired risk factors. At this time, uniform screening of children with major illnesses, and/or those who require CVCs, for congenital prothrombotic disorders in order to provide prophylactic therapy cannot be recommended. The contribution of congenital prothrombotic disorders to venous thrombosis in pediatric patients remains to be clarified. Few children develop thrombosis due to a heterozygote congenital prothrombotic condition, without also having an acquired risk factor.[45,68,69,89-96]

In summary, the data supporting inherited thrombophilia as a major factor in thrombosis in childhood is conflicting. In the PICU, it is likely that the dominant factors are clinical risk factors for thrombosis and that, if it contributes at all, thrombophilia may act as an additional hit in a multi-hit pathogenesis. However, there remains no evidence to support routine screening for thrombophilia, and there are certainly no data to support primary prophylaxis of children with inherited heterozygous thrombophilia. Further, there is no evidence that the presence or absence of thrombophilia changes acute treatment once a thrombosis is diagnosed. Given the inherent difficulties in interpreting at least the functional assays of protein levels in acutely sick children, there seems little role for thrombophilia testing in the PICU.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) occurs in approximately 3% to 5% of adults exposed to unfractionated heparin (UFH) and is typically associated with a reduced platelet count, occurrence 5 to 10 days after heparin exposure, and an increased risk of thrombosis despite the thrombocytopenia. HIT is the result of a complex antigen-antibody interaction, and the most important therapeutic intervention once HIT is diagnosed is the immediate withdrawal of all heparinoid anticoagulants, and substitution with non-heparinoid drugs until the risk of thrombosis is ameliorated.[97]

A number of case reports of pediatric HIT have described patients ranging in age from 3 months to 15 years.[98-102] UFH exposure in these cases ranged from low-dose exposure during heparin flushes used in maintaining patency of venous access devices, to supratherapeutic doses given during cardiopulmonary bypass and hemodialysis. Studies specifically examining the frequency of HIT in children have varied in their reported results, likely related to differences in patient inclusion and laboratory techniques.[103-108] Reported rates vary from almost nonexistent in unselected heparinized children[106] up to 2.3% in children in the PICU.[107] However, HIT appears to occur far less frequently in children than in adults and the rationale for this is unclear.[106] Many patients in the neonatal intensive care unit/PICU who are exposed to UFH have multiple potential reasons for thrombocytopenia and/or thrombosis, and recent papers confirm that many positive HIT tests are in fact false positives.[109] Danaparoid, hirudin, and argatroban are alternatives to UFH in children with HIT;[100-102,110-113] however, these drugs have significant risks in children.[114] Until such time as the true clinical incidence of HIT in children is understood, the diagnostic tests have higher sensitivity and specificity, and there are safe and reliable alternatives to heparin therapy in acutely sick children, the diagnosis of HIT in children should be made with caution. Careful attention to the diagnostic criteria, exclusion of other causes, and rationale use of test results are all required.

Clinical Features

The clinical symptoms and complications of venous thrombosis in children can be classified as acute or long-term. The acute clinical symptoms include loss of CVC patency; swelling, pain, and discoloration of the related limb; swelling of the face and head with superior vena cava syndrome; and respiratory compromise with pulmonary embolus (PE). The long term complications include prominent collateral circulation in the skin (face, back, chest, and neck as sequelae of upper venous thrombosis, and abdomen, pelvis, groin and legs as sequelae of lower venous thrombosis), repeated loss of CVC patency, repeated requirement for CVC replacement, eventual loss of venous access, CVC-related sepsis, chylothorax, chylopericardium, recurrent thrombosis necessitating long-term anticoagulation and its risk of bleeding, and post-thrombotic syndrome.

In adults, asymptomatic thromboses are not necessarily treated and thrombosis experts argue that these thrombi are probably inconsequential. Symptomatic thrombi are treated to prevent embolism and extension. However, in children, asymptomatic thrombosis that is radiographically detected (and which constitutes a large proportion of the thrombosis diagnosed in children), is of clinical importance for a number of reasons. First, there is increasing evidence supporting the relationship between CVC-related sepsis and CVC-related thrombosis.[115] Second, PE in children is frequently not diagnosed during life due to the subtle symptoms and the presence of other illnesses, but can cause sudden respiratory compromise. However, PE most commonly results from CVC-related thrombosis and can cause death.[116] Third, in a child with a patent foramen ovale (or some other cardiac right-to-left shunt) and venous thrombosis, stroke may occur as a result of the right-to-left intracardiac connection. Fourth, the long-term consequences of CVC-related thrombosis may be significant and include death and loss of venous access. Sudden death has been described in a few case reports from rupture of an intrathoracic collateral vessel thought to have resulted from previous CVC placement years earlier. Loss of venous access is a devastating complication of CVC-related thrombosis in children requiring vascular access for organ transplant, lifelong TPN, or dialysis.

The clinical presentation of pulmonary embolus in children is often masked. In critically ill children, sudden cardiorespiratory deterioration can be due to a multitude of causes, and the difficulty in performing appropriate imaging to confirm the diagnosis of PE often means the diagnosis is either not considered, or unable to be substantiated. Further, previously healthy children tend to tolerate large pulmonary embolus remarkably well, so often shortness of breath or dyspnea is transient, and the resolution of symptoms betrays the significance of the underlying pathology. Many children with substantial PE have no symptoms at all, until they demonstrate those of chronic venous hypertension, or a subsequent further PE has fatal consequences. Clinical suspicion for PE must be high in all critically unwell children, especially those with central venous access devices in situ.

The clinical presentation of arterial thrombosis in children is often more straightforward, with cold, pale, pulseless limbs acutely related in time to the placement of an arterial catheter. However, other systemic arterial thrombosis, for example, emboli to abdominal organs, may present with vague and nondiscriminatory symptoms. Arterial thrombosis related to transplanted vessels may present as sudden graft loss.

Diagnosis

Venous Thrombosis

Little is known about the precision and accuracy of the noninvasive imaging techniques that are commonly used to make the diagnosis of venous thrombosis in neonates. There are

few studies comparing currently used diagnostic tests. The low pulse pressure and small vessels in premature newborns can make ultrasound more difficult to interpret. Similarly, the presence of CVCs makes compressibility difficult to assess and, accordingly, greatly reduces the sensitivity of ultrasound. In neonates with umbilical vein catheters, Doppler ultrasound was shown to be poor compared to contrast venography in detecting asymptomatic thrombi.

The exception is renal vein thrombosis (RVT), where ultrasound is the radiographic test of choice because of its sensitivity in detecting an enlarged kidney, as distinct from the ability to detect intravascular thrombosis. In the first week after RVT, the affected kidney swells and becomes echogenic with prominent echo-poor medullary pyramids. Subsequently, the swelling decreases and the kidney becomes heterogeneous, with loss of corticomedullary differentiation. Ultimately, depending on the degree of recovery, ultrasound may demonstrate focal scarring or atrophy. Color Doppler ultrasound may demonstrate absent intrarenal and renal venous flow in the early stages of RVT. Magnetic resonance imaging (MRI) and computerized tomography (CT) have also been used for RVT, but have no apparent advantages over ultrasound.

In summary, in neonates with suspected venous thrombosis, venography remains the gold standard where possible. Clinicians will often be forced to use a combination of clinical assessment and suboptimal imaging to make clinical decisions, because the gold standard is practically unachievable. This must be factored into progressive decision-making.

In older children, there is a little more data about diagnostic strategies. A well-designed substudy of the PAARKA investigation compared venography versus ultrasound for the diagnosis of asymptomatic upper venous system CVC-related venous thromboembolism. Ultrasound was demonstrated to have a sensitivity of 20% for intrathoracic thrombosis, yet diagnosed jugular thrombi that were missed on venography.[25] The Lineogram, Ultrasound, and Venogram (LUV) study compared linogram, ultrasound, and venography for the diagnosis of symptomatic upper venous system CVC related thrombosis.[117] Most of the thrombi in this study were located in the jugular veins and diagnosed by ultrasound (80% sensitivity) but not venography.[118] Another study compared magnetic resonance venography (MRV) to ultrasound and linogram in 25 children with multiple CVC insertions who were suspected of having major central venous thrombosis.[118] Linogram consistently underestimated the extent of thrombosis. Ultrasound detected only seven of 18 thromboses seen on MRV, and underestimated the extent of four of the seven. In all cases, ultrasound identified jugular thrombosis but failed to identify more central thrombosis. Further, MRV identified a patent vein for reinsertion of CVC in 22 of 25 children. At operation, venous patency was confirmed in 20 patients (91%). There are no studies determining the sensitivity and specificity of diagnostic testing for lower venous system CVC-related thrombosis in children.

In summary, for children with suspected upper system thrombosis, a combination of ultrasound (jugular veins) and bilateral upper limb venography (subclavian and central veins) is recommended. The temptation to extend ultrasound imaging below the clavicles should be resisted. MRV may be a viable alternative to formal venography depending on local expertise. For children with suspected lower system thrombosis, ultrasound is a reasonable alternative for veins distal to the groin, based on adult experience. As in adults, serial ultrasound may be required to exclude thrombosis in specific circumstances. For more proximal veins, venography or MRV should be considered. Of importance, while there is considerable literature about the value of sensitive D-dimer assays in excluding DVT in adults, there is no such data in children. Furthermore, given the preceding medical and surgical therapies that most children with DVT have received, D-dimer is unlikely to be of use. At this time, D-dimer is not part of the recommended diagnostic strategy for venous thrombosis in children.

Pulmonary Embolus

There are no studies determining the sensitivity and specificity of diagnostic testing for PE in children. However, literature would support that PE is significantly underdiagnosed in children, especially those in intensive care settings. A number of potential difficulties with interpreting ventilation/perfusion (V/Q) scans in children at risk from PE have been identified. This is particularly the case in children following specific cardiac surgeries such as Fontan surgery, where total pulmonary blood flow may not be assessed by isotope injected into an upper limb. The true impact of these difficulties on diagnostic accuracy remains to be determined. In addition, there are concerns about the safety of perfusion scanning in children with significant right-to-left cardiac shunts, as it is likely that significant amounts of macroaggregated albumin will lodge in the cerebral circulation, and the impact of this is unknown.[119] Ventilation-perfusion scanning remains the recommended first-line investigation for PE in neonates and children. Pulmonary angiography remains the gold standard. Clinicians will frequently need to make a presumptive diagnosis based on clinical findings and the presence or absence of source thrombosis. CT pulmonary angiography may be an alternative, especially in the specific populations in whom V/Q scanning is more worrisome (e.g., large right-to-left shunts), but CT may miss small peripheral pulmonary emboli. Further, repeated CT angiogram may cause significant radiation exposure to breast tissue in young female patients.[116]

Arterial Thrombosis

There is little specific information related to diagnostic strategies in neonates. Contrast angiography remains the gold standard. Peripheral arterial thrombosis is usually diagnosed clinically. Ultrasound remains unproven, although serial measurements may provide useful information. Aortic thrombosis, usually secondary to umbilical artery catheterization, requires radiological diagnosis. Contrast angiography is rarely feasible in critically ill newborns. Noninvasive imaging techniques have not been validated. In fact, in one of the only comparative studies, ultrasound failed to visualize aortic thrombosis in four patients, three of whom had complete aortic obstruction by contrast angiography. Thus clinicians must often use clinical findings and suboptimal imaging to make clinical decisions.

In older children, many arterial thromboses are diagnosed on clinical grounds alone, for example, after femoral artery puncture. False negatives are reported using ultrasound to diagnose spontaneous femoral artery thrombosis in children. False-positive magnetic resonance angiography has been reported for chronic femoral artery obstruction when compared with formal angiography. In suspected peripheral artery thrombosis, clinicians should consider the possibility

of intramural or external hematoma causing arterial compression as a differential diagnosis, and for peripheral arteries, ultrasound may be sufficiently sensitive to exclude this phenomenon.

Other important arterial thromboses are those that occur in the arterial supply to transplanted organs. For hepatic artery thrombosis after liver transplant, serial testing with pulsed Doppler combined with real-time ultrasound of the liver parenchyma has a sensitivity of approximately 70%. Both false-positive and false-negative results occur, such that angiography is usually required to confirm the diagnosis. Computerized tomography of the liver may be of aid in equivocal cases. Spiral CT has been shown to be sensitive and specific in adults. The value of MRI is yet to be fully determined.

Intracardiac Thrombosis

Three studies have specifically compared transthoracic echocardiography (TTE) to transesophageal echocardiography (TEE) in the diagnosis of intracardiac thrombosis following Fontan surgery.[120-122] Stumper et al.,[122] in a cross-sectional survey of 18 patients, found three intracardiac thromboses using TEE, only one of which was detected by TTE. Fyfe et al.,[121] in a similar study, found six thrombi in four pediatric patients using TEE, only one of which was detected by TTE. Balling et al.[120] performed a cross-sectional study of 52 patients after Fontan surgery. Seventeen patients (33%) had thromboses seen on TEE, only one of which was identified on TTE. Several other publications reported intracardiac thromboses diagnosed by TEE or angiography that were not detected using TTE. Thus transthoracic echocardiography is likely insufficient to exclude intracardiac thrombosis in children after Fontan surgery, although the studies published had a number of design flaws.

The validity of transthoracic echocardiography in other clinical situations is unknown, and clinicians should consider the local expertise, availability of TEE, and the clinical situation before determining the diagnostic approach in any individual child.

Management

Overall, the management of thrombosis in children is based around anticoagulation. There are a multitude of reasons why anticoagulation therapy in children is more difficult to manage than anticoagulation therapy in adults, and some of these are listed in Table 80-2.[123] The indications for surgical intervention or thrombolysis are few and far between. A limited drug arsenal exists in terms of drugs for which there is experience in children. No anticoagulants are formally approved for use in children and so all anticoagulants are used off label. In critically unwell children, there are often multiple relative or even absolute contraindications to anticoagulation, and the balance of risk versus benefit is difficult to ascertain due to the lack of well-designed studies. In general, anticoagulation is best managed by a pediatric hematologist experienced in thrombosis and anticoagulation, in consultation with the critical care team. At all times, the overall management of the child's underlying condition must be kept in perspective versus the management of an individual thrombosis.

In terms of specific guidelines for managing thrombosis in children, the American College of Chest Physicians regularly publishes evidence-based guidelines and the reader is referred to the most up-to-date version of these guidelines as the best overall guide to antithrombotic therapy in children.[123]

Table 80–2 Factors that Increase the Complexity of Anticoagulant Therapy in Children Compared with Adults

Factor	Impact
Epidemiology of thrombosis	Increased proportion of sick children with multiple comorbidites
Developmental hemostasis	Affects response to therapeutic agents
Pharmacokinetic differences	Volume of distribution, binding, and clearance of drugs vary with age
Concurrent illnesses	Increased frequency of intercurrent infections (and hence medications) in children
Less diagnostic certainty	Requirement for general anesthetic to perform diagnostic studies impairs ability to investigate and monitor thrombosis in children
Limited vascular access	Delivery of intravenous therapy and monitoring of anticoagulant therapy more difficult
Drug formulations	All anticoagulants are "off label" in children and there are no specific pediatric preparations, making accurate dosing difficult
Dietary differences	Formula-fed versus breast-fed infants have vastly different responses to certain drugs (e.g., vitamin K antagonists)
Compliance	Age significantly affects ability to understand and cooperate with therapy
Parental supervision	Children in dysfunctional families present special management issues not seen in adults

The most common drug used is critically unwell children is unfractionated heparin. Of all currently available anticoagulants, it is the only intravenous preparation with short half-life and rapid onset and offset for which there is a known antidote. Low-molecular-weight heparins such as enoxaparin, tinzaparin, and dalteparin are all indicated for subcutaneous use in children. While there are many situations in which LMWH are advantageous, their long half-life and lack of reversibility with protamine usually make them poor anticoagulants for critically unwell children. Oral anticoagulation with coumarin derivatives such as warfarin are suitable for long-term anticoagulation, but the need for oral administration, slow onset of action, and long half-life make them unsuitable for acute anticoagulation of critically unwell children. There are a multitude of newer anticoagulants available for use in adults, and their use in children has been reviewed recently.[114] To date, the outcome of these newer drugs when used in children has been poor. The lack of antidote for most of them is an important limitation when considering their use in critically ill children. Thus until further research identifies an alternative anticoagulant that has the advantageous properties of UFH, UFH will remain the anticoagulant of choice in pediatric intensive care units.

Unfractionated Heparin in Children

UFH can be used as a first-line intervention to treat arterial and venous thromboses in infants and children. In addition, UFH also has numerous indications for primary thromboprophylaxis in infants and children, including cardiac angiography, artificial circuits (e.g., cardiopulmonary bypass, hemodialysis, extracorporeal membrane oxygenation), arterial cannulation, and venoocclusive disease prevention during bone marrow transplantation. The short half-life of UFH makes it the ideal antithrombotic agent for use in critically ill children who are at greater risk of bleeding complications but who nonetheless require antithrombotic therapy.[124]

Unfractionated heparin is a complex glycosaminoglycan capable of binding to many circulating proteins as well as to the vascular endothelium.[125-129] The anticoagulant effect of therapeutic doses of UFH is largely limited to its interaction with two naturally occurring anticoagulants: antithrombin and tissue factor pathway inhibitor. Antithrombin is a natural inhibitor of all serine proteases except factor VIIa and protein C, although the majority of its anticoagulant effect is mediated through thrombin and factor Xa.[130,131] Unfractionated heparin binding to AT occurs via a unique pentasaccharide sequence present in approximately one third of UFH molecules.[127,129] The UFH:AT complex produces a thousandfold increase in AT inhibition of coagulation protein activity compared to AT alone.[130,131] Following intravenous administration of UFH, TFPI release from the vascular endothelium increases in a dose- and concentration-dependent manner.[132] Unfractionated heparin is believed to increase the antithrombotic effect of TFPI by increasing its affinity for factor Xa by simultaneously binding to both proteins (Table 80-3).[134,135]

The monitoring of UFH therapy in the PICU is a major problem. For many indications, there is no clear therapeutic range, and certainly no clinical outcome data in pediatrics to support any particular therapeutic range. In addition, each of the monitoring tests available has significant limitations, particularly in children. Clearly, global measures of hemostasis such as the APTT will always be limited by confounding variables that affect results. Direct measurement of UFH's ability to inhibit specific coagulation proteins (e.g., factor Xa), while producing definitive values, only represents one component of UFH's inhibitory effect on in vivo coagulation. Protamine titration has been viewed as the gold standard with respect to the measurement of UFH; however, the lack of automation renders protamine titration less clinically practical. A summary of the available tests for monitoring UFH and their shortcomings in pediatrics is presented in Table 80-4.

The most important adverse effect from heparin therapy in children is bleeding. One cohort study reported bleeding in 1.5% (95% CI, 0.0% to 8.3%) of children treated with UFH for DVT/PE.[136] However, many children were treated with subtherapeutic doses of UFH (compared to the target APTT) in this study.[136] A more recent single-center cohort study reports a major bleeding rate of 24% in children in pediatric intensive care receiving UFH therapy.[137] Further studies are required to determine the true frequency of UFH-induced bleeding in optimally treated children. There are only three case reports of pediatric UFH-induced osteoporosis. In two of these, the patient received concurrent steroid therapy.[138-140] The third received high-dose intravenous UFH therapy for a prolonged period.[141] However, given the convincing relationship between UFH and osteoporosis in adults, clinicians should avoid long-term use of UFH in children when alternative anticoagulants are available. HIT has been discussed previously in this chapter.

Table 80–3 Factors in Children that Affect the Action of Unfractionated Heparin

UFH Factor	Age-Related Difference
UFH acts via AT mediated catabolism of thrombin and factor Xa	Reduced levels of AT [3,4,142] Reduced capacity to generate thrombin[10,11] Age-related difference in anti Xa/anti IIa activity[143]
UFH is bound to plasma proteins, which limits free active UFH	Alterations in plasma binding[144,145]
Endothelial release of TFPI	Age-related differences in amount of TFPI release for same amount of UFH[145]

When considering bleeding as an adverse effect of UFH, clinicians frequently view this complication as a consequence of trying to manage the balance between bleeding and clotting in critically ill children. However, in reality, one of the most common reasons for heparin-associated bleeding is due to accidental overdose of UFH. This often occurs in children who are receiving low-dose UFH flushing of vascular access devices, intended, for example, to be 50 units UFH/5 mL. Errors in vial selection and failure of bedside checking procedures result in 5000 units UFH/5 mL being injected, and in small infants this results in a massive overdose of UFH. While reports of such events rarely occur in the medical literature, and in fact there are no specific reports of this in the literature for over 20 years, the popular press is littered with reports of medicolegal activity and deaths of children due to such errors. A Google search of heparin overdose in children will highlight many recent incidents, many with fatal outcomes. Figure 80-3 summarizes the range of heparin preparations found in a typical PICU. It is not hard to see how such errors occur in busy units that operate 24 hours per day. Units should actively manage the choices of UFH preparations available to their staff to minimize the risk of confusion. Staff should be educated in the dangers of UFH, and encouraged to be vigilant at all times when administering a drug that consistently ranks in hospital lists of the drugs most commonly involved in medication errors.

Another adverse event from UFH only recently reported has been anaphylaxis, which in 2007-2008 accounted for over 80 deaths due to an unintended contaminant introduced in the manufacturing process. Again, while there is almost nothing in the medical literature describing these events, the FDA released a number of warning statements, and one impact of this has been changes to the labeling of UFH. The potential for contamination of drug products made from biological sources will always be real. An important mechanism to minimize this risk is to ensure that children only receive UFH when the risks are clearly outweighed by the benefits. UFH has been described as being ubiquitous in PICUs, and clinicians should actively minimize unnecessary exposure.

In summary, anticoagulation in children in PICU is common, and UFH is the most common agent currently utilized. While there remain many concerns about the potential adverse

Table 80–4 Assays Used in the Monitoring of UFH Therapy

Assay	Common Uses	Advantages	Disadvantages in Children
APTT F-Clot	Coagulation screening assay Therapeutic UFH monitoring	Low cost Easy to perform Widely available	Baseline APTT often prolonged in children Wide variability in reagent sensitivity to age-related differences Nonphysiologic measure of UFH effect No validation of therapeutic ranges in children
TCT F-Clot	Coagulation screening assay Therapeutic UFH monitoring (rarely)	Easy to perform	Patients previously exposed to topical thrombin may have antibodies causing prolongation of the clotting time Optimal concentration of thrombin used for the assay is unknown No validated reference range for UFH in children
ACT F-clot	CPB, extracorporeal circuits	Easy bedside whole blood test Extensive experience in most PICUs	Does not correlate with any specific measures of heparin activity Analyzer dependent
Anti-Xa F-Ch	Calibration of APTT reference ranges Therapeutic UFH monitoring	Direct measure of UFH inhibition of Xa Easy to perform	Not as widely available as APTT and costs significantly more Does not measure other mechanisms of UFH effect (e.g., Anti-IIa) and assumes constant ration of effect, which is not true in children Some kits have exogenous AT, others have dextran sulphate, both of which will introduce in vitro error in small children for different reasons
Protamine Titration Q	Not used clinically Used by reference laboratories	Only assay that directly measures UFH concentration Low cost	Not widely available Automated methods have not been validated for management of therapeutic UFH and manual methods labor intensive

F-Clot, Functional, clot-based assay; *F-Ch,* functional, chromogenic assay; *Q,* quantitative assay

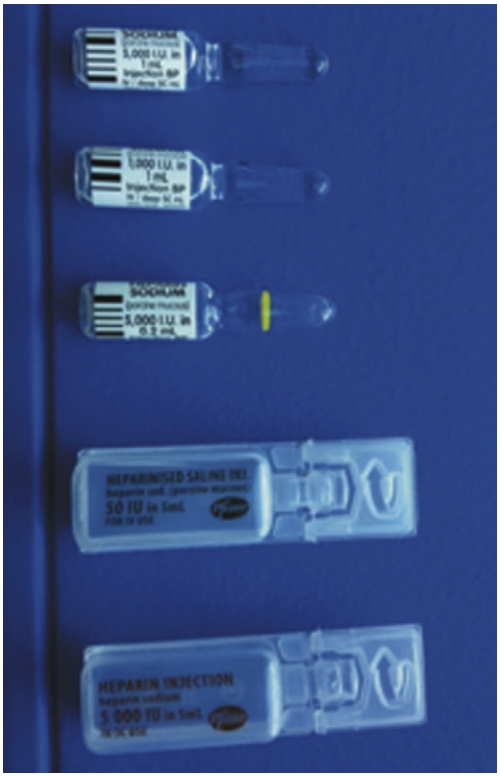

Figure 80–3. Preparations of UFH commonly found on an Australian pediatric ward. Note the minimal differences in packaging, and the significant differences in UFH concentration, such that there is potential for a 100-fold overdose should a selection error be made.

effects of UFH, there are currently no real alternative anticoagulant agents available for intravenous use in sick children. Many adverse events are related to dosing errors, and it is likely that PICUs can significantly improve the safety of UFH by developing systems to prevent medication errors. In addition, there is emerging evidence that our understanding of the pharmacokinetics of UFH in children and of the assays used to monitor UFH in children is far from ideal. Urgent research is required to improve the safety and utility of UFH in critically ill children.

Conclusions

Thromboembolic disease is now a major cause of mortality and morbidity in critically ill children, in the context of children having marked differences in the hemostatic system compared to adults, which appear to be age related. There remains much to be learned about the etiology and clinical presentations of thrombosis. Diagnostic strategies are mostly extrapolated from adult studies, but are likely suboptimal. Similarly, management strategies and the use of anticoagulants in children for either treatment or primary prophylaxis are guided by minimal evidence, and there is a desperate need for further research. In the meantime, clinical decisions must be made, and for the time being, these decisions require considerable consideration of the individual risk-benefit ratios for each individual patient.

References are available online at http://www.expertconsult.com.

Hematology and Oncology Problems in the Intensive Care Unit

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PEARLS

- Proactive treatment measures for tumor lysis syndrome include hydration with hypotonic or isotonic saline solution, alkalinization, use of allopurinol or urate oxidase, avoidance of exogenous potassium, close monitoring of fluid status, and frequent monitoring of serum potassium, sodium, chloride, bicarbonate, calcium, phosphorus, uric acid, blood urea nitrogen, and creatinine concentrations.
- Clinically significant hyperleukocytosis occurs with white blood cell count greater than 200,000/μL in acute myeloid leukemia and greater than 300,000/μL in acute lymphocytic leukemia.
- Concurrent thrombocytopenia and hyperleukocytosis increase risk of morbidity including intracranial hemorrhage and death. Aggressive therapy to correct coagulopathy with fresh-frozen plasma and vitamin K and to maintain platelet count greater than 20,000/μL is critical.
- Oxygen consumption may become delivery dependent when the hemoglobin concentration falls below 5g/dL or less.
- Signs of significant cardiovascular compromise may not become evident until the child has acutely lost at least 25% of total blood volume.
- Neutropenic patients have a decreased ability to manifest a coordinated proinflammatory and immunoregulatory response against infectious pathogens. Restoration of adequate intravascular volume and broad-spectrum antibiotic therapy are the most important therapeutic intervention for neutropenic patients in septic shock.
- In the absence of other hemorrhagic risks, platelet counts 10,000/μL and greater are associated with little risk of serious bleeding.
- Gastrointestinal bleeding is an important cause of morbidity and mortality in patients with end-stage renal disease.
- Intravenous administration of desmopressin acetate at a dosage of 0.3 μg/kg over 30 minutes improves platelet dysfunction caused by uremia within 1 hour, and the effect is maintained for 4 to 8 hours.
- Childhood mediastinal masses produce few symptoms until they have occluded a substantial portion of the cross sectional area of the trachea or main-stem bronchi or the superior vena cava. Diagnosis should be established with the least invasive means available, because these patients are at significant risk for anesthetic complications.
- Spinal cord compression most frequently occurs as metastatic disease and requires emergent treatment with 1 mg/kg of dexamethasone over 30 minutes.
- Hemophagocytic lymphohistiocytosis (HLH) produces severe illnesses that may be confused with other forms of systemic inflammatory response syndrome, such as sepsis. Appropriate diagnosis is tantamount as untreated HLH is almost always fatal.

A variety of hematologic and oncologic disorders may cause critical illness resulting in admission of a child to the intensive care unit (ICU). Hematologic abnormalities arising from other conditions or their treatment may pose a challenge to physicians caring for the critically ill child. This chapter addresses the more frequently encountered problems. Chapter 84, "Hemoglobinopathies," addresses the complications of sickle cell anemia. Chapter 83, "Critical Illness Involving Children with Hematopoietic Stem Cell Transplantation," addresses the complications related to hematopoietic stem cell transplantation.

Hematologic Emergencies

Anemia

Anemia results from a deficiency in the oxygen carrying capacity of the blood. The deficit may be in the number of red blood cells (RBCs), the RBC hemoglobin concentration, or both. Because hemoglobin serves as the primary transport molecule for oxygen, anemia may affect the delivery of oxygen (O_2) to the tissues with wide-ranging potential complications.

O_2 delivery is the product of cardiac output and arterial O_2 content (Cao_2). Hemoglobin concentration and the percentage of O_2-hemoglobin binding (% saturation) are the primary determinants of Cao_2. Oxygen dissolved in the plasma normally contributes a negligible amount to overall O_2 delivery. Cardiac output is a product of stroke volume and heart rate. Abnormalities in any of these parameters may impair tissue oxygenation.

Under steady-state conditions, oxygen consumption remains constant and is independent of oxygen delivery until it falls below a critical level, which varies for each organ system. When the hemoglobin concentration decreases to approximately 5 g/dL or less, oxygen delivery and consumption may be altered.[1] Below this level, O_2 consumption becomes delivery dependent.

The body responds to acute, normovolemic anemia by increasing cardiac output, through increases in stroke volume, heart rate, or both. As the hematocrit falls, blood viscosity diminishes, thus increasing venous return and augmenting preload. In the patient with chronic anemia, increases in cardiac output are supplemented by increased levels of 2,3-diphosphoglycerate shifting the oxyhemoglobin curve to the right and augmenting O_2 delivery at the tissue level.

Anemias generally are classified either by the mechanism resulting in the hemoglobin deficit—decreased production, accelerated destruction, or loss of erythrocytes—or by the morphologic appearance of the erythrocyte (Box 81-1).[2] Decreased RBC production may result from a variety of causes, including congenital defects, such as Fanconi anemia and Diamond-Blackfan anemia, or from postnatal causes, including acquired aplastic anemia, erythropoietin deficiency associated with renal disease, bone marrow suppression secondary to drugs or infectious agents, nutritional deficiencies, and bone marrow infiltration.

RBC loss may stem from enhanced destruction as seen with erythrocyte membrane defects, (e.g., hereditary spherocytosis); with deficits in RBC enzymes such as glucose 6-phosphate dehydrogenase; and with microangiopathic processes, including hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation (DIC). Antibody-mediated red cell destruction, whether autoimmune, alloimmune, or drug related, may result in profound anemia. Blood loss secondary to trauma, surgery, hemorrhage, or even frequent phlebotomy may also lead to severe anemia.

Morphologic classifications of anemia are based on either erythrocyte size, as defined by mean corpuscular volume and mean corpuscular hemoglobin concentration, or by abnormalities in the erythrocyte shape (Box 81-2).[2] The normal values for mean corpuscular volume and mean corpuscular hemoglobin concentration vary with the child's age. A wide variety of conditions, some intrinsic to the erythrocyte and others related to extrinsic factors, may result in abnormal RBC morphology.

The more common causes of profound anemia encountered in the pediatric intensive care setting are reviewed below. These causes include hemorrhagic anemia, decreased RBC production, and hemolytic anemia. Chapter 84, "Hemoglobinopathies," provides a discussion of sickle cell anemia, other hemoglobinopathies, and their complications.

Box 81–1 Physiologic Classification of Anemia

A. Disorders of Red Cell Production in Which the Rate of Red Cell Production Is Less than Expected for the Degree of Anemia

1. Marrow failure
   - a. Aplastic anemia
     - (i) Congenital
     - (ii) Acquired
   - b. Pure red cell aplasia
     - (i) Congenital
     - (ii) Diamond-Blackfan syndrome
     - (iii) Aase syndrome
     - (iv) Acquired
     - (v) Transient erythroblastopenia of childhood
     - (vi) Other
   - c. Marrow replacement
     - (i) Malignancies
     - (ii) Osteopetrosis
     - (iii) Myelofibrosis
     - (iv) Chronic renal disease
     - (v) Vitamin D deficiency
   - d. Pancreatic insufficiency-marrow hypoplasia syndrome
2. Impaired erythropoietin production
   - a. Chronic renal disease
   - b. Hypothyroidism, hypopituitarism
   - c. Chronic inflammation
   - d. Protein malnutrition
   - e. Hemoglobin mutants with decreased affinity for oxygen

B. Disorders of Erythroid Maturation and Ineffective Erythropoiesis

1. Abnormalities of cytoplasmic maturation
   - a. Iron deficiency
   - b. Thalassemia syndromes
   - c. Sideroblastic anemias
   - d. Lead poisoning
2. Abnormalities of nuclear maturation
   - a. Vitamin BI; deficiency
   - b. Folic acid deficiency
   - c. Thiamine-responsive megaloblastic anemia
   - d. Hereditary abnormalities in folate metabolism
   - e. Orotic aciduria
3. Primary dyserythropoietio anemias (types I, II, II, IV)
4. Erythropoietic protoporphyria
5. Refractory sideroblastic anemia with vacuolization of marrow precursors and pancreatic dysfunction deficiency

C. Hemolytic Anemias

1. Defects of hemoglobin
   - a. Structured mutants
   - b. Synthetic mutants (thalassemia syndromes)
2. Defects of the red cell membrane
3. Defects of red cell metabolism
4. Antibody mediated
5. Mechanical injury to the erythrocyte
6. Thermal injury to the erythrocyte
7. Oxidant-induced red cell injury
8. Infectious agent-induced red cell injury
9. Paroxysmal nocturnal hemoglobinuria
10. Plasma lipid-induced abnormalities of the red cell membrane

Box 81–2 Classification of Anemias Based on Red Cell Size

A. Microcytic Anemias
1. Iron deficiency (nutritional, chronic blood loss)
2. Chronic lead poisoning
3. Thalassemia syndromes
4. Sideroblastic anemias
5. Chronic inflammation
6. Some congenital hemolytic anemias with unstable hemoglobin

B. Macrocytic Anemias
1. With megaloblastic bone marrow
   a. Vitamin B_{12} deficiency
   b. Folic acid deficiency
   c. Hereditary orotic aciduria
   d. Thiamine-responsive anemia
2. Without megaloblastic bone marrow
   a. Aplastic anemia
   b. Diamond-Blackfan syndrome
   c. Hypothyroidism
   d. Liver disease
   e. Bone marrow infiltration
   f. Dyserythropoietic anemias

C. Normocytic Anemias
1. Congenital hemolytic anemias
   a. Hemoglobin mutants
   b. Red cell enzyme defects
   c. Disorders of the red cell membrane
2. Acquired hemolytic anemias
   a. Antibody mediated
   b. Microangiopathic hemolytic anemias
   c. Secondary to acute infections
3. Acute blood loss
4. Splenic pooling
5. Chronic renal disease (usually)

Hemorrhagic Anemia

Bleeding may be either acute or chronic. Chronic bleeding generally causes anemia through depletion of iron stores.[3] In response, patients adapt mechanisms to increase O_2 delivery and to avoid hypovolemia permitting them to tolerate hemoglobin levels well below the normal range, with mild clinical findings. Signs and symptoms of acute hemorrhage result from poor end-organ perfusion, with consequent diminished O_2 delivery. However, diagnosis of the presence and degree of blood loss may be difficult in an otherwise healthy child. Signs of impending shock, such as pallor, anxiety, and tachypnea, may be subtle.[4] Signs of significant cardiovascular compromise may not become evident until the child has lost at least 25% of total blood volume. Patients who have lost more than 25% of blood volume usually manifest age-related systolic hypotension.[4] Initial management should include achieving hemostasis, establishment of a secure airway, maintenance of ventilation, and initiation of volume replacement via an adequate intravenous catheter.[5] Either crystalloid or colloid solutions are effective in restoring circulating volume, but an important debate currently exists over appropriate fluids and timing of resuscitation in acute traumatic hemorrhage that is beyond the scope of this chapter.

RBC transfusion should be given if O_2 delivery to the end organ is impaired.[6] Either whole blood or packed RBCs can be used, but the former has many difficulties related to storage and transport. If packed RBCs or plasma-poor red cells are used to correct O_2-carrying capacity during massive blood loss, deficits of coagulation factors develop earlier than during transfusion of whole blood. Hypofibrinogenemia generally develops first, followed by deficits in other clotting factors and later by thrombocytopenia. Fresh-frozen plasma should be used to treat coagulopathy that develops during replacement of massive blood loss with RBCs. Transfusion of platelets should be guided by serial platelet counts.[7]

Central venous pressure should be monitored to allow for rapid administration of RBCs and volume replacement while decreasing the risks of hypervolemia. Blood and other fluids may be administered very rapidly until central venous pressure rises to between 6 and 7 mm Hg. Chapter 29 discusses the diagnosis and management of shock.

Anemia Secondary to Bone Marrow Failure

Several hematologic diseases are associated with diminished blood cell production. Acquired aplastic anemia, characterized by pancytopenia and hypocellular or acellular bone marrow, is defined by at least two of the three following: granulocytes less than 500/μL, platelets less than 20,000/μL, and anemia with a corrected reticulocyte count less than l%, in conjunction with markedly hypocellular bone marrow.[8] The majority of cases have no definable cause but the pathophysiology appears related to immune mediated with destruction of blood-forming cells by lymphocytes. Excessive production of interferon-γ, tumor necrosis factor, and interleukin-2 has been noted.[9] Altered immunity results in CD34 cell death and in intracellular pathways leading to cell cycle arrest.[10] A minority of cases follows chemical or drug exposure. Post-hepatitis aplastic anemia typically occurs in young males, with pancytopenia presenting several weeks after severe liver inflammation.[11] Serologic testing for known hepatitis viruses generally reveals no pathogen.[12]

Acquired aplastic anemia can be distinguished from bone marrow failure resulting from Fanconi anemia by specific assays for chromosomal susceptibility to chemical cross-linking agents that characterize Fanconi anemia.[13] Other constitutional syndromes may be suspected based on the presence of a pedigree of typical physical stigmata. Cytogenetic studies usually are normal in aplastic anemia, whereas aneuploidy or structural abnormalities are relatively common in myelodysplasia.[10] Myelodysplasia may evolve in patients treated for aplastic anemia. Some patients with paroxysmal nocturnal hemoglobinuria develop bone marrow failure; conversely, paroxysmal nocturnal hemoglobinuria may evolve years after aplastic anemia is diagnosed.[10] In paroxysmal nocturnal hemoglobinuria, flow cytometry shows a deficiency of CD59 on erythrocytes and leukocytes.

Irrespective of the etiology of bone marrow failure, life-threatening complications may arise from blood cytopenias. The most common causes of death are bacterial sepsis and fungal infection secondary to refractory granulocytopenia.[14] Broad-spectrum antibiotics should be used to treat suspected infection in the granulocytopenic patient. Historically, gram-negative organisms were the most frequent cause of fulminant

infection in this patient population. With the increased use of central venous catheters, gram-positive organisms now predominate.[15] Antifungal therapy should be instituted in patients who fail to defervesce within 3 to 5 days of treatment with antibiotics. Persistent, unexplained fever requires thorough evaluation to look for evidence of invasive fungal infection.

Platelet transfusions should be used judiciously in an effort to avoid alloimmunization to platelet antigens, generally being reserved for episodes of active bleeding. Similarly, RBC transfusions should be reserved for patients whose oxygen delivery may be compromised as a result of profound anemia. The patient should not receive blood products donated by family members to avoid sensitization to leukocyte and platelet antigens of potential bone marrow donors. All blood products should be irradiated and leukodepleted to decrease the risk of graft-versus-host disease.[15] Treatment of severe acquired aplastic anemia involves either the use of immunosuppressive therapy or replacement of bone marrow through stem cell transplantation. The patient and immediate family members should undergo human leukocyte antigen typing. The treatment of choice, bone marrow or peripheral blood stem cell transplantation from a histocompatible sibling, produces long-term survival rates of 75% to 80%.[16] Unfortunately, up to 70% of patients may lack a suitably matched sibling donor. Stem cells are harvested from matched unrelated donor, or umbilical cord blood, produce poorer outcomes because of the higher rate of graft-versus-host disease. For these patients, immunomodulation, which usually includes a combination of antithymocyte globulin, cyclosporin, and corticosteroids, often with use of hematopoietic growth factors, has resulted in response rates of 70% to 80%.[17,18] Not all responders achieve a complete remission, however; late relapses, as well as evolution to myelodysplasia and leukemia, are reported.[19]

Hemolytic Anemia

Hemolysis, the destruction of RBCs with liberation of hemoglobin, may occur either within the blood vessels (intravascular hemolysis) or the reticuloendothelial system (extravascular hemolysis). Anemia results when the rate of RBC destruction exceeds new RBC production in the bone marrow.[20] Laboratory findings in patients with hemolytic anemia usually include increased reticulocyte count and elevated serum concentrations of unconjugated bilirubin and lactate dehydrogenase. Intravascular hemolysis usually results in decreased serum haptoglobin concentrations.

Premature destruction of RBCs may result from intrinsic RBC abnormalities, such as hemoglobinopathies or red cell membrane defects, or from a variety of extrinsic factors (Figure 81-1).[2] Numerous hemoglobin variants resulting in shortened RBC survival have been identified. Individuals with sickling hemoglobinopathies may suffer a variety of complications that require treatment in an ICU (see Chapter 84). Abnormalities in the structure of the RBC membrane, as in hereditary spherocytosis, or decreased quantities of RBC enzymes, as in G6PD deficiency, also decrease red cell survival. Hemolysis in these settings occurs primarily extravascularly. Mechanical disruption of the red cell membrane secondary to factors extrinsic to the RBC may lead to macroangiopathic hemolytic anemia, as with turbulent flow around a prosthetic heart valve, or microangiopathic hemolytic anemia, caused by

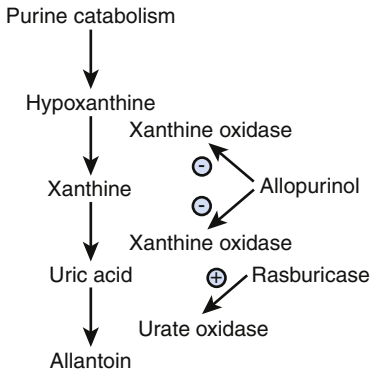

Figure 81–1. Causes of premature destruction of the red blood cell. *CU*, Copper; *DIC*, disseminated intravascular coagulation; *G6PD*, glucose 6-phosphate dehydrogenase; *HS*, hereditary spherocytosis; *PK,* pyruvate kinase; *PNH*, paroxysmal nocturnal hemoglobinuria.

fibrin deposition in the microvasculature. The latter process is seen in consumptive disorders, including DIC, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura.[21] In these entities, hemolysis is primarily intravascular. Schistocytes are characteristically seen on the blood smear.

The hemolytic processes that result from abnormal interactions between erythrocytes and the immune system are known collectively as autoimmune hemolytic anemia (AIHA).[2] AIHA can be classified as either primary, in which there is no identifiable systemic illness except possibly a history of a recent viral-like illness, or secondary, in which the hemolytic anemia is present in the context of another illness. AIHA has been reported as a manifestation of autoimmune disorders (e.g., lupus erythematosus), immunodeficiency disorders, malignancies, specific infections, or as a drug reaction (Box 81-3).[21] AIHA also may be classified by the thermal sensitivity of the autoantibodies. The most common form is the result of warm-reactive immunoglobulin (Ig) G autoantibodies directed against RBC membrane proteins. Extravascular hemolysis occurs, with sensitized erythrocytes cleared primarily in the spleen. Cold-agglutinin disease, the second most common form of AIHA, most frequently occurs with *Mycoplasma pneumoniae* infections, but it also is associated with other infectious agents, including Epstein-Barr virus, cytomegalovirus, and mumps virus. In this disorder, IgM autoantibody binds to the RBC and fixes complement. The erythrocytes may undergo intravascular hemolysis, or they may be cleared by the reticuloendothelial system, primarily in the liver. Paroxysmal cold hemoglobinuria, a rare variant of AIHA in which an IgG autoantibody binds at cold temperature to the P-antigen of the erythrocyte, fixing complement (the Donath-Landsteiner antibody) and producing intravascular hemolysis. It usually follows a viral illness.[21] Although drug-induced autoantibodies occur uncommonly in children, they may follow exposure to some antibiotics, including penicillins and cephalosporins.[22,23] Mechanisms of drug-induced hemolysis may include autoantibody formation and adsorption of the drug onto the red cell membrane, with immune complex formation with IgG or IgM.[24]

Patients with AIHA usually present with pallor, jaundice, and splenomegaly on physical examination. The reticulocyte count is generally elevated, although initially it may be low or normal. Spherocytes and polychromasia are present on the peripheral blood film, and nucleated RBCs are frequently seen.

Box 81–3 Classification of Autoimmune Hemolytic Anemia in Children

A. Primary AIHA*
1. Warm-reactive autoantibodies, usually IgG
2. Paroxysmal cold hemoglobinurla, usually IgG
3. Cold-agglutinin disease, usually IgM

B. Secondary AIHA†
1. Systemic autoimmune disease (e.g., lupus)
2. Malignancy (Hodgkin and non-Hodgkin lymphoma)
3. Immunodeficiency
4. Infection (*Mycoplasma*, viruses)
5. Drug induced

*Occurs in the majority of affected children and often follows a nonspecific viral-like syndrome, but in the absence of another systemic illness.
†Occurs in association with another systemic process.
AIHA, Autoimmune hemolytic anemia; *IgG*, immunoglobulin G.

RBC agglutination may be present in cold-reactive AIHA. The direct antiglobulin test (Coombs test) demonstrates the presence of antibodies or complement on the red cells. The indirect antiglobulin test measures the presence of unbound antierythrocyte antibodies in the patient's serum.

Therapy depends on the type of AIHA and the severity of clinical symptoms. Profound anemia, usually with a hemoglobin level of less than 5 g/dL, may result in cardiovascular compromise and requires erythrocyte transfusion to increase O_2-carrying capacity. The presence of autoantibodies often makes cross-matching blood difficult, and the patient may require transfusion with "least incompatible" blood.[25] Significant hemolytic transfusion reactions are infrequent.[25] However, severe hemolysis occurs on rare occasions, with hemoglobinemia and hemoglobinuria resulting in renal failure. Therefore transfusions should be started at a slow rate, and both plasma and urine samples should be checked regularly for free hemoglobin.[21] Patients with cold-reactive antibodies should be kept warm, and a blood warmer should be used for the transfused blood.[26] Even in the absence of transfusion, significant intravascular hemolysis may occur in patients with cold-reactive antibodies. Maintaining good renal blood flow and careful monitoring of urine output in this setting may help obviate renal injury.[27] Corticosteroids appear to slow the hemolytic process, particularly in patients with IgG autoantibodies, in whom they appear to inhibit Fc receptor-mediated clearance of sensitized erythrocytes.[28] The usual dosage is 1 to 2 mg/kg methylprednisolone given intravenously every 6 hours until the patient is clinically stable. The patient then can be switched to oral prednisone (2 mg/kg/day for 2 to 4 weeks, followed by a slow taper over 1 to 3 months).[21]

Corticosteroids may also be effective in cold agglutinin disease, although the response is less predictable.[29] High-dose intravenous γ-globulin (IVIG, 1 g/kg/day for 5 days), produces response in approximately one third of patients with warm-reactive disease.[30] Plasmapheresis and plasma exchange may be beneficial, particularly in patients with IgM autoantibodies.[31] The overall prognosis for children with AIHA is good. Cold-reactive AIHA generally resolves completely. Some patients with warm-reactive antibodies have a chronic course, marked by remissions and exacerbations.[21]

Thrombocytopenia

Thrombocytopenia may be secondary to either decreased platelet production or increased platelet destruction. Decreased platelet production may result from primary bone marrow failure states or from bone marrow infiltration by malignant cells as in leukemia, lymphoma, and metastatic solid tumors. Bone marrow suppression, a common side effect of antineoplastic therapy including both chemotherapy and radiotherapy, frequently leads to periods of thrombocytopenia. Thrombocytopenia or platelet dysfunction may result in bleeding, usually involving the skin and mucous membranes. Clinical manifestations include petechiae and purpura, epistaxis, gastrointestinal bleeding, hematuria, and menorrhagia. Intracranial hemorrhage is an infrequent manifestation of thrombocytopenia.

Indications for platelet transfusion in these settings vary with the underlying cause of thrombocytopenia and the patient's clinical status. Patients with primary bone marrow failure, who likely will experience prolonged thrombocytopenia, generally receive transfusions only for active bleeding because of the risk of alloimmunization. In addition, exposure to multiple platelet donors may jeopardize the success of bone marrow transplantation by increasing the risk of graft rejection.[32] In the absence of other hemorrhagic risks, platelet counts of 10,000/dL or greater usually carry little risk of bleeding.[33] The threshold for transfusion may need to be set higher in patients with sepsis, decreased humoral coagulants, or other risk factors. In the perioperative setting, platelet counts should be maintained at higher than 50,000/dL and greater than 100,000/dL for neurologic or ophthalmologic surgery.[34] Use of ABO-compatible donors and leukoreduction diminishes the risk of platelet alloimmunization.[33] Single-donor apheresis units reduce donor exposure compared with pooled platelet concentrates, but whether such usage reduces the incidence of platelet alloimmunization remains unclear.[35]

Immune Thrombocytopenia

Immune platelet destruction may be caused by autoantibodies, drug-dependent antibodies, or alloantibodies. Alloantibodies result from exposure to polymorphic epitopes expressed on foreign platelets to which the patient has been exposed (see previous section). Drug-induced thrombocytopenia may be suggested by the patient's medication history. Laboratory tests for specific drug-associated antiplatelet antibodies are available.

In immune thrombocytopenia purpura (ITP), autoantibodies to platelets may be associated with other autoimmune disorders or immune deficiency states, or after viral illness or immunization.[36] The incidence of childhood ITP was found to range from 5 to 7 per 100,000 per year, with 25% of the children subsequently developing chronic ITP.[37] Frequently, no predisposing condition is identified (idiopathic thrombocytopenia purpura). Regardless of cause, the reticuloendothelial system removes antibody-coated platelets, with the bulk of the destruction occurring in the spleen. These children typically present with petechiae, purpura, and bleeding from mucous membranes and isolated thrombocytopenia. The bone marrow responds with increased platelet production. The rapid turnover in platelets results in younger, somewhat larger, platelets entering the blood. Hence, serious bleeding rarely

occurs because of the increased effectiveness of platelets.[38] In a recent retrospective review, a low admission mean platelet volume value (<8 μL) and a history of viral prodrome were found to be independent prognostic variables that predicted durable remission.[39]

The primary goal of therapy in children with ITP is to limit bleeding especially from the central nervous system. Therapy does not appear to affect the natural history of the illness. There is no consensus regarding the management of acute ITP and the need for intervention in the absence of significant hemorrhage remains the subject of debate.[40] Intracranial hemorrhage remains rare, and there are no data that treatment actually reduces the incidence of intracranial hemorrhage. Therapy is directed at slowing clearance of sensitized thrombocytes in the spleen and reducing antibody production. Initial medical management usually involves the use of corticosteroids (prednisone 2 mg/kg/day) or IVIG (1 g/kg/day for 1 to 2 days).[41,42] High-dose methyl-prednisolone (30 mg/kg/day intravenously for 3 days) also is effective.[43,44] Bone marrow evaluation to rule out malignancy before corticosteroid therapy should occur. Infusion of anti-Rh(D) immunoglobulin (50 to 75 μg/kg) for individuals who have Rh(D)-positive RBCs prolongs survival of antibody-coated platelets in patients with ITP. As with IVIG, the major mechanism appears to include blockage of Fc receptors on reticuloendothelial cells.[45] Use of these agents usually halts bleeding and raises platelet counts to safe levels within a few days, although evidence indicating their influence on the course of the disease remains lacking.

Intracranial hemorrhage, the most devastating complication of ITP, although rare requires immediate intervention. Consequently, patients presenting with headaches, persistent vomiting, or neurologic symptoms require emergent computed tomography (CT) scan of the head. Therapy for intracranial hemorrhage usually includes, IVIG, corticosteroids, and emergency splenectomy.[46] Platelet transfusions in ITP rarely result in an increase in the platelet count because of rapid consumption of transfused platelets. Nevertheless, intermittent (2 to 4 IU/m^2 every 6 to 8 hours) or continuous (0.5 to 1 IU/m^2/hr) platelet transfusions have been administered for life-threatening hemorrhage, with decreases in bleeding reported.[47,48] Plasmapheresis may be beneficial in patients who do not respond to these interventions.[49] A splenectomy should be performed if a craniotomy is required, to maximize the perioperative platelet count.[47]

Nonimmune Thrombocytopenia

DIC occurs when generalized activation of the plasma coagulation pathways occurs within small blood vessels with formation of fibrin and depletion of circulating levels of humeral clotting factors and platelets. DIC usually follows a systemic insult, most often sepsis or shock. Treatment should be directed to the underlying cause. Hemorrhage frequently occurs at platelet counts greater than 10,000/μL because of concomitant depletion of clotting factors. Control of bleeding may necessitate platelet and plasma transfusions. DIC had been thought to be the etiology of much of the multiorgan system failure in ICU patients, with formation of a large number of microthrombotic foci leading to organ microcirculation failure and subsequent failure of the organ itself.[50] More recently, some studies have suggested that vascular endothelial damage induced by humeral mediators is the primary cause of thrombocytopenic multiorgan system failure.[51] In these instances, thrombocytopenia may be a marker of poor prognosis rather than a cause of ICU mortality.[52]

Increased platelet consumption with resultant thrombocytopenia occurs in diseases associated with extensive vascular endothelial damage, including hemolytic uremic syndrome and thrombotic thrombocytopenic purpura.[53,54] Aggregates of activated platelets become trapped in small blood vessels, causing a microangiopathic hemolytic anemia. Schistocytes usually are present on the peripheral blood film. Platelet transfusions should be given only for life-threatening bleeding because they may worsen the thrombotic process.[55]

Thrombocytopenia caused by splenic sequestration develops in individuals with massive splenomegaly. The etiology of splenomegaly includes infectious, infiltrative, neoplastic, obstructive, and hemolytic causes. The Kasabach-Merritt syndrome is an association of a giant hemangioma with localized intravascular coagulation causing thrombocytopenia and hypofibrinogenemia. Rare congenital thrombocytopenic syndromes include congenital amegakaryocytic thrombocytopenia, thrombocytopenia-absent radius and Wiskott-Aldrich syndrome.

Bleeding in Uremia

Hemorrhagic manifestations in patients with renal failure are characterized by purpura and bleeding from mucous membranes and puncture sites. Gastrointestinal bleeding may contribute to morbidity and mortality in patients with end-stage renal disease.[56] Concurrent hypertension increases the risk of subdural hematoma. The hemostatic defect in uremia is multifactorial, resulting in part from altered metabolism of platelets and vascular endothelial cells and from abnormal interactions between platelets and vascular endothelium.[57]

When uremia is present, clinical bleeding may be increased relative to the degree of thrombocytopenia resulting from secondary platelet dysfunction. Intravenous administration of desmopressin acetate (0.3 μg/kg over 30 minutes) improves platelet dysfunction caused by uremia within 1 hour with a duration of the effect for 4 to 8 hours.[58] Tachyphylaxis may occur after two to three doses. Intravenous conjugated estrogens or oral estrogens cause slower but more sustained improvements in bleeding time.[56] Dialysis results in improved platelet function through reduction of azotemia.

When severe anemia is present, platelets travel closer to the midstream and are less likely to interact with the vascular endothelium. In addition, RBCs exert metabolic effects on platelets by enhancing adenosine diphosphate and thromboxane A2 release. Therefore use of red cell transfusions or erythropoietin to increase the hematocrit to 30% helps to correct the bleeding time.[59] Further increase in hematocrit increases the risk of thrombosis, particularly of arteriovenous shunts and the extracorporeal hemodialysis circuit.

Oncologic Emergencies

Tumor Lysis Syndrome

As the name suggests, tumor lysis syndrome (TLS) results from the death of tumor cells resulting in the rapid extravasation of intracellular contents into the blood.[60] The release of intracellular contents may cause metabolic derangements and/or produce end-organ damage. Careful monitoring and

rigorous attention to organ function may help to obviate the majority of complications from this syndrome.

Although the lysis of malignant cells usually begins after the institution of chemotherapy, spontaneous TLS occurs.[61] Important considerations in TLS include the level of tumor burden and the sensitivity of the cells to the antitumor agents.[62] In children, hematologic malignancies such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) and Burkitt lymphoma provide the majority of cases of TLS.[63] TLS usually occurs with new-onset disease, preexisting renal dysfunction, when nephrotoxic drugs are used and with dehydration. Diagnosis of TLS generally requires some combination of hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia in the face of a tumor. Yet no definitive classification or grading system exists although some differentiate between laboratory and clinical TLS.[64] The value of the classifications that have been published has not been established.

Pathophysiology

Tumor cells possess normal or supranormal quantities of many intracellular contents that pour into the circulation on cell death.[60] Potassium is the primary intracellular cation but cells have abundant nucleic acids, inorganic phosphates, and proteins. The metabolism of nucleic acids results in the production of uric acid. With high tumor burden, the release of these chemical may overwhelm normal homeostatic mechanisms, threatening the patient with hyperkalemia, hyperphosphatemia, hyperuricemia, and end-organ damage.

Hyperkalemia can acutely threaten cardiovascular status by altering cardiac rhythm. Levels of potassium greater than 6.5 to 7 mmol/L may lead to widening of the QRS complex and peaked T waves that can progress to disorganized ventricular rhythms and severe cardiac dysfunction. Other symptoms include irritability, fatigue, muscle weakness and cramps, paresthesias, nausea, emesis, and diarrhea. Hyperkalemia must be addressed emergently.

In addition to potassium, tumor cells possess substantial quantities of phosphates, often much higher than nonmalignant cells, which bind avidly to calcium depleting serum calcium levels.[65] The resultant calcium phosphate may precipitate in the renal tubules. High levels of phosphate, which are often exacerbated by renal dysfunction, may produce fatigue, lethargy, weakness, nausea, and emesis. Hypocalcemia may also result in muscle cramps as well as tetany, seizures, and dysrhythmia. Counterintuitively, low levels of calcium must be addressed by treating the elevated phosphate rather than by administering intravenous calcium.

Uric acid, the final product of purine nucleotide metabolism, is excreted in the urine but has low solubility, especially in acidic urine.[66] Production of uric acid depends on the enzyme xanthine oxidase. High levels of uric acid may injure renal tubules especially in the context of dehydration and administration of nephrotoxic medications. Increasing serum uric acid levels have been associated with increasing risk for TLS.

Uremia may also occur in patients at risk for TLS either from TLS itself or from preexisting renal injury or a combination of these factors. In TLS, the most common cause of renal injury results from precipitation of uric acid crystals in the renal tubule but can be due to calcium phosphate or xanthine crystals, nephrotoxic drugs, tumor infiltration, or obstruction and infection.[65]

Therapy

The key concepts in therapy include hydration to assure adequate end-organ perfusion, especially of the renal vascular bed, and some hemodilution. Additionally, altering the production of uric acid and the use of ion binders/antagonists help to protect end organs.

Hyperkalemia is a medical emergency, especially when the level exceeds 6.5 to 7.0 mEq/dL. Therapy includes oral and/or rectal cation exchange resins, intravenous calcium (gluconate or chloride) to antagonize the action of K^+ on the cardiac myocyte, and sodium bicarbonate to correct acidosis and increase the gradient of K^+ into the cells. Insulin and glucose encourage the movement of K^+ into cells. Diuretic therapy or, in the face of renal dysfunction, dialysis may help the excretion of K^+.

Therapy to obviate complications of elevated uric acid includes alkalinization of the urine, which increases the solubility of uric acid, to limit or avoid precipitation of uric acid crystals in renal tubule. Allopurinol, a xanthine analogue, inhibits the conversion of xanthine and hypoxanthine to uric acid by competitively blocking the enzyme xanthine oxidase.[67,68] Allopurinol decreases the formation of uric acid and reduces the incidence obstructive uropathy caused by uric acid in patients at risk for TLS. Allopurinol cannot, however, lower elevated uric acid levels that may precede therapy. Also inhibition of xanthine oxidase may increase the levels of xanthine and hypoxanthine, the former of which may produce renal tubular damage. Furthermore, allopurinol blocks the metabolism of purine-based chemotherapeutic agents (azothiopurine, 6-mercaptopurine) employed in the treatment of leukemias, rendering these agents less effective.[69]

Elevated levels of uric acid represent a difficult problem beyond the reaches of allopurinol. Urate oxidase, a nonhuman proteolytic enzyme, cleaves uric acid to allantoins, which are highly soluble at urinary pH decreasing the risk of renal injury. Rasburicase, a recombinant form of the enzyme, has high costs but appears to be effective at lowering uric acid levels, decreasing serum creatinine and phosphorus levels, and preventing the need for dialysis, permitting early institution of chemotherapy.[70] The decreased need for dialysis and other ICU therapies appear to render Rasburicase, when used in the initial management of high-risk patients cost effective as well.[71] Rasburicase is contraindicated in patients with a known G6PD deficiency (certain patients of African-American, Mediterranean, or Southeast Asian descent) and in pregnant or lactating females.[70]

Elevated levels of serum phosphates result in an initial increase in urinary excretion and decreasing tubular reabsorption, but this mechanism has its limits. The ability to excrete phosphates will be impaired by renal injury. Hyperphosphatemia may result in precipitation of calcium phosphate crystallizes causing or worsening renal dysfunction. This crystallization appears to increase when the calcium-phosphate multiple exceeds 70 and when the urine has been alkalinized.

Hyperleukocytosis

Hyperleukocytosis, defined as a white blood cell (WBC) count greater than 100,000/μL, is seen in 5% to 20% of children diagnosed with leukemia, most often in patients with ALL.[73] Clinically significant hyperleukocytosis usually occurs with

WBC count greater than 200,000/μL in AML, greater than 300,000/μL in ALL, and greater than 600,000/μL in chronic myeloid leukemia.[74] Myeloblasts and monoblasts, which tend to be larger and more rigid than lymphoblasts and granulocytes, are more likely to obstruct vessels, even in smaller numbers. Other benign causes of hyperviscosity include leukemoid reaction, polycythemia vera, and accumulation of abnormal hemoglobin in sickle cell disease.

As WBC counts increase, the viscosity of the blood raises dependent both the leukocyte and erythrocyte volumes as well as the deformability of the cells.[75] Substantial increases in WBC counts produce aggregation of leukocytes which may obstruct small blood vessels.[75] Leukostasis results in local hypoxia as well as invasion of the blood vessels by leukemic cells, producing organ and vascular damage and/or hemorrhage. Leukemic cells adhere to the endothelium, a process mediated by cytokines interleukin-1 and tumor necrosis factor-α released by the blasts themselves, and then migrate into the perivascular space. The adhesion molecules expressed by leukemic blasts and their chemotactic response to cytokines may be as important as cell number in causing leukostasis.[68] This may explain the variability in clinical presentation among patients with a range of peripheral blast counts and why some patients but not others develop leukostasis.

Children with hyperleukocytosis have higher rates of mortality and morbidity including neurologic complications (intracranial hemorrhage), pulmonary leukostasis, and tumor lysis syndrome than other children with leukemia. The most dramatic concern includes intracranial parenchymal hemorrhage, which typically is limited to the white matter, centered at intravascular microscopic leukemic nodules. Symptoms may include headache, mental status changes, seizures, or visual disturbance. Respiratory symptoms found with pulmonary leukostasis may include hypoxemia, respiratory failure, and adult respiratory distress syndrome. Arterial measurement of oxygenation should be promptly obtained rather than relying on pulse oximetry because elevated met-hemoglobin concentration may be present.[71] Chest radiograph findings of pulmonary leukostasis may be normal or reveal diffuse interstitial infiltrates. Immediate cytoreduction is indicated when excessive O_2 metabolism of leukocytes causes tissue hypoxemia. Elevated serum lactate levels have been described as an early sign of microcirculatory failure.[72]

Children with AML and hyperleukocytosis have a higher risk of early morbidity and mortality than patients with non-hyperleukocytotic AML or with ALL and hyperleukocytosis, but the true incidence of these complications is not well elucidated.[76] Central nervous system hemorrhage with high WBC counts occurs in 5% to 33% of patients with AML and hyperleukocytosis, usually correlating with the degree of hyperleukocytosis.[75] Complications of leukostasis in ALL patients commonly occur when WBC counts exceed 400×10^9/L and at presentation.[75] The frequency of CHS hemorrhage appears to be much lower in patients with ALL and hyperleukocytosis. In one study, nearly half of children with AML and WBC of 100×10^9/L or greater developed complication before or during the first 14 days after initiation of chemotherapy.

Therapy for hyperleukocytosis has not undergone rigorous analysis. Diuretic therapy and packed red cell transfusion both increase viscosity and are best avoided. Concurrent thrombocytopenia and hyperleukocytosis increase risk of death from bleeding complications. Aggressive therapy with fresh frozen plasma and vitamin K to correct coagulopathy and maintenance of platelet count greater than 20,000/μL are critical.[73] Hydration, alkalinization, and allopurinol have been used in patients with WBC counts higher than 100,000/μL.[74] More aggressive therapies must be considered for symptomatic patients, those with laboratory evidence of hypoxia or ischemia, or in certain patients depending on malignancy type and WBC. Both exchange transfusion and leukapheresis can be used to rapidly lower WBC. No randomized trials of cytoreduction have been performed, and although a reduced incidence of electrolyte abnormalities has been shown, no improvement in pulmonary status, central nervous system outcome, or mortality has been demonstrated.[77] Complications of leukapheresis include difficulty with vascular access, rapid rebound of WBC count, and need for anticoagulation. Cytoreduction by leukapheresis, exchange transfusion, or other methods may modulate cell-cycle distribution and nucleoside transporters in leukemic cells by increasing the fraction of the S-phase. No beneficial role has been demonstrated for use of steroids or emergency cranial radiation.[75] After leukapheresis, the blast counts often rebound rapidly unless cytoreductive medications are initiated.

Spinal Cord Compression

Compression of the spinal cord by malignancy occurs uncommonly but still represents an important cause of morbidity in children, affecting between 2.7% to 5% of children with cancer. Most frequently, compression occurs as metastatic disease spread rather than primary spinal cord tumors themselves. Ewing sarcoma, neuroblastoma, and primitive neuroectodermal tumors appear to be the most frequent diagnoses although compression may be found with Hodgkin lymphoma, nephroblastoma, and germ cell tumors.[76,78]

Most cord compression results from epidural compression due to extension of paravertebral tumor through the intervertebral foramina, or, less commonly, extension of the tumor in the vertebral column. Compression of the vertebral venous plexus by epidural tumor causes vasogenic cord ischemia, edema, venous hemorrhage, and myelin loss.[79] The spinal cord compression usually localizes to the dorsal and lumbosacral regions (42% each). Patients frequently develop back pain, motor dysfunction, sphincter abnormalities, and alteration in sensation. Such findings represent harbingers of potential permanent loss of neurologic function, necessitating emergent evaluation including magnetic resonance imaging.

Confirmation of tumor compression of the spinal cord requires emergent medical action. A history of progressive spinal cord dysfunction and focal deficit or percussion tenderness of the spine requires 1 mg/kg dexamethasone intravenously over 30 minutes. Treatment of a cord-compressing lesion next mandates a decision between immediate surgical decompression, radiation therapy, or chemotherapy. This decision is influenced by a number of factors, including presence of a histologic diagnosis, likelihood of response to chemotherapy or radiotherapy, as well as degree and rate of progression of neurologic deficit. Although controversy exists, decompressive laminectomy is indicated for tumors without a diagnosis, patients with small cell tumors with very rapid neurologic deterioration or complete loss of motor function, and sarcoma, with the exception of osteogenic sarcoma.[76] However, laminectomy in children often leads to scoliosis,

kyphosis, and anterior subluxation. Consequently, the decision must be made with this issue in mind as laminectomy patients often require subsequent treatment for orthopedic sequelae.[81] Among children with complete sensory and motor loss below the level of spinal cord compression, 30% to 60% of treated children experience neurologic recovery.[76,78,82]

Acute Airway Compromise in Anterior Mediastinal Tumors

Superior Vena Cava Syndrome

Childhood mediastinal masses pose difficult diagnostic and therapeutic challenges. Such masses often produce few symptoms until they have occluded a substantial portion of the trachea or main-stem bronchi or the superior vena cava. Complete airway occlusion in these children represents a potentially fatal complication the risk of which increases at the time of sedation for diagnostic procedures. An estimated 9% to 15% of pediatric patients with anterior mediastinal masses and airway obstruction have been reported to develop life-threatening complications with anesthesia.[83-85] Over the past two decades, increased awareness of the potential for airway or cardiovascular collapse in pediatric patients with anterior mediastinal masses has led to improved management. Major airway complications are now more likely to occur in the postanesthetic care.[86] Superior vena cava syndrome, left atrial compression, and pericardial effusion may lead to a state of fixed cardiac output.

Mediastinal masses are classified by their anatomical compartment and anterior mediastinal masses represent 46% of all such masses in children.[87] The most common tumors found in the anterior mediastinal compartment include hematological malignancies: T-cell lymphoblastic leukemia, Hodgkin disease, and T-cell lymphoblastic non-Hodgkin lymphoma.[88-90] Children with anterior mediastinal mass often present with nonspecific findings including orthopnea, dyspnea, cough, pleural effusion, wheezing, superior vena cava (SVC) syndrome, pain, and stridor.[90-92] Mediastinal masses are far more common in older children and teenagers than in children younger than 5 years. Barking cough and stridor in an older child or teenager rarely occurs with croup and therefore needs further investigation

Important risk factors for airway compromise include computed tomography findings of more than 50% decrease in across-sectional area of the trachea, peak expiratory flow less than 50% of predicted value, anterior mediastinal mass, tracheal compression, main-stem bronchus compression, larger median mediastinal mass ratio, lymphoma, vena cava syndrome, pericardial effusion, pleural effusion, history of recurrent chest infections, stridor, orthopnea, cough, wheeze, and shortness of breath.[83,84,91,93] The predictive value of these risk factors remains controversial, however. Unfortunately, compression at the level of the carina or bronchi may contribute appreciably to respiratory compromise, even in patients with a cross-sectional area above 50% of predicted.[90] A computed tomography scan will provide evidence of airway compression at a tracheal and/or bronchial level as well as the existence of exacerbating factors such as pleural effusion that may limit a patient's physiological reserve.

The preoperative evaluation of patients with critical airway from compression by an anterior mediastinal mass should include an experienced multidisciplinary pediatric team of oncologist, anesthesiologist, interventional radiologist, surgeon, and intensivist.[83,91] Computed tomography provides the most useful, rapid test for airway compromise. Unfortunately, severe or rapid progressive symptoms may preclude lying supine for the scan. In such, cases diagnostic procedures under local anesthesia with ultrasound guidance or commencement of therapy before a cellular diagnosis may be required. Such use of empirical treatment can distort the histopathological appearance, hinder the making of a correct diagnosis, and lead to inappropriate treatment although in one study an accurate diagnosis was made in 95% of patients receiving steroids.[88] Bone marrow or lymph node biopsy and pleural fluid analysis may be helpful in patients who are not unstable. Complete blood count and α-fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase levels should be obtained. Image-guided needle biopsy performed under local anesthesia for mediastinal mass or lymph node by skilled interventional radiologist remains the diagnostic test of choice.[90]

SVC syndrome encompasses the signs and symptoms related to compression or obstruction of the SVC, which in childhood most commonly results from anterior mediastinal mass, middle mediastinal lymph nodes, or occlusion of the SVC itself.[94] SVC obstruction may be accompanied by compression of other mediastinal structures, large airways, pulmonary vessels, and aorta. SVC syndrome is most often caused by lymphoid malignancy, including non-Hodgkin lymphoma, acute lymphocytic leukemia, and Hodgkin disease. In addition to malignancies, indwelling catheters, previous cardiac surgery, previous extracorporeal life support.[95] right-sided congenital diaphragmatic hernia,[96] and ventriculoperitoneal shunts are other causes of SVC syndrome in pediatric patients.

In children, respiratory symptoms usually predominate; air hunger, dyspnea, wheezing, and anxiety occur, particularly with position change. The gradual development of SVC syndrome may manifest with periorbital edema, conjunctival suffusion, facial swelling, dizziness, syncope, and cough. SVC syndrome may occur in conjunction with spinal cord compression (Rubin syndrome), where significant venous obstruction usually develops before the spinal cord compression. Patients with SVC syndrome and back pain should be evaluated with magnetic resonance imaging of the vertebral spine when their condition is stable.

Evaluation of anterior mediastinal mass is described previously. As in airway compression, SVC syndrome places a patient at significant risk for anesthetic complications during diagnostic procedures. CT should be pursued without sedation and may require prone positioning because compression of the great vessels may occur despite a patent airway, resulting in profound hypoxia and reduced cardiac output. In addition, echocardiography can evaluate cardiac motility and the degree of venous return. In one study, 16% of children with anterior mediastinal masses and SVC syndrome developed potentially life-threatening airway compromise, although all survived without sequelae. Seven percent required chemotherapy or radiotherapy before successful extubation. The authors conclude that general anesthesia should be performed only when spontaneous ventilation can be preserved.

Diagnosis should be established with the least invasive means available, with empiric anticancer therapy required if no histologic sample can be obtained safely. Tissue for definitive diagnosis should be obtained as soon as the patient's

clinical status allows to decrease the likelihood that empiric therapy will permanently obscure the diagnosis.

Septic Shock in Pediatric Oncologic Patients

Septic shock poses a grave threat to immunocompromised children. The need for early diagnosis and rapid, thorough treatment cannot be exaggerated.[97-99] In childhood cancer patients, shock most commonly occurs with bacterial sepsis but distributive shock may also occur in the context of an addisonian crisis among children who have received high dose steroid therapy in the prior 6 months.

Risk factors for sepsis in pediatric cancer and hematopoietic stem cell transplant patients include neutropenia, impaired mucosal barriers, preexisting end-organ failure, and graft-versus-host disease. Neutropenic patients have a decreased ability to manifest a coordinated proinflammatory and immunoregulatory host response against infectious pathogens. Prolonged neutropenia worsens infectious complications and mortality rates.[100]

Clinically children may present without fever, particularly those with neutropenia or receiving corticosteroids. Cardiovascular insufficiency may result in tachycardia, decreased blood pressure and altered pulse pressure, signs of poor perfusion, and signs of respiratory insufficiency (e.g., respiratory distress, increased work of breathing). Other signs of inadequate end-organ perfusion include altered level of consciousness, diminished urine output, and lactic acidosis. Blood cultures should be obtained from all lumens of vascular catheters without impeding treatment. Other cultures should be obtained based on clinical suspicion. A chest radiograph should be obtained in all patients. The presence of pulmonary infiltrates should prompt consideration of a computed tomography scan and/or bronchoscopy for microbiologic diagnosis.

Early goal-directed fluid resuscitation has been shown to improve outcome in children and adults with severe sepsis and septic shock.[97,99,101] Restoration of adequate intravascular volume improves tissue oxygen delivery and attenuates the inflammatory response. Inaccuracy in assessing shock state severity and delay of adequate fluid resuscitation increases mortality. Surviving Sepsis Campaign guidelines recommend that intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis[102] because this may be the most important therapeutic intervention for patients in septic shock.[98] Chest radiograph infiltrates should prompt coverage for community-acquired pneumonia and possible invasive fungal infections. Progression to multiple organ failure may necessitate more complex therapies including granulocyte-colony stimulating factor, mechanical ventilation, inotropic support, and renal replacement therapy.

Pediatric ICU mortality of septic shock in pediatric oncologic patients ranges from 38% to 77%,[103-107] affected by a number of factors including diagnosis, numbers of failed organs, and need for nonhematologic organ support.[103,104] Fiser et al.[108] reported in a recent large retrospective review of severe sepsis in pediatric oncology patients a 30% mortality for pediatric hematopoietic stem cell transplant patients and 12% mortality for non–hematopoietic stem cell transplant patients. But pediatric ICU mortality reached 64% when those patients required mechanical ventilation and inotropic support. Fungal pathogens were responsible for 63% of pediatric ICU mortality.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) describes a syndrome of conditions rather than a specific disease entity that is marked by hyperinflammation resulting from riotously elevated circulating cytokines.[109] HLH represents an emergency because it shares many clinical features with the severe inflammatory response syndrome (SIRS) or sepsis syndrome rendering diagnosis difficult but it requires a much different treatment algorithm.[110] Inadequately treated HLH results in very poor outcome; indeed, HLH has been seen in a variety of clinical scenarios, including inherited defects as well as acquired conditions.[111]

HLH arises because of defects, acquired or inherited, in cytotoxic activity, which diminishes elimination of cellular targets and impairs downregulation of the immune response.[109] All HLH defects appear to arise from abnormalities involving the process by which cytotoxic vesicles migrate to contact site of the target cell, attach, fuse, and release their contents. Familial HLH results from inherited abnormities in one of three protein involved in the activity of cytotoxic vesicles.[109] Perforin, a cytotoxic protein stored in secretory granules of cytotoxic cells, acts as an effector molecule for the cytotoxic function of natural killer cells and CD8+ cytotoxic lymphocytes as well as contributing to lymphocyte homeostasis. MUNC 13-4 has a crucial role in cytolytic granules. The final mutation discovered thus far is in the syntaxin-11 believed to be involved in cytotoxic granule release or trafficking. In addition to these syndromes, several immune deficiency syndromes (Chediak-Higashi syndrome, Griscelli syndrome and X-linked lymphoproliferative syndrome) place patients at risk for HLH.[109,112,113]

HLH may be acquired under a variety of circumstances, but the mechanism of impairment of natural killer cells and cytotoxic lymphocytes in secondary HLH remains unclear but occurs in all age groups.[109] These defects occur more commonly than genetic HLH but incidence data are lacking. Secondary HLH appear to be caused most frequently by infections, autoimmune disease, and malignant diseases. Less common causes include Kawasaki disease, metabolic disease such as lysinuria protein intolerance, multiple sulfatase and Wolman's disease. Macrophage activation syndrome, first described in 1985, appears to be a special form of HLH occurring in patients with underlying autoimmune disorders, most commonly rheumatoid arthritis.[114]

Patients typically present with signs and symptoms of systemic infection or SIRS including prolonged fever (usually unresponsive to antibiotics), hepatosplenomegaly, and cytopenias.[109] Because HLH often mimics other conditions, a high index of suspicion remains paramount. Fortunately, diagnostic guidelines exist (Box 81-4), but again must be considered because of the substantial overlap with other severe sepsis, SIRS, and multiple organ dysfunction syndrome. In some patients, neurologic symptoms, seizures, and cranial nerve palsies may occur.

Laboratory study often aids in diagnosis but may not be obtained routine in patients who may have provisional diagnoses such as sepsis syndrome. Diagnostic criteria require a ferritin level higher than 500 ng/mL, but the levels are usually much higher, exceeding 10,000, unlike in sepsis where

Box 81–4 Diagnostic Criteria for HLH

A. Familial Disease/Known Genetic Defect

B. Clinical and Laboratory Criteria (5 of 8 Criteria)

1. Fever
2. Splenomegaly
3. Cytopenia ≥2 cell lines
4. Hemoglobin <90 g/L (below 4 weeks <120 μg/L)
5. Platelets $<100 \times 10^9$/L
6. Neutrophils $<1 \times 10^9$/L
7. Hypertriglyceridemia and/or hypofibrinogenemia
   a. Fasting triglycerides >3 mmol/L
   b. Fibrinogen <1.5 g/L
8. Ferritin >500 lg/L
9. sCD25 = >2400 U/mL
10. Decreased or absent natural killer cell activity
11. Hemophagocytosis in bone marrow, CSF or lymphnodes

serum ferritin is elevated but appears to be generally below 2000. Serum triglycerides are elevated. Soluble interleukin-2 receptor (sCD 25) soluble FAS (CD178) are elevated. Hemophagocytosis may be absent early in the disease and can also be missed on bone marrow aspiration.

Treatment depends on whether HLH is primary or secondary. Initial treatment is meant to suppress hyperinflammation using immunosuppressive and cytostatic treatment with corticosteroids, cyclosporine A, or etoposide.[109] Identification of infection should prompt immediate treatment. Unfortunately, in cases of HLH appropriate antimicrobial therapy does not usually alter the hyperinflammation. Patients with primary HLH or underlying immune deficiency may require stem cell transplantation. Evidence of macrophage activation syndrome should prompt rheumatologic consultation.[114]

Anthracycline-Induced Cardiogenic Shock

The anthracyclines daunorubicin, doxorubicin, epirubicin, and idarubicin are used for a wide variety of solid tumor and hematopoietic malignancies of childhood.[115-117] Unfortunately, 15% of all pediatric cardiomyopathies occur in patients treated for childhood or adolescent malignancies.[118] In one prospective study, after anthracycline treatment, 5% of the children developed heart failure and 19% presented abnormal left ventricular function.[119] Shortening fractions declined proportionately to cumulative dose. Furthermore, differential susceptibility to cardiotoxicity became apparent early in treatment. Hence, patients at high risk of risk of important anthracycline cardiotoxicity may be identifiable early in treatment by regular echocardiography. Pediatric age and female gender are known risk factors for anthracycline cardiotoxicity.[120,121]

Anthracycline-induced acute myocardial injury is a rare form of cardiotoxicity that may occur immediately after a single dose or after a course of anthracycline therapy, with clinical symptoms usually occurring within a week of treatment.[115,116,122-124] Acute cardiotoxicity ranges from relatively benign arrhythmias to serious conditions such as fatal ventricular arrhythmias, myocardial ischemia/infarction, congestive heart failure, and cardiomyopathy.[122,123,125]

The pathophysiology of anthracycline-induced cardiotoxicity may include free-radical–mediated myocyte damage, adrenergic dysfunction, intracellular calcium overload, and release of cardiotoxic cytokines.[121,126] The myocardium appears susceptible to free radical damage from low levels of superoxide dismutase, catalase, and glutathione peroxidase activity.[127] Cardiac mitochondria contain a unique enzyme (reduced nicotinamide adenine dinucleotide dehydrogenase) in their inner membrane that reduces anthracyclines to their semiquinones, producing severe oxidative damage to mitochondrial DNA, reductions in cellular energy production and myocyte apoptosis.

Prevention of cardiotoxicity remains the ultimate goal. There is evidence that dexrazoxane reduces the cardiotoxicity associated with some anthracyclines without affecting the efficacy of anthracycline therapy.[128] The antioxidant CoQ10 is an integral component of the mitochondrial respiratory chain and has successfully been used in the treatment of cardiac failure.[129]

The outcome of anthracycline-induced cardiogenic shock during chemotherapy remains poor. The myocardium has limited regeneration ability.[117] The mortality rate related to anthracycline-associated heart failure is substantial; heart transplantation is often the only option for long-term survival.[115] Supportive treatment including mechanical support (e.g., extracorporeal life support or ventricular assist devices) may stabilize patients while decisions about longer-term care can be made.[116,129-132]

References are available online at http://www.expertconsult.com.

V

Chapter 82

Transfusion Medicine

Jacques Lacroix, Marisa Tucci, Alan Tinmouth, France Gauvin, and Oliver Karam

PEARLS

- The decision to prescribe the transfusion of any blood product must be based on individualized indications and must take into account specific health problems.
- Acute severe anemia (hemoglobin concentration <5 g/dL) can lead to death in some severely ill patients.
- There is no evidence that a red cell transfusion is beneficial in stable critically ill children if their hemoglobin concentration is greater than 7.0 g/dL. A hemoglobin concentration of 7.0 g/dL or higher may be required in unstable critically ill children and in pediatric intensive care patients with heart disease, particularly those with cyanotic heart disease, but the best threshold is unknown.
- Plasma can be useful to treat multiple coagulation factors deficiencies. It should not be used as a volume expander.
- Platelets can be useful to treat bleeding caused by low platelet counts and/or platelet dysfunction.
- In pediatric intensive care units, most transfusion-related adverse events are linked to immuno-mediated effects of blood products rather than to transfusion-transmitted infectious diseases.

In this chapter, the authors will review the rationale for the transfusion of red blood cells (RBC), plasma, and platelets in pediatric intensive care units (PICU). In addition transfusion reactions are discussed at the end of the chapter.

Red Blood Cells

RBCs contain hemoglobin (Hb), which binds and carries oxygen (O_2) to cells, thus facilitating efficient adenosine triphosphate (ATP) production via cellular respiration. Because energy expenditure is high in critically ill patients, it would seem rational to maintain their Hb level in the normal range. Anemia is observed in 74% of critically ill children.[1] RBC transfusion is the only effective way to rapidly increase the Hb level. However, the safety of RBC transfusion has been questioned in recent years. Infections transmitted by blood products were the most important concern in the 1980s. In the 1990s, nosocomial infections and multiple organ dysfunction syndrome (MODS) observed in critically ill adults who received an RBC transfusion have become a cause of concern.[2] Also transfusion-related immune modulation (TRIM),[3] and transfusion reactions like transfusion-related acute lung injury (TRALI) and transfusion-associated cardiac overload (TACO)[4] have become significant concerns. There are few data on these adverse events in PICU. Actually, the impact of RBC transfusion on risk/benefit and the cost/benefit ratios among critically ill children is not well characterized.

In the following sections, the authors will discuss anemia and O_2 delivery (DO_2), review evidence on the effectiveness and usefulness of RBC transfusion in the intensive care setting, and discuss the recommendations found in guidelines on RBC transfusion in critically ill children.

Red Blood Cell Transfusion: Why and Why Not

Anemia and O_2 Delivery

O_2 Delivery in the Critically Ill. Anemia decreases the capacity of blood to deliver oxygen because of lower hemoglobin content. Global DO_2 is dependent on cardiac output and the arterial concentration of O_2 (CaO_2): DO_2 = cardiac output (stroke volume × heart rate) × CaO_2. Arterial concentration of O_2 (CaO_2) is defined by the formula:

$$CaO_2(\text{mL } O_2 / 100 \text{ mL}) = (\text{Hb} \times SaO_2 \times 1.34) + (0.003 \times PaO_2)$$

In this formula, the Hb level is expressed in grams per deciliter, arterial O_2 saturation (SaO_2) is expressed as a fraction rather than a percentage, and PaO_2 is expressed in mm Hg or torr. Because global DO_2 is directly linked to the Hb concentration, the most rapid and effective way of increasing DO_2 (within minutes) is by increasing the Hb concentration, and this represents the most common rationale underlying RBC transfusion in critically ill patients. More modest augmentation in global DO_2 can be attained by increasing cardiac output and/or SaO_2. Indeed, a prospective study conducted in 2005 involving 30 North American PICUs showed that about 50% of critically ill children received at least one transfusion of packed RBC unit during their PICU stay.[1]

Adequate O_2 delivery to cells does not imply necessarily that O_2 consumption (VO_2) is adequate, and that cells produce enough energy. The formula used to calculate global VO_2 is:

$$VO_2 = (CaO_2 - CmvO_2) \times \text{Cardiac output}$$

in which $CmvO_2$ is the mixed venous O_2 concentration. VO_2 depends on substrate availability and on metabolic demands; it can be amplified by increasing cellular O_2 extraction rate (O_2ER), or by increasing DO_2 if there is VO_2/DO_2 dependence (Figure 82-1).

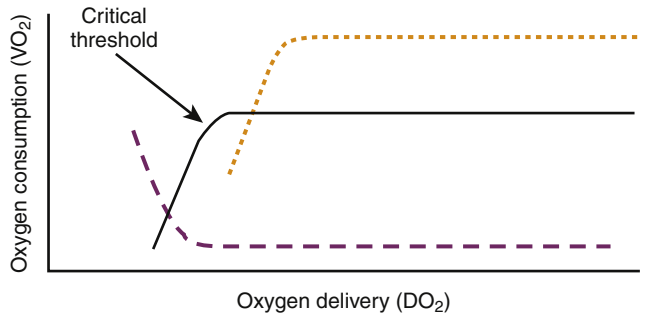

Figure 82–1. This figure illustrates the relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2) in normal patients (black full line), of DO_2 and blood lactate level in normal patients (blue dashed line), and of DO_2 and VO_2 in critically ill patients with sepsis (red dotted line). Under the "critical threshold" marked by an arrow, VO_2 and blood lactate level diminishes if DO_2 decreases. Over this threshold, a fall in DO_2 does not cause a drop in VO_2 because it is compensated by an increase in oxygen extraction rate. In critically ill patients, the VO_2 is frequently higher than normal and the DO_2/VO_2 curve is shifted upwards to the right (red dotted line).

The relationship between O_2 delivery and consumption is characterized by two phases: a directly linear relationship between VO_2 and DO_2 up to a "critical threshold" (often referred to as the critical DO_2), and a flat section above this threshold (see Figure 82-1). Below the threshold, VO_2 diminishes if DO_2 decreases. Above this threshold, a fall in DO_2 does not cause a drop in VO_2 because it is compensated by mechanisms such as an increase in O_2ER; these mechanisms are limited though, which explains why there is a critical threshold of DO_2 under which O_2ER cannot increase any further, and under which VO_2 begins to fall.

The stress of critical illness increases metabolic rate and VO_2, and shifts the critical level of DO_2 to the right and up. Moreover, the compensatory mechanisms are limited. Thus, the critically ill patient rapidly finds himself or herself in a situation in which O_2ER can increase no further and in which other adaptive mechanisms are maximal, thus resulting in a situation where a higher DO_2 is critical to allow for energy requirements to be met.

Adaptive Mechanisms to Anemia

Anemia significantly decreases blood O_2 carrying capacity. However, in the normal host, the amount of O_2 delivered to tissues exceeds resting O_2 requirements by a two- to fourfold factor.[5] When the Hb concentration falls below 10 g/dL, several adaptive processes maintain VO_2. These processes include (1) increased O_2ER; (2) increased heart rate and stroke volume, which increase cardiac output; (3) redistribution of blood flow from nonvital organs toward the heart and brain, at the expense of O_2 delivery to less vital vascular beds, such as the splanchnic vasculature; and (4) rightward shift of the oxy-Hb-dissociation curve, which decreases affinity between Hb and O_2, thereby increasing the amount of O_2 released to cells.

Increasing O_2ER is an important way to adapt to anemia. The upper range of normal O_2ER is 30%; O_2ER increases if O_2 requirements are not met. Higher O_2ER is frequently observed in severely ill patients, which translates into low $SmvO_2$ and $ScvO_2$ (central venous O_2 saturation). When maximal O_2ER is attained and other adaptive mechanisms are overwhelmed, VO_2/DO_2 dependence appears and may result in O_2 debt, with is associated with mortality. The O_2 requirements of patients with sepsis and MODS is increased while they may have impaired left ventricular function and abnormal regulation of their vascular tone, which can restrict DO_2 and disturb redistribution of blood flow to local tissues; this may increase O_2 debt even more.

A number of host characteristics specific to children and infants may also impair their adaptive mechanisms. An increase in cardiac output can compensate for anemia. Because myocardial compliance is decreased during the first weeks of life, there is a significant impairment in diastolic filling, which limits stroke volume increase. In addition, an elevated heart rate at rest in newborns (about 140 ± 20/min) and infants (about 130 ± 20/min) also limits the ability to increase cardiac output. Congenital heart disease is frequently observed in PICU patients, and could also directly impair DO_2. Energy requirements in young infants are much higher than in adults. This difference is mostly attributable to growth and implies a greater need for substrates including O_2. In addition to increased metabolic demands, there are also major differences in O_2 transport between adults and children in the first years of life. The proportion of fetal Hb is significantly higher during the first months of life, causing a leftward shift of the oxy-Hb saturation curve. Physiologic anemia is normal during this period, and explains at least partly why the normal Hb concentration range is broad in the newborn and the infant. Moreover, the health status of children before ICU entry is generally better than that of adults, and might in part explain the lower PICU mortality rates seen in children. All these characteristics specific to critically ill children may alter their capacity to cope with a lower Hb concentration; further studies are needed to determine their clinical consequences.

O_2 Kinetics in the Critically Ill

Tissue hypoxia from low DO_2 may be due to low Hb concentration (anemic hypoxia), low cardiac output (stagnant hypoxia) or low Hb saturation (hypoxic hypoxia).[5] A significant number of intensivists use RBC transfusion to increase DO_2 in critically ill children.[6] RBC transfusion indeed increases DO_2, but there is no clear evidence that RBC transfusion improves tissue VO_2 in ICU patients.[2] Many mechanisms may explain why VO_2 does not always increase in such instances. Mitochondrial dysfunction is frequent in critically ill patients; this may prevent O_2 utilization (see Chapter 74).[7] Moreover, O_2 delivery to tissue is impaired in ICU patients, and there is some evidence that RBC transfusion may worsen that problem.

Regulation by Red Blood Cells of DO_2 to Tissue

Although RBC transfusion certainly increases systemic DO_2 in the central circulation, it does not mean that local O_2 delivery to tissues is improved. There is indeed evidence that RBC transfusion may disturb local DO_2. For example, Kiraly et al.[8] showed that tissue SO_2 (StO_2) in critically ill patients who received a transfusion of RBC units stored more than three weeks declined from about 89% to 81%, whereas this did not happen in controls. However, data on local DO_2 are inconsistent, their clinical significance remains to be determined, and the mechanisms are not well characterized; blood viscosity, microcirculatory flow, local DO_2, and cellular respiration may be involved.

Erythrocyte transfusion increases blood viscosity. Higher viscosity of blood can lead to microcirculatory stasis and impaired DO_2 to tissues. In the sickle cell literature, a Hb of 10 g/dL or hematocrit of 0.3 is often discussed as the level above which blood viscosity starts to increase. However no hard data indicate that blood viscosity is a clinically important problem unless the Hb is higher than 20 g/dL.

Activation of white blood cells (WBC) in packed RBC units and cytokine generation in the supernatant of transfused RBC units may also have a microcirculatory effect: some cytokines can mediate vasoconstriction or thrombosis of small vessels and cause local ischemia.[9] However, most packed RBC units are now prestorage leukocyte-reduced, which significantly decreases cytokine levels in the supernatant.[10] The clinical impact of cytokines in the supernatant of prestorage leukocyte-reduced packed RBC units remains to be determined.

There is evidence that RBC transfusion can cause vasoconstriction of small blood vessels via a mechanism involving an interaction between the Hb in RBC and the nitric oxide released by small vessels. With local tissue hypoxia, Hb in the microvasculature releases nitric oxide and triggers local vasodilatation; conversely, if there is sufficient O_2 in the microvasculature, Hb binds nitric oxide resulting in vasoconstriction. This regulatory mechanism is almost immediately lost once RBCs are stored: it has been shown that in vitro exposure of blood vessels to RBC units stored 3 hours or more causes vasoconstriction.[11] However, the level of nitric oxide increases rapidly after transfusion.[12] Although the clinical significance of these observations is not clear yet, these findings nonetheless suggest that local DO_2 can be disturbed by RBC transfusion.

Packed RBC units undergo several changes during storage, which are generally referred to as "storage lesion."[13] For example, the level of 2,3-diphospho- glycerate (2,3-DPG) in stored RBC decreases over time and can induce a leftward shift in the oxy-Hb dissociation curve, which impedes O_2 release to tissues even if DO_2 is increased. In addition, RBC deformability decreases after 2 or 3 weeks of storage, which may alter their capacity to pass through the capillary bed. Furthermore, hemolysis in older packed RBC units releases substantial amounts of free Hb ranging from 0.5 mg/dL in a 1-day-old RBC unit to 250 mg/dL in a 25 day-old unit[14]; free intravascular Hb has the ability to bind nitric oxide and therefore likely mediates vasoconstriction.[15]

Thus, whereas RBC transfusions certainly increase systemic DO_2, some available evidence suggests that impaired microcirculatory flow and O_2 availability can occur, which may have adverse effects on tissue oxygenation and cellular respiration.

Transfusion of Red Blood Cells: Indications (When)

Blood is clearly indicated for the treatment of hemorrhagic shock.[2] In such instances, the decision to prescribe RBC transfusions should be based on the physiologic state, the estimated amount of blood loss, and risk of ongoing hemorrhage, not on the Hb concentration.

RBC transfusion is more questionable if the hemorrhage is not clinically significant or if there is no hemorrhage. Pediatric intensivists have stated in two surveys that their decision to prescribe a RBC transfusion would be based on reasons such as a low DO_2 or VO_2, cardiovascular insufficiency, respiratory failure, or use of certain specific technologies such as extracorporeal membrane oxygenation (ECMO), hemodialysis, hemofiltration, plasmapheresis, or exchange transfusion; nonetheless, the most frequent reason to transfuse RBCs was reported to be a low Hb concentration.[1,6] The Hb level that should prompt a pediatric intensivist to prescribe RBC transfusion remains a matter of debate, but there is some evidence in the medical literature that can guide practitioners.

Evidence-Based Medicine: Clinical Studies

Four case series are applicable to critically ill children: two in children with septic shock,[16,17] another in postoperative cardiac surgery patients,[18] and the last in children with cyanotic heart disease undergoing elective cardiac catheterization.[19] These studies assessed hemodynamic parameters before and after a 0 to 20 mL/kg packed RBC transfusion; all reported a significantly increased Hb level as well as a greater DO_2 after transfusion, but only one study reported an increase in VO_2.[16] These findings support the hypothesis that RBC transfusion increases systemic DO_2, but does not necessarily increase VO_2.

There is evidence that severe anemia increases mortality and morbidity among severely ill children. In two studies involving patients who refused blood products for religious reasons, the risk of mortality increased significantly with a postoperative Hb level less than 4 g/dL in healthy adults[20] and less than 10 g/dL in adults with heart disease.[21] There are three prospective descriptive studies addressing this issue in pediatrics. Lackritz et al.[22] followed 2433 African anemic children younger than 12 years among whom 20% received a RBC transfusion. They reported that RBC transfusion was beneficial if the Hb level was below 4.7 g/dL and if the patient presented some respiratory distress. Lackritz et al.[23] subsequently published another prospective study examining 1223 consecutively hospitalized children in Kenya. Local guidelines suggested that an RBC transfusion should be given to all children with an Hb level less than 5 g/dL. The Hb level was less than 5 g/dL in 303 cases; 116 (38%) did not receive a transfusion, mostly because packed RBC units were not available. Each child with severe anemia was paired with the next child hospitalized with an Hb greater than 5 g/dL. The death rates were: 19.5% in 303 patients with Hb greater than 5 g/dL who were not transfused, 21.4% in 187 patients with Hb less than 5 g/dL who were transfused, and 41.4%% in 116 patients with Hb less than 5 g/dL who were not transfused. English et al.[24] completed a prospective cohort study of 1269 children with malaria hospitalized in Kenya; they reported that RBC transfusion decreased mortality if anemia was severe (Hb level <4 g/dL), or if a Hb level less than 5 g/dL was associated with dyspnea. These three studies suggest that the risk of mortality increases significantly in severely ill children requiring hospitalization if their Hb concentration is lower than 5 g/dL particularly if respiratory symptoms are present.

Two randomized clinical trials evaluated RBC transfusion strategies in children. The first trial was performed in Africa in 106 children with malaria crisis (hematocrit: 12% to 17%); RBC transfusion did not improve mortality rate (1/53 vs. 2/53) in patients without respiratory or cardiovascular compromise.[25] In the TRIPICU study, a large multicenter international randomized clinical trial involving 637 stable critically ill children with Hb level lower than 9.5 g/dL, 320 patients were allocated to a RBC transfusion threshold of 7 g/dL of Hb (restrictive group) and 317 to a threshold of 9.5 g/dL (liberal group). A statistically significant noninferiority

was found: 38 and 39 patients respectively developed new or progressive MODS, and there were 14 deaths in both strategy groups within 28 days postrandomization. The conclusion of this study was that a restrictive strategy is as safe as a liberal strategy in stable critically ill children. Moreover, given that 174 patients (54%) in the restrictive group received no RBC transfusion compared to 7 (2%) in the liberal group (P <.0001) and that patients in the restrictive group received 54% fewer RBC transfusions, the findings supported adopting a restrictive transfusion strategy for stabilized critically ill children.[26] Subgroup analyses were subsequently undertaken in patients with sepsis[27] and those having undergone noncardiac surgery[28]: both showed trends very similar to those reported in the original TRIPICU study.

Red Blood Cell Transfusion: Current Recommendations

Guidelines from many organizations emphasize that the decision to administer RBC should not be determined solely by an Hb value, but should be based on sound clinical judgment.[2,29,30] RBC transfusion in PICU is indeed associated not only with a low Hb level, but also with admission for cardiac disease (odds ratio [OR], 8.07; 95% confidence interval [CI], 5.14 to 14.65), higher severity of illness (PRISM score >10: OR, 4.83; CI, 2.33 to 10.04), and presence of MODS (OR, 2.06; CI, 1.18 to 3.57).[31] In a survey,[6] pediatric intensivists declared that they might consider prescribing a RBC transfusion based on the following markers: Hb concentration, low SaO_2, low PaO_2, low cardiac output (poor DO_2), high blood lactate level, low $ScvO_2$ or $SmvO_2$, poor VO_2, high severity of illness, active bleeding, and emergency surgery. However, how these determinants of RBC transfusion interacted with each other was unclear.

Many physicians advocate "goal-directed transfusion therapy."[32,33] Although it is theoretically rational to base the decision to transfuse RBCs on physiologic need, it is still a matter of debate what parameters best determine that need. It has been suggested that a RBC transfusion is indicated for patients with symptomatic anemia, but most critically ill children are unable to report these symptoms. Some have suggested it would be better to use global markers of oxygenation deficit, such as systemic VO_2, VO_2/DO_2 dependence, blood lactate level, $ScvO_2$, $SmvO_2$, or O_2ER.[34] Others propose the use of measurements that reflect local, regional, or tissue oxygenation deficit, such as brain tissue O_2 pressure ($PbtO_2$),[35] gastric tonometry[36] StO_2 measured by near-infrared spectroscopy[8] or digital O_2 extraction rate measured by noninvasive devices. Actually, it is presently not known what markers are best suited for this purpose and what cutoff values should be used to determine the need for RBC transfusion in critically ill children. The concept of goal-directed transfusion therapy is laudable, but is presently vaguely defined, and not supported by hard data. Recommendations specific to goal-directed transfusion therapy remain undetermined at the present time.[32]

In practice, a low Hb concentration remains the most frequent and the primary justification for pediatric intensivists to prescribe a RBC transfusion.[1] Therefore it makes sense that the Hb concentration be the first parameter assessed when a RBC transfusion is considered. Given the available evidence, RBC transfusion is recommended for all critically ill children who present with a Hb concentration below 5 g/dL. In stable patients, including septic patients,[27] patients having undergone noncardiac surgery,[28] and severely burned children,[37] it is suggested by experts to consider a RBC transfusion if the Hb concentration is lower than 7 g/dL, but a transfusion is not recommended if the Hb concentration is above this level.[2] These thresholds are not so far from current practice: Goodman et al.[38] have reported that all critically ill children with a Hb ≤5.3 g/dL and that 93% of those with a Hb of 6.4 g/dL or less received at least one RBC transfusion. However, determinants other than the Hb concentration must be considered including age, severity of illness or evidence of organ dysfunction or O_2 dependency, such as a high blood lactate level or low $ScvO_2$. For example, it would seem appropriate to consider a higher threshold and a more aggressive RBC transfusion strategy in unstable patients, but the optimal and safe lower limit of the transfusion threshold has not been established for such patients. Moreover, any recommendations made must also factor in specific considerations for disorders such as sickle cell disease, hemolytic uremic syndrome, and some cardiac diseases.

Many experts in the field of pediatric cardiology and cardiac surgery believe that the optimal Hb concentration for patients in the postoperative phase of cardiac surgery should be significantly higher, and advocate levels as high as 14 to 18 g/dL in cases of uncorrected cyanotic congenital cardiopathy.[39,40] Few clinical studies have addressed RBC transfusion in cyanotic heart disease. Experience with bloodless cardiac surgery for congenital heart disease in children whose families refuse transfusion for religious reasons seems to suggest that a lower Hb level may be well tolerated. This is supported by a randomized clinical trial involving 59 children with bidirectional Glenn or Fontan procedures. In this trial, patients were randomized either to a restrictive or liberal transfusion strategy (respective Hb concentration thresholds of 9 or 12 g/dL). The mean postoperative Hb was 11.1 ± 13 and 13.9 ± 0.5 g/dL, and the mean number of RBC transfusions was 0.47 ± 0.6 and 2.03 ± 1.2 per patient in the restrictive and liberal groups. No difference was found with respect to outcomes like peak blood lactate level (3.0 ± 1.5 vs. 3.1 ± 1.3 mmol/L), ventilator or pressor duration, ICU or hospital length of stay, or survival. More data are required before implementing a restrictive transfusion strategy in patients with cyanotic heart disease.[41] Beekman's 1985 statement that "The optimal Hb concentration for children with cyanotic heart disease has yet to be determined" remains true today.[19]

On the other hand, there is some evidence that a 7 g/dL threshold may be safe in the postoperative care of noncyanotic congenital heart disease in stabilized patients older than 28 days.[42] Willems et al.[43] analyzed a subgroup of 125 postoperative cardiac patients enrolled in the TRIPICU study after a cardiac surgery. No significant difference was found between the restrictive and liberal groups in new or progressive MODS (12.7% vs. 6.5%; P = .36), PICU length of stay (7.0 ± 5.0 vs. 7.4 ± 6.4 days) or 28-day mortality (two vs. two deaths). The British Society of Haematology[30] supports the acceptance of a postoperative hemoglobin level of 7 g/dL in children when there is good postoperative cardiac function unless there is a cyanotic heart lesion persisting. The Society of Thoracic Surgeons makes a similar recommendation for all cardiac surgery patients.[44] Data reported by Willems et al.[43] support these recommendations.

There is a debate on the usefulness of blood transfusion as a preventive measure. Some evidence suggests that this may be appropriate in critically ill children who have certain forms of congenital anemia (for example, sickle cell disease,[45] and in patients who require ECMO (a Hb threshold of 13 to 15 g/dL is suggested[46]) or surgery.[47] However, there are few hard data to support such recommendations in the latter two groups.

Prevention of Red Blood Cell Transfusion

"Bloodless medicine" is a popular concept in many American hospitals; it refers to all the strategies that can be used to provide medical care without allogeneic RBC transfusion, including blood conservation.[48] There are indeed many strategies that can prevent and/or significantly decrease the need for RBC transfusions and exposure to a transfusion. Adopting a restrictive RBC transfusion strategy in stable critically ill children is one of them; other possible means range from raising the Hb concentration before an elective surgery to using blood products only when necessary, limiting blood losses and administering the patient's own blood.

Bloodless medicine begins before surgery. Among the possible strategies in the preoperative period, the use of erythropoietin and iron supplementation to optimize the preoperative Hb level, collection of autologous donations to prevent some allogeneic transfusion,[49] avoidance of any medication that increases the risk of bleeding, including herbal medicine (e.g., garlic, ginseng, ginger[33]), and optimal control of any existing coagulation disorders just prior to surgery should be considered.

During surgery, maximal attention should be given to limiting blood loss[50] and ensuring good hemostasis and rapid control of all bleeding. In some instances, desmopressin,[51] fibrin sealants, or antifibrinolytic agents such as aprotinin or tranexamic acid[48] may be used to stop a hemorrhage. Recombinant activated factor VII (rFVIIa) is also advocated by some practitioners, but it is associated with a significant risk of thrombosis; the cost/benefit ratio of rFVIIa in children is not well evaluated and its use should be limited to situations with uncontrolled bleeding that is life-threatening.[52] The safety and cost-effectiveness of intraoperative blood conservation strategies such as normovolemic hemodilution,[53] autologous blood cell salvage modalities,[54] intraoperative autotransfusion, and deliberate hypotension[50] remain to be determined in children.

Postoperative and ICU management of anemia and bleeding is also important. A restrictive transfusion strategy is in line with the concept of "permissive anemia" supported by the British Committee for Standards in Haematology Transfusion Task Force.[30] A prospective study reported that 73% of blood loss in PICU is attributable to blood draws.[1] The number and the frequency of blood tests must be limited, and the amount of blood collected reduced. Many devices can help to minimize blood loss, including the use of loop sampling, pediatric blood collection tubes, microanalysis techniques requiring small volumes of blood, and in-line measurement of parameters such as blood gases and Hb concentration.[55-57] The erythropoietin response to anemia is blunted[58] and poorer than expected in critically ill patients.[59] In spite of this, there are data suggesting that erythropoietin can prevent anemia in critically ill adults,[60] in low-birth-weight preterm infants[61-63] and in the postoperative care of neonates.[64] In critically ill children, there are no data to support the use of erythropoietin as a preventive measure because most RBC transfusions are administered within 2 or 3 days after PICU admission,[1,65] a period of time too short to allow for a response to erythropoietin that generally requires several days.[66] The standard use of erythropoietin is presently not recommended in PICU.[65,67] In addition, iron supplementation is not indicated because most critically ill patients are not iron depleted.[59]

An RBC transfusion should be administered only if the anticipated benefit outweighs the potential risk. A threshold Hb concentration of 7 g/dL is adequate in most stable critically ill children.[68] The optimal Hb concentration or transfusion threshold above which the benefits outweigh the risks and costs remains to be determined in unstable patients and in patients with congenital heart disease.

Types of Packed Red Blood Cell Units

Many types of RBC units are available: standard, washed, irradiated, cytomegalovirus (CMV) negative, autologous and directed.

Standard Packed RBC Units

Storage of RBC units is made possible by refrigeration at about 4° C and by storage in preservative anticoagulant solutions that contains dextrose, sodium citrate, citric acid, and sodium diphosphate. Erythrocytes use dextrose and phosphate to generate ATP, which is essential for their survival. Citrate blocks coagulate by chelating calcium; it is also transformed into bicarbonate, which stabilizes the stored RBC unit pH above 6.4. Citrate-phosphate-dextrose (CPD) solution can be stored up to 28 days. Citrate-phosphate-dextrose-adenine (CPDA-1) contains more dextrose (2 g vs. 1.6 g/63 mL) and more adenine (17.3 mg/63 mL) than CPD; it can be stored up to 35 days because the level of ATP remains normal after 21 days of storage and is about 50% after 35 days. Packed RBC units are prepared by removing 200 to 250 mL of plasma from one unit of whole blood by centrifugation. To support the nutrient needs of RBCs after plasma is removed, additive solutions were developed, such as AS-1 (Adsol), AS-3 (Nutricel), and AS-5 (Optisol), and saline-adenine-glucose (SAG) or SAG-mannitol (SAGM)[69]; these additive solutions further decrease RBC lysis and allow for storage up to 42 days.[70]

The volume of a CPDA-1 unit is about 250 mL, including 63 mL of preservative solution; it must be diluted with 75 mL of NaCl 0.9% before transfusion (final volume: 325 mL). The volume of an AS-3 unit is about 350 mL and the volume of a SAGM unit is about 300 mL; both include approximately 100 mL of preservative solution and do not require any dilution.

Other Types of Packed Red Blood Cell Units

Whole Blood. The use of whole blood has been advocated mostly for first-line therapy in hemorrhagic shock as it contains RBCs, coagulation factors, and platelets. However, it is generally not available. Additionally, refrigeration in storage solution for even several hours results in decreased levels of coagulation factors, oxygen-carrying capacity, as well as platelet function. In practice, component therapy is standard practice and it is usually easier to give one or more packed RBC units diluted with normal saline along with plasma and/or

platelets. Whole blood units are also used by some for neonatal exchange transfusions, and in small children when priming for cardiac bypass procedures or continuous hemoperfusion. Whole blood is not recommended in normovolemic patients because it can cause a cardiac overload. The volume of a typical whole blood unit is about 450 mL.

Leukocyte-Reduced Packed Red Blood Cell Units. Packed RBC units contain some nonviable platelets, small amounts of coagulation factors, and WBCs that can release proinflammatory and antiinflammatory mediators during storage. Prestorage leukocyte reduction is a standard procedure for all blood components in many countries, such as Australia, Canada, and the United Kingdom; it can decrease the number of WBCs in packed RBC units from 1×10^9 to less 1×10^6 per product, and it decreases the concentration of cytokines in the supernatant, as well as some T cells that regulate immunomodulation.[71] In 2005, 88% of packed RBC units given in American PICUs were leukocyte-reduced at collection.[1] Transmission of intracellular viruses such as CMV and herpes is less frequent if there are fewer WBCs.

Washed Packed Red Blood Cell Units. RBCs can be washed with sterile saline; the process removes not only 98% of the plasma, but also up to 20% of the RBC. Erythrocyte washing increases the hematocrit up to 0.8, but the procedure takes up to 2 hours; thus it is impossible to use washed packed RBC units on an emergency basis unless they are prepared in advance. Washed units must be used within 24 hours after processing. Multiple wash cycles are required. The procedure may not reduce the proteins enough to prevent hypersensitivity reactions (e.g., hypersensitivity to immunoglobulin [Ig]A). The overall volume of a washed RBC unit is significantly decreased (about 200 mL rather than 350 mL for an AS-3 RBC unit), making them sometimes useful to limit the volume administered in some patients. Washed RBC units can also be considered for patients with severe, recurrent allergic reactions to blood and some patients with anti-IgA deficiency. Washed RBC units should not be considered leukocyte reduced.

Irradiated Packed Red Blood Cell Units. Some WBCs remain in RBC and platelets units, even in prestorage leukocyte-reduced units. The objective of irradiation is to induce enough DNA damage to prevent leukocyte proliferation.[72] Irradiation destroys the ability of transfused lymphocytes to divide and therefore to respond to host foreign antigens, thereby decreasing the risk of developing transfusion-associated graft versus host disease (TAGVH) in susceptible recipients. However, irradiation is not without some drawbacks. For example, it can damage the RBC membrane causing the release of significant amount of free Hb and potassium. Moreover, the shelf life of irradiated RBC units is reduced from 42 to 28 days.[73]

Irradiated RBCs are indicated for all children with congenital or acquired cellular immune deficiency (for example, allogeneic stem cell transplant recipients, certain hematologic malignancies, myeloablative chemotherapy recipients) to prevent TAGVH. Because diGeorge syndrome is not rare among infants with congenital heart disease undergoing cardiac surgery, these patients should receive irradiated units. Irradiation is also indicated in patients receiving directed donation from family members. Irradiation is not mandatory for most solid tumors, routine immunosuppressive therapy (corticosteroids), solid organ transplants, non-myeloablative chemotherapy recipients, or humoral immunodeficiency.

Cytomegalovirus-Negative Packed Red Blood Cell Units. A large proportion (30% to 70%) of blood donors are CMV positive. Most CMV infections are of little clinical consequence, but CMV can be fatal in patients with immunodeficiency. Fresh frozen plasma is not known to transmit CMV infection, but RBC units are. Although it would be ideal to administer only CMV-negative RBC units to CMV negative patients, the high prevalence of CMV infection among donors does not permit this.[74] Nevertheless, prestorage leukocyte reduction of blood products decreases transmission of CMV to 1% to 2% (similar to the rate of infection following the transfusion of CMV negative units) compared to standard products for which transmission is 13% to 37%. Administration of a CMV positive RBC unit is generally not an issue for immunocompetent patients. Established indications for CMV-negative units include CMV-negative recipients of organ or bone marrow transplants from CMV-negative donors, CMV-negative bone marrow transplant recipients, and intrauterine transfusions. Less well-established indications include CMV-negative patients who are potential candidates for autologous or allogeneic bone marrow transplant, CMV-negative patients undergoing splenectomy, potential seronegative donors for bone marrow transplant and CMV-negative patients with HIV.

Directed Packed Red Blood Cell Units. Directed blood is donated by family members or friends. Parents frequently believe that giving their own blood decreases the risks of transfusion, which, in practice, is not the case. A small increase of transfusion-transmitted infectious diseases has been reported.[46] Moreover, the risk of contracting a TAGVH is increased even in immunocompetent patients. In spite of this, directed blood donation remains popular; good clinical studies are warranted to better estimate the risk/benefit ratio of this practice. All directed RBC units must be irradiated pretransfusion.

Autologous Packed Red Blood Cell Units. Older healthy children can give their own blood a few weeks before elective surgery. It is frequently believed that autologous RBC units are free of risk, but this is untrue. These units are usually quite old by the time transfusion is required, which raises significant concerns with respect to RBC unit length of storage.[75] Moreover, autologous RBC units are not leukocyte-reduced, at least in Canada. The risk/benefit ratio of autologous RBC units remains to be determined.

RBC substitutes and other alternatives to RBC transfusion

Hemoglobin-based oxygen carrier solutions (semisynthetic or synthetic preparations of Hb) and perfluorocarbon derivatives can carry O_2.[76,77] Both were developed as alternatives to RBCs, but there are serious concerns about their safety and usefulness. None can be recommended presently.

Transfusion of Packed Red Blood Cells: How

Erythrocyte transfusion is the best way to rapidly increase the Hb concentration. The practitioner must address a few questions after a decision is made to prescribe a RBC transfusion:

what type of RBC unit (see the previous section), what blood type, how much (volume), how the unit is infused and what monitoring must be performed.

Blood Types

Table 82-1 describes the compatibility of different blood products. A completed cross-match is mandatory before any transfusion is given, with few exceptions. Transfusion of group O Rh negative RBC and/or group AB Rh positive plasma can be lifesaving, but this must be reserved for very severe and acute situations. It takes 15 to 20 minutes to complete ABO and Rh typing of a patient. If there are no RBC antibodies, fully compatible blood or immediate spin cross-match may be issued quickly. In the case of RBC antibodies or other anomalies, a full serologic cross-match is required, which will take more time. The risk of severe reaction to typed, but not cross-matched blood RBC units, is about 1 in 1000 if the patient has never received a transfusion; the risk is decreased by tenfold if a cross-match is done. If the patient has received at least one transfusion, the risks are respectively 1 in 100 with no cross-match and 1 in 1000 if a cross-match is done. It was recommended that similar units be used until patient recovery if a patient receives more than 20% of his blood volume with uncross-matched packed RBC units. However, this practice is a little outdated, as there is very little plasma in AS-3 and SAGM RBC units. If anti-A/B antibodies are detected on blood typing then antigen negative blood should be provided; otherwise ABO-identical units should be used when they become available. Repeat verification that the correct blood unit has been delivered to a given patient is essential because blood mismatch is the most important cause of severe transfusion reaction.

For high-risk elective procedures, type and cross-matching performed before bleeding event allows for compatible RBC units to be reserved for the patient. If an unforeseen emergency transfusion is required within minutes for an actively bleeding patient, it is impossible to deliver RBC units that are typed and cross-matched within a reasonable time frame and group O Rh negative RBC units must be administered. STAT ordering a transfusion means that it must be started within a few minutes after the prescription; STAT ordering is usually not required, unless the patient is actively bleeding.

Table 82–1

Blood Product	Receiver	Donor
Packed RBC unit and whole blood	A, O	
	B	B, O
	O	O
	AB	AB, A, B, O
	Rh^+	Rh^+ or Rh^-
	Rh^-	Rh^-
Plasma or platelets	A, AB	
	B	B, AB
	AB	AB
Platelets	Rh^+	or Rh^-
	Rh^-	Rh^- or Rh^{+*}

*Give as an anti-D vaccine (Win Rho SDF) if the receiver is Rh^- and the platelet concentration is Rh^+.

Volume and Number of Units

Prescribing the right volume of packed RBC units is important as this prevents cardiac overload and limit exposure to several donors. An easy to remember, albeit simplistic, rule of thumb suggests that administration of 10 mL/kg of packed RBC units should increase the blood Hb level by 2 to 3 g/dL. If the Hb concentration is stable in a patient that is not actively bleeding, it is more precise to calculate the difference between the Hb concentration observed before transfusion and the targeted Hb level. The following formula can be used to calculate more precisely the volume of packed RBCs that should be given:

$$\text{Volume(mL)} = [(\text{Hb}_{\text{targeted}} - \text{Hb}_{\text{observed}}) \times \text{Blood volume}] / \text{Hb}_{\text{RBC unit}}$$

where $Hb_{targeted}$ is the Hb concentration targeted posttransfusion (e.g., 10 g/dL), $Hb_{observed}$ is the most recently measured Hb concentration of the patient (g/dL), and $Hb_{RBC\ unit}$ is the average Hb concentration in the packed RBC units (g/dL) delivered by the blood bank. Hb concentration in RBC units may vary from one center to another and with different preservative solutions. For example, the hematocrit of RBC units with AS-3 (Nutricel) is approximately 0.55, and $Hb_{RBC\ unit}$ concentration is about 19.5 g/dL (range, 18-21 g/dL); the hematocrit of CPDA-1 is 0.75 to 0.65, and the $Hb_{RBC\ unit}$ is about 25 g/dL. The blood volume can be calculated according to the following formula:

$$\text{Total body blood volume} = \text{Weight} \times \text{Blood volume}$$

where weight is expressed in kilograms, and blood volume is in liters per kilogram (0.08 L/kg for a child younger than 2 years, 0.07 L/kg for child aged 2 to 14 years). For example, if the $Hb_{observed}$ in a 2-week-old baby weighing 3 kg is 6.5 g/dL, his blood volume is 0.24 L (0.08 L/kg × 3 kg), and the $Hb_{RBC\ unit}$ is 19.5 g/dL (AS-3), and if the physician targets a Hb concentration ($Hb_{targeted}$) of 10 g/dL, the volume of RBC unit to be transfused would be:

$$\text{Volume} = [(10\ \text{g/dL} - 6.5\ \text{g/dL}) \times 0.24\ \text{l}] / 19.5\ g/\text{d} = 0.043\ \text{L} = 43\ \text{mL}$$

If the volume needed to reach the $Hb_{targeted}$ is greater than the volume of one unit of packed RBCs, blood should be transfused one unit at a time to minimize exposure to multiple donors. Before the administration of additional packed RBCs, the Hb concentration should be measured after allowing at least 30 minutes posttransfusion for Hb and hematocrit values to equilibrate.[78] The transfusion can be completed with another unit or partial unit if a reasonable Hb level is not attained.

If the volume of packed RBCs required is less than one unit, a partial unit can be given. Whole packed RBC units can be subdivided in half (standard division) or in small pediatric 75 mL transfer packs (Pedi-Pak). Partial units should be prepared sterilely where possible. Partial units prepared nonsterilely expire 24 hours after the preparation. On the other hand, partial units prepared sterilely can be kept as long as the original unit (up to 42 days for AS-3). A small volume of packed RBC unit placed in a syringe must always be administered within 24 hours.

Length of Storage

Regulatory agencies and scientific societies such as the Food and Drug Administration and the American Association of Blood Banks mandate that packed RBC units can be stored up to 42 days based on the premise that at least 75% of transfused RBC will be alive 24 hours posttransfusion.[46,79] However, a "storage lesion" occurs over time, which raises many concerns.[13] These changes are associated with a number of biochemical and biomechanical changes including RBC ATP depletion, low 2,3-DPG levels, membrane phospholipid vesiculation and loss, protein oxidation, lipid peroxidation of RBC membranes, and RBC loss of deformability.

Prolonged storage changes the supernatant as well as the RBCs themselves. In the storage medium, studies have noted the generation of cytokines and other bioreactive substances,[80] including histamine,[81] complement activators, O_2 free radicals, lyso-phosphatidyl-choline species, and microvesicles containing lipids shed by RBCs. These bioactive substances may stimulate pro-inflammatory pathways and perhaps change flow patterns in the microcirculation.[11] The latter observation might explain the effect of RBC transfusion reported by Kiraly et al.[8] on StO_2 in critically ill trauma adults. A significant decline in StO_2 was observed in 17 patients who received RBC units stored since more than 21 days in the posttransfusion period compared to baseline. This was not observed in 15 patients who received fresher blood, nor in 16 patients who were not transfused.

Other well-documented time dependent changes in the storage medium are described, including a progressive fall in pH, an increase in plasma potassium and release of free Hb from lysed RBCs. On the other hand, fresh blood products stored for less than a week are not without risk and can be associated with transmission of certain intracellular viruses as well as TAGVH.[82,83]

There is presently controversy regarding the impact of RBC storage time in critically ill patients, both adult and pediatric. Some descriptive studies suggest that the outcome in critically ill adults is better if they receive fresher RBC units, while other studies do not support this.[84] Two prospective descriptive studies undertaken in critically ill children suggest that outcome is less favorable with transfusion of packed RBC units stored for more than 2 or 3 weeks.[85,86] On the other hand, a large retrospective study conducted in neonates undergoing cardiac surgery suggests that fresh blood may be more detrimental.[87]

The societal impact of implementing a "fresh RBC strategy" can be enormous: presently, RBC unit wastage is less than 1%; it is estimated that wastage would approach 30% if the allowable length of storage is decreased from 42 to 21 days.[79] Thus it is unethical to implement a fresh RBC transfusion strategy without strong evidence to support its usefulness. Whether the length of storage of RBC units really affects outcome in critically ill children remains to be determined by randomized clinical trials. The ABLE study (ISRCTN44878718) is such a trial and has been enrolling adults since 2009, whereas a pediatric trial is in preparation. Until hard evidence is available, the use of fresh rather than "old" blood cannot be recommended for PICU patients.

Perfusion, Warming, and Filtration

A RBC transfusion must be completed within 4 hours after the unit is delivered by the hospital blood bank. A packed RBC unit is usually given over 1 to 3 hours, but it might be given more slowly (up to 4 hours) or divided in two transfusions if there is some risk of cardiac overload.[46]

The viscosity of packed RBC units is high, which implies it is preferable to use larger bore needles to administer them.[88] No drugs should be given in the line used for packed RBC unit perfusion. It is also inappropriate to mix RBC units with dextrose or hypotonic solutions (risk of hemolysis), with Ringers lactate (risk of coagulation), or calcium.

Packed RBC units must be warmed before administration to diminish the viscosity of the blood product and to avoid hypothermia. Blood viscosity decreases by about 7% for each 1° C increase, thus reducing resistance and making it easier to administer blood products through catheters. Erythrocyte units are stored at 1 to 6° C and could cause significant hypothermia if given to a patient without warming. All blood products are warmed to room temperature (about 20° C) before delivery to the bedside. Warming to body temperature (37° C) may be required for patients weighing less than 10 kg or if large amounts need to be given corresponding to more than 20% to 30% of the circulating blood volume. Standard blood-warming devices must be used to raise the temperature of whole blood or packed RBC units, not microwave ovens that can cause severe hemolysis.

Because all packed RBC units (even prestorage leukocyte-reduced RBC units) contain fibrin, platelets, and WBC aggregates, a filter (with 80, 179, or 260 μm pores) must always be used to bind these aggregates before they are administered. Although their cost-usefulness has not been determined, filter with 20 to 40 microns micropores are more effective, and some evidence suggests that they can prevent some cases of TRALI. Filters with smaller micropores are not considered standard treatment.

Monitoring and Reporting Adverse Events

Patients should be monitored closely while receiving a transfusion. Vital signs should be taken before transfusion as well as within the first 15 minutes and every hour up to four hours after the transfusion.

Plasma

Plasma is separated from the RBC after collection of whole blood or it is collected using an apheresis machine; it is then frozen for storage to preserve the levels of coagulation factors. It is named "fresh frozen plasma" if the unit is refrigerated within 8 hours of collection, and "frozen plasma" within 24 hours of collection. There is a slight reduction in factor VIII levels in frozen plasma, but in clinical practice these two types of plasma are essentially interchangeable.[89] The acronym FP (frozen plasma) is used in this section to designate both of them.

Frozen plasma units are collected from a single donor, whereas units of solvent detergent (SD) plasma (Octaplas, Octapharma) is constituted from a pool of frozen plasma collected from approximately 700 donors and is processed using the SD process for inactivation of lipid-enveloped viruses. SD plasma is not currently licensed in the United States, but it is licensed and available in Europe. In some countries, only FP may be available, but in many countries including the United States fresh FP is still available in the year 2010.

FP units are systematically leukocyte-reduced by filtration before storage in many countries, but not in the United States. FP volume is about 200 to 250 mL/unit,[46] whereas the volume of SD plasma is about 200 mL/unit. On average, FP contains 1 unit/mL of all coagulation factors, but there is significant variability among individual units, which is attributable to

biological variation in factor levels among individual donors, and differences in processing, storage and preparation for transfusion.[90] The levels of coagulation factors in SD plasma are more standard with little variation among units as it is a pooled plasma product. FP is stored at −18° C up to one year after collection. Solvent detergent plasma can be stored for up to 48 months.

Transfusion of Plasma: Indication (When)

Generally, FP is transfused to correct multiple coagulation factor deficiencies (or single-factor deficiencies when no recombinant or plasma-derived coagulation factor concentrates are available) to patients with active bleeding or before invasive procedures when no alternative therapies are available or appropriate. Common coagulopathies for which FP may be given include liver disease and symptomatic disseminated intravascular coagulation (DIC). However, the use of plasma to treat disseminated intravascular coagulation is controversial because thrombosis is frequently a component of this disorder.[46] Frozen plasma can also be given for the emergency reversal of warfarin or vitamin K deficiency when prothrombin complex concentrates are not available.[91] Guidelines suggest transfusing FP only when the international normalized ratio (INR), the prothrombin time (PT), or the activated partial thromboplastin time (aPTT) is more than 1.5 times normal as coagulation factors are generally adequate for hemostasis below this level. However, some data suggest that FP is not very effective at normalizing mild abnormalities of coagulation tests, like an INR below 1.85,[92] and the potential clinical benefit of FP transfusion seems minimal when the INR is less than 1.7.[93]

Frozen plasma may also be administered during massive transfusion of packed RBC units. Some experts advocate early replacement of FP in a 1:1 ratio with RBC units in trauma patients with massive transfusion, whereas others suggest that FP transfusions should be guided by the presence of abnormal coagulation test results as previously listed or of whole blood: it should be administered in patients who have received more than 1.5 their circulating blood volume, even if there is no bleeding, or in patients who have received more than one circulating blood volume and who have clinical evidence of oozing or microvascular bleeding.[29,91,94]

Other indications for FP transfusion include plasma exchange for thrombotic thrombocytopenic purpura (TTP).[91] Some physicians advocate transfusion of plasma to treat cases of hemolytic uremic syndrome and to restore the blood volume of patients in shock, but there is no hard evidence to support such uses.

There is no evidence that FP should be given in prophylaxis to nonbleeding patients. Plasma should not be used as a volume expander; crystalloids, synthetic colloids, or purified human albumin solutions are preferred. Solvent detergent plasma has lower levels of protein C and S, which may contribute to increased thrombotic events and therefore should be used with caution in patients with severe liver disease, including liver transplant patients.

Transfusion of Plasma: How

One milliliter of FP contains about 1 unit of each of the coagulation factors. For most deficiencies, 30% of normal factor activity is enough to ensure hemostasis. Surgical hemostasis may be achieved with factor II levels 5% to 50% of normal, factor V approximately 30% of normal, factor VII 25% of normal, and factor VIII 30% to 60% of normal.[33] Practitioners usually administer 10 to 20 mL/kg of plasma initially; this should increase the level of the individual coagulation factors above 30%. As the levels of coagulation factors vary among units, the response to FP is not consistent. Therefore, the effectiveness of FP transfusion should be estimated by clinical judgment of ongoing bleeding and, if necessary, repeat coagulation testing. Additional doses of FP may be required for ongoing bleeding with persistently elevated coagulation tests. However, normalization of coagulation tests often does not occur and, therefore, should not be used as the only guide for additional FP transfusions.[95]

Frozen plasma transfusions should be ABO compatible but are not required to be identical. In contrast to RBC, group AB-positive plasma is the universal plasma donor and can be given in emergency situations when a blood group is not available. Cross-matching is not required because FP units are screened for antibodies against non-ABO and Rh antibodies, which may cause hemolytic reactions.

FP must be thawed (20 to 30 minutes) before transfusion. Warming FP can be shortened to 7 minutes using microwave ovens specifically constructed for this task (standard microwave oven can disable coagulation factors). A thawed unit of FP is ideally transfused within 4 hours, but thawed plasma can be relabeled and stored for up to 5 days in some countries including the United States (AABB Technical Manual). The clinical indications for thawed plasma are similar to FP but there is some decrease in the labile coagulation factors (factor V and VIII). A 80 or 170 μm pore filter must be used.

Platelets

The prevalence of thrombocytopenia, defined by a platelet count less than 150,000/μL (<150 × 10^9/L), is 17.3% on admission into PICU; 25.3% of children are thrombocytopenic at some point during their PICU stay.[96] Thrombocytopenia arises from decreased platelet production, increased platelet destruction, and dilutional or distributional causes.[97] In PICU, most thrombocytopenia is caused by sepsis, disseminated intravascular coagulation, MODS, or hemolytic uremic syndrome; however, heparin-induced thrombocytopenia,[98] massive transfusion,[99] and reactive hemophagocytic syndrome are not so rare.[100] In critically ill children, thrombocytopenia at PICU entry is associated with increased mortality (17.6% vs 2.5%)[96], bleeding complications, thrombosis, and prolonged PICU and hospital length of stay.

Platelet dysfunction is also observed quite frequently in PICU. Rarely platelet dysfunction can be caused by hereditary disease (e.g., Bernard-Soulier disease, etc.), but, more commonly, it is caused by specific treatments (hypothermia, pentastarch, and hetastarch,[101] etc.) or antiplatelet drugs (e.g., low-dose aspirin. nonsteroidal antiinflammatory drugs).

Standard Platelet Concentrates

Different methods can be used to obtain platelet concentrates: they may be whole blood derived platelets, either by the platelet-rich plasma (United States and United Kingdom) or the buffy-coat method (Europe and Canada) or by apheresis (single-donor) platelets (United States, Europe, and Canada). For

whole blood-derived platelets, platelet concentrates are often pooled (up to 6 units) for a single platelet transfusion.

Maximum platelet lifespan is 10.5 days.[102] Each platelet unit contains about 55×10^9 platelets. When stored at 20° C to 24° C and gently agitated in a continuous manner, platelets can be used up to 5 days after they were collected, but will become active only 4 hours after transfusion to the recipient. If they are stored at 4° C, they are active immediately, but cannot be stored for more than 48 hours. In practice, most platelets units are stored at 20° C.

Special Platelet Concentrates

Leukocyte-Reduced Platelets

A platelet concentrate must contain les than 8.3×10^5 WBCs to be labeled leukocyte reduced.[46] Prestorage leukocyte reduction is a standard procedure in many countries. Bedside leukocyte reduction filter should not be used when prestorage leukocyte reduction was done because it is useless and it can decrease the number of platelets.

Irradiated Platelets

The risk of TAGVH is increased in patients who receive HLA-compatible platelets. Therefore pretransfusion irradiation is mandatory for all human leukocyte antigen (HLA)-compatible platelet concentrates. Irradiation is also recommended for intrauterine transfusion and infants at risk of TAGVH.[46]

Cytomegalovirus-Negative Platelets

Platelet concentrates can transmit CMV. The indications for CMV-negative platelet and RBC are similar.

Platelets Substitutes

There is no alternative to platelets transfusion. However, cryoprecipitate can be used to treat platelet dysfunction caused by uremia if therapy like dialysis is not successful.[46]

Transfusion of Platelets: Indication (When)

Over 1.5 million platelet products are transfused in the United States each year.[103] Platelet transfusions are indicated for the prevention or treatment of bleeding in patients with thrombocytopenia or platelet dysfunction. As platelet transfusions will only result in modest elevations for 1 to 3 days in patients with persistent thrombocytopenia, the purpose of platelet therapy is not to eliminate all bleeding, but to prevent or stop major hemorrhagic events.

Therapeutic platelet transfusions are given to treat clinically significant bleeding associated with a low platelet count. There is evidence that correction of thrombocytopenia reduces mortality of critically ill patients,[96,104] but a platelet transfusion should be considered only if the platelet count in an actively bleeding patient is less than 50,000 to 100,000/μL.

More than 50% of platelets transfusions are given to prevent bleeding, even though the need for prophylactic transfusions has not been conclusively proven. There is insufficient evidence to support a particular threshold for prophylactic platelet transfusion in children. Most recommendations come from guidelines developed for adults, based on expert opinion. For patients with hypoproliferative thrombocytopenia (e.g., chemotherapy induced), a platelet transfusion threshold of 10,000/μL is recommended.[46] This is based on clinical trials in adults, which showed no increases in bleeding rates when comparing platelet transfusion thresholds of 10,000 vs. 20,000/μL.[102]

In the ICU, higher platelet transfusion thresholds are usually employed. Intensivists prescribe platelets for patients on ECMO if their platelet count is less than 100,000/μL; the same threshold is frequently used when a central nervous system procedure is undertaken. When the platelet count is less than 50,000/μL, platelets are usually given just before an invasive procedure (surgery, insertion of central venous catheter); it can also be considered in mechanically ventilated patients because the risk of pulmonary hemorrhage is significant. A threshold of 10,000 or 20,000/μL is recommended for lumbar puncture.

The platelet count must be monitored closely if a large amount, more than one blood volume, of crystalloids, and/or packed RBC units is given because this can significantly dilute the circulating platelet volume.[105]

The platelet count is not the only element to consider when deciding whether to administer platelets: increasing the threshold that triggers platelet transfusion may be appropriate if a rapid decrease in the platelet count is observed, if the risk of bleeding is higher, or if platelets are dysfunctional. Platelets are contraindicated in patients with thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia because of the increased thrombotic risk.

The capacity of platelets to stop a hemorrhage is not only related to their number, but also to their function. Many tests can be used to estimate platelet function: thromboelastogram, Sonoclot coagulation analyzed, Plateletworks analyzer, Hemostatus platelet function test, Platelet function analyzer, VerifyNow (Ultegra) System, and so on.[33] However, the results of these tests are not available on an emergency basis in most hospitals. Measurement of platelet mass may be a practical alternative. There is evidence that larger platelets exhibit increased hemostatic activity.[106] The results of a randomized clinical trial conducted in a neonatal ICU suggest that using platelet mass (Platelet count × Mean platelet volume) rather than platelet count to trigger a platelet transfusion may reduce the number of transfusions.[107] Nevertheless, it must be underlined that the clinical usefulness of all these tests remains undetermined in PICU.

There is significant diversity in the stated practice pattern with respect to platelet transfusions.[108] Most guidelines are based on experts' opinion, and not on hard data.[29,30] Significant work needs to be done to better determine when platelets should be administered in critically ill children.

Transfusion of Platelets: How

A simple rule of thumb suggests giving 1 or 2 platelet units per 10 kg, but not more than 6 units per transfusion. For children weighing less than 10 kg, the platelet dose can be 5 to 10 mL/kg of pooled or apheresis platelet unit. Transfusion of one platelet concentrate per m^2 of body surface generally increases the platelet count by 7000 to 11,000/μL. By body weight, the administration of one unit per 10 kg should increase the platelet count by 30,000 to 50,000/μL. However, a clinical trial, where platelet dose was estimated

by body surface area, evaluated low (1.1×10^{12} platelets/m^2), medium (2.2×10^{12} platelets/m^2), and high (3.3×10^{12} platelets/m^2) dose prophylactic platelet transfusions and did not find any differences in bleeding among adult or pediatric patients.[109] Platelet units must be used within 4 hours after they are delivered by the blood bank, but there is some evidence that the platelet count raises more if the unit is given within an hour. A filter with 80 or 170 micron pores must be used to remove aggregates that can form between harvesting and transfusion.

The volume of a platelet-rich unit is about 50 to 70 mL, whereas that of an apheresis platelet unit ranges from 200 to 300 mL; 90% to 95% of this volume is plasma. It is important to note that this plasma is not an adequate source of coagulation factors because their concentration drops rapidly during platelet storage. Platelet units can be volume reduced (removal of plasma) before transfusion, but this process can decrease the platelet count by 15% to 20%, shortens the storage time to 4 hours and delays platelet release from the blood bank by approximately 1 hour. Volume reduction can only be considered if there is a risk of severe cardiac overload, but is not recommended as a standard procedure because it can activate platelets.[46]

Unlike RBC units, ABO compatibility is not mandatory with platelets. However, it is better to use ABO compatible platelet unit in young patients with small blood volumes. Moreover it is recommended to deliver ABO compatible platelets when inventory and time permit, unless the plasma component has been substantially reduced. On the other hand, Rh compatibility is desired because all platelet units contain some RBCs. Transfusion of a Rh-positive unit to a Rh-negative patient can cause Rh alloimmunization; an anti-D immunoglobulin (Win Rho SDR) should be administered within 48 hours to prevent this complication when Rh positive platelets are given to an Rh-negative patient, particularly in female patients.[103]

The percent platelet increment (difference between post- and pretransfusion on pretransfusion platelet count) should be higher than 20% if the dose is adequate and if a repeat platelet count is performed 10 to 60 minutes posttransfusion; it should be higher than 10% if measured 18 to 24 hours posttransfusion.[103] Platelet refractoriness can occur because of nonimmune factors such as disseminated intravascular coagulation, in which platelet consumption can be high, acquired hemophagocytic syndrome, drugs such as amphotericin or heparin, or immune factors involving antiplatelet antibodies, and so on.[100,103,110] Treatment of the underlying problem is mandatory in such instances, for example stopping heparin administration. Patients with anti-IgA antibodies should receive washed platelets or platelets collected from IgA deficient donors.

Cryoprecipitate

Cryoprecipitate is a concentrated source of fibrinogen, factor VIII, factor XIII, and von Willebrand factor. It is stored at a minimum of −18° C for a maximum of 1 year. It is used in patients with congenital or acquired hypofibrinogenemia and patients with coagulopathy and significant bleeding. It is also used in patients with von Willebrand disease and hemophilia A only if specific factor concentrates are not available. The dose is 1 or 2 IU/10 kg (maximum, 12 units), which should increase fibrinogen level about 60 to 100 mg/dL (46). A blood filter (80 or 180 μm) should be used. The recommended rate of delivery is 30 minutes (maximum, 4 hours).

Transfusion Reactions and Complications

Transfusions of labile blood products (RBC, plasma, platelets) can cause immediate or delayed transfusion reactions and various complications. Immediate reactions usually occur during the transfusion or within six hours after the end of the transfusion. Delayed reactions can occur after a few days, weeks, or even years.

Red Blood Cells, Plasma, and Platelets

Immediate Transfusion Reactions

The incidence of typical immediate transfusion reactions to RBC, FP, and platelets is reported in Table 82-2. Acute transfusion reactions are probably underdiagnosed in critically ill children. In a study conducted in the PICU of Sainte-Justine Hospital, all transfusions between February 2002 and February 2004 were prospectively monitored.[111] A total of 2509 transfusions were administered to 305 patients; 40 acute transfusion reactions (1.6%) occurred: 24 nonhemolytic febrile reactions, 6 minor and 1 major (anaphylactic shock) allergic reactions, 4 isolated hypotensive reactions, 3 bacterial contaminations, 1 hemolytic reaction, and 1 TRALI.

The SHOT report on transfusion reactions observed in children in the United Kingdom from 1996 to 2005 estimated the incidence of adverse outcomes to be 18 per 100,000 RBC units issued for children less than 18 years, 37:100,000 for infants less than 12 months, and 13:100,000 for adults.[112] Among the 321 adverse reports in children, 82% were instances of incorrect blood component transfused, and 50 cases (14%) were acute transfusion reactions. The most important acute transfusion reactions are described below.

Respiratory System

TRALI is one of the most dangerous transfusion reactions. Two pathophysiologic mechanisms are currently proposed.[113,114] (1) According to the antibody hypothesis, TRALI is caused by an antigen-antibody reaction.[115] The antibodies (granulocyte antibodies and/or HLA class I or II antibodies) are present in the donor plasma and react with the recipient's WBC antigens (or rarely vice versa). The administration of such antibodies can directly injure the lung or can activate neutrophils, monocytes, and complement, creating an inflammatory reaction that may result in pulmonary damage.[115] (2) According to the "two-hit" or "neutrophil priming" hypothesis, recipients must first have a predisposing factor that "primes" their neutrophils, such as a septic state; then, the recipient's neutrophils are activated by donor plasma that contains leukocyte antibody or pro-inflammatory molecules like cytokines and bioactive lipids.[116]

The diagnosis of TRALI is made on the basis of clinical signs and symptoms, chest X-ray suggestive of pulmonary edema, and time relationship with transfusion (onset per-transfusion or within 6 hours posttransfusion). Causes of pulmonary edema other than TRALI should also be excluded, such as

Table 82–2 Incidence of Transfusion Reactions in Canada (Adults and Children)

	Risk per 1 Unit of Blood Component*			
	All Products	**RBC**	**FP**	**Platelets†**
EARLY TRANSFUSION REACTIONS (ONSET USUALLY <6 HOURS AFTER TRANSFUSION)				
Cardiorespiratory System				
*TRALI[152]	1:19,783	1:15,595	1:31,960	1:23,350
*TACO[152]		1:34,091	1:32,690	1:32,971
*‡Isolated hypotension[152]	+	1:102,273	1:108,968	1:98,914
§Cardiac arrhythmias[153]	–	+	+	–
Hematologic and Immunologic Systems				
*Acute hemolytic reactions[152]	1:31,189	1:26,914	1:18,161	–
*ABO incompatability[152]	1:15,595	1:85,227	1:108,968	1:98,914
*Major allergic reaction (anaphylaxis)[152]	1:6182	1:3889	1:11,117	1:23,350
Minor allergic reaction (urticaria)[134]	+	1:100	+	+
Other Acute Transfusion Reactions and Complications¶				
Febrile nonhemolytic reaction[127,154]	–	1:10	1:50 to 1:200	1:300
*Bacterial contamination[152]	1:31,189	1:51,136	1:65,381	1:49,457
DELAYED TRANSFUSION REACTIONS (ONSET USUALLY DAYS AFTER TRANSFUSION)				
Transfusion-associated graft-versus-host disease[82]	1:1 million	+	+	+
*Delayed hemolytic transfusion reactions[152]	1:255,682	1:163,452	–	–
*Posttransfusion purpura[152]	1:85,277	1:108,968	–	1:31,189
Transfusion-transmitted nonbacterial infections	See Table 83-3	+	+	+

TRALI, Transfusion-related acute lung injury; *FP,* frozen plasma; *RBC,* red blood cell; *TACO,* transfusion-associated circulatory overload.
*Reported in 2003.
†Risk per pool of 5 units of platelet.
‡Hypotension can be caused by allergic or hemolytic reactions, septicemia, citrate toxicity, reaction to leukocyte reduction filters, and bradykinins in the supernatant of blood products.
§One retrospective study involving 143 critically ill adults with sepsis or septic shock reported more atrial fibrillation ($P = .04$), cardiac arrest ($P = .03$), and "all cardiac events" ($P = .001$) in recipients of packed RBC units.[153]
¶Metabolic complications include hypothermia, metabolic alkalosis,[4] hypocalcemia,[155] hypomagnesemia,[4] hyperkalemia,[155] hyponatremia,[12] and hyperglycemia.[156]

fluid overload or cardiac dysfunction. A panel of experts suggested a consensus definition of TRALI in 2004[117]; the list of diagnostic criteria advocated by these experts is detailed in Box 82-1. The experts defined TRALI as a new ALI for which no other risk factor than the transfusion can be found. They suggested to use the term "possible TRALI" if another risk factor can be temporally related to the ALI. TRALI is a clinical syndrome, and no laboratory test is pathognomonic of TRALI, but the presence of HLA and/or neutrophil antibodies in the donor plasma is highly suggestive[113]; however, the absence of such antibodies does not exclude a typical case of TRALI.

The diagnostic criteria advocated by the panel of experts in 2004 exclude the possibility that a TRALI appears in a patient who already presents an ALI or an ARDS, a frequent occurrence in PICU. There is indeed some evidence that a TRALI should also be considered in some patients with ALI/ARDS before a transfusion if their respiratory dysfunction deteriorates significantly during or after a transfusion. Marik at al.[118] suggested expanding the definition of TRALI in ICU to ALI/ARDS observed within 72 hours after the transfusion of a blood product: they reported that such "delayed TRALI syndrome" occurred in up to 25% of critically ill adults receiving a blood transfusion. Church et al.[119] also reported an association between the transfusion of plasma and/or packed RBC units and ALI/ARDS. The bioactive substances contained in packed RBC and plasma units can cause or add to the severity of cases of ALI/ARDS.[119,120] Further investigation is required to better characterize the epidemiology, the mechanisms and the clinical impact of transfusion-related ALI/ARDS in PICU.

All blood products that contain plasma, even in minute quantities, can cause a TRALI. When such reaction occurs, the transfusion must be stopped immediately and supportive treatment administered with oxygen (in 100% of the cases) and mechanical ventilation (in 70% of the cases). The associated hypotension may be unresponsive to fluid administration and may require use of inotropes/vasopressors.[121] Diuretics are not useful; they are contraindicated in hypotensive patients.[122] All suspected TRALI reactions must be reported to the blood bank, because the donor's other blood products have to be withdrawn.

The prognosis of cases of TRALI is usually good if the patient survives, but mortality rate of 6% is reported. In survivors, resolution is usually rapid (within 96 hours) and there are no long-term sequelae.[122]

Box 82–1 Diagnostic Criteria of TRALI and Possible TRALI[117]

TRALI*

Diagnostic criteria of ALI:
- Acute onset
- Hypoxemia: PaO_2/FiO_2 ≤300 or SpO_2 <90% on room air
- Bilateral infiltrates on frontal chest radiograph
- No evidence of left atrial hypertension (i.e., no circulatory overload)

No preexisting ALI before transfusion
Onset during or within 6 hours posttransfusion
No temporal relationship to an alternative risk factor of ALI (see list of factors below)

Possible TRALI

ALI
No preexisting ALI before transfusion
Onset during or within 6 hours posttransfusion
A clear temporal relationship to an alternative risk factor for ALI:
- Risk factors of direct lung injury: aspiration, pneumonia, toxic inhalation, lung contusion, near drowning
- Risk factors of indirect lung injury: severe sepsis, shock, multiple trauma, burn injury, acute pancreatitis, cardiopulmonary bypass, drug overdose

*All criteria must be present.

Cardiovascular System

TACO figures among the most frequent potentially severe adverse events attributable to RBC transfusion.[123] Its incidence in PICU is not well characterized. It is most commonly associated with a rapid or massive transfusion that causes pulmonary edema secondary to heart failure.[124] Reduced cardiac reserve, chronic and severe anemia (Hb <5 g/dL), and age (infants and elderly patients) are risk factors. The main symptoms are respiratory distress, hypoxemia, tachycardia, and hypertension. When a TACO is suspected, the transfusion must be stopped and supportive treatment with oxygen and diuretics administered. Slow transfusion (≤1 mL/kg/h) in at-risk patients can prevent TACO.

Isolated hypotensive reactions are increasingly recognized,[125] but their etiology remains uncertain. They are probably attributable to bradykinin generation, which can happen when a blood product is exposed to negatively charged surfaces (e.g., filters). The risk of hypotensive reaction is increased in patients receiving angiotensin-converting enzyme inhibitors or with diminished bradykinin metabolism.[126] Hypotensive reactions are more frequently associated with platelets than with RBC and plasma. The hypotension may happen alone or with some flushing; it occurs rapidly after the transfusion begins. The treatment is straightforward: the transfusion must be stopped and supportive treatment (i.e., fluid bolus) should be undertaken.

Other Acute Transfusion Reactions

Nonhemolytic febrile reaction is the most frequent and benign acute transfusion reaction. In addition to fever, it can be accompanied by chills, discomfort, headache, nausea, or vomiting.[127] The symptoms usually occur toward the end or soon after a transfusion. These reactions are mediated by pyrogenic substances that accumulate during storage, or by recipient's antibodies that bind with leukocytes from the donated blood, which allow activation of the complement system and production of cytokines.[80] Acetaminophen can be used to minimize fever, but premedication with acetaminophen, diphenhydramine, or steroids is not useful.[128,129] A decrease in the incidence of these reactions is reported with prestorage leukocyte reduction.[130,131]

Acute hemolytic reactions may be much more serious. They are caused by lysis or accelerated destruction of RBC from immunological incompatibility between donor and recipient blood.[132] The mortality rate associated with transfusion errors is less than 10%.[133] ABO mismatch is the most frequent and most severe of the blood group incompatibilities, with hemolysis (1 in 60,000) and death (1 in 600,000) as the results.[29] In most instances, the patient received a packed RBC unit that was prepared for another patient. The risk that such error happens is obviously higher in an emergency setting and its prevention warrants careful verification by medical staff of all blood products administered. The reaction is characterized by fever, chills, discomfort, diffuse pain, and hemoglobinuria; hypotension, shock, renal failure, and disseminated intravascular coagulation are also observed in some cases. When such reaction is suspected, the transfusion must be stopped immediately and supportive treatment must be administered. To avoid these hemolytic reactions, the donor and recipient's compatibility must be thoroughly checked (ABO and Rh types, unit identification number) and the recipient must be properly identified (name and medical record number) when the sample is taken for pretransfusion analyses as well as before the transfusion is started.

Nonimmune hemolysis can be caused by mechanical trauma to RBCs, rapid administration through a small catheter, excessive warming or freezing, or contact with hypotonic solution.

Allergic transfusion reactions result from the interaction between donor allergens and recipient antibodies (IgE) that provokes a type I hypersensitivity reaction.[134] Other possible mechanisms are: preexisting class-specific anti-IgA in patients with IgA deficiency, preexisting antibodies to polymorphic forms of other serum proteins (e.g., IgG, albumin, haptoglobin) that the patient is lacking, transfusion of allergens to which a patient is presensitized, (drugs, chemicals, etc), and passive transfer of IgE antibodies to transfused patients.[134] The reaction can be minor (e.g., isolated urticaria) or major (e.g., hypotension, anaphylactic shock, respiratory distress, digestive disorders). A severe reaction usually occurs quickly, whereas a benign reaction may occur up to 4 hours after the transfusion is completed. When an allergic reaction is suspected, the transfusion must be stopped and supportive treatment undertaken with antihistamines, steroids, and epinephrine if required. Prevention must be considered. Premedication of patients with antihistamines is suggested if they have already presented two minor episodes. In patients with major reactions, premedication can be used with steroids and antihistamines. Washed RBC and platelets units can also be used. Patients with anti-IgA antibodies must receive blood products from donors with IgA deficiency or products that have been washed several times. Leukocyte reduction does not offer any benefit.

Bacterial contamination is more frequent with platelets than with RBC units or plasma since platelet concentrates are stored at 20° C to 24° C. Contamination may be due to unsuspected bacteremia in the donor, skin flora when taking a blood sample from the donor or the environment, and product handling.[135] The most common germs are: gram-negative bacteria such as *Klebsiella pneumoniae*, *Serratia marcescens*, and Pseudomonas species, and gram-positive such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus cereus*. The reaction is characterized by fever and chills and may lead to septic shock. Symptoms usually appear during or within 4 hours after transfusion. When a bacterial contamination is suspected, the transfusion must be stopped immediately, wide spectrum antibiotics must be given (third-generation cephalosporin or beta-lactam in combination with aminoglycoside) and supportive treatment administered. The blood bank must be informed immediately, as other blood products from the same donor may need to be withdrawn.

Delayed Transfusion Reactions

Among the 321 adverse events reported in children by SHOT in UK from 1996 to 2005,[112] there were five cases of severe delayed transfusion reactions, including two cases of TAGVH disease. Transfusion-associated graft versus host disease is rare but very serious.[82,83] It may occur when viable lymphocytes from a donor are infused to a recipient who is unable to reject them because of immuno-suppression or partial HLA matching (closed donor genetic profile). Donor leukocytes can then persist in the recipient; because these lymphocytes recognize the recipient's HLA antigens as foreign, an immune reaction is triggered. Signs and symptoms (generalized skin rash, diarrhea, abnormal liver function, or fever) appear 8 to 10 days after transfusion.[136] Associated complications are aplastic anemia with pancytopenia, which may lead to hemorrhage and severe infections. The mortality rate is 90%. The risk of TAGVH is 1 in 700 after cardiopulmonary bypass in some immunocompetent adult populations.[137] The risk is also high in premature babies and if a patient with a congenital or acquired immunodeficiency receives a nonirradiated RBC unit or if the blood was a directed donation collected from a relative. Neoplasia (e.g., leukemia, solid tumors), chemotherapy and transplantation (stem cell, bone marrow, solid organ),[138] intrauterine transfusions, and exchange-transfusions are other risk factors. No effective treatment is recognized. Prevention can be accomplished by irradiating blood products that will be transfused to at-risk patients or that result from directed donations.

Delayed (extravascular) hemolytic reactions result from the interaction between recipient irregular alloantibodies and donor RBCs. They involve either antibodies that were present before transfusion, but were missed because they were undetectable by cross-matching, or antibodies that appear after the transfusion. Involved antibodies are usually E, Jk^a, c, Fy^a, and K.[139] These reactions occur 3 days to 2 weeks after the transfusion. Symptoms include anemia and jaundice. The outcome is usually good except in some patients with sickle cell anemia. There is no specific treatment, but using only appropriate RBC units can prevent cases.

Posttransfusion purpura is characterized by dramatic, sudden, and self-limiting thrombocytopenia. The pathogenesis is unclear, but it is presumably related to the development of platelet-specific antibody following transfusion. The platelet count drops below 10,000/μL 5 to 10 days after a transfusion was given to a patient with a history of sensitization by pregnancy or prior transfusion.[140] Purpura and diffuse hemorrhages (mucosal, gastrointestinal, urinary, cerebral) may be observed. The thrombocytopenia is refractory to platelet transfusion. The mortality rate is 8%. Treatment includes steroids, plasmapheresis, and immunoglobulins.

Complications Related to Massive Red Blood Cell Transfusion

Massive transfusion is defined by giving more than one circulating volume of blood within 24 hours, or more than 50% of the circulating blood volume in three hours or less, or 10 RBC units in adults.[99] A number of complications may occur: (1) coagulopathy and dilutional thrombocytopenia, which may trigger bleeding[141]; (2) hypothermia due to a rapid infusion of cold blood products, which can lead to arrhythmias, platelet dysfunction, and cardiac dysfunction; (3) citrate toxicity that may trigger hypocalcemia, hypomagnesemia, and metabolic alkalosis[142]; and (4) hyperkalemia. These complications can be avoided by implementing the following precautions: use a blood heater if the transfusion rate exceeds 50 mL/kg/h; monitor the coagulation profile and transfuse platelets, plasma or cryoprecipitate to maintain a platelet count greater than 50,000/μL, an INR less than 1.5 to 2.0, and fibrinogen level greater than 0.1 g/dL; monitor hypocalcemia, and administer $CaCl_2$ if necessary.[138]

Transfusion Transmitted Infections

In the United States, blood donation is tested at least for the following infectious agents: hepatitis A, B and C, human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), West Nile virus (seasonal), and syphilis.[46] These tests and better donor selection leads to a significant decrease in the risk of transfusion-transmitted infectious diseases. However, there will always be some residual risk, attributable to the "window period" (time from the beginning of an infection to the time when tests can detect the infection) and to false-negative results. Table 82-3 lists the risks of contracting specific infections with transfusion.

Transfusion-Related Immunomodulation

There is strong evidence that transfusions might generate and/or enhance both anti- and proinflammatory reactions. Clinically important immune suppression is described in recipients of RBC units. For example, transfusions of packed RBC units have been reported to improve renal and cardiac allograft survival. This immune suppression might explain the increased rates of nosocomial infections reported in transfused critically ill adults.[143,144]

On the other hand, many proinflammatory molecules are found in RBC units, and may initiate, maintain, or enhance an inflammatory process.[13] The WBC and these substances may trigger or maintain a systemic inflammatory response syndrome in the recipients of RBC units. Administering a RBC transfusion to a critically ill patient with systemic inflammatory response syndrome may stimulate their inflammatory syndrome and constitute a "second hit," which can cause additional organ dysfunction, contribute to MODS,[145] and

Table 82–3 Transfusion-Transmitted Nonbacterial Infectious Diseases in Canada

Infection	Risk per Units of Blood Component*
HIV (AIDS)†	<1:4 million
Hepatitis B†	1:82,000 to 1:275,000
Hepatitis C†	<1:2.8 million
HTLV type I/II†	<1:1 million
Parvovirus B19†	1:5000 to 1:20,000
Cytomegalovirus†	Rare
Other infections‡	Low

HIV, Human immunodeficiency virus; *HTLV,* human T-cell lymphotropic virus.
*Most transfusion-transmitted infections are attributable to RBCs. However, there is historic evidence that the following infectious agents can be transmitted by plasma-derived products: HIV, hepatitis B and C, HTLV, and parvovirus B19—but not cytomegalovirus or parasites.[152]
†Reference 152.
‡Many other agents can be transmitted by a transfusion, such as West Nile virus, insect-borne zoonoses (e.g., malaria,[157] babesiosis,[158] *Bartonella quintana,*[159] and variant Creutzfeld-Jacob disease[160]).

perhaps ultimately result in higher mortality rates.[143] Some clinical data suggest that these risks decrease significantly if the packed RBC unit is leukocyte-reduced before storage.[68,146] However, in vitro data suggest that some inflammatory mediators are active even in leukocyte-reduced packed RBC units.[147] There are presently no data on this issue in pediatrics. The clinical impact of RBC transfusion on the immunological responses of critically ill children remains to be determined.

Complications Specific to Plasma Transfusion

Overall, the noninfectious and infectious complications associated with FP are similar to those of RBC transfusions, excluding hemolysis. The most notable risks associated with FP transfusion are TRALI and TACO. There are antibodies and other biologically active substances in plasma, but data suggest that SD plasma may be associated with a reduced incidence of TRALI. Frozen plasma is known to have immunomodulative properties,[148] which may explain why plasma is associated with an increased risk of MODS, ALI/ARDS,[119,149] and nosocomial infections.[150] Additionally the large volumes of FP transfused can result in TACO. Allergic reactions are also relatively common with FP transfusions (1% to 3%).

The risk of transfusion-transmitted viral infections is the same for FP and RBC units. Solvent detergent plasma has a reduced risk of infection related to enveloped viral pathogens, but the risk for nonenveloped viruses is not affected and the risk could be higher with regard to emerging nonenveloped viruses.

Complications Specific to Platelet Transfusion

The overall risk of clinically symptomatic adverse transfusion reactions attributed to a platelet transfusion was 10.9 per 100 pooled units in Canada.[123] Major allergic reactions and bacterial contamination are the most frequent severe complications associated with platelet transfusion.[123] Serious noninfectious complications of platelet transfusion are similar to those reported with plasma and RBC with the exception of hemolytic transfusion reactions. Rarely, hemolytic transfusion reactions can be seen after the transfusion of non-ABO identical platelets, which contain anti-A or anti-B antibodies. Platelet transfusion may also be associated with specific adverse effects including platelet refractoriness due to HLA alloimmunization. Prestorage leukocyte-reduced platelet products are available in most North American blood banks, which significantly decrease the risk of HLA alloimmunization and platelet refractoriness, nonhemolytic febrile reactions, and CMV transmission.

The most important infectious complication associated with platelet transfusion is bacterial infection. As platelet concentrates are stored at room temperature, the incidence of bacterially contaminated platelet products is higher than with RBCs. The risk of bacterial infection can be significantly reduced, but not eliminated, by bacterial testing (e.g., routine culture). The risk of other transfusion-transmitted infections is similar for platelets and other blood components.

Treatment of Transfusion Reactions

The following symptoms and signs suggest that an acute blood reaction occurred: fever, shivering (rigors), pain, anxiety, agitation, dyspnea, hypotension, hypertension, hemorrhage, shock, and hemoglobinuria (pink or red urine).

If a transfusion reaction is suspected, the transfusion must be stopped immediately, an intravenous access with NaCl 0.9% must be maintained, all measures to insure patient stability must be undertaken, verification that the patient received the correct unit must be done, a visual inspection of the unit must be done and described in the patient hospital chart, clinical data on the event must be detailed in the hospital chart, and the patient should be monitored for at least a few hours. In many centers, the unit that was being transfused, the filter and the tubing being used, and the remaining blood product are returned to the blood bank. A workup must be done to assess for infection as well as to measure antibodies, antigens, free Hb, and sometimes other markers of metabolic disturbance (acidosis, hyperkalemia, hypocalcemia, etc.). For example, collecting blood samples from the patient, including cultures, is mandatory if bacteremia is suspected, and it can be useful to measure antibodies, antigens, free Hb, or other markers of metabolic disturbance (acidosis, hyperkalemia, hypocalcemia, etc.). All possible transfusion reactions must be reported to the appropriate blood agency, which is the blood blank in many hospitals.

Conclusion

A transfusion can save a life, but it can also cause significant problems. The risk of death attributable to the transfusion of a labile blood product is low: only 1 death over 2,845,459 blood component units was reported in the United Kingdom during year 2008.[151] However, serious reactions and severe complications can happen. A transfusion is a serious matter: it should be prescribed only if deemed necessary. Closed monitoring of the recipient is mandatory while a transfusion is given.

References are available online at http://www.expertconsult.com.

Critical Illness Involving Children Undergoing Hematopoietic Progenitor Cell Transplantation

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PEARLS

- Patients undergoing allogeneic hematopoietic progenitor cell transplant (HPCT) experience prolonged immune dysregulation and are at risk for both opportunist infection and graft-versus-host disease (GVHD).
- HPCT patients experiencing respiratory symptoms including a new oxygen requirement deserve prompt evaluation by the critical care team as they are at risk for rapid development of respiratory failure.
- Outcomes for HPCT patients requiring intensive care unit care have improved over the past decade.
- Patients who develop GVHD are at high risk for developing other transplant related toxicities.

Hematopoietic progenitor cell transplantation (HPCT) has evolved as treatment for a variety of congenital and acquired malignant and nonmalignant disorders. Over the years the name of this procedure has changed in an attempt to be more accurate. Throughout the literature, it has been referred to as bone marrow transplant or HPCT and now is sometimes referred to as hematopoietic progenitor cell transplant (HPCT).

The first successful human bone marrow transplant occurred in pediatrics for severe combined immunodeficiency. Reported in 1968, the patient received marrow from a human leukocyte antigen (HLA)-matched sibling.[1] Presently, in adults and children, the majority of allogeneic transplants are performed for the treatment of malignant disorders such as leukemias and lymphomas, although the field continues to expand to include nonmalignant disorders such as autoimmune disorders, metabolic diseases, immune deficiencies, and hemoglobinopathies. Since its inception, the field of pediatric HPCT has demonstrated vast improvements in morbidity and mortality related to transplantation; however, there are still many hurdles that we need to overcome. The major barriers that still contribute significantly to the morbidity and mortality of allogeneic transplantation are relapse of disease, toxicity from treatment, infection, and graft-versus-host disease (GVHD).

Sources of Hematopoietic Progenitor Cells and Identification of Donors

HPCT involves transplanting hematopoietic progenitor cells from a donor source into a recipient. These stem cells are capable of self-renewal and terminal differentiation that ultimately give rise to myeloid cells, lymphocytes, erythrocytes, and platelets (Figure 83-1). The donor source of these stem cells can be from the patient/recipient themselves (autologous) or from another individual (allogeneic). The source of the donor (autologous vs. allogeneic) is generally dependent on the indication for which the transplant is being performed. Autologous transplants can be used for the treatment of nonhematologic malignant diseases, whereas allogeneic transplants are used for hematologic malignancies and marrow failures or dysfunction. Traditionally, HPCT has been performed using stem cells obtained from bone marrow. However, stem cells can be mobilized into the peripheral blood by the use of cytokines (e.g., granulocyte-colony stimulating factor [G-CSF]) or upon recovery from chemotherapy. These peripheral blood stem cells (PBSCs) allow for faster hematopoietic recovery and possibly less tumor contamination than bone marrow for autologous transplantation. However, there may be more side effects in the allogeneic setting (increased incidence of graft versus host disease).[2] Umbilical cord blood has also been shown to contain large numbers of stem cells capable of reconstituting hematopoiesis. The first HPCT using cord blood was performed in 1988 on a 5-year-old child with Fanconi anemia using the patient's HLA-identical sibling.[3] Since then, unrelated cord blood stem cells have been used and numerous public cord blood banks have been established worldwide. In circumstances in which there is no matched unrelated donor or cord blood found in a timely fashion, a haploidentical transplantation can be performed using a parent or a sibling. Histoincompatibility barriers of a mismatched transplantation are overcome by using mega-doses of stem cells. However, for this to be successful, a majority of the T cells have to be removed from the graft to prevent severe GVHD. Unfortunately, this increases the

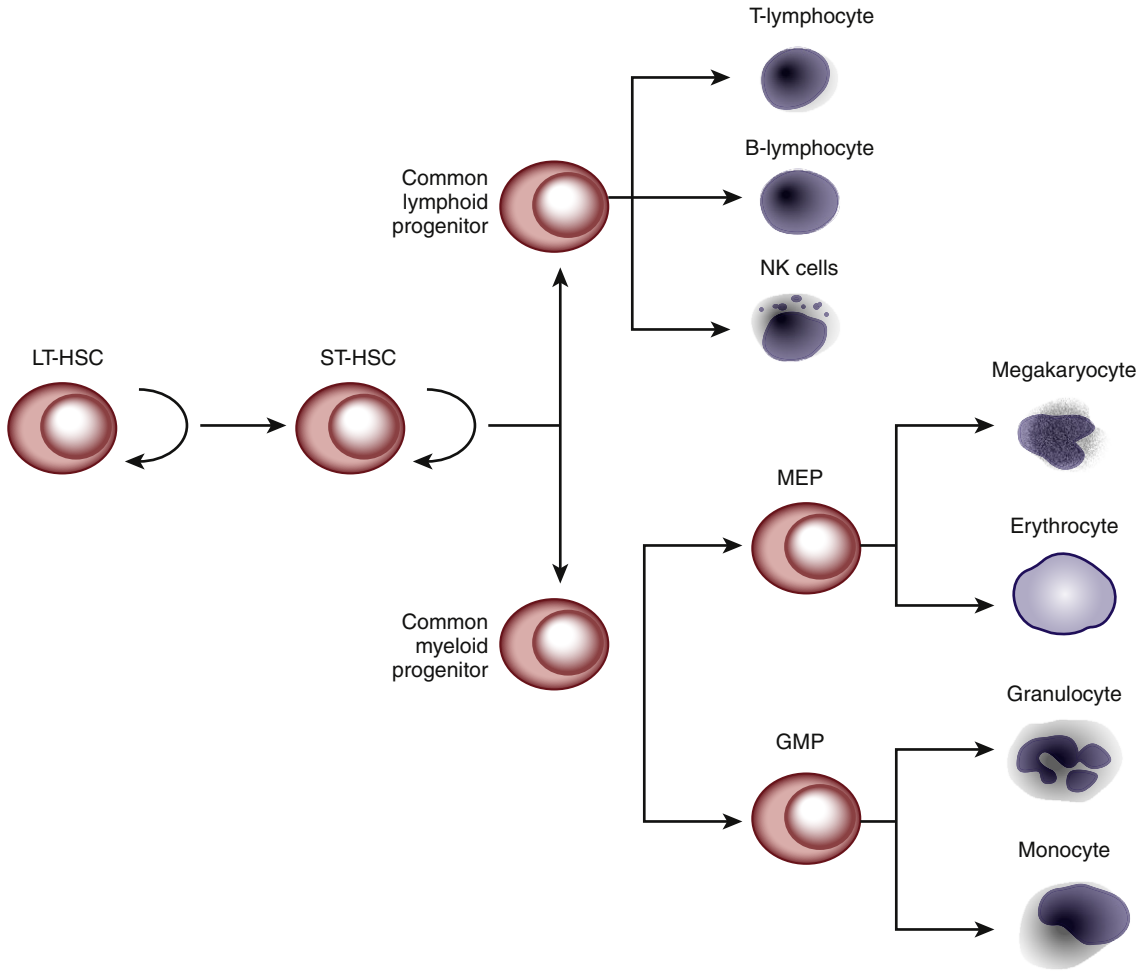

Figure 83–1. As hematopoietic stem cells divide, they give rise to common lymphoid and common myeloid precursor cells that eventually generate all mature blood lineages of the body. *GMP,* Granulocyte-monocyte precursors; *LT-HSC,* long-term hematopoietic stem cells; *MEP,* megakaryocyte-erythrocyte precursors; *NK,* natural killer; *ST-HSC,* short-term hematopoietic stem cells. *(Modified from Leung AYH, Verfaillie CM: Stem cell model of hematopoiesis. In* Hematology: basic principles and practice, *ed 4, Philadelphia, 2001, Elsevier.)*

risk for severe infection and relapse of the patient's original disease.[4,5]

HLAs are expressed on the surface of various cells, in particular white blood cells (WBCs). These antigens are also known as the major histocompatibility complex with relevant genes on the short arm of chromosome 6.[6] This genetic region has been divided into chromosomal regions, called classes. Classes I and II are important in transplantation.

Class I is made up of HLA-A, HLA-B, and HLA-C and class II is made up of HLA-DR, HLA-DP, and HLA-DQ, as well as variations on these genes. Traditionally, the loci critical for matching for a bone marrow donor are HLA-A, HLA-B, and HLA-DR. HLA-C and HLA-DQ have recently gained importance and are now considered in determining the best available donor.[6,7] Ideally a matched sibling donor is the best donor for a patient. However, only 25% of patients with siblings are fortunate to have a matched sibling donor. If there is no sibling donor, an alternative donor is identified using the National Marrow Donor Program (NMDP) that has approximately 9 million potential donors and nearly 150,000 cord blood units available for patients who need a hematopoietic cell transplant (bone marrow, PBSC, or cord blood transplant).[8] As the degree of mismatch between patient and donor increases, so do the risks of complications from transplant, especially GVHD and rejection of the graft.

Indications and Outcomes

HPCT has been used for a variety of diseases. Autologous transplantation has traditionally been used to treat nonhematologic malignant diseases by escalating the doses of chemotherapy to myeloablative doses to hopefully eradicate the cancer. Recently, successive (two or three) autologous transplants have been performed with nonmyeloablative doses of chemotherapy particularly in brain tumors. The rationale of giving hematopoietic stem cells after the chemotherapy is completed is to minimize the period of neutropenia that will hopefully reduce the number of infections.[2]

Allogeneic HPCT has been performed for hematologic cancers that in children are most commonly leukemias including acute lymphoblastic leukemia and acute myelogenous leukemia. It has also been used to treat hematologic diseases including sickle cell anemia, thalassemias, and severe aplastic anemia. A variety of immune deficiencies and metabolic disorders have been cured by allogeneic transplant including severe combined immune deficiency and hemophagocytic lymphohistiocytosis (Table 83-1).[2]

Survival from HPCT has improved in the recent years. Typically for autologous transplantation the incidence of treatment related mortality is less than 10%; however, the majority

Table 83–1 Indications for Pediatric Hematopoietic Progenitor Cell Transplantation

AUTOLOGOUS TRANSPLANTATION
Malignant Disorders
High-risk neuroblastoma
Relapsed non-Hodgkin lymphoma
Relapsed Hodgkin disease
Medulloblastoma
Germ cell tumors
Brain tumors
Relapsed Ewing sarcoma
Nonmalignant Disorders
Autoimmune disorders
ALLOGENEIC TRANSPLANTATION
Malignant Disorders
Acute myelogenous leukemia
Acute lymphoblastic leukemia
Chronic myeloid leukemia
Myelodysplastic syndromes
Juvenile myelomonocytic leukemia
Nonmalignant Disorders
Aplastic anemia
Fanconi anemia
Severe combined immunodeficiency
Thalassemia major
Diamond-Blackfan anemia
Sickle cell anemia
Wiskott-Aldrich syndrome
Osteopetrosis
Inborn errors of metabolism
Hemophagocytic lymphohistiocytosis
Shwachman-Diamond syndrome
Congenital immune deficiencies

of failures of transplant are due to recurrent disease. Specifically the event-free survival rate for autologous HPCT for high risk neuroblastoma ranges from 33% to 57%.[9-11] For recurrent or refractory non-Hodgkin lymphoma the event-free survival in autologous HPCT ranges from 27% to 59%.[12] In relapsed or refractory Hodgkin disease the event-free survival ranges from 20% to 62%.[12] The NMDP and the Center for International Bone Marrow Transplantation Research data from 1998 to 2006 for acute lymphocytic leukemia shows the probability of survival at 5 years in matched sibling allogeneic HPCT for early or intermediate disease is approximately 50% versus 25% for advanced disease.[13] For unrelated donors the 5-year survival for pediatric patients is significantly increased for patients in first complete remission (CR1) (54%) and second complete remission (CR2) (49%) compared with patients with advanced disease (26%) (log-rank $P < .0001$).[14] Advanced disease is defined as third complete remission or refractory disease. For acute myelogenous leukemia the 5-year survival for pediatric patients (<18 years of age) transplanted for acute myeloid leukemia with unrelated donors is significantly increased for those patients transplanted in CR2 compared with those transplanted in CR1 or with advanced disease. However, a greater percent of patients transplanted in CR1 had poor-risk cytogenetics compared to those patients who were transplanted in CR2 (log-rank $P < .0004$). The 5 yr survival rates are 31% for CR1, 51% for CR2, and 29% for advanced disease.[15] However, the data for pediatric patients with AML in CR1 with a matched sibling shows a survival rate at 5 years of 65%.[16]

For patients with Fanconi anemia and severe aplastic anemia, the 5-year survival is 55% for allotransplants with unrelated donors facilitated by the NMDP in children younger than 18 years.[17] Pediatric survival rates after matched sibling HPCT for SAA are now excellent, 85% and even higher in some series.[18] In Wiskott-Aldrich disease and severe combined immune deficiency, the 5-year survival is approximately 75% to 80%.[19,20] For inherited metabolic disorders, the overall survival of pediatric patients with adrenoleukodystrophy/metachromatic leukodystrophy is approximately 50% and for Hurler syndrome is approximately 60% when using unrelated donor transplants facilitated by the NMDP from 1998 to 2006 (Table 83-2).[21]

Transplant Procedure

Conditioning Regimen

Patients undergoing HPCT are subjected to a treatment regimen referred to as a conditioning regimen or preparative regimen prior to infusion of the hematopoietic progenitor cells. The purpose of this preparative regimen is multifold. In cases of malignant disorders, it provides cytoreduction and/or eradication of disease. In addition, the preparative regimen must be immunosuppressive in allogeneic transplantation to allow the donor cells infused to establish themselves in the marrow cavity and overcome host rejection. The precise conditioning regimens can include chemotherapy alone or in combination with radiation. Numerous regimens have been explored and are dependent upon the disease for which the transplant is required and the research interests of the institution performing the transplant.

Stem Cell Harvesting/Collection/Cryopreservation

Stem cells can be collected or harvested from either bone marrow or peripheral blood. For patients or donors undergoing bone marrow harvest, general anesthesia or regional anesthesia is given with the patient in the prone position. Bone marrow is generally aspirated using special bone marrow harvest needles percutaneously from the posterior iliac crests using numerous passes. The amount of marrow taken is based on the size of the recipient. If there is a significant size discrepancy between the donor and the recipient (recipient larger than the donor), the donor may lose a significant amount of blood because bone marrow is well perfused with blood. Donors can be placed on iron therapy after harvest, or they can electively store autologous blood ahead of time. A newer technique allows for the collected marrow to be processed with removal of red blood cells (RBCs) (particularly necessary in cases of major ABO incompatibility between donor and recipient), and these RBCs can be transfused to the donor postoperatively.

Peripheral blood stem cells can be mobilized in patients recovering from chemotherapy (autologous) or by giving allogeneic donors cytokines such as G-CSF. Their stem cells then can be collected using an apheresis machine in an outpatient setting. Collection of sufficient cells for transplantation may require several apheresis procedures. Stem cells for allogeneic transplantation usually are collected on the day they are anticipated to be reinfused into the patient. Autologous collection

Table 83–2 Survival Rates for Pediatric Diseases Undergoing Hematopoietic Progenitor Cell Transplantation

		Survival Rate		
			Allogenic Transplantation	
	Stage	Autologous Transplantation	Sibling Donor	Unrelated Donor
Acute lymphocytic leukemia	Complete response (CR1 to CR2)	NA	50%	49%–54%
	Advanced disease	NA	25%	26%
Acute myeloid leukemia	CR1	NA	65%	31%
	CR2	NA	45%	51%
	No remission	NA	NA	29%
Hodgkin disease	Relapsed/refractory	20%–62%	NA	NA
Non-Hodgkin lymphoma	Relapsed/refractory	27%–59%	NA	NA
Neuroblastoma stage IV		33%–57%	NA	NA

NA, Not applicable.

of stem cells requires cryopreservation of the cells until the day of reinfusion. Dimethyl sulfoxide is added to the collection product to ensure cell viability, and the cells are frozen in liquid nitrogen until needed.

Stem cells can be collected from umbilical cord blood. After delivery of the infant, sterile umbilical venous access is obtained and the blood is collected into anticoagulated tubes. This can be done either before or after delivery of the placenta. A sample of this cord blood is used for HLA typing and infectious disease testing; the remainder is cryopreserved.

Reinfusion

The day of stem cell reinfusion is referred to as day 0 for the transplant period. Cryopreserved stem cells are thawed in a water bath under sterile conditions and may be washed to remove the dimethyl sulfoxide cryopreservant. Stem cells then are infused into the patient though the indwelling central venous catheter. These cells are capable of migrating into the bone marrow on their own. Blood transfusion–like complications can occur with reinfusion of stem cells, and patients are generally placed on cardiac monitors with emergency medications available at the bedside during the infusion. The infusion procedure is generally short, lasting anywhere from approximately 10 minutes to 4 hours, depending on the volume of cells infusing.

Recovery Period

After the reinfusion of stem cells, patients wait for count recovery to occur and receive treatment for any toxicities they have developed. Allogeneic transplant patients receive immunosuppressive medicines to prevent GVHD. Most patients are hospitalized for the entire transplant procedure, starting with the conditioning regimen. However, there is a trend toward outpatient HPCT, particularly in the autologous setting. A typical hospitalization for HPCT is 4 to 6 weeks, but it may be prolonged if umbilical cord blood is used or shortened for autologous transplants.

Complications

Patients undergoing HPCT are at high risk for complications that may require a stay in the pediatric intensive care unit (PICU). In one series, 19% of pediatric HPCT patients required a PICU admission.[22] In other published series, 6% to 25% of pediatric HPCT patients required mechanical ventilation.[23,24] Because of the high use of critical care services by HPCT patients, it is beneficial for the pediatric intensivist to be familiar with their complications.

The reasons for these patients being at such high risk for critical illness are multifactorial. Many of these patients are undergoing HPCT for an underlying disease that places them at risk for critical illness such as malignancies, severe immunodeficiencies, and metabolic disorders. To make room for the new hematopoietic progenitor cells, patients are given conditioning regimens with high doses of toxic chemotherapy and/or radiation. This makes them severely immunocompromised; placing them at high risk for opportunistic infections. The conditioning agents themselves cause significant oxidative stress, and may be the common denominator behind many of these complications.[25]

While mortality rates for HPCT patients requiring ICU care are quite high in comparison to the general ICU population, they appear to be improving. Data from the 1980s showed mortality rates for mechanically ventilated pediatric HPCT patients to be near 90%.[24,26] However, more recent data indicate the mortality rates to be closer to 60%.[24,27,28] In a single institution report, HPCT patients requiring vasopressor or inotropic support due to sepsis had PICU mortality rates of 30%. In the subgroup of septic patients requiring both inotropic and/or vasopressor support and mechanical ventilation, mortality rates were 74%.[29] Some of the improvements seen in outcomes over the years may be due to differing characteristics of the patients, as very few studies reported severity of illness scores.[26] In any case, no series reporting on mortality of pediatric HPCT patients was able to predict with 100% certainty that a given patient would not survive. Therefore it remains up to the critical care team in conjunction with the transplant team to use their best judgment when making recommendations to families regarding appropriateness and duration of critical care services for this complex patient population.

Cardiac Complications

Cardiac complications following HPCT can occur acutely during the immediate transplant period or as a late sequelae in survivors. The heart may be injured during the transplant

process from a variety of pathophysiological etiologies.[30,31] First, previous cardiotoxic treatments and therapies such as anthracyclines and iron overload from frequent red cell transfusions may predispose the heart to subsequent injury during transplantation. In addition, cardiotoxic therapies such as cyclophosphamide and irradiation used as part of the preparative regimen may further injure the recipient heart.[32,33] Moreover, hyperhydration therapies, blood product transfusions, and impaired renal function may place further stress on the heart. Finally, sepsis, that commonly affects the HPCT patient, has been found to decrease cardiac contractility.[34]

Despite these potential cardiac problems, cardiac complications are relatively rare in the early posttransplant period after HPCT. In an analysis of 2821 adult and pediatric patients, only 26 (0.9%) experienced a major or fatal cardiac complication in the first 100 days after transplant.[35] Seven of the 26 cardiac complications occurred in children, and given the median age of 22 years in that trial, an incidence of approximately 0.5% may be inferred for pediatric HPCT recipients. Among the 26 patients with significant cardiac complications, 11 had evidence of heart failure, 5 had pericardial tamponade, and 10 had dysrhythmias.[35] All 11 patients with heart failure died compared with only one each with tamponade or a dysrhythmia. All cases of heart failure occurred between day −6 and day +35. Four of the seven pediatric patients had heart failure. In another report, the Associazione Italiana Ematologia Oncologia Pediatrica-BMT Group described their transplant-related toxicity in 636 pediatric patients transplanted for acute leukemia.[36] In their experience, the incidence of moderate or severe cardiac toxicity in the first 90 days posttransplant varied by the type of transplant with autologous recipients experiencing an incidence of 1.9% (4 in 216, two deaths) and allogenic recipients of a compatible related donor experiencing a comparable incidence of 2.4% (7 in 294, four deaths). However, recipients of an allogeneic alternative donor experienced a 6.4% rate of these cardiac complications (8 in 126) with all eight experiencing an early death. In that study, the presence of moderate or severe cardiac toxicity increased the relative risk of an early posttransplant death more than ninefold (relative risk, 9.1; 95% confidence interval, 2.8 to 29.6), and more so than any other organ system toxicity.

The manifestations of the cardiac disease are varied and include myocardial ischemia, dysrhythmias, pericardial effusion, pericarditis, and progressive congestive heart failure. An accepted scoring system based on previously published grading of cardiac toxicities following stem cell transplantation consists of the following.[35]

Grade I: (1) cardiomegaly on chest radiograph without symptoms, (2) mild electrocardiogram changes not requiring treatment, (3) asymptomatic pericardial effusion

Grade II: (1) moderate electrocardiogram changes requiring and responding to medical intervention, (2) congestive heart failure requiring and responding to afterload reduction, diuretics, and digitalis, (3) pericarditis

Grade III: (1) severe electrocardiogram abnormalities with no or only partial response to medical intervention, (2) congestive heart failure requiring inotropic support, (3) cardiogenic shock, (4) a decrease in QRS voltage by more than 50%, (5) pericardial tamponade

Grade IV: fatal toxicity

Late cardiovascular toxicity occurring a year or more after HPCT is also being reported.[37,38] Late cardiovascular complications following HPCT include heart failure, dysrhythmias, hypertension, and cerebrovascular accidents. Several pathologic mechanisms of late congestive heart failure have been offered including those of acute heart failure such as previous cardiotoxic agents (anthracyclines, alkylating agents, thoracic irradiation) in conjunction with cyclophosphamide and total body irradiation during conditioning regimens. However, other factors such as the presence of chronic GVHD and patient characteristics such as age, size, and gender may play a role in late congestive heart failure. In one report of 155 long-term pediatric survivors of HPCT with a median length of follow-up of 9 years, 14 were found to have hypertension, 4 were found to have abnormal asymptomatic electrocardiograms, and 4 were found to have abnormal asymptomatic echocardiograms.[38] All patients in that report had a left ventricular shortening fraction greater than 30%. In another report of 112 children who received an allogeneic HPCT and survived at least 1 year, 11 had abnormal echocardiographic findings, 8 had hypertension, and 2 had cerebrovascular accidents.[39] The probability of developing a cardiovascular complication at 10 years was 11% ± 3% in that report. Moreover, among patients who developed a cardiac complication, all had received total body irradiation. Total body irradiation both alone, and in conjunction with pretransplant anthracycline use, was also associated with a negative impact on cardiac function 5 years after transplant in a cohort of 162 pediatric patients who underwent allogeneic HPCT for both malignant and nonmalignant diseases.[40] In that study, 14 (12%) of the 119 patients with pretransplant echocardiograms were found to have abnormal shortening fractions at the time of transplant. The cumulative incidence of shortening fraction abnormalities increased to 26% by the fifth year of follow-up in that report. In another study, assessing cardiac function during cardiopulmonary exercise testing revealed a significantly decreased maximal cardiac index in 33 children who had undergone HPCT in longitudinal follow-up.[41] Although no patient experienced a dysrhythmia or had electrocardiographic evidence of ischemia, four patients were found to have a shortening fraction less than 28%. Based on the finding of a decreased maximal cardiac index and a normal peak heart rate, the authors concluded that this provided evidence of long-standing subclinical cardiac dysfunction in this patient population.

In summary, cardiac toxicity appears to be an uncommon, although serious, complication following HPCT. It may present as an acute finding in the immediate posttransplant period with evidence of progressive heart failure, dysrhythmias, and pericardial effusions with tamponade. Late cardiovascular complications are also being studied. Although clinically evident late cardiac complications are being reported, there appears to be a number of subclinical findings detected by more involved testing. The importance of these subclinical findings is likely to be better understood as these children age further.

Pulmonary Complications

In adults the incidence of pulmonary complications after HPCT ranges from 30% to 60%.[42] The incidence in children is reported between 12% and 25%.[43,44] The need for mechanical ventilatory support is the most frequent reason for admission of HPCT patients to the PICU.[22,28]

Pulmonary complications can be divided into early and late complications (Table 83-3). Early complications occur within the first 100 days after transplant. The division into

Table 83–3 Pulmonary Complications of Hematopoietic Progenitor Cell Transplantation

Complications	Characteristics	Treatment
EARLY-ONSET PULMONARY COMPLICATIONS		
Infection	Positive test for infection	Antimicrobials
Diffuse alveolar hemorrhage	Progressive bloody return on BAL	Corticosteroids, FFP, plasmapheresis
Idiopathic pneumonia syndrome	Diffuse noninfectious lung injury	Etanercept
Engraftment syndrome	Periengraftment pulmonary edema	Corticosteroids
LATE ONSET PULMONARY COMPLICATIONS		
Bronchiolitis obliterans	Obstructive lung disease	Corticosteroids, macrolides
Bronchiolitis obliterans organizing pneumonitis	Restrictive lung disease	Corticosteroids
Idiopathic pneumonia syndrome	Diffuse noninfectious lung injury	Etanercept
Pulmonary veno-occlusive disease	Pulmonary hypertension	Sildenafil, prostacyclin, defibrotide

BAL, Bronchoalveolar lavage; *FFP,* fresh frozen plasma.

early and late complications is not absolute but may help the clinician in developing a differential diagnosis. Early complications include infection, diffuse alveolar hemorrhage (DAH), engraftment syndrome causing pulmonary edema, and idiopathic pneumonia syndrome.[45] Late-onset complications occur beyond 3 months after HPCT and include bronchiolitis obliterans (BO), bronchiolitis obliterans organizing pneumonia (BOOP), and idiopathic pneumonia syndrome (IPS).[46]

Early Pulmonary Complications

Engraftment Syndrome

Engraftment syndrome occurs just as patients begin to show signs of neutrophil recovery. This syndrome is likely caused by pulmonary leukoagglutination and inflammatory cytokines. Patients may develop fever, rash, fluid retention, capillary leak, and pulmonary edema. In severe cases patients can develop multiorgan involvement.[47] Engraftment syndrome may be related to a graft-versus-host response or in some cases a host-versus-graft response. In mild cases, no treatment is necessary.[47] In more severe cases, particularly if there is lung involvement, corticosteroids can be very beneficial.[47-49]

Diffuse Alveolar Hemorrhage

Alveolar hemorrhage may be infectious or noninfectious in etiology. However, the term DAH in an HPCT patient generally refers to a noninfectious etiology. The reported incidence ranges from 1% from 21% of HPCT patients. It usually occurs in the early posttransplant period and is characterized by widespread alveolar injury, absence of infection, and progressively bloodier return of BAL fluid during bronchoscopy.[50] The exact etiology of DAH is unknown but like other noninfectious pulmonary complications it is associated with GVHD and engraftment.[51-53] Endothelial injury from chemotherapy and radiation, inflammation, undiagnosed infections and immune mediated damage related to GVHD have all been postulated as the cause.[50,52]

Successful use of high dose corticosteroids has been reported in case reports of DAH.[50,54] However no prospective studies have proven the benefit of this therapy.[50,52] Fresh frozen plasma transfusions and plasmapheresis have been tried but are of uncertain benefit.[50] Aminocaproic acid used in conjunction with corticosteroids has been described in a series of eight patients with DAH refractory to corticosteroids. The overall 100-day mortality for these eight patients was 44%, an improvement over those treated with steroids alone where the overall 100-day mortality was 83%.[55]

Idiopathic Pneumonia Syndrome

Incidence and Diagnosis. The incidence of IPS in pediatric HPCT patients has been reported between 2% and 11.8%.[44,46,56] IPS is usually considered an early complication of transplant, but has also been described as a late complication of transplant. The diagnosis is made by meeting the diagnostic criteria set by an expert panel convened by the NIH in 1993. Patients must show evidence of widespread lung injury as evidenced radiographically by bilateral lung disease, signs and symptoms of pneumonia (cough, dyspnea or rales), abnormal lung function (increased alveolar to arterial oxygen gradient, pulmonary function testing with restrictive lung disease), and absence of an infectious etiology.[57]

The term IPS is often used interchangeably with idiopathic pneumonitis and interstitial pneumonitis in the literature. However, interstitial pneumonitis is the histopathologic description in some cases of IPS. Other cases of IPS will show histopathologic findings consistent with DAH or BOOP.[57] In any case, IPS, interstitial pneumonitis, DAH, BOOP, and BO are all considered noninfectious pulmonary complications of transplant. As prevention and treatment of infectious pulmonary complications have improved, these noninfectious complications are now the more troublesome.[42]

The literature continues to be confusing regarding the nomenclature of these noninfectious pulmonary complications of transplant. It is important for the critical care physician at the bedside to treat their patient appropriately without becoming anguished over the particular name of the disease. Though steroids and etanercept (tumor necrosis factor-alpha [TNF-α] receptor antagonist) may prove to be beneficial, at the present time no large clinical trials have shown any therapy to be effective for any of these noninfectious pulmonary complications. Therefore, paying close attention to fluid balance and utilizing lung protective strategies during mechanical ventilation are likely the most important aspects of care we can provide.

Etiology of Idiopathic Pneumonia Syndrome. Inflammation likely plays a significant role in the development of IPS. GVHD is known to be associated with high levels of inflammatory cytokines. GVHD has consistently been shown to be associated with IPS.[46,56,59] Because of this association, there is debate in the literature if IPS actually represents GVHD of the lung.[57]

In the mouse models of IPS when TNF-α knockout mice are used as recipients, the mice develop IPS like wild type mice. However, when TNF-α knockout mice are used as donors for wild type recipients, the severity of IPS is significantly less. In this model, TNF-α is derived from donor T-cells.[60] This animal model fits the clinical observation that patients who receive T-cell-depleted grafts have a lower incidence of pulmonary complications.[58,61]

Some cases of IPS may be caused by an unidentified infection. A retrospective study of stored BAL samples from HPCT patients with pulmonary complications detected human metapneumovirus in 5 (3%) of 163 patients. Three of the five patients were diagnosed with IPS. On review of these patient's medical records, they initially presented in the first 40 days after transplant with typical upper respiratory symptoms: fever, cough, nasal congestion, and sore throat. Four of the five patients died of rapidly progressive acute respiratory failure. Three of the five had DAH.[62]

Treatment of Idiopathic Pneumonia Syndrome. Because of the role of inflammation in IPS, corticosteroids have been used as therapy but have not been shown to be efficacious.[46,63] Therefore, since TNF-α has been shown to be an important mediator in mouse models of IPS, the soluble TNF-α-binding protein, etanercept has been used in recent years. It is currently under investigation in a large multicenter trial of both pediatric and adult patients who develop IPS from HPCT. Preliminary results look promising with 10 of the first 15 patients reported to have a complete response. The 28-day survival rate is 73% thus far.[64] This is a significant improvement from previous reported mortality rates approximating 50%.[46,58,64]

Continuous veno-venous hemofiltration has also been used in patients with acute lung injury after chemotherapy and HPCT. In a series of 10 patients, seven had a noninfectious lung injury. Four of these 7 were HPCT patients. All patients were mechanically ventilated and met criteria for ARDS. Three of the four HPCT patients with noninfectious lung injury survived to extubation.[65]

Lung transplantation has been reported in four children who have developed chronic respiratory failure as a complication of HPCT. Of the four patients reported, two are alive without significant complications 2 and 7 years after lung transplant.[66]

Calfactant (calf lung-derived surfactant) may play a role in the treatment of acute lung injury after HPCT. A post hoc analysis of a multicenter trial of calfactant in mechanically ventilated pediatric patients with acute lung injury showed possible benefit in the subgroup of immunocompromised patients. Twenty-seven of the 52 immunocompromised patients analyzed had undergone HPCT. In this subgroup analysis, patients who received calfactant had a 50% mortality rate, whereas those receiving placebo had a 60% mortality rate.[67] A trial of calfactant in pediatric patients with acute lung injury with leukemia, lymphoma, or history of HPCT is currently underway.

Extracorporeal membrane oxygenation (ECMO) has infrequently been used as a heroic measure for HPCT patients with severe lung injury. In a recently published review of the Extracorporeal Life Support Organization database there were no ECMO survivors with a history of recent HPCT.[68] However, there is one case report in the literature of an 8-month-old girl with SCIDS who was transplanted while symptomatic with bronchiolitis. ECMO was used successfully as a bridge to engraftment.[69]

Late Pulmonary Complications

Bronchiolitis Obliterans/Bronchiolitis Obliterans Organizing Pneumonia

BO and BOOP are late onset noninfectious pulmonary complications of HPCT. Both of these complications are associated with chronic graft-versus-host disease.[61,70] Patients with BO have an obstructive pattern on pulmonary function testing. On high resolution chest computed tomography (CT) both high and low attenuation areas are seen as are bronchial dilatation, bronchial thickening, vascular attenuation, and expiratory air trapping. Biopsy specimens show submucosal bronchiolar fibrosis and luminal narrowing and obliteration.[70]

Patients with BOOP have patchy air space disease on chest radiograph. High-resolution chest CT shows ground-glass opacifications, areas of consolidation, and pulmonary nodules.[70] As opposed to patients with BO, pulmonary function testing in BOOP shows a restrictive lung disease pattern. Biopsy specimens of BOOP show granulation tissue in the distal airways, alveolar ducts and peribronchial alveolar space.[42,71]

For both BO and BOOP it is recommended that patients undergo bronchial alveolar lavage to rule out infection. BO may be diagnosed on clinical grounds to avoid open lung biopsy and its associated risks. The diagnosis of BOOP generally requires biopsy. However, unlike BO, a transbronchial specimen is often sufficient.[70]

The number of patients with BO or BOOP reported in the literature is small. Therefore, it is difficult to make firm recommendations regarding treatment or prognosis. However, these complications may respond better to steroids than other noninfectious pulmonary complications of HPCT.[42,46] Macrolide therapy may be of benefit in patients with BO after HPCT but requires further study.[72] Other therapies such as inhaled cyclosporine, etanercept, infliximab and extracorporeal photochemotherapy have been described in case reports for BO.[70]

Pulmonary Veno-occlusive Disease

Case reports of pulmonary veno-occlusive disease (PVOD) in HPCT patients have been infrequently described. Patients have presented both early and late after HPCT. Patients present with increasing dyspnea and signs of right heart failure. Cardiomegaly and pulmonary edema are seen on chest x-ray. Pulmonary hypertension is seen on echocardiogram. In patients who have undergone cardiac catheterization, high right atrial pressure, right ventricular pressure, and pulmonary artery pressures are seen, whereas the pulmonary artery wedge pressure is frequently normal. Pathologic specimens show fibrosis of the venules and small pulmonary veins, whereas the larger pulmonary veins are typically normal. Because the resistance to flow in the pulmonary veins is typically normal in PVOD, the pulmonary artery wedge pressure appears normal despite having increased resistance through pulmonary venules and small pulmonary veins. Pulmonary

arterial intimal fibrosis and hypertrophy may also be seen. Steroids, other immunosuppressive agents, and anticoagulation have been used without notable benefit. Sildenafil with prostacyclin has been reported to be of some benefit in treating the pulmonary hypertension. Defibrotide may be beneficial given its efficacy in hepatic VOD, but there are no available reports of its use in patients with pulmonary VOD.[73,74]

Dilemmas in the Diagnosis of Pulmonary Complications

As HPCT patients with pulmonary complications are frequently tenuous, placing these patients at risk for complications from diagnostic procedures is a difficult decision. Although it is difficult to treat these critically ill patients without a firm diagnosis, it is also unpalatable to worsen the patient's condition while performing a diagnostic procedure that does not result in a diagnosis. Therefore, the debate continues in the literature and at the bedside regarding the risk/benefit ratio of invasive diagnostic procedures such as bronchial alveolar lavage (BAL) and lung biopsy.

St. Jude Children's Hospital recently published data regarding the diagnostic yield of BAL at their institution.[75] BAL identified the cause of respiratory symptoms in 53 (67.9%) of 78 of their allogeneic patients and 7 (63%) of 11 autologous patients. The most common finding diagnosed on BAL was bacterial infection (52%). The patients tolerated the procedure well with complications noted in less than 20%. In their series, transbronchial biopsy added additional information in only two of seven patients. They also noted that 14 of 16 patients who underwent open lung biopsy already had a positive BAL. The authors concluded that BAL had a beneficial risk/benefit profile and was useful in identifying patients who had an infectious etiology to their lung injury. However, biopsy did not add significantly more information but carried an unacceptable morbidity rate of 47%.

In contrast, a second study from Taiwan looked at the diagnostic yield of open lung biopsy versus BAL in a cohort of both pediatric and adult BMT patients with diffuse pulmonary infiltrates.[76] They found open lung biopsy resulted in a change in clinical management in 63% of their patients while BAL only offered a diagnosis in 30.7% of patients. This series found a shorter duration of intubation in patients who underwent open lung biopsy as opposed to BAL. The authors concluded this was due to a more accurate diagnosis leading to appropriate treatment in the open lung biopsy patients. In this cohort of patients the most common diagnoses were idiopathic interstitial pneumonitis and cytomegalovirus (CMV) pneumonitis as opposed to the St. Jude cohort where bacterial pneumonia was the most common. The difference in underlying diagnoses could explain the differences seen in the utility of BAL versus open lung biopsy.

Hepatic Complications

Hepatic complications of HPCT include infectious hepatitides (viral, fungal, bacterial), cholestasis, drug toxicity, VOD, and GVHD.

Viral hepatitis can be caused by any viral pathogen, including hepatitis C, CMV, Epstein-Barr virus, hepatitis B, adenovirus, herpes simplex, and varicella zoster. The diagnosis of these pathogens is based on clinical manifestations, with identification of the virus determined (1) histologically, (2) by culture of blood or tissue, or (3) by the presence of viral antigen or deoxyribonucleic acid within serum or liver tissue. Treatment is dependent upon identification of the viral pathogen. Herpes simplex and varicella zoster are treated with acyclovir, whereas CMV is treated with ganciclovir or foscarnet. Epstein-Barr virus-induced donor lymphocytes have been used *to treat* Epstein-Barr virus-associated lymphoproliferative disorders after allogeneic bone marrow transplantation.[77]

Fungal involvement of the liver is often seen in conjunction with widespread dissemination. There may be granulomas, abscesses, cysts, fungus in biliary ducts, or infarcts from vascular occlusion. Typically, Candida species are seen; however, any fungal pathogen can occur. Ultrasound or CT scan may help identify a lesion. Ultrasound-guided fine-needle aspiration can confirm the diagnosis. Bacterial infections of the liver occur less commonly but present similarly.

Gallbladder stones from poor oral intake, cytoreductive therapy causing exfoliation of gallbladder mucous-containing cells, and increased biliary excretion of precipitable material (cyclosporine A [CSA], antibiotics) all contribute to a 70% incidence of gallbladder sludge.[78,79] Numerous medications required for HPCT can have direct toxicity on the liver, including antibiotics, fluconazole, and CSA. Histologically, drug effect should be suspected when there is significant hepatocellular necrosis and minimal inflammation.

VOD after allogeneic HPCT was first reported in 1979[80] and now is recognized as a major cause of morbidity and mortality in the first 100 days of transplant. The pathogenesis is believed to result from hepatic venule and sinusoidal endothelial injury.[81] Histologically, subendothelial edema, endothelial cell damage with microthrombosis, fibrin deposition, and expression of factor VIII and von Willebrand factor within venular walls is seen.[82] Hepatic necrosis occurs, and collagen deposition in the sinusoids, venular wall sclerosis, and collagen deposition in the venular lumen is seen as the disease progresses.[83] Risk factors can include elevated transaminases before the conditioning regimen,[84-86] use of methotrexate for GVHD prophylaxis,[87] presence of oral mucositis,[88] interstitial pneumonitis,[89] or transfusional iron overload.[90] Certain preparative regimens have also been found to have a higher incidence of VOD, including those with high doses of total body irradiation, higher doses of cyclophosphamide, or the combination of busulfan and cyclophosphamide, or etoposide and carboplatin.[85,86,91,92] A recent trial of adults undergoing HPCT using everolimus and sirolimus for GVHD prophylaxis was terminated prematurely because of an unacceptably high rate of severe VOD and thrombotic microangiopathy.[93] The authors felt that busulfan use in conditioning may have been a contributing factor.

Clinically, VOD presents with hyperbilirubinemia, painful hepatomegaly, and fluid retention. The incidence varies based on risk factors and the criteria used but reportedly are as high as 55%,[84] with mortality rates ranging from 3% to 67%.[94] Significant variability in mortality results from differing conditioning regimens and definitions of VOD. Two sets of criteria have been used for VOD. Jones et al.[85] first described VOD and modified this criterion as hyperbilirubinemia greater than 2 mg/dL with at least two of three other findings: hepatomegaly, ascites, or 5% or greater weight gain.[85] McDonald et al.[84] in Seattle defined VOD in their series as two of the following criteria occurring within 20 days of transplant: hyperbilirubinemia greater than μg/dL, hepatomegaly or right upper quadrant pain, or sudden weight gain greater than 2% of body weight.[84]

Clinically, most patients with VOD develop symptoms between day 6 and 7 after transplant; peak around 10 days after onset; and return to baseline, if they are going to recover, 10 days later.[85] Multiorgan failure is seen more frequently in patients with VOD.[84,86] Pulmonary dysfunction, pleural effusions, hepatorenal syndrome, sodium retention with subsequent edema, and congestive heart failure all can occur and contribute to the high mortality rate. Liver ultrasound with Doppler study showing reversal of portal flow is a late finding in VOD.[95]

In some patients it is difficult to differentiate between VOD and hepatic GVHD and more invasive procedures are needed. Transvenous liver biopsy and hepatic venous pressure gradient measurement can be performed safely,[97] and have been found in a limited setting to have predictive value, with hepatic venous pressure gradient greater than 30 Hg associated with poor outcome.[96] Hepatic venous pressure gradient levels greater than 10 mm Hg have been shown to be highly specific for diagnosis of VOD.[98,99]

Given that the pathogenesis is thought to involve endothelial injury and coagulation factor deposition, attempts have been made to reduce the hypercoagulable state with several agents, including heparin, prostaglandin, and bile salts. Use of heparin as a continuous infusion has been explored most extensively with conflicting results, although randomized studies to date have not shown any benefit.[100-102] Ursodiol in historical studies and randomized trials has been shown to cause mild to moderate reduction in VOD occurrence.[103,104] Fresh frozen plasma and antithrombin III have been used as prophylaxis, both showing potential benefit in small nonrandomized studies.[105,106] Three separate nonrandomized trials using defibrotide as VOD prophylaxis have been reported. All three trials showed a reduction in incidence and severity of VOD, but used historic controls for comparison.[107-109]

Thrombolytic therapy with recombinant tissue plasminogen activator has been used successfully.[110,111] Pediatric dosing has been with low-dose recombinant tissue plasminogen activator at 0.25 to 0.5 mg/kg for 4 days.[111] Careful monitoring for bleeding complications is required because these patients already are at high risk with thrombocytopenia and hepatic dysfunction. Defibrotide appears promising with recent phase II trials showing 30% to 60% remission rates, even in patients with severe VOD.[112] N-acetylcysteine, a thiol antioxidant, and nitric oxide have been tried in anecdotal reports.[113,114]

Hepatic GVHD usually occurs when GI GVHD is present. Clinically, cholestatic jaundice with increased serum alkaline phosphatase and hyperbilirubinemia occur. Hepatocellular dysfunction with ascites and coagulopathy are unusual unless there is multiorgan end-stage disease. Histologically, portal inflammation is the hallmark feature. Treatment includes increase or change in immunosuppressant medications, although normalization of liver test results may take weeks or months.

Myelosuppression and Hematologic Complications

Myelosuppression and Immune Dysregulation

Stem cell transplant conditioning results in an extended period of neutropenia, anemia, and thrombocytopenia. Neutrophil engraftment is typically defined as an absolute neutrophil count of greater than or equal to $0.5 \times 10^3/\mu L$ on 3 consecutive days. The duration of time from stem cell infusion to engraftment depends on the intensity of conditioning, the type of transplant, the stem cell source and dose, the type of graft-versus-host disease prophylaxis used, and the degree of HLA matching. Neutrophil engraftment occurs 2 to 4 weeks following stem cell infusion. Factors associated with more rapid neutrophil engraftment include autologous transplant, the use of reduced intensity conditioning regimens, T-cell depleted transplantation, peripheral blood stem cell source, full HLA matching, and higher stem cell dose.[115] When peripheral blood progenitor cells are used engraftment typically occurs 1 to 6 days sooner than when bone marrow is used as the stem cell source.[116] Engraftment occurs slower when umbilical cord blood is used compared to PBSC and bone marrow.[117] Granulocyte stimulating factors are commonly used following autologous HPCT and umbilical cord blood transplant to reduce the time to stem cell engraftment.[118] Platelet engraftment generally occurs 1 to 2 weeks following neutrophil engraftment, but can take weeks to months. A platelet count less than 100,000 on day 100 following transplant is associated with poor outcome.[119]

Neutrophil engraftment does not signify the reconstitution of a fully functional immune system. It is crucial to remember that engrafted post-HPCT patients remain significantly immunocompromised and are at risk for life-threatening opportunistic infections. The restoration of normal immune function can take as long as a year in patients without significant post-HPCT complications and longer in patients with chronic GVHD.[120] Typically, natural killer cell recovery takes approximately one month and T-lymphocyte recovery takes 6-12 months.[121] Restoration of normal B-cell function takes approximatey 3 to 6 months post-HPCT in the absence of GVHD.[122]

Infectious Complications

Patients undergoing HPCT have increased susceptibility to many infections because of a combination of (1) neutropenia, (2) breakdown of physical barriers (mucositis, indwelling venous catheters), and (3) defects in cellular and humoral immunity as a result of the conditioning regimen and immunosuppressive therapy needed. The susceptibility to any particular organism varies over the course of the transplant period. During the first 2 to 4 weeks of the transplant, while the patient is neutropenic, bacterial infections account for approximately 90% of the infections. Enteric gram-negative bacilli (e.g., *Escherichia coli*, *Klebsiella, Enterobacter, Pseudomonas aeruginosa*) can cause rapid hemodynamic instability. The gram-positive infections (*Staphylococcus* and *Streptococcus*) are frequent causes of infections, due to the presence of central venous catheters. Therefore empiric antibiotic coverage for fevers during this time must be broad spectrum and provide adequate coverage for these organisms. Monotherapy with cefipime or imipenem is effective, simple, and has little toxicity.[123-125]

Fungal infections are increasing in frequency with better treatment and prophylaxis of bacterial and viral infections, particularly after allogeneic transplantation. Fungal pathogens in HPCT patients include the yeasts (e.g., *Candida* spp., *Cryptococcus neoformans*), molds (e.g., *Aspergillus, Fusarium, Mucormycosis*), and dimorphic fungi (e.g., *Coccidioides, Histoplasma, Blastomyces*). Of these, *Candida* and *Aspergillus* are most common. *Candida* spp. colonize the gastrointestinal

tract in more than half of healthy people,[126] but they become opportunistic infections in HPCT patients.

Candidal infections can occur as superficial mucosal infections (e.g., thrush) or deeply invasive (hepatosplenic candidiasis). Esophageal candidiasis is associated with dysphagia and retrosternal pain. This may be difficult to distinguish from chemotherapy or radiation-induced mucositis or herpetic mucositis. Endoscopy may be necessary to diagnose and appropriately treat. Candidemia may present with fever and systemic symptoms and is frequently not associated with tissue involvement. Because most HPCT patients receive fluconazole prophylaxis, candidemia should be treated with amphotericin B. Patients with documented candidemia or persistent/recurrent fevers should undergo evaluation for multiorgan involvement, including CT or magnetic resonance imaging (MRI) of the brain and chest abdomen/pelvis, and an ophthalmologic examination.

Aspergillus spores are routinely inhaled and in immunocompromised or HPCT patients can cause invasive infections. Neutropenia and GVHD with immunosuppressive treatment are risk factors for this. Outbreaks of Aspergillus can occur in areas of construction or with contaminated ventilation. Invasive aspergillosis occurs most commonly in the lungs with fever, cough, dyspnea, and ultimately hemoptysis as the disease progresses. The characteristic radiographic appearance is a cavitary lesion, but nodular infiltrates and bronchopneumonia are also seen. BAL should be performed initially. However, up to 50% of patients have a negative BAL and open-lung biopsy should be considered in this case.[127]

CMV is one of the most problematic viral infections for HPCT patients posttransplant. CMV emerges in the allogeneic patient between 1 and 3 months posttransplantation if either the patient or donor were CMV positive before transplant. CMV lays dormant after the initial clinical infection. However, in immunosuppressed patients, this virus can reactivate and result in interstitial pneumonitis, enteritis, or bone marrow suppression. CMV infection is defined as the identification of CMV from any site or the seroconversion to CMV positivity. CMV disease is defined as the clinical manifestations seen in the presence of CMV infection. The use of CMV-negative blood products and leukofiltration of blood products has helped reduce the risk of CMV infections in patients undergoing transplant. Interstitial pneumonitis from CMV presents with hypoxia and fever and an interstitial pattern on chest x-ray film. Untreated, there is an 80% mortality rate.[128] Ganciclovir and intravenous (IV) immunoglobin is the recommended treatment for CMV interstitial pneumonitis.[129] Ganciclovir is dosed at 10 mg/kg daily for 21 days followed by 5 mg/kg/day 5 days per week until day 180 posttransplantation. IV immunoglobin is given at 500 mg/kg every other day for 21 days, followed by 500 mg/kg weekly until day 180. With this regimen, survival is 80%. For patients resistant to ganciclovir, foscarnet may be given at 60 mg/kg three times daily for 7 days, then 90 mg/kg/day until day 180.[130,131] Ganciclovir can cause neutropenia, and growth factor (e.g., G-CSF, granulocyte macrophage–CSF) should be given if the absolute neutrophil count falls below 1000/ul. If the absolute neutrophil count falls below 500/μL, the drug should be held. In addition, renal adjustment may be necessary because both ganciclovir and foscarnet can be renal toxic.

CMV enteropathy presents with dysphagia, abdominal pain, nausea, vomiting, diarrhea, or gastrointestinal bleeding. These symptoms can be seen with GVHD as well, and endoscopy should be performed to aid in the diagnosis. Treatment is similar to that of CMV pneumonia.

Prophylaxis of CMV with ganciclovir is prohibited by its marrow-suppressive effects. However, monitoring of CMV now is available with improved antigenemia testing and polymerase chain reaction, allowing for preemptive therapy if results of these tests become positive before onset of clinically apparent disease. Ganciclovir then is given at 5 mg/kg twice daily for 7 to 14 days, then 5 mg/kg/day until day 120 posttransplantation.[132]

Graft Rejection

Primary graft rejection is an uncommon, potentially lethal complication of HPCT. It is defined as failure of the stem cell graft to recover hematopoietic function by day 30, though some patients successfully engraft later than day 30. The risk of graft rejection is increased with HLA-disparity between donor and host and when transplant is done for a nonmalignant hematologic condition. It is rare in sibling donor transplants. Graft rejection is an emergency as the risk of death increases with the duration of neutropenia and because there are few effective therapies.

Hematologic Complications

Patients require frequent blood product transfusions during the acute transplant phase due to conditioning-associated myeloablation and potentially increased consumption of platelets and RBCs. For most patients, the need for blood product transfusions declines rapidly following hospital discharge. However, some patients need transfusion support for months after transplant. All blood products should be gamma-irradiated to rid the product of competant donor T-cells that can cause transfusion associated-GVHD.[133] Additionally, blood products must be CMV negative to prevent transmission of the virus to nonimmune patients. This can be achieved by using blood from CMV seronegative donors or with leukofiltration.[134]

There is no commonly accepted standard transfusion parameter for either packed RBCs or platelets. Recent studies have investigated the use of a platelet transfusion threshold of 10,000. Most studies have found the use of this lower trigger safe for nonbleeding patients, but it is not supported in all studies.[135-137] A Cochrane review of the prophylactic transfusion at thresholds of $10 \times 10^3/\mu L$, $20 \times 10^3/\mu L$, and $30 \times 10^3/\mu L$ was recently reported.[138] The review found no difference in mortality rate or severe bleeding events between the groups. Similar studies are needed to assess RBCs transfusion parameters. Although transfusion parameters can be clinically useful, they do not replace clinical judgment.

Donors and recipients who are HLA matched are not necessarily ABO matched. ABO matching is not required for successful transplant and is a secondary consideration when choosing a donor. However, ABO mismatching puts the recipient at risk for immune-mediated hemolytic anemia. The risk for and severity of the potential hemolytic anemia depends on the degree of compatibility and is divided into four groups: (1) ABO-matched; (2) minor ABO mismatch, in which there is potential for hemolysis of the recipient RBCs by donor isoagglutinins; (3) major ABO mismatch, in which case the

recipient isoagglutinins are directed against donor/graft RBCs and donor RBCs after engraftment; and (4) bidirectional mismatch, which combines minor and major ABO mismatch.[139] When there is a major or bidirectional mismatch, the stem cell product must be RBC-depleted or the patient must have the offending isoagglutinins removed by pheresis prior to infusion to prevent a hemolytic reaction. Minor incompatibility, in which the recipient RBCs are incompatible with components of the donors plasma (e.g., donor is O and the recipient is B), puts the recipient at risk for an immune mediated transfusion reaction. Plasma depletion of the product prior to infusion reduces the risk. Even when plasma depletion is used mild hemolysis can exist for weeks to months due to antibody production from newly produced B-lymphocytes against residual recipient RBCs.

There are many described late hemolytic complications of transplant and most are uncommon. Autoimmune hemolytic anemias, thrombocytopenia, and neutropenias from post-HPCT immune dysregulation can occur months to years after transplant and are typically managed with immune suppression, immune modulation, or IV immunoglobin.

Post-HPCT thrombotic microangiopathic processes include hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).[140,141] Both are reported with increased frequency in patients who received cyclosporine as part of the GVHD prophylaxis regimen.

HUS is a potentially life-threatening, uncommon post-HPCT complication. It presents with hemolysis and mild to moderate renal dysfunction or with additional symptoms of seizures and severe hypertension at a median time of 5 months post-HPCT.[142] Many cases of post-HPCT HUS gradually self-resolve, although patients may be left with residual renal dysfunction. Post-HPCT TTP classically presents earlier than HUS with thrombocytopenia, schistocytes on the peripheral blood smear, and elevated LDH. Endothelial damage from transplant conditioning, GVHD, and calcinerin inhibitors are thought to contribute to the development of post-HPCT TTP.[143] It differs from classic TTP of childhood in that ADAMTS13 deficiency is not present.[141,143] Additionally, standard therapies for idiopathic TTP, such as plasma exchange, do not appear to be effective for the treatment of post-HPCT treatment.

Iron Overload

Iron overload is increasingly recognized as an important posttransplant complication. HPCT patients are at risk for increased iron burden due to repeated blood transfusions pre- and post-HPCT and disturbed iron metabolism.[144] Adverse effects from iron overload include increased susceptibility to infection, VOD, chronic liver disease, and cardiac dysfunction.[1,107,145] Studies show that iron overload has an adverse impact on survival in patients undergoing HPCT for beta-thalassanemia major and hematologic malignancies.[144,146,147]

There are multiple ways to diagnose iron overload posttransplant. Liver biopsy remains the gold standard, but frequently the diagnosis is made with imaging and laboratory studies. The serum ferritin is elevated in iron overload. However, ferritin is a nonspecific marker of inflammation that makes this a sensitive, but not specific indicator of iron overload. Serum iron studies are useful adjuncts for diagnosis and are often used when monitoring the efficacy of therapy. MRI can provide a quantification of organ specific iron burden.[148]

Phlebotomy is the standard treatment for post-HPCT iron overload.[149,150] Iron chelation is effective, but limited by the practical considerations in the case of deferoxamine infusion and potential toxicities of the treatments.[151]

Graft-Versus-Host Disease

GVHD is the most common complication of allogeneic HPCT. GVHD develops when donor T-lymphocytes respond to proteins on recipient cells.[152] Activated donor T-lymphocytes, monocytes, and macrophages triggers a self-propogating cycle of cytokine production and inflammation. GVHD was historically categorized as acute if symptoms developed before day 100 after transplant or chronic if the presentation was after day 100. The traditional definitions of acute and chronic GVHD have evolved. The current National Institutes of Health consensus recommends classification based on the clinical presentation rather than posttransplant day.[153] This classification recognizes two main categories of GVHD (acute and chronic), each with subcategories. Acute GVHD includes classic acute GVHD that develops within 100 days after transplant and persistent, recurrent, or late-onset acute GVHD that clinically resembles acute GVHD, but occurs greater than 100 days after transplantation. Chronic GVHD includes classic chronic GVHD with manifestations that are specific to chronic GVHD. The chronic GVHD category includes an overlap syndrome, which has features of chronic GVHD and features typical of acute GVHD.[153]

The skin, gastrointestinal tract, and liver are the most common involved systems in acute GVHD. The cutaneous presentation is typically an erythematous maculopapular rash, although there are a wide variety of possible skin findings. Diffuse bullous lesions with skin sloughing are the most severe manifestation of cutaneous GVHD. Acute gastrointestinal GVHD is characterized by diarrhea that is often bloody and may contain tissue. Hepatic acute GVHD typically presents with a cholestatic pattern of elevated bilirubin and alkaline phosphatase. Isolated transaminase elevation is uncommon. Less common presentations of acute GVHD are oral inflammation with possible ulceration and ocular inflammation. Acute GVHD is graded according to severity of the systems involved (Table 84-4).

The clinical presentation of chronic GVHD is more varied. The skin is the most commonly involved system. Patients may have persistent erythematous rash, severely dry skin, atrophy, changes in skin pigmentation, hair loss, or nail changes. The most severe clinical presentation of chronic cutaneous GVHD is scleroderma. Chronic hepatic GVHD is clinically similar to acute hepatic GVHD. The differential diagnosis includes viral infection and medication toxicity. A liver biopsy can aid diagnosis, but must be performed with caution in patients with increased bleeding risk.

The diagnosis of chronic pulmonary GVHD is controversial as there are no pathologically defined criteria for GVHD of the lungs. Bronchiolitis obliterans may represent the pulmonary equivalent of GVHD. This is an uncommon complication of transplant characterized by irreversible pulmonary obstruction. Post-HPCT bronchiolitis obliterans has a high mortality rate.[154] Steroid-resistant disease has an especially poor prognosis. Gastrointestinal tract chronic GVHD may present as anorexia, nausea, vomiting, diarrhea, or weight loss. Other manifestations of chronic GVHD are sicca syndrome, oral

Table 83–4 Consensus Criteria for Clinical Staging and Grading of Acute Graft-Versus-Host Disease

	Skin	Liver	Gut
STAGE			
1	Rash* <25% or persistent nausea†	Bilirubin 2–3 mg/dL‡	Diarrhea >500 mL/day§
2	Rash 25%-50%	Bilirubin 3–6 mg/dL	Diarrhea >1000 mL/day
3	Rash >50%	Bilirubin 6–15 mg/dL	Diarrhea >1500 mL/day
4	Generalized erythroderma with bullae	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
GRADE‖			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	—	Stage 2–3 or	Stage 2–4
IV	Stage 4 or	Stage 4 or	Stage 4¶

From Przepiorka D, Weisdorf D, Martin P, et al: 1994 consensus conference on acute GVHD grading, *Bone Marrow Transplant* 15:825-828, 1995.
*Use "rule of nines" or burn chart to determine extent of rash.
†Persistent nausea with histologic evidence of graft-versus-host disease in the stomach or duodenum.
‡Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin can be documented.
§Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.
‖Criteria for grading given as degree of organ involvement required to confer that grade.
¶Grade IV may include lesser organ involvement with Karnofsky performance status <50%, so patients with stage 4 gut GVHD usually are grade IV.

scarring with salivary gland scarring, fasciitis, and genitourinary scarring. Immune dysfunction independent of immunosuppressive medications is characteristic of chronic GVHD. Patients with chronic GVHD have abnormal splenic function and often need prophylaxis against encapsulated bacteria.

GVHD prevention regimens differ between institutions. Agents commonly used for prevention include cyclosporine, tacrolimus, methotrexate, rapamycin, and corticosteroids. Corticosteroids are the mainstay of treatment for GVHD. Other upfront treatments that specifically target affected systems are oral dexamethasone and tacrolimus rinses and corticosteroid or tacrolimus topical therapies. There are many available second-line agents and treatment strategies for steroid refractory GVHD, but none are considered standard. The choice of second-line therapy depends on the individual clinical situation. Due to prolonged treatment with corticosteroid some patients with chronic GVHD are adrenally insufficient. When a patient with chronic GVHD needs intensive care one should consider the use of stress dose corticosteroid.

Neurologic Complications

Neurologic complications contribute significantly to the morbidity and mortality following HPCT and are much more common following HPCT than in nontransplant oncology patients.[36,155-157] Seizures appear to be the most common clinical manifestation following HPCT occurring in approximately half of the reported cases.[155,156] Other symptoms include encephalopathy, motor function deficits, cranial nerve palsies, visual disturbances, and impaired coordination.[36,155-157] In one report, encephalopathy was reported in 26 (6.4%) of 405 pediatric patients following allogeneic HPCT.[157] In that report, the encephalopathy developed within the first 100 posttransplant days in all but one patient. Leukoencephalopathy was commonly reported in that study and others.[156-159]

Leukoencephalopathy primarily occurs in HPCT patients who receive cranial radiation and/or intrathecal chemotherapy before and after transplantation. Clinically, this condition manifests days to months after transplantation and may present with dysarthria, ataxia, dysphasia, confusion, or decreased sensorium in severe cases. The white matter changes can be detected with either CT or MRI. Peripheral nervous system neurotoxicity also occurs posttransplantation as an immune-mediated complication. Inflammatory degenerating polyneuropathy, myasthenia gravis, and polymyositis have all been described posttransplant.[160-162] These conditions present with muscle flaccidity, hypoactive deep tendon reflexes, and absence of extensor plantar reflexes.

Depending on the complications assessed, the length of follow-up time, and the patient population studied, clinical analyses report a wide range of neurologic complications in pediatric HPCT patients with more recent studies reporting a range of 10% to 24%.[36,155,156,158,163,164] However, an autopsy study of both children and adults (age range, 1 to 48 years; average, 23.7 years) demonstrated neuropathological abnormalities in more than 90% of patients who died after HPCT.[165] In one pediatric report, 11 (10%) of 133 children experienced a life-threatening neurologic complication within the first 3 months following HPCT.[163] In a more recent analysis, 40 (24%) of 165 pediatric HPCT patients were found to experience neurologic complications.[156] In that study, neurologic complications were categorized as either (1) transient and nonrepetitive symptoms lasting less than 24 hours and without abnormalities on MRI or on CSF analysis or (2) persistent (lasting more than 24 hours) or repetitive symptoms associated with radiographic cerebral imaging and/or CSF analysis abnormalities. Nineteen (12%) of the 165 patients satisfied the criteria of the second group approximating the incidence of the earlier study.

In that report, neurologic complications occurred most commonly in children who had undergone unrelated allogeneic transplantation (39%), more than related allogeneic transplants (21%) or autologous transplantations (11%). The finding of neurologic complications occurring more commonly in allogeneic rather than autologous HPCT recipients has been

previously noted.[158,166,167] These data support the finding that neurologic complications following HPCT are related to the presence of GVHD and immunosuppression.[156,158,163,168-170] GVHD and the need for prolonged immunosuppression are clearly associated with many of the etiologies of neurologic complications in this patient population. Common etiologies of neurologic complications in these children include CNS infections, intracranial hemorrhage and stroke, metabolic disturbances, medication toxicity, and CNS involvement of the underlying disease.[155-157]

CNS infections are a consequence of neutropenia and immunosuppression. Depending on the time period after transplant, patients may develop bacterial meningitis, aspergillus invasion of the brain parenchyma and vessels, cerebral toxoplasmosis, or viral encephalitis. These CNS infections contribute significantly to the morbidity and mortality following HPCT.[171] In addition to the association of GVHD with CNS infections, the medications used to treat GVHD are common causes of neurologic complications in this patient population. Neurotoxicity from CSA or tacrolimus, used for GVHD prophylaxis or treatment, can include tremor, seizures, headaches, cortical blindness, neuropathy, or mental status changes. Frequently, these symptoms are observed with levels above the therapeutic range, but this is not always the case. These effects usually are reversible with elimination of the drug. These medications may also be associated with the posterior reversible leukoencephalopathy syndrome.[156] As many as 5% to 6% of HPCT patients taking CSA may experience seizures.[172,173] Phenytoin, phenobarbital, or carbamazepine, that may be used to treat seizures, can alter cytochrome P-450 activity and interfere with CSA or tacrolimus levels. Valproic acid may be a better alternative in this situation.[174] Several other chemotherapy agents that may be used in the HPCT conditioning regimen can have neurotoxicity. High-dose carmustine, frequently used for autologous transplants for Hodgkin disease or lymphomas, has been associated with seizures. Busulfan, usually used in allogeneic transplants, can also cause seizures and epileptiform activity on electroencephalogram. In fact, phenytoin is given prophylactically during busulfan administration. Glucocorticoids used for immunosuppression can be associated with mood swings, dysphoria, agitation, or frank psychosis.

CSA, tacrolimus, and chemotherapeutics may also cause renal wasting of magnesium resulting in hypomagnesemia and lowering of the seizure threshold. In addition to hypomagnesemia, other metabolic abnormalities may occur in this setting contributing to seizures. Moreover, metabolic derangements resulting in encephalopathy has been considered the most common neurologic complication following HPCT with an incidence estimated to be as high as 37%.[175] A more recent pediatric analysis suggests that metabolic derangements remain a significant cause of encephalopathy after HPCT, but with a much lower incidence (14%) than this earlier study.[157] Hypoxia, ischemia, hepatic failure, electrolyte imbalance, or renal failure have all been found to be etiologies of these metabolic derangements resulting in encephalopathy. Clinically, patients are delirious or have a depressed mental status and no focal neurologic signs. Idiopathic hyperammonemia can occur in patients after high-dose chemotherapy, as in the transplant conditioning regimen. Altered mental status and respiratory alkalosis with elevated plasma ammonia occur acutely. Left untreated, irreversible cerebral edema may result.

Neurovascular complications are not uncommonly reported as one of the neurologic toxicities associated with HPCT. Thromboembolic episodes, subdural hemorrhages, and intracerebral hemorrhages are common examples. Thrombotic thrombocytopenic purpura has also been reported as a cause of encephalopathy following pediatric HPCT.[157] In a recent report, two (10%) of 21 children with a definitive diagnosis of encephalopathy following HPCT were found to have TTP and one other (5%) had evidence of a stroke.[157] In that report, one (5%) of the 22 children with intracranial imaging was found to have a subdural hematoma and two (10%) were noted to have infarctions. In another report, two (11%) of the 19 children with persistent neurologic symptoms (>24 hours) after HPCT were diagnosed with intracranial hemorrhage.[156] In a study of patients receiving HPCT or conventional chemotherapy alone in a pediatric oncology center, nine (12%) of the 76 patients who experienced a neurologic complication were found to have a vascular event.[155]

In terms of prognosis, neurologic complications appear to portend a poor prognosis. Nearly 60% of the children with persistent/repetitive symptoms and either radiographic or cerebrospinal fluid abnormalities following HPCT died; more than a third of them as a result of their neurologic complication.[156] In another study of 113 pediatric allogeneic HPCT patients, children with a neurologic complication following HPCT were significantly more likely to die than those who did not experience such a complication.[163] Thirty-three (32%) of 102 patients without a neurologic complication had died at 6 years of follow up as compared with 10 (91%) of the 11 patients with a neurologic complication ($P < .001$). In another study, neurologic complications were also associated with a higher mortality among pediatric HPCT patients, but only in the early post-transplant period.[158] Similarly, in the Associazione Italiana Ematologia Oncologia Pediatrica prospective study of 636 pediatric patients transplanted for acute leukemia, CNS toxicity was associated with early treatment-related death.[36] In that report, severe CNS toxicity was related to a threefold increase in the risk of treatment-related death as compared with absent or mild toxicity ($P = .02$). However, in a logistic regression model of all organ toxicities, the relationship between CNS toxicity and early treatment-related death was not statistically significant (relative risk, 2.2; 95% confidence interval, 0.8 to 5.5; $P = .11$). Finally, in a study of encephalopathy after pediatric HPCT, 17 (65%) of 26 patients died; 12 never recovered from their encephalopathy.[157] In that report, only four (15%) of the 26 patients experienced a full recovery of their encephalopathy.

Late Effects

A complete discussion of the late effects of HPCT is beyond the scope of this chapter. However, some potential late effects are relevant to intensive care providers. Patients who have been treated with total body irradiation or focal lung radiation and some chemotherapeutic agents are at risk for chronic lung disease including pulmonary fibrosis, obstructive lung disease, and restrictive changes.[38] Post-HPCT cardiac late effects include cardiomyopathy, congestive heart failure, or arrhythmia. Anthracycline chemotherapy is primary cause of cardiomyopathy. Anthracycline-related cardiomyopathy is dose dependent and treatment given before transplant contributes largely to the risk of developing cardiac dysfunction. Cardiac

late effects related to radiation include fibrosis, arrhythmia (related to fibrosis), and restrictive cardiomyopathy. Children who received radiation are at increased risk for myocardial infarction and congestive heart failure.[176]

Nutritional Support in the Critically Ill Hematopoietic Progenitor Cell Transplantation Patient

HPCT patients may begin their course malnourished that could put them at risk for the development of micronutrient deficiencies during transplant.[177,178] Deficiencies of micronutrients including magnesium, phosphorus, zinc, selenium, vitamin E, vitamin D and β-carotene have been described during conditioning.[177,179-182] HPCT patients are also at significant risk for development of severe mucositis and vomiting, making oral enteral nutrition difficult. However, enteral nutrition may be the preferred method of nutrition when possible as there is evidence that patients who are enterally fed are at decreased risk for developing GVHD.[183-185]

A few studies have shown an association between micronutrient deficiencies and transplant complications. Low zinc levels during the transplant course were associated with more febrile episodes, longer duration of febrile episodes, and more positive blood cultures.[186] Persistently low vitamin D levels were associated with more severe GVHD.[182]

Biochemical markers of oxidative stress during conditioning have been seen in HPCT patients. Decreased glutathione and α and γ-tocopherol levels have been documented during conditioning.[187] Increased serum Fe levels and a decreased total radical trapping antioxidant parameter of plasma (measure of antioxidant reserve) and linoleic acid concentrations have also been documented in HPCT patients.[188]

There is also increasing evidence for oxidative stress in critically ill patients with sepsis, systemic inflammation and lung injury; all common reasons for ICU admission of HPCT patients.[189-195] Therefore it is likely that the critically ill HPCT patient who has recently undergone conditioning may be under a significant amount of oxidative stress.

To date three trials examining antioxidant supplementation during HPCT have been published, only one in the English language. The single trial published in English came from Children's Hospital of Boston. Thirty-seven pediatric HPCT patients were given ursodeoxycholic acid, vitamin E, folinic acid, and total parenteral nutrition with traditional amounts of vitamins, minerals, and trace elements. There was no control group. They designed the study with the main outcome being feasibility of patients taking oral supplements. Most patients tolerated the oral medications well and the authors were able to prove feasibility. In these patients they also noted less mucositis, less hepatic toxicity, and a shorter time to engraftment in comparison to a historical control group.[196]

Although common sense dictates that some type of nutrition is good and prolonged lack of any nutrition would lead to death, little is known about the optimal nutrition for critically ill pediatric HPCT patients.[197] Critical illness and HPCT cause significant oxidative stress. Therefore, it is possible that critically ill HPCT patients may benefit from specialized nutritional strategies that optimize antioxidant capacity. This is a field that begs for further study.

References are available online at http://www.expertconsult.com.

Hemoglobinopathies

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PEARLS

- The pathophysiology of sickle cell disease is multifactorial, involving hemoglobin polymerization, oxidative damage to cell membrane proteins, white blood cell activation and inflammation, activation of the clotting cascade, and chronic hemolysis resulting in disturbances in nitric oxide metabolism.
- Acute chest syndrome is responsible for up to 25% of deaths in sickle cell disease, and its management should include antibiotic therapy with both a cephalosporin and a macrolide, oxygen to maintain saturations greater than 94%, prevention of atelectasis with incentive spirometry or biphasic positive airway pressure, diligent fluid resuscitation, adequate pain control, and bronchodilators.
- The default should always be to trust a patient's self-assessment of sickle cell pain.
- Up to 30% of patients with sickle cell disease have pulmonary hypertension and the threshold to treat must be lower than for other etiologies as even mild elevations in positive airway pressure (30 mm Hg) correlate with a significantly increased risk of death.
- The major cause of death in thalassemia major is cardiac failure secondary to iron overload; therefore, a thalassemic patient presenting in cardiac failure must be assessed for cardiac iron content and if present, undergo continuous chelation therapy.

Perspective

The evolution of animals is dependent on high concentrations of hemoglobin in red cells unattainable by most biochemists. This relies on the extraordinarily robust and coordinated synthesis of the α- and β-like globin polypeptide chains, and iron containing heme rings. Each has a highly evolved structure essential for optimal pairing of α- and β-like chains, as unpaired peptide initiates cellular damage. The resultant $\alpha_2\beta_2$ hemoglobin heterodimers play a critical role in the transport and regulation of carbon dioxide, pH, and nitric oxide (NO) in addition to O_2. Thus hemoglobin synthesis is a high stakes process in which any mutation may affect hemoglobin production, stability, function, or result in unpaired globin chains leading to devastating downstream effects. The approach to any hemoglobin alterations must consider the qualitative effects (i.e., how the plethora of hemoglobins' functions is altered), and quantitative effects (i.e., the amount of hemoglobin and unpaired globin chains).

Hemoglobinopathies are plentiful as many provide a protective effect to malaria. Although 5% of humans have hemoglobin variants, an estimated 300,000 affected homozygotes are born annually.[1] Contrary to popular beliefs, hemoglobinopathies do not provide resistance to infection, but rather diminish the chance of death once infected, allowing the development of partial immunity. Although sickle cell and thalassemia trait increase fitness, homozygotes in malaria endemic areas often do not survive into their teens. Although this strong protective effect resulted in a high incidence of hemoglobinopathies in the equatorial malaria zones, the slave trade and more recent voluntary migrations has led to the worldwide distribution of these conditions.

The Globin Gene Loci

The α- and β-like genes reside within multigene loci and are transcribed at unparalleled levels in both tightly tissue specific, and developmentally specific patterns.[2] This, and their involvement in human disease, has made these loci paradigms for gene regulation and pathophysiology. The β-globin gene was the first sequenced, and sickle cell was the first molecularly defined and diagnosed disease. Most forms of mutation (e.g., point, splicing, deletion, gene rearrangement) are observed in thalassemia, making these the quintessential teaching loci. This high variety and incidence of mutations result in frequent compound heterozygotes with a wide spectrum of clinical manifestations.

The five genes of the β-globin locus reside in a cluster on chromosome 11. The genes are expressed in an erythroid, and developmentally stage-specific manor; the ε, Aγ and Gγ, and δ and β genes being expressed primarily during the embryonic, fetal, and postnatal periods, respectively. At birth 95% of β-like chains are γ, with the rest being β. This ratio gradually inverts during the first year of life, explaining why phenotypes limited to the β-globin gene such as sickle cell and most β-thalassemias do not manifest until several months of age. Expression of the chromosome 16 based α-like genes differs; the embryonic ζ-gene parallels the expression of ε, but the twin α-genes are expressed from the fetal period onward. Thus α abnormalities manifest in utero, potentially with devastating consequences (e.g., hydrops fetalis). The resultant hemoglobin α-, β-heterotetramers (HbS) are developmentally

Appendix materials for this chapter are available online at http://www.expertconsult.com.

expressed; embryonic: Hb Gower1 (ζ_2,ε_2), Hb Gower2 (α_2,ε_2), and Hb Portland (ζ_2,γ_2); fetal: HbF (fetal) (α_2,γ_2) and adult: HbA2 (α_2,δ_2) and HbA (Adult) (α_2, β_2) (Appendix Figure 84-A). Although many suggest HbF, with its higher oxygen affinity, evolved to aid the fetus in "stealing" oxygen from the mother, this is not supported experimentally, the advantage of HbF may in fact lie in differential transport of NO or carbon dioxide. Unfortunately, despite the intensive study, multiple Nobel prizes and the clinical importance of the globin loci, little of the molecular understanding of the loci has been translated to clinical care. The holy grail of manipulating expression from the β-locus remains elusive. Inhibiting adult sickle or thalassemic genes, while concomitantly activating expression from the normal fetal genes would alleviate most disease, obviating the need for this chapter.

Sickle Cell Disease

Molecular Description and Epidemiology

Sickle cell disease (SCD) is a group of single gene, autosomal recessive disorders common in people originating from specific regions of Africa or India and in those of Hispanic descent. SCD encompasses a group of disorders characterized by the presence of a single nucleotide change in the adult β-globin gene, and a second abnormal allele allowing the sickle hemoglobin to polymerize. Substitution of an adenine (A) for a thymidine (T) in codon 6 results in replacement of a hydrophilic glutamic acid residue with a hydrophobic valine residue. The allosteric changes in hemoglobin structure occurring with deoxygenation leads to exposure of a destabilizing valine-containing pocket. The high concentration of hemoglobin in erythrocytes (MCHC) allows for the alignment of these pockets, leading to polymerization and transition to the classic sickle cell morphology (Figure 84-1) and the initiation of downstream events leading to pain and chronic end-organ damage. The presence of HbA in sickle trait, or HbF in the newborn, attenuate polymerization, diminishing the clinical consequences of HbS. In the United States, approximately 1 in 14 and 1 in 400 African Americans have sickle trait and SCD, respectively, with approximately 100,000 cases and approximately 1000 new births per year (in contrast to approximately 1 million births per year in Africa). With increased ethnic mixing, compound heterozygous forms of SCD are increasingly being observed (e.g., S/β-thalassemia or HbS/E). Sadly, though simple public health measures have dramatically decreased mortality rates in the United States, the countries with the highest incidence of SCD often lack such resources and children with SCD often do not reach their teens.

Sickle Cell Trait

Once the presence of HbS has been confirmed, the differential diagnosis consists of severe forms, less severe forms, and carrier states. Sickle cell trait (SCT) is distinguished from SCD by the presence of a normal β-globin allele and more HbA than HbS (typically 40% HbS) (Table 84-1). SCT does not result in the classic spectrum of sickle-related complications or alter red cell indices, but can lead to clinical abnormalities. Impaired renal concentrating abilities and intermittent microhematuria is common. Although of unclear clinical significance, this damage may interact with other pathophysiology in the African-American population (e.g., diabetes), explaining the high risk of chronic renal disease. In addition, there may be an increased risk of venous thromboembolism.[3] Most controversial is the concern that extremes of physical exertion, dehydration, and/or altitude may induce sickle cell vaso-occlusive events in some individuals with sickle cell trait.[4] This is particularly relevant to student athletes for whom no formal activity restrictions are recommended, but empirically, aggressive hydration during extremes of physical exertion is generally recommended.

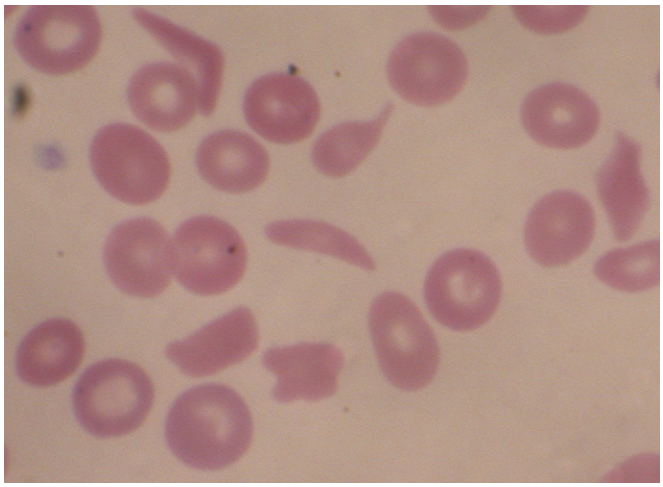

Figure 84–1. Morphology of sickled cells. Note that although a subset of cells has a high degree of polymerized HbS and has taken on the classic sickle shape, that the majority of cells maintain normal morphology. *(Courtesy Dr. Min Xu, Seattle Children's Hospital.)*

Spectrum of Sickle Cell Disease Genotypes

Although homozygous sickle cell (Hb S/S, often called *sickle cell anemia*) is most common, it is essential to be aware of additional genotypes that result in a similar spectrum of disease (see Table 84-1). That said, once in the intensive care unit (ICU), the form of SCD plays little role in decision-making. In HbS/β^+-thalassemia and HbSβ^0-thalassemia, the lower the expression of β-like chains from the thalassemic allele, the lower the hemoglobin concentration (Hgb) and MCV, and the higher the percentage of HbS and polymerization, resulting in a more severe clinical phenotype. In contrast, when HbS is expressed in conjunction with HbC, HbD, or Hb O-Arab or several other variants, near normal amounts of hemoglobin are made, but these forms are less able to attenuate HbS polymerization than HbA and result in milder sickle syndromes.

Natural History

The clinical manifestations of SCD result from intermittent episodes of vascular occlusion leading to tissue ischemia/reperfusion injury and variable degrees of hemolysis, both of which contribute to multiorgan dysfunction. The severity of disease manifestations varies widely in individuals with the same genotype and is affected by (1) known genetic modifiers, e.g., α-thalassemia that lowers the MCHC; (2) genetic modifiers of additional pathways contributing to the pathophysiology of SCD (below); (3) behavioral and environmental factors, (e.g., family and community support, racial disparities and access to health care); and

Table 84–1 Hematologic Characteristics of Sickle Hemoglobinopathies

Diagnosis*	Predominant Hemoglobins After Age 1 Year†	Phenotype‡	Hematologic Studies After Age 1 Year§		
			Hgb	MCV‖	HbA_2 (%)¶
HbA	A	nl	nl	nl	nl
HbA/S (trait)	A > S[a]	nl[b]	nl	nl	nl
HbS/S	S	Hemolysis and anemia by age 6–12 mo	⇊	nl	nl
HbS/β^0-thalassemia	S	Hemolysis and anemia by age 6–12 mo	⇊	⇊	nl or ↑
HbS/β^+-thalassemia	S > A	Milder hemolysis and anemia	↓	↓	nl or ↑
HbS/C	S ≅ C	Milder hemolysis and anemia	↓	nl or ↓	nl

Table shows typical results; exceptions occur.
*The β-thalassemias are divided into β^+-thalassemia, in which reduced levels of normal β-globin chains are produced, and β^0-thalassemia, in which there is no β-globin chain synthesis.
†Hemoglobins are reported in order of quantity. Only the most prominent hemoglobins are listed.
‡Overview of phenotype.
§Values vary during the first year of life. Some patients values continue to change after age 1 year.
‖Must use age-specific values. MCV can be lowered by α-thalassemia trait and increased by hydroxyurea.
¶HbA_2 results vary depending on laboratory method.
[a]In sickle trait, HbS is ~40% of total hemoglobins.
[b]Although patients do not have severe sequelae, patients may have subtle abnormalities.
Hb, Hemoglobin type; *Hgb,* hemoglobin concentration; *nl,* normal; ↑, increased; ↓, decreased.
From Bender MA, Hobbs W: *Sickle cell disease GeneReviews at GeneTests: medical genetics information resource,* Seattle, 2009, University of Washington.

(4) psychological factors, (e.g., coping with chronic disease, recurrent pain, and a high rate of depression). The spectrum of manifestations changes with age, and is beautifully described in Gill et al.[5] Previously, median survival in the United States for those with SCD was 42 years for men and age 48 years for women[6]; however, considerable improvements in longevity have been suggested.[7,8] The main causes of death are infection, acute chest syndrome, pulmonary artery hypertension, and cerebrovascular events.[9,10] What is not fully appreciated by pediatricians is that this increased lifespan is often associated with significant morbidity related to chronic organ damage.

Laboratory and Diagnostics

Though all newborns in the United States are now tested for SCD, states vary in when testing was initiated and the status of most immigrants is unknown, thus a need for testing in the ICU remains. Limitations in the acute setting include the lack of definitive SCD testing on an emergent basis, and that screening tests lack sensitivity and specificity. The prominence of HbS in conjunction with diminished or absent HbA defines SCD. Cellulose acetate electrophoresis or high pressure liquid chromatography laboratory diagnostics are most often used, but are rarely available on an emergent basis. HbS screening tests (e.g., Sickledex, Sickleprep, or Sicklequick) making use of the relative insolubility of deoxygenated HbS are available emergently; however, results must be interpreted with extreme caution as they lack sensitivity and specificity. In particular: (1) they do not distinguish SCD from sickle trait; (2) high levels of HbF may cause false-negative results, particularly important in neonates; (3) profound anemia can result in false negatives; (4) lipemia can cause false-positives results; and (5) some clinically significant forms of SCD can be missed (e.g., HbS/C). Although imperfect, screening tests in conjunction with a complete blood count, smear, and measure of iron status (e.g., zinc-protoporphyrin) help distinguish between SCD and SCT. Therefore in the setting of significant clinical suspicion of a hemoglobinopathy, consultation with lab medicine and hematology is recommended.

Pathophysiology

Although unable to fully provide the elegant details of the rapidly evolving insights into the multifaceted pathophysiology of SCD, this chapter outlines key pathways with direct relevance to management basics. While the initial era of understanding pathophysiology focused on HbS polymerization and red cell "sickling," this was followed by an awareness of the critical role of endothelial interactions and inflammation and later, of hemolysis and perturbations of NO metabolism (Figure 84-2).[11-14]

Hemoglobin Polymerization

Exposure of the hydrophobic pocket of deoxyhemoglobin leads to polymerization. Crystallization is enhanced by a high hemoglobin concentration (MCHC), low pH, and low temperature, whereas HbA and HbF attenuate it. A key determinant of sickling is the capillary transit time (CTT). The longer a red cell is exposed to the relatively deoxygenated, cold, and acidotic environment of the capillary and post-capillary venule, the more time exists for HbS polymerization to occur. This drives the basics of patient education, prevention and medical management including hydration, warmth, avoiding acidosis and vasoconstriction, ambulation, and assuring oxygenation. It also is the rationale for inducers of HbF and agents to prevent cell dehydration.

Red Cells, Inflammation, and the Endothelium

Crystallization leads to deformation of erythrocytes and oxidative damage to cell membrane proteins, leading to the activation of pathways contributing to the stimulation of white cells and inflammation, endothelial damage and the initiation of the clotting cascade and platelet aggregation. Membrane damage triggers movement of phosphatidylserine to the outer leaf of the red cell membrane where it acts as a substrate for factor V and VIII binding, promoting the clotting cascade.

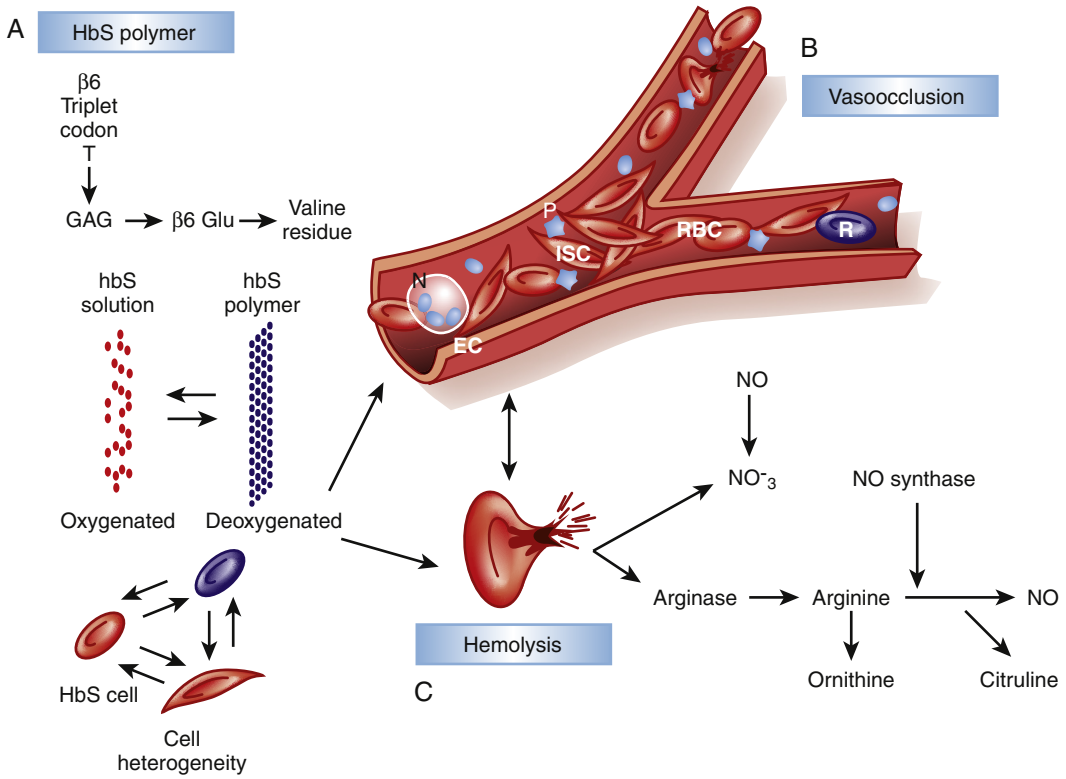

Figure 84–2. Summary of multiple interacting steps contributing to the pathophysiology of sickle cell disease. While an oversimplification and additional pathways are involved, the three predominant pathophysiologic steps are summarized. **A,** Polymerization of HbS. A single nucleotide change results in HbS, which polymerizes on prolonged deoxygenation, leading to sickled cells. **B,** Red cells, inflammation, and the endothelium. Activation of adherence receptors, coagulation, platelet aggregation, and inflammatory pathways lead to slowed flow, sickling of red blood cells, and eventual occlusion of blood flow *N,* Neutrophil; *EC,* endothelial cell; *ISC,* irreversibly sickled cell; *RBC,* red blood cell; *R,* reticulocyte; *P,* platelet. **C,** Hemolysis and NO homeostasis. Hemolysis releases free hemoglobin, which breaks down NO, whereas release of arginase converts the substrate for NO, arginine, to ornithine. Thus less NO is generated and more is destroyed. *(Modified courtesy Dr. Martin Steinberg, Boston University School of Medicine.)*

Reticulocytes and sickled cells expose increased adherence proteins, slowing flow and increasing CTT and enhancing binding to other cell types. Binding to platelets leads to platelet activation and aggregation, whereas binding to neutrophils stimulates the oxidative burst, damaging endothelium and exposing tissue factor, further promoting coagulation, platelet aggregation, and clot formation. In addition, bound white cells release cytokines, increasing inflammatory cell recruitment and division, perpetuating the process. Thus, sickle cell represents an activated, inflammatory state in which the CTT is easily compromised. This increases the likelihood of additional cells sickling and blood flow becoming further compromised, resulting in ischemic damage, inflammation, and propagation of the cycle. This activation and integration of multiple pathways explains the tremendous clinical heterogeneity observed in people with the same hemoglobin genotype, as well as why patients can show rapid clinical decline. The clinical importance of these paths in SCD is re-enforced by an elevated white blood cell (WBC) count being a risk factor for pain episodes, acute chest syndrome, and early death.[6,15] This also explains why infection and trauma are frequent triggers for sickle related pain, and why granulocyte-colony stimulating factor (G-CSF) has led to death in SCD.[16] Therapeutically, this points to the importance of nonsteroidal anti-inflammatory drugs (NSAIDs) in affecting the underlying pathophysiology as well as providing analgesia, and why clinical response to hydroxyurea is best correlated with a decrease in WBC.[17,18] Finally the identification of these interacting pathways identifies potential targets for new therapies affecting inflammation and cell-endothelial interactions.

Hemolysis and Nitric Oxide Homeostasis

In contrast to the vaso-occlusive complications that correlate with a high WBC and diminished HbF, recently a subset of complications including pulmonary hypertension, skin ulcers, and priapism were found to correlate with increased lactate dehydrogenase and bilirubin and reticulocyte count.[12-14] This defines a hemolytic phenotype arising from disturbances in NO hemostasis, and as described at the end of this section, this may be responsible for the inverse association of hemolysis and pain. Hemoglobin accelerates destruction of NO several thousand-fold. Normally laminar flow positions red cells centrally in vessels sequestering hemoglobin away from the endothelium where NO is synthesized and utilized. Hemolysis releases hemoglobin (Fe^{++}) that is now free to diffuse and reduce NO to nitrate with resultant formation of methemoglobin (Fe^{+++}). In addition, hemolysis releases erythrocyte arginase, resulting in arginine depletion, the precursor for NO synthesis. Thus chronic hemolysis leads to decreased NO synthesis and increased destruction, resulting in altered NO

hemostasis and increased tone of small vessels, slowing flow and increasing sickling. Optimal management of hemolysis related pathophysiology remains uncertain. Hemolysis prevention with hydroxyurea is appropriate and well accepted, and agents to prevent cellular dehydration (e.g., Mg^{++} or ICA-17043) are being investigated, but neither is appropriate for acute management. NO metabolism is directly modified with class 5 phosphodiesterase inhibitors (e.g., sildenafil) or by administering NO or related metabolites, and both approaches are being actively investigated for both acute and chronic use. Endogenous sulfur compounds may be tightly integrated with NO pathways, thus a therapeutic role of sulfur compounds may emerge.

In an exciting new paradigm for understanding SCD pain suggested by Gladwin and colleagues,[19] NO has been found to affect the processing of nociceptive signals, that may explain why patients with more severe hemolytic disease have fewer vaso-occlusive events (VOE). NO and resultant cGMP signaling increase the hyperexcitability of nociceptive neurons.[20] Thus as hemolysis depletes NO, it potentially attenuates pain signaling. Conversely, this may explain why SCD patients with fewer markers of hemolysis have more VOE. The implications of this biochemical pathway on pain management in SCD and other states of high hemolysis such as cardiac bypass are not known (see "Pain" below).

Clinical Manifestations

Although a summary of clinical problems and management are listed in the following section, the reader is referred to the National Heart Lung and Blood Institute standard of care guidelines[21] for more details: www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf.

Pain

See Appendix Table 84-A for a detailed care plan, and Appendix Figures 84-B, C, and D for overviews of pain management.[22] Vaso-occlusive events, defined as the acute onset of severe pain secondary to ischemic tissue injury, are a hallmark of SCD. The complexities of SCD pain are best summarized by Shapiro and Ballas: "Vaso-occlusion is a physiological process, but the resultant pain is a biopsychosocial phenomenon. Psychosocial issues such as coping skills, social context, personality, mood, and interactions with the health care system mingle with the biologic factors and contribute to the expression of the illness."[23] SCD pain can be acute, recurrent and/or chronic, and is complicated by co-existing chronic disease as well as social and racial overlays. The need for aggressive and rapid treatment is critical and well documented in guidelines of the American Pain Society and British Society of Hematology and should be consulted.[24,25] Although aggressive intervention is essential for humane care and physiologic improvements (e.g., improving respiratory mechanics when having rib infarct pain), too often racial attitudes and concerns of drug seeking prevent sufficient delivery to patients in excruciating pain.[26] Pain is the most common reason for hospitalization in SCD. The impact of pain is extremely heterogenous in SCD, likely because of differences in genetic background affecting the pathways described above, environment and psychosocial and behavioral variables. In one cooperative study, 80% of patients sought care once or less per year, whereas 5% of patients accounted for one third of hospitalizations.[27] Recent daily pain diary assessments suggest these prior studies underestimate the routine pain many experience.[28] Risk factors for pain include a high Hgb, high WBC, coexisting alpha thalassemia, and increased levels of cell free DNA, whereas HbF is protective.[27,29,30]

Pathophysiology, Diagnosis, and Presentation. Pain can start spontaneously but common precipitating factors relate to the pathophysiology and include weather changes (especially cold), dehydration, inflammation, and infections, all of which increase CTT. Occlusion results in ischemic/reperfusion injury and the release of multiple inflammatory mediators that activate nociceptors, evoking a pain response. Pain may involve any part of the body though most commonly affecting the back and long bones. The unpredictability of the pain contributes to the psychological component of pain, potentially interfering with coping mechanisms.[31] Recurrent and chronic pain contribute to a decreased quality of life, decreased function, depression and suicidal ideations.[28,32,33] Diagnosis is based on a qualitative description, typically biting or gnawing, throbbing, and fatiguing; and quantitative description, that must be trusted (Figure 84-E). The description is essential to help rule out other etiologies of pain, because no physical exam, laboratory, or radiographic studies can confirm or negate this subjective complaint. Physical findings can include swelling, warmth, erythema and tenderness, but exams can be normal and critically, it must be re-enforced that patients can appear without distress. The role of laboratory and radiologic studies is to rule out other etiologies of pain; particularly important for sickle mesenteric pain that must be distinguished from other causes of abdominal pain (e.g., ultrasound to rule out appendicitis or cholecystitis, or tapping a joint to rule out infectious bone or joint processes). Serial quantitative assessments with a developmentally stage specific pain scale is standard of care, though fraught with problems.

Management. See Appendix Table 84-A for a detailed care plan, and Appendix Figures 84-B to 84-D for overviews of pain management.[22] An effective management strategy addresses the underlying tissue damage, nociception, history of pain episodes, and doses of medications required to achieve acceptable analgesia, baseline pain medications, history of tolerance, and how people process pain and coexisting depression. Although many are tempted to begin with analgesic medications, there are several other key components to management, such as the following: (1) environmental manipulation. A dark, calm, quiet environment with supportive interactions supports pain reduction. (2) Complementary methods. Many benefit from distraction, prayer, biofeedback, self-hypnosis and similar modalities. (3) Addressing pathophysiology and triggers. Fluids to maintain euvolemia, warmth and NSAIDs decrease CTT and promote conditions less likely to result in vaso-occlusion. (4) Adjuncts. Physical therapy, ambulation, and incentive spirometry should be encouraged to maintain blood flow and prevent atelectasis and acute chest syndrome (ACS). Additional adjuvants such as massage and acupuncture have been tried. After these have been addressed, providers may focus on analgesic medications.

Patients with SCD are the experts in their own pain management. Ideally patients and staff have agreed on individualized, predefined guidelines for pain management taking

into account the patient's degree of opiate tolerance, and side effect profile, and these are documented online or on a patient identification card. Early initiation of NSAIDs is essential, although the choice of NSAID is controversial (e.g., ibuprofen is a better anti-inflammatory, whereas ketoralac is a better analgesic). Notably, half of children will have resolution of pain with intravenous ketorolac.[34] For severe episodes, rapid and repeated doses of opiates (dosed every 20 minutes), followed by transition to patient controlled analgesia (if developmentally appropriate) is the accepted standard.[35] Although no consensus on the opiate of choice exists, many controversies remain. There are conflicting reports regarding an increased incidence of acute chest syndrome with morphine, with some suggesting decreased rates when nalbuphine is used.[36,37] Many avoid meperidine due to concerns of increased seizures and neuroexcitation.[38] The goal of opiate use is to balance providing sufficient pain relief to allow one to rest and perform incentive spirometry, while avoiding oversedation, which contributes to the development of pulmonary processes. Certain subsets of patients may benefit from regional anesthesia including epidural,[39] dexmedetomidine,[40] clonidine, gabapentin, ketamine, and intranasal diamorphine[41]; although few data exist evaluating their efficacy. One additional promising agent is low molecular weight heparin, which targets the prothrombotic and inflammatory state in SCD, Notably a recent trial reported fewer days of severe pain and length of stay with this intervention.[42]

As mentioned in the discussion of the pathophysiology of SCD, hemolysis leads to depletion of NO and this may attenuate nociceptive signaling through modulation of cGMP signaling.[19] This has substantial implications for SCD where, as described in the following section, modulators of NO metabolism are being increasingly employed therapeutically. Expected outcomes are not obvious as additional signaling pathways modulate cGMP activity, and NO and cGMP production can decrease pain under some conditions.[20] Some of this complexity is explained by the differential effects of modulating distinct sets of NO synthase genes and proteins.[20] Thus, ultimately agents that specifically modulate distinct arms of these pathways in specific regions of the body (e.g., periphery versus central nervous system) will be required to extract the full clinical benefits of NO metabolism manipulation for SCD while maintaining the benefit of NO deletion on chronic pain.

Sepsis

See Appendix Figure 84-F for a detailed care plan.[22] Sepsis is a major cause of morbidity and mortality in SCD. Strikingly, in the 1970s, 20% of SCD patients in the United States died before age 6 years, primarily from sepsis with encapsulated organisms, particularly *Streptococcus pneumoniae.*[5] Many patients were diagnosed with SCD when presenting with sepsis, and diagnosed families often did not appreciate that fever in a toddler was an emergency. This led to newborn screening programs and the development of comprehensive care programs focused on education and immunizations. As expected, this did not affect the incidence of sepsis, but deaths from sepsis plummeted,[43,44] and further decreased with the initiation of prophylactic penicillin in those younger than 6.[45] Widespread use of pneumococcal and Hib vaccines further decreased severe pneumococcal disease to 2.3 events per 100 patient-years, with ages 6 to 36 months being the highest risk group.[46,47]

Pathophysiology and Etiology. The developmental timing of sepsis risk correlates with decreased splenic function because of infarcts leading to functional asplenia, which can be observed as early as 3 months. The resultant defects in cellular immunity, the alternate complement pathway and decrease in memory cells and opsonizing antibodies reduces clearance of encapsulated organisms. Together these lead to a lessened response to the 23-valent polysaccharide vaccine requiring routine reimmunization and results in a 100 to 400 times increased risk of bacteremia with encapsulated pathogens. SCD patients have shown a strong response to the conjugated PCV-7 vaccine, resulting in a two-thirds reduction in invasive pneumococcal disease.[48] Serotypes not covered by the PCV-7 are increasing in prevalence, prompting the development of the PCV-13 vaccine. Although *S. pneumoniae* accounts for the majority of invasive infections other major pathogens include *Haemophilus influenzae* type b, *Escherichia coli* urosepsis, and *Salmonella* and *Staphylococcus* osteomyelitis.[49]

Management

See Figure 84-F for a detailed care plan.[22] Although the pathophysiology, diagnosis, and management of sepsis are presented in Chapter 103, several aspects are unique to SCD, including (1) a focus on prevention with aggressive vaccinations with PCV-13, the conjugated 23-valent vaccine (and recurrent boosters from falling titers), Hib, and meningococcus[50]; (2) prophylactic penicillin given through age 6 years; (3) the critical role of family and provider education in seeking medical care and parenteral antibiotics emergently for fevers higher than 38.3° C. Pneumococcus has doubling time of 20 minutes; thus a 2-hour delay can result in a 50-fold increase in bacterial burden; (4) antibiotic choice should be driven by clinical presentation, but for empiric therapy ceftriaxone is preferred over cefotaxime and cefuroxime due to increasing resistance of pneumococcus; and (5) possible transfusion if cardiovascularly unstable. Evolving care practices will need to account for (1) the influence of hydroxyurea, (2) increasing antibiotic resistance, and (3) the recent release of the PCV-13 vaccine. (Hydroxyurea can result in regrowth of splenic tissue, and early use in young children may prevent autoinfarction, but how this correlates with preservation of immune function and resistance to encapsulated organisms is unknown.)

Acute Chest Syndrome

See Appendix Table 84-B for a detailed care plan.[22] ACS is clinically heterogeneous and its definitions vary in the literature, making comparisons of studies difficult. The most general definition is a new nonatelectatic infiltrate on chest radiograph in a patient with SCD, though others add requirements for fever or respiratory symptoms (Figure 84-3). ACS is the second leading cause of hospitalization in SCD. ACS can progress in hours resulting in a mortality rate of 1% in children (vs. 4% in adults), with most deaths occurring in children younger than age 3 years.[51] ACS accounts for 25% of deaths.[51] Risk factors include a history of asthma, high baseline Hgb and low HbF. Factors associated with mortality include a prior episode of ACS, development of respiratory failure within 48 hours of presentation, sepsis, and simultaneous presentation with pain.[51] Etiologies vary by age and included bacterial infections with typical and atypical organisms, viral infections, fat emboli, and pulmonary hemorrhage

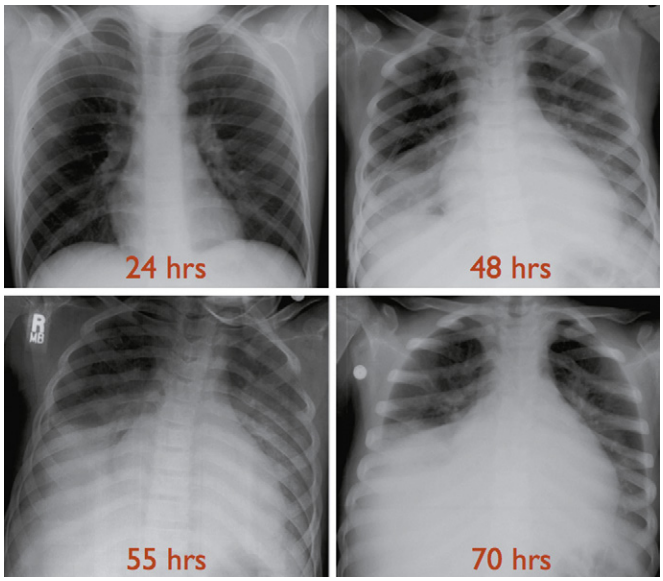

Figure 84–3. Rapid progression of acute chest syndrome. Serial chest radiographs of a 13-year-old male with homozygous sickle cell disease admitted for pain. Hours from admission are noted. Notably acute chest syndrome typically presents 2 to 3 days into an admission for a vaso-occlusive events.

and multiple etiologic factors are often present (see also Appendix Figure 84-G).[52]

Presentation. ACS frequently occurs 2 to 3 days into a VOE. Consistent with the variety of etiologies, presenting signs and symptoms are variable and vary with age (e.g., young children are more likely to present with fever while older adolescents are more likely to present with chest pain).[51] Notably, no single or pattern of signs and symptoms predicts ACS, and up to 35% of patients will have a normal pulmonary exam.[51] Therefore there should always be a low threshold to obtain a chest radiograph. Infiltrates are most common in the lower lobes, and pleural effusions are more common in adults.[51,52] Leukocytosis and significant drops in hemoglobin and platelets are common.[51] Significant morbidity is associated with ACS including pneumothorax and empyema and 14% of patients developed respiratory failure in one study.[52] Risk factors for respiratory failure include (1) extensive lobar involvement, (2) platelet count less than 199,000/μL and (3) history of cardiac disease.[52]

Management

See Appendix Table 84-B for a detailed care plan.[22] Management of ACS can be addressed in stages; initial conservative interventions are followed by transfusion for clinical decline or if severely ill and finally biphasic positive airway pressure (BiPAP) or ventilatory support if needed. Initial care should consist of (1) antibiotics: a cephalosporin to cover encapsulated organisms, particularly *S. pneumoniae*, and a macrolide because *Mycoplasma* and *Chlamydia* are the most common infectious pathogens; (2) oxygen to maintain saturations more than 94%; (3) judicious fluid resuscitation to maintain euvolemia while avoiding overly aggressive fluid resuscitation that may worsen cardiac and respiratory status due to a combination of severe anemia and decreased cardiac function; and (4) prevention of atelectasis. Incentive spirometry (IS) has been shown to prevent progression, and chest physiotherapy and ambulation may be of benefit.[53] Although IS is often limited by chest pain and patient compliance, use of a positive expiratory pressure (PEP) device has been shown to be as effective and better tolerated.[54] The use of BiPAP or continuous positive airway pressure (CPAP) as a preventive measure is untested but appropriate as early intervention may prevent the need for intubation. (5) Opiates should be carefully titrated to minimize splinting and allow IS, while minimizing respiratory depression (small opiate boluses before IS may be helpful). Pain relief can improve respiratory mechanics, improving clinical status. (6) Bronchodilators are indicated as asthma is common in SCD and its presence increases the risk of ACS, and a subset of patients respond independent of documented wheezing.[55] (7) The use of corticosteroids remains controversial. Although a randomized trial showed a decrease in hospital stay and transfusion, a subsequent retrospective review revealed a higher readmission rate, independent of a history of asthma.[56,57]

Transfusion has been shown to significantly improve oxygenation and clinical status in ACS.[52] Although transfusion is usually effective at reversing ACS, because of the risks, including alloimmunization, transfusion not part of initial management unless severely ill. For most patients serial observations, with a low threshold for repeat chest radiographs is appropriate; reserving transfusion for progression despite conservative management. The decision of when to transfuse is contentious and data have been lacking. Promising studies suggest elevated secretory phospholipase A2 (sPLA2) levels predict the development of ACS in SCD.[58] sPLA2 cleaves phospholipids, releasing free fatty acid, and is increasingly being associated with cardiovascular and pulmonary damage, including meconium aspiration. A randomized trial suggests early transfusion guided by sPLA2 levels, can prevent ACS.[58] Though promising, sPLA2 assays are not routinely available and their role in management remains to be determined.

Although 20% to 70% of patients with ACS are transfused, views differ on performing a simple transfusion targeting a Hgb of approximately 10, or an exchange transfusion targeting the same Hgb while lowering the HbS to under 30%.[51,52] Although both approaches improve oxygenation and are safe and effective, exchange transfusion requires exposure to more donors, increasing allo-immunization, is more time consuming, and may require central access in this population with increased thrombotic risk. Thus a simple transfusion is recommended for most situations.[59,60] The decision between direct and exchange transfusion in worsening ACS patients with a high Hgb (>9 g/dL) remains unclear as a minimal amount of red cells can be transfused.

Although lacking formal studies, the use of BiPAP or CPAP in an attempt to stave off intubation makes sense pathophysiologically. There is no consensus as to when to intubate or the optimal ventilation strategy in ACS, thus patients are often treated as children with acute lung injury or ARDS. For those patients with refractory hypoxemia, both high-frequency oscillatory ventilation and venovenous extracorporeal membrane oxygenation have been successful.[61-63] Several promising approaches to ACS including improving NO metabolism with inhaled NO or oral arginine, a precursor of NO; and inhibitors of sPLA2.[64]

Patients with ACS have developed plastic bronchitis. A review of 29 children hospitalized with ACS found 72% had plastic bronchitis, one requiring mechanical ventilation, suggesting there may be a role for intratracheal DNase.[65,66]

Stroke

See Appendix Table 84-C for a detailed care plan and Appendix Figure 84-H for a diagnostic approach.[22] One of the most debilitating and under-appreciated complications of SCD is a cerebrovascular accident (CVA), or the acute disruption of cerebral blood supply resulting in loss of brain tissue function lasting longer than 24 hours.[67] In contrast, transient ischemia attacks resolve within 24 hours, and usually less than 1 hour. This section will focus on CVA related to SCD; a detailed discussion of stroke can be found in Chapter 63. Before screening and prevention programs, 11% of children with HbS/S or HbS/β-thalassemia developed overt strokes (peak, 2 to 9 years), with another 17% having silent infarcts.[68,69] Risk factors include anemia, moya moya, history of CVA, and high velocities upon transcranial Doppler (TCD) ultrasound.[70] Additional risks for ischemic stroke include ACS and hypertension, whereas leukocytosis is a risk for hemorrhagic stroke. Patients with HbS/C disease and other compound heterozygotic states do not have such a significantly increased risk. Strokes are heterogeneous, being due to ischemia, hemorrhage, or thromboembolic events and involving large, medium, and small vessels. The type of CVA varies by age, with ischemic events more common in the first decade and hemorrhagic events more common after age 20 years. Pathophysiology varies tremendously depending on the type and site of stroke, for example anemia is associated with watershed infarcts, whereas thrombus formation and emboli affect more midsize to small vessels, and hemorrhagic strokes likely result from intimal hyperplasia and dilation at the site of previous insults.

Natural History. The natural history of overt ischemic infarcts has changed dramatically with screening TCDs and chronic transfusions. If untreated, 67% of patients have a recurrent infarct within 9 years, and this is reduced to 10% with chronic transfusions targeting a HbS of under 30%.[71-73] Screening TCDs using a standardized approach identifies patients with high cerebral vessel flow, associated with an excessively high stroke risk within 3 years.[74] This can now be decreased to 10% with chronic transfusions.[75] Although physical manifestations often show significant improvement after a stroke, persistent neurocognitive abnormalities are common. A subgroup of patients have moya moya, multiple constrictions of large arteries leading to collaterals at high risk of hemorrhage, aneurysm and clot (see Appendix Video 84-1). This group may have particularly severe disease and may represent some of the 10% resistant to chronic transfusions. The natural history of hemorrhagic infarcts varies in large part with their severity at presentation and location, because these dictate possible neurosurgical or radiology-guided interventions. Silent infarcts can result in difficulties with academic attainment and achievement and cognitive dysfunction similar to that in overt strokes.[76] Executive function deficits are most common, having a tremendous effect on a patient's function in society, and ability to navigate the health care system.

Diagnosis. See Appendix Figure 84-H for a diagnostic approach.[22] While diagnosis is suggested by a history of acute neurologic changes and abnormalities on neurologic physical exam, magnetic resonance imaging (MRI) and magnetic resonance angiogram confirm it. Notably, headache and signs of increased cranial pressure are more common in hemorrhagic stroke (see Chapter 59). Neurosurgical intervention for a hemorrhagic lesion should never be delayed; thus an emergent noncontrast CT is obtained to immediately rule out any surgically amenable lesions and MRI may be deferred, potentially until after therapy has been initiated (see Appendix Figure 84-H).[77] Other etiologies of childhood stroke must be considered and ruled out including infection, thrombosis (thrombosis panel and anticardiolipin antibodies), cardiac embolic disease, masses and trauma with vascular damage.

Management. See Appendix Table 84-C for a detailed care plan.[22] Acute care and monitoring is similar to that for other children with CVAs except exchange transfusion is suggested. Careful attention to signs of increased intracranial pressure and urgent neurosurgical consult in the setting of hemorrhagic stroke, assuring oxygenation, treating fevers to decrease metabolic demands, maintaining adequate cerebral perfusion pressure and monitoring blood sugars and electrolytes are discussed in detail in Chapter 63). Seizures should be treated, but there is no role for prophylaxis. Although tissue plasminogen activator (t-PA) has a role in non-SCD stroke, t-PA or anticoagulant therapy is not recommended in children, in part due to the different pathophysiology. While no studies have assessed the need for acute transfusion, the prevention of secondary events with a chronic transfusion program and the underlying pathophysiology has led to acute transfusion with a goal of maintaining a HbS under 30% being standard of care.[77] This is most efficiently done with exchange transfusion with a final Hgb of 10g/dL. Care must be taken to avoid hypotension with blood withdrawal during the exchange. Once stabilized, extensive evaluation by physical, occupational, and speech therapy, as well as a neurocognitive evaluation are essential to define new postevent baselines and guide future needs.

Aplastic Crisis

See Appendix Figure 84-I for a detailed care plan.[22] An acute worsening of baseline anemia (by 1 to 2 g/dL of Hgb) associated with decreased reticulocyte count (typically <1%), suggests aplastic crises and is caused by acute infection such as parvovirus B19. Sickle RBCs survive 10 to 14 days (vs. 60 to 100 days for normal cells); thus patients are dependent on a threefold to fivefold increased reticulocyte production and any decrease can lead to a transient red cell aplasia with rapid development of a profound anemia. Monitoring of Hgb (both absolute and compared with the individual's baseline), reticulocyte count, and cardiovascular status are essential. Most parvovirus B19 will spontaneously resolve, however, intravenous gammaglobulin should be considered to hasten viral clearance if reticulocytopenia persists. Transfusion may be necessary if cardiovascularly unstable or if the hemoglobin acutely falls more than 2 g/dL. Profound anemia or cardiac compromise may require a slow transfusion (2 mL/kg/hr), diuretics, or even exchange transfusion to avoid congestive heart failure.

Splenic Sequestration

See Appendix Figure 84-I for a detailed care plan.[22] Sequestration is characterized by an acutely enlarging spleen with a Hgb more than 2 g/dL below an individual's baseline value. Mild to moderate thrombocytopenia may also be present. Splenic

sequestration occurs in 10% to 30% of children with SCD, most commonly between the ages 6 months and 3 years, often following a febrile illness. Abdominal pain, nausea, and vomiting are common, and severe episodes of sequestration may progress rapidly to cardiovascular collapse and death. Transfusion is indicated when signs of cardiovascular instability are present and, as with aplastic crises, caution should be taken to avoid contributing to congestive heart failure. Though rare, emergent splenectomy may be required. Elective splenectomy is indicated for recurrent episodes of sequestration with cardiovascular compromise.

Pulmonary Hypertension

Despite being a major cause of death in SCD, pulmonary hypertension (PHTN) is underappreciated, in part due the uniquely high morbidity associated with mild elevations in pulmonary artery pressures (PAP).[78] Adults with estimated PAPs greater than 30 mm Hg or a tricuspid regurgitation velocity jet velocity (TR jet) of greater than 2.5 m/sec have a strikingly higher mortality rate; thus it is essential to have a significantly lower threshold for aggressive intervention for PHTN in the hemoglobinopathy patient than in others.[78] Pulmonary hypertension in children (defined as a PAP greater than 25 mm Hg at rest or greater than 30 mm Hg with activity) is present in approximately 30% of children, as well as adults, with SCD. With approximately 100,000 SCD patients in the United States, this translates to 30,000 cases, making SCD the leading cause of PHTN. Despite this, there is little awareness of this relationship in the hematology and cardiology communities.

Pathophysiology and Etiology. Assessment and management is complicated as multiple etiologies and risk factors contribute (see Chapter 48). Unlike most PHTN in childhood in which there is a single dominant cause (e.g., congenital malformation), multiple pathways contribute to the manifestation of PHTN in SCD and each must be addressed for optimal management. Pulmonary hypertension is more common in SCD patients with a "hemolytic phenotype" associated with priapism and leg ulcers, but independent of VOE. Thus patients often have a high LDH, bilirubin, and reticulocyte count, and low HCT which are associated with decreased NO production and increased NO destruction, that result in a NO resistant state. Frequently confounding factors in SCD include (1) hypoxic PHTN due to the high incidence of enlarged tonsils, obstructive sleep apnea, asthma, and chronic lung disease; (2) arterial obstructive PHTN secondary to increased coagulation and embolic disease; and (3) pulmonary venous hypertension due to cardiomyopathy. Contributing to the high morbidity in SCD are the protean manifestations of mild pulmonary hypertension (30 to 44 mm Hg). The majority of patients with SCD and PHTN will be asymptomatic or have mild decreases in exercise tolerance (e.g., 6-minute walk) yet have a 10-fold increased risk of death.[78] Adults with PHTN may not experience significant effects until pressures become moderate to severe, which for SCD portends a high mortality not observed in other patient populations with comparable pressure. The dilemma is that while mild PHTN is a major risk for death in adults, the natural history in children is unknown, and a recent study suggested no increased risk of death within three years of diagnosis.[79] Thus it is not clear how aggressively to treat children with SCD and PHTN.

Diagnosis. Though cardiac catheterization is the gold standard for determination of PAP, the indications for catheterization are debated within the sickle cell community. Noninvasive quantitation of the TR jet by echocardiography is most commonly used as it correlates with catheterization data. Catheterization is reserved for a subset of the patients initiating PHTN specific therapies.

Management. Though no consensus has been reached, a three-part approach to treatment is reasonable. (1) Optimization of SCD care, with the goal of decreasing the hemolysis fueling NO imbalance. Hydroxyurea and chronic transfusions are typically used though these are not acute interventions. (2) Aggressive diagnosis and treatment of confounding factors (e.g., tonsillectomy and adenoidectomy, BiPAP or CPAP, and nighttime O_2. (3) PHTN specific interventions, discussed in detail in Chapter 48. The mainstay of treatment of PHTN in the ICU is inhaled NO (iNO), which provides both direct vasodilation of the pulmonary vasculature and simultaneous reversal of the underlying disruption in NO metabolism. The major challenge with iNO is the development of rebound PHTN on discontinuation of therapy and difficulty in administration, thus driving a focus on alternative therapies. The phosphodiesterase (PDE)-5 inhibitor sildenafil is effective in facilitating weaning from iNO and in decreasing PAP over time in non-SCD PHTN[80,81]; however, a recent trial of sildenafil for PHTN in SCD was discontinued because of increased rates of VOE. Additional therapies that deserve consideration include (1) intravenous prostacyclin (epoprostenol), which reduced PAP in a small number of patients with SCD undergoing cardiac catheterization[82]; (2) endothelin receptor antagonists (e.g., bosentan and ambrisentan), which reduced PAP and improved 6-minute walk in adults with SCD and PHTN[83]; (3) inhaled iloprost, a prostacyclin analogue used in Europe, that has shown promising results in idiopathic PHTN, but its safety and efficacy in SCD has not been determined; and (4) oral arginine therapy, which reduced PAP within 5 days of therapy in a small number of patients with SCD and PHTN.[84]

Multiorgan Failure

Multiorgan failure syndrome is defined as severe pain associated with failure of at least two of the following organs: liver, lung, and kidney. It is often associated with severe pain in patients with previously mild disease and a relatively high Hgb.[85] Widespread vaso-occlusion is thought to be responsible, though data is lacking. Patients present with an atypically severe VOE, fever, and sudden deterioration including a drop in Hgb and platelets, diffuse encephalopathy, and rhabdomyolysis. Death has been reported in up to 25% of patients.[86] Exchange transfusion should be considered early, and can result in rapid recovery of organ function as well as survival. Antibiotics are often used, though many patients are culture negative. There are isolated reports of success with NO or plasma exchange in those with transfusion resistant disease.

Priapism

See Appendix Table 84-D for a detailed care plan.[22] Priapism is common in males with SCD, often starting in childhood and frequently occurring during the early morning hours. Stuttering priapism is intermittent episodes lasting fewer than 2 to 4 hours, and is often recurrent and may precede a more

severe episode. Severe episodes, lasting over 2 to 4 hours, need rapid intervention as they may result in permanent tissue damage and impotence.[87] Initial interventions include hydration, warmth, micturition, activity, and analgesia. Pseudoephedrine can be used for prevention and treatment though no efficacy data is available. If these measures fail to lead to detumescence in 4 to 6 hours aspiration and irrigation with a dilute α-agonist (e.g., epinephrine, phenylephrine) by a urologist has been shown to be effective if done within 24 hours.[88] Prevention with PDE-5 inhibitors is being investigated.

Skin Ulcers

Though rarely discussed, lower extremity ulcers are a major cause of morbidity, affecting comfort, ambulation, and increasing the risk for depression. Although no standard of care has been established, ulcers can be resistant to conventional therapies. As a result exchange transfusions and experimental interventions such as topical G-CSF, endothelin inhibitors and fetal cell transplants are under investigation.

Cholelithiasis

The prevalence of "stones" increases with age, and many centers suggest screening ultrasounds. Though often asymptomatic, cholecystectomy should be considered as soon as stones become symptomatic; avoiding the risk of infection or emergent surgery. Cholecystectomy is the most common general surgery procedure in SCD and is increasingly done laparoscopically, increasing operating room time, but decreasing recovery time.

Renal Conditions

Passage through the vasa recta exposes red cells to hypoxia, acidosis, and hypertonicity, which are extreme enough conditions to make some trait cells sickle, and causing damage to the renal medulla. This can lead to multiple complications that can affect fluid balance and renal function including (1) Hyposthenuria, an inability to concentrate urine. It is critical to remain aware of this in the ICU as the production of dilute urine cannot be used as a marker for being euvolemic, and, patients are prone to dehydration, leading to pain episodes. This results in enuresis being common and worsened in the ICU by continuous intravenous fluids and opiates. (2) Hematuria: This can range from micro-, to gross hematuria associated with papillary necrosis. Conservative management with bed rest and maintenance of high urine output to avoid the development of clots usually suffices. Vasopressin has been used with some success, as has ε-amino caproic acid, though the latter should be used with caution as it can lead to clot. If recurrent transfusions are required or bleeding becomes life-threatening, resection of the involved region may be indicated. (3) Tubule dysfunction including an incomplete renal tubular acidosis worsened by the hyposthenuria, and hyperkalemia associated with the use of potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, or β-blockers. (4) Chronic renal failure associated with glomerular injury and proteinuria and can progress to nephrotic syndrome. End-stage renal disease develops in 40% of patients with nephrotic syndrome, thus persistent proteinuria is an indication for an in-depth evaluation. Risk factors include hypertension, hematuria, proteinuria, and worsening anemia. Although there is no clear cure, angiotensin-converting enzyme inhibitors can reduce the proteinuria, and NSAIDs should be avoided. Worsening anemia can be treated with erythropoietin, though patients often need higher doses than others. Alternatively, transfusions can be done, keeping in mind the increased risk of fluid overload. Kidney transplantation is appropriate, and outcomes are similar to that of African Americans, albeit less than other Americans. Current success using combined hematopoietic stem cell and kidney transplants in a canine model raise the exciting possibility of curing both the hemoglobinopathy and renal failure simultaneously.[89]

Ocular Conditions

Retinal arteriolar occlusions are thought to lead to ischemia and damage, resulting in release of vascular growth factors, causing a proliferative retinopathy. The goal is to treat with laser photocoagulation (or other techniques) before the development of severe disease. If untreated, retinal detachment and vitreous hemorrhage can occur, and may require retinal microsurgical intervention. Interestingly, whereas HbS/C tends to be less severe, the risk of retinopathy and avascular necrosis are both higher.

Avascular Necrosis

Occlusion of endarterial vessels can lead to necrosis of juxta-articular bone. This occurs disproportionately in patients with concomitant α-thalassemia or HbS/C disease. Avascular necrosis can lead to significant pain and decrease in function. Conservative management with NSAIDs, opiates, and reduced weight bearing can allow for limited function while boney remodeling occurs, though with age this is less successful and progressive destruction leads to degenerative arthritis. Targets relate to size and weight bearing, with the hips, knees, and shoulders being most affected. In an attempt to avoid hip replacement, surgical core decompression had been promoted, but a specific, aggressive physical therapy program has been shown to be as effective.[90] For severe cases, hip replacement is indicated.

Iron Overload

Unlike thalassemia, the iron overload of sickle cell is purely related to transfusion. Whereas sickle cell and thalassemic patients may show different patterns of iron deposition, the acute management in the ICU is similar, and is discussed in the thalassemia section.

Sleep Conditions

SCD patients are at increased risk for sleep-disordered breathing and obstructive sleep apnea, though the importance of this remains under debate.[91,92] It has been suggested sleep disturbances increase the risk of VOE and pulmonary hypertension, though data is inconsistent. The etiology is not clear, but notably, SCD patients tend to have enlarged tonsils and adenoids and children with SCD have more severe nocturnal desaturations and hypercapnia than others with obstructive sleep apnea. Tonsillectomy and adenoidectomy often leads to resolution. Alternatively, auto-CPAP has been well tolerated in SCD and shown to improve sleep and cognitive function.[93]

Depression and Suicide

With recurrent pain and complications that can occur without warning, it is not surprising that anxiety and depression are increased in SCD.[94,95] Interestingly, rates are higher than in cystic fibrosis, spina bifida, or diabetes, with 49% having anxiety symptoms in one study, and the risk of suicide in adults being increased.[33,95-97]

Table 84–2 Indications for Transfusion in Sickle Cell Disease

	Duration	Consensus	Method	Goal*
Stroke, acute	Single	+	Ex	HbS <30%
Stroke, ongoing care	Chronic	+	Either	HbS <30%
High-velocity TCD	Chronic	+	Either	HbS <30%
ACS, initial episode	Single	+	Dir > Ex	Hgb 10
ACS, recurrent	6–12 months	+	Either	
PHTN	Chronic	+	Either	
Multiorgan failure	Single	+	Ex	
Major surgery	Single	+	Dir	Hgb 10
Acute anemia	Single	+	Dir	
Recurrent spleen sequestration	Chronic	+		
Sepsis/meningitis	Single	+	Dir	
Severe chronic pain	6–12 months	+		
Congestive heart failure	Chronic	+		
Silent infarct with abnormal neuropsychology	Chronic	–		
Pregnancy		–		
Anemia/renal failure	Chronic	–		
Leg ulcers	6–12 months	–		
Severe growth delay		–		
Severe eye disease		–		
Priapism		–		

Dir, Direct; *Ex,* exchange; *Hb,* hemoglobin type; *Hgb,* hemoglobin concentration; +, consensus reached; –, consensus not reached.
*Goal of transfusion if a consensus has been reached.

Surgery and Anesthesia

See Appendix Table 84-E for a detailed care plan.[22] Major surgery in sickle cell is associated with increased perioperative risks including VOE pain, acute chest syndrome, and death, but these can be minimized with specific perioperative care. Preoperative transfusion was thought to provide benefit, leading to a randomized trial in which perioperative care was standardized and direct transfusion targeting a Hgb of 10 was compared with exchange transfusion targeting a Hgb of 10 with a HbS less than 30%.[98] Outcomes for both arms appeared better than observed historically, and the two groups were equivocal except the exchange arm was exposed to more units of blood and had more alloimmunization. Thus a direct transfusion is preferred as it minimizes exposure to blood. Communication and coordination between anesthesia, surgery, and hematology is essential, and institutions are encouraged to have a standard perioperative care plan for SCD. Most patients are admitted overnight for O_2, aggressive IS and observation, even if cleared to return home from a surgical standpoint. Because of poor compliance with incentive spirometry the use of BiPAP in the immediate post-operative period may be of use.[99] Specific recommendations should be followed (Appendix Table 84-E), though some feel that with modern improvements in perioperative care, that routine transfusion is no longer needed.[99,100]

Therapies and Interventions

The impact of public health policy and family education focused on prevention, early detection, and early intervention cannot be overstated. Morbidity, mortality, and quality of life have all improved. Although specific therapies were listed above, additional management guidelines follow. Increasingly treatments target specific mechanisms involved in the pathophysiology of SCD (see Appendix Figure 84-J for an overview).

Hydroxyurea

Although hydroxyurea is not an acute intervention, the intensivist should be aware that many SCD patients are (or should) be prescribed hydroxyurea, as it can decrease pain, ACS episodes, and transfusion need while increasing hemoglobin and lifespan.[10,101] Originally used in SCD to stimulate HbF production, the primary clinical benefits may stem from the relative leukopenia induced by this oral chemotherapeutic (see "Pathophysiology" above). Although good data exist for its use in adults, its role in children, especially the very young is an ongoing research question, but looks promising.[102] Clinicians should remain aware that in addition to cytopenias, hydroxyurea can lead to a red cell macrocytosis and should not be alarmed by MCVs greater than 115.

Transfusion

Though a mainstay of therapy, guidelines for transfusions in SCD are complex and vary by indication (Table 84-2).[103-106] See Chapter 82 for general information regarding blood transfusion. SCD specific issues follow.

Choice of Product. Packed RBCs should be leukodepleted to minimize febrile reactions and alloimmunization. Although transfusion from sickle trait donors is safe and effective, HbS negative blood should be requested to allow accurate

determination of posttransfusion HbS levels if needed. Due to racial, and therefore antigenic, differences between patients and the primarily white U.S. donor pool, alloimmunization is common, even after a single transfusion. This can significantly hinder the ability to provide future transfusion support. An extended cross-match for antigens of clinical significance that vary between racial groups should always be requested and should include Rh (Cc, D, Ee), and Kell in addition to ABO.[105] The intensivist must be aware that this matching, or finding compatible units for highly immunized patients, may take considerable time, thus a type and cross should be sent well before blood is needed, and in some emergencies extended matching may need to be forgone. Unlike patients with hematologic malignancies there is no need for blood product irradiation or CMV negative selection.

Type and Goals of Transfusion. Transfusion increases O_2 carrying capacity while decreasing the percent of HbS and different modes of transfusion affect these differentially. Few clinical trials are available but for several acute indications direct and exchange transfusions provided similar benefit, thus in these instances direct transfusion is preferred to minimize alloimmunization. The decision in chronic transfusion is more difficult as exchange transfusion results in less iron overload at the cost of increased exposure to blood. Manual exchange transfusions can be initiated rapidly with a single intravenous infusion, but are laborious and time consuming. Automated exchange (erythrocytapheresis) is rapid but not universally available, requires two large-bore intravenous infusions or a central pheresis-specific catheter and cannot be done in small children because of the significant volume and pressure shifts (size limits vary with the machine used). The target hemoglobin concentration or HbS percentage varies with indication (see Table 84-2) but in most cases the final Hb should never be higher than 11. Studies suggest higher Hb increase oxygen carrying capacity, but O_2 delivery falls. Formulas for calculating blood volumes for routine and exchange transfusions are available (Appendix Figure 84-K).

Indications. The reflective tendency to transfuse SCD patients should be avoided. Because of alloimmunization and other risks, attempts should be made to avoid transfusion unless there is a clear clinical indication. Transfusions may be one-time, or chronic, the latter not being an ICU issue. Table 84-2 summarizes guidelines and additional information is in specific sections.[103,104,106]

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) remains the one cure for SCD and is recommended for young patients with severe disease and a suitable donor. This is not appropriate in the acute setting, and there is debate over what defines a young patient and suitable donor, as well as what the optimal conditioning regime is. The major role of the ICU is supportive care post-transplant (see Chapter 83). Pediatric patients receiving a matched sibling transplant after a myeloablative conditioning regime had an 85% event-free survival and an approximately 94% overall survival with approximately 10% graft failure (reverting to their endogenous marrow) and 12% to 20% significant GVHD.[107,108] Attempts to adapt a less toxic, nonablative "mini transplant" regimen have been hampered by a high incidence of graft failure, potentially contributed to by a long history of exposure to donor antigens in transfusions. Initial attempts have found current regimes overly toxic to adults, presumably due to the accrued end-organ damage from SCD before transplant. Currently multiple SCD research transplant studies are available and address optimizing the conditioning regime and extending transplants to older patients, and to using alternate donors (unrelated, cord blood, haplo-identical).

Gene Therapy

Modification of autologous HSCs to correct the sickle mutation or add a normal gene avoids many of the problems of routine HSCT but remains experimental with limited number of clinical trials (see "Thalassemia" below).

Nitric Oxide

SCD often results in a NO resistant state. Both hemolysis related and vaso-occlusion related complications may directly benefit from NO-related therapies. Because NO is incredibly labile, multiple modes of delivery are being investigated, including providing substrate (e.g., arginine), providing cofactors for its generation (e.g., 6R-BH4), providing NO or direct metabolites intravenously or by inhalation, or modulating the effects of NO (e.g., sildenafil).[109]

Induction of β-like Chains

Many agents have been used to induce fetal globin genes with variable success. Refer to this topic in the "Thalassemia" section below for a more detailed discussion.

Antioxidants

SCD is associated with increased reactive oxygen species, RBC membrane damage, and depleted antioxidant stores. As a result multiple antioxidants are being investigated including L-glutamine and a variety of herbal or natural products.

Endothelial Protectants

As SCD results in endothelial disruption and inflammation, statins are being investigated including simvastatin and atorvastatin.

Thalassemia

Molecular Description and Epidemiology

In contrast to a single mutation being responsible for sickle cell, and the mutant peptide directly leading to the pathophysiology, a broad spectrum of mutations lead to thalassemia and it is the residual unpaired phenotypically normal globin chains that incite damage. The hallmark of thalassemia is an imbalance in the ratio of α- and β-chains, not a deficiency in chains. The distinction becomes important when one considers α-/β-thalassemia compound heterozygotes, or duplicated (excess) globin genes. The broad spectrum of mutations responsible for thalassemia truly represents a textbook compendium of mechanisms of mutation, but common to all is an altered level of chain production. Gene deletions account for the majority of α-thalassemias, leading to quantum incremental changes in phenotype depending on whether 1, 2, 3, or all 4 adult α-globin genes are missing. In contrast to α-thalassemia, a broad range of mutations lead to β-thalassemia, resulting in a continuum of clinical phenotypes. As with sickle cell trait, thalassemia trait is thought to provide increased fitness in malaria zones.

It is estimated that 1.5% of humans are heterozygous for a thalassemia, with about 0.05% having clinically significant disease. Because of the coexistence of α-/β-thalassemia in the same regions compound heterozygotes are common, leading to a huge spectrum of disease and complicating diagnostics.

Laboratory and Diagnostics

Although the sine quin non of diagnostics is the demonstration of an α- to β-globin chain imbalance, this is not practical for routine testing, thus most clinical laboratories rely on a variation of a thalassemia screen. The screen distinguishes thalassemia from iron deficiency, and α- from β-thalassemia. Due to the wide range of defects, and frequent mixed α- and β-thalassemia patients, it is impossible to state absolutes for diagnostic interpretation, and there should be a low threshold to consult with hematology. Components of the screen include (1) a complete blood count where emphasis is placed on the MCV which is decreased in proportion to hemoglobin production, the RBC to assess the degree of compensation for the decreased cell size, the hemoglobin and the smear; (2) a hemoglobin electrophoresis or HPLC to quantitate normal, and variant hemoglobins; (3) an inclusion body or Brilliant Cresyl Blue preparation to semi-quantitatively assess excess β-like chains and distinguish α- and β-thalassemia, and a (4) zinc-protoporphyrin or similar screen to exclude iron deficiency. α-Thalassemia results in excess β-like chains that form tetramers (β4: Hb H, γ4: Hb Barts) that precipitate in proportion to the number of missing α-genes, resulting in a positive inclusion body prep (Table 84-3). A negative study in the face of adequate iron is suggestive of β-thalassemia. The diagnosis of β-thalassemia is less direct. Excess α-chains are less stable and degrade, thus the inclusion body prep is normal and no α-tetramers are detectable on electrophoresis or HPLC. Frequently β-thalassemia results in up regulation of HbA_2 or HbF; thus the presence of either is suggestive of the diagnosis. Many mistakenly exclude the diagnosis if HbA_2 or HbF is not elevated, but this is not appropriate (e.g., deletion of the δ and β genes results in thalassemia but HbA2 is not elevated).

DNA testing is increasingly available and cost-effective though it remains problematic as no single assay or panel detects all abnormalities. PCR assays for the most common α-thalassemia deletions are available, and their utility is dependent on the frequency of the specific deletion in the patient's ethnic background. Due to the variety of mutations leading to β-thalassemia, β-locus sequencing is most efficacious, but misses most deletional forms. The use of CGH (comparative genome hybridization) arrays is being developed for assessment of the α-locus to allow a more comprehensive and less biased approach.

Pathophysiology

The pathophysiology of thalassemia is complex but in overview, unpaired globin chains lead to ineffective erythropoiesis and hemolysis, the degree of which depends on the specific form of thalassemia and patient's genetic background (Appendix Figure 84-L). Free globin chains increase reactive oxygen species while decreased glutathione and antioxidant stores result in oxidative damage to the fragile red cell membrane, as well as to apoptosis in a Fas-mediated process. The end result is a cadre of processes contributing to the heterogeneity of disease presentation. Phosphatidyl serine moves to the outer leaf of the red cell membrane, enhancing macrophage-mediated destruction in the spleen and marrow. Phosphatidylserine also acts as a substrate for factor V and VIII binding, enhancing generation of thrombin, which together with decreased protein C and S levels and increased platelet activation and adhesion leads to increased thrombosis. In an attempt to compensate for the hemolysis and ineffective erythropoiesis, medullary and extramedullary erythropoiesis is increased leading to skeletal abnormalities such as the thalassemic facies, and thinning of the cortex of long bones (Appendix Figure 84-M). The latter, along with endocrine abnormalities (see the following section) lead to increased fractures. High levels of non-transferrin bound iron from red cell destruction, increased intestinal absorption from inappropriately low levels of hepcidin, and transfusions lead to iron deposition, resulting in liver, cardiac, and endocrine dysfunction.

Forms and Variations

α-Thalassemia

Most mutations are deletions entirely eliminating a gene's activity. With deletion of each subsequent gene, hemoglobin synthesis, and thus MCV, is decreased, there are more unpaired β-like chains, which increases the precipitations on the inclusion body prep and worsens ineffective erythropoiesis, resulting in a lower hemoglobin. (See Appendix Table 84-F for typical laboratory findings). A one-gene deletion (silent carrier) is clinically benign; two-gene deletions (thalassemia trait) lead to a borderline low Hgb and decreased MCV, thus are easily confused with iron deficiency. A three-gene deletion (HbH disease) leads to anemia and significant microcytosis, which can be worsened by viral suppression or oxidizing drugs, such as those avoided in G6PD deficiency. Although individuals do not have increased morbidity or mortality, in rare instances they can display growth delays or acute drops in Hgb requiring PRN transfusions. A subset of HbH patients, those with HbH with a HbCS (Constant Spring) allele, are severely affected and more likely to require transfusion. A four-gene deletion (hydrops fetalis) typically results in fetal demise while presenting significant medical risk to the mother. With the aid of serial in utero transfusions, some fetuses survive and once born will require life-long transfusions as described for β-thalassemia major.

β-Thalassemia

In contrast to α-thalassemia, the plethora of β-gene mutations leads to a continuous spectrum of disease. β^0-thalassemia denotes non-expressing alleles, whereas β^+-thalassemia is used for genes that express a reduced amount of normal protein. Most mutations do not eliminate ε- or γ-gene expression, thus it is unusual for clinical complications to occur until several months of life, when infants become dependent on β-globin chains. Nomenclature is based on this continuum of phenotypic severity rather than genotype. β-thalassemia trait, also referred to as thalassemia minor, is due to a single silent allele and is benign and clinically similar to α-thalassemia trait. Although the term thalassemia major (aka Cooley anemia) is reserved for transfusion dependent phenotypes, those patients with clinical sequelae, but who are not dependent on transfusions for survival are referred to as having thalassemia intermedia. The latter require the most clinical decision-making as

Table 84–3 Distinguishing Laboratory Features of α- and β-Thalassemias

Diagnosis*	BCB Prep†	HbA_2‡	HbF	HbH	Hb Barts in Newborn§
Normal	–	nl	nl	nl	–
α-Thalassemia	+	nl	nl	nl or ↑	+
β-Thalassemia	–	nl or ↑	nl or ↑	nl	–

Can be negative for a one α-globin deletion (silent carrier), for compound heterozygotes with combined α- and β-thalassemia, and other hemoglobinopathies (e.g., HbE or HbS). Table shows typical results; exceptions occur.
*All forms of α -or β-thalassemia are pooled; specific results will vary.
†Brilliant cresyl blue (*BCB*) or inclusion body prep. Results vary by lab, but this can be done semiquantitatively. This can be negative when a one α-globin deletion (silent carrier) is present. This assay is unreliable in the presence of other hemoglobins (e.g., HbS or HbE). This can be negative when α- and β-thalassemia are simultaneously present.
‡HbA_2 results vary depending on laboratory method.
§Hb Barts increases with the degree of α-thalassemia.
Hb, Hemoglobin type; *nl,* normal; ↑, increased; –, negative; +, positive.

there is increasing awareness of the high morbidity in many of these patients.

HbE/β^0-Thalassemia

Of the numerous hemoglobin variants, this compound heterozygous state is worth special mention. The HbE mutation is common throughout Southeast Asia and results in a RNA splicing abnormality and a destabilizing amino acid substitution, leading to a thalassemic allele. When combined with another β-thalassemic allele the phenotype is extraordinarily variable, with some thriving, and a subset being transfusion dependent. Management is similar to other thalassemias.

Combined Mutations

Patients with combined α- and β-thalassemia are an elegant demonstration that a significant degree of the pathophysiology is due to unpaired globin chains and not solely decreased chain production. As an example, the clinical severity of β-thalassemia decreases as patients have additional deletions of α-globin genes. Having both decreased α- and β-chains leads to low MCV and MCH, but with fewer unpaired globin chains cells are more stable, thus patients have a higher RBC and improved Hgb than with either mutation alone.

Natural History

Natural history is highly variable depending on the genotype, modifying genetic factors, and critically, what interventions are available, and at what stage of illness. When a patient comes to medical attention depends on the severity of anemia, type of thalassemia, family history and awareness, and, critically, local medical expertise and resources. If not diagnosed by newborn screening or from a known familial risk, children can present with anemia, growth delays, boney abnormalities, and most important for the intensivist, congestive heart failure. With time, whether transfused or not, toxicity from iron overload and deposition develops.

Assessment of Iron Overload

Serum ferritin is a poor indicator of iron stores.[110] Though inexpensive and easily obtained, it is elevated with inflammation and does not correlate well with tissue iron content, especially in patients receiving chelation therapy. Serial observations may help track trends but this is not a substitute for direct tissue measurements. While previously liver biopsy was the gold standard for assessment of liver iron content (LIC) it is limited by (1) its invasiveness and risk, (2) it not correlating with accumulation in the heart and other target organs, and (3) sampling errors, as only a small region of liver is assessed while iron accumulation is heterogeneous throughout the liver. MRI-based assessment of iron overload is based upon relaxation times correlating with iron content. These techniques are evolving rapidly, making it essential to discuss options with local radiologists, as standards and practices vary greatly. Ferriscan was the first Food and Drug Administration-approved MRI assessment of iron, obviating biopsies, but it is limited to the assessment of hepatic iron.[111] In contrast, T2* imaging is increasingly available and allows simultaneous assessment of hepatic and cardiac iron, and potentially, other target organs.[112] A lower T2* correlates with higher degrees of iron overload (see "Cardiac Failure" below).

Spectrum of Disease

Although a summary of clinical problems and management are listed below and in Appendix Figure 84-N, please refer to the Northern California Comprehensive Thalassemia Center standard of care guidelines[113] for more details: http://thalassemia.com/documents/thalhandbook2008.final.pdf.

Anemia

Although there is much debate as to the optimal Hgb that should be targeted, in the ICU one must factor in the acuteness of the anemia, the degree of cardiovascular compromise, and the patient's baseline Hgb. A baseline level of under 7 g/dL is often the threshold for initiating chronic transfusions, though a higher threshold is used if growth, skeletal malformations or extramedullary erythropoiesis become problematic. The goal should be to maintain a Hgb of 9 to 10 g/dL pretransfusion (10 to 12 g/dL if cardiac disease is present), but no higher than 14 g/dL posttransfusion. As with SCD, profound anemia or cardiac compromise may require a slow transfusion, diuretics, or even exchange transfusion to avoid congestive heart failure. Blood products should be leuko-reduced to minimize alloimmunization, febrile nonhemolytic transfusion reactions, and CMV transmission. As with SCD, blood should be matched for ABO, Rh (Cc, D, Ee), and Kell. Family and related donor transfusion should be avoided if a hematopoietic stem cell transplant is to be considered as alloimmunization to donor antigens increases graft rejection.

Transfusion-Related Complications

Chronic or frequent transfusions increase infectious risk (described in Chapter 82) as well the risk of alloimmunization. Because of inappropriately low hepcidin levels, the ability of the body to absorb iron is unopposed, leaving blood loss and sloughing of endothelial and skin cells as the only mechanism to decrease iron in the face of iron overload. This is estimated to lead to a loss of 1 mg/day in an adult that pales in comparison to the approximately 200 mg of iron in each unit of blood. Although previous focus was on hepatic iron overload and cirrhosis, there is increasing awareness of iron overload in the heart, pituitary and endocrine organs leading to dysfunction (the the following section), and excessive melanin production leading to "bronze" pigmentation. Iron overload requires chelation, which can result in additional complications (Appendix Table 84-G).[113] Because of its short half-life, deferoxamine therapy is given continuously (subcutaneously or intravenously), and complications may include oto- or ophthalmologic toxicity, allergic reactions with life threatening hypotension (primarily when given intravenously), growth failure, metaphyseal cartilaginous dysplasia, bacterial infections (e.g., *Yersinia*), and inadvertent chelation of other cations including zinc, copper, selenium, and calcium. The need for continuous subcutaneous infusions often leads to problems with compliance, in part overcome by the use of oral deferasirox. Though quality of life may be improved, compliance issues remain, and more than 30% of patients on deferasirox have a reversible increase in creatinine; renal and hepatic failure has been reported.[110] Optimal dosing of either drug is determined over time, taking into account the degree of overload, transfusion regime, and whether a neutral, or negative iron balance is desired. Please see the cardiac failure section for emergent dosing and new approaches.

Cardiac Failure

Cardiac failure, defined as a low ejection fraction with a component of cardiomyopathy, is the major cause of death in thalassemic patients with iron overload. A thalassemic patient in failure should be assumed to have cardiac iron overload until proven otherwise. Risk factors include transfusion history and underchelation. Excess unbound iron from transfusion and inappropriate gastrointestinal absorption freely penetrates cardiac myocytes leading to progressive tissue damage. Iron accumulates predominantly in the epicardial portion of the ventricular septum and ventricular free walls, stimulating the production of free radicals, resulting in peroxidative tissue damage, decreased cardiac contractility and dysrhythmias. This, in combination with the high output state from chronic anemia, results in the early development of cardiac failure. Cardiac iron overload occurs years after the liver becomes overloaded. Initial cardiac iron deposition increases the influx of additional iron resulting in a rapid accumulation and the potential for rapid decline, a wide range of dysrhythmias and failure after years of normal function. The clinical presentation is that of congestive heart failure; however, some present solely with abdominal pain due to liver distension. Clinicians should always have a low threshold to evaluate for cardiac dysfunction. Before the introduction of iron chelation therapy in the 1960s, the majority of patients with thalassemia died from congestive heart failure by age 16 years. With advances in both transfusion and chelation therapy survival has increased, with 80% of patients living to age 40 years.[114] Lifespan is highly dependent on the underlying thalassemia as well as the transfusion and chelation history.

Assessments

Cardiac iron accumulation and function must both be assessed. Ferritin and assessments of LIC cannot be used, because kinetics of iron loading and unloading differ between the organs. Iron assessment by T2* is invaluable as one can assess cardiac iron, as well as LIC.[112] A T2* of over 20 ms is not associated with increased cardiac risk. In contrast, a value of 10 to 20 ms denotes overload and increased cardiac risk, and a T2* of under 10 ms portends a high risk of cardiac dysfunction and an emergent situation requiring aggressive chelation (Appendix Table 84-H).[110,113,115] Echocardiography is essential, and left ventricular dysfunction is highly suggestive of iron overload.[116] Given the high output state, some suggest the cutoff for a normal ejection fraction in thalassemics should be 60%.[117] Electrocardiogram often revels biventricular dysfunction with left ventricular hypertrophy, a prolonged PR interval, bradycardia, ST-T wave change, and T-wave inversions. Iron-related parathyroid, and thyroid and adrenal dysfunction, as well as vitamin D and thiamine status should be investigated for as these impact cardiac function.

Management

The key to management of iron-related cardiac dysfunction is chelation. High-risk cardiac patients (failure, arrhythmias, a cardiac T2* <10 ms, or an LIC >30 μg/g dry weight) demand emergent intervention. Conservative therapy consists of continuous deferoxamine. It should be given around the clock, seven days a week due to its short half-life and having higher efficacy than the same dose given intermittently. Dosing should be at least 50 mg/kg/day, intravenously through a central line, or subcutaneously and increased to 100 mg/kg/day (6 g/day maximum) as tolerated. Ascorbic acid (2 to 4 mg/day) releases iron, facilitating chelation while drug is present, but should not be used in the absence of a chelator as the increased release of iron may lead to cardiac damage. Total iron must be assessed to avoid toxicity from overchelation. Afterload reduction, diuresis and inotropic support should be considered, and serial echos to follow shortening and ejection fractions are indicated. Additional measures to optimize cardiac function include maintaining a Hgb of 10 to 12 g/dL, protecting oxidative damage with carnitine, correcting thyroid and parathyroid deficiencies and the administration of intravenous calcium with oral vitamin D to maintain cardiac contractility. Liver dysfunction predisposes to hypoalbuminemia, increasing the risk of acute renal failure due to the combination of poor cardiac output and aggressive diuresis. Therefore, administration of albumin may be indicated. Unless emergent, interventions such as pacemakers and cardiac transplant should not be considered until after cardiac iron has been reduced because dysfunction is often reversible with chelation.

Optimal chelation strategies in emergent situations are evolving rapidly, thus a hematologist or local expert on chelation should be consulted. While deferoxamine is proven to chelate cardiac as well as liver iron, increasing data suggests that deferasirox may be effective as well. Deferiprone (L1) is small molecular weight oral chelator awaiting Food and Drug Administration approval that has been used extensively in

Europe and studies suggest it may be superior for removal of cardiac iron, but its major limitation is the risk of agranulocytosis. The availability of additional agents is leading to new regimes for cardiac iron removal making use of dual therapy with agents with nonoverlapping toxicity profiles.

Hepatic Dysfunction

The liver is a target for damage from iron overload, transfusion-related viral hepatitis, medications, autoimmune disease, and genetic factors such as α_1-antitrypsin deficiency and Wilson disease. Routine screening for liver synthetic function, LFTs and hepatitis serologies is essential. Assessment of liver damage is often multi-modal, requiring a T2* for LIC, and CT or routine MRI to assess tissue damage and cirrhosis. Liver biopsy may be necessary to more fully assess the underlying damage.

Endocrine Abnormalities

Iron deposition can lead to hypopituitarism, hypothyroidism, hypoparathyroidism, diabetes, delayed puberty, and growth failure, as well as testicular or ovarian failure. Early detection of deficits and early supplementation is essential. Growth and sexual maturation is attenuated by chronic anemia. Growth hormone has had limited efficacy. Although hormone replacement is often effective in treating hypogonadotropic hypogonadism in males, this is far less successful in females.

Growth, Osteoporosis, Osteopenia, and Fractures

Chronic anemia, endocrine dysfunction, and chelation interact with extra-medullary hematopoiesis to limit growth, and lead to thinning of the cortex and decreased mineralization, resulting in extreme and potentially chronic pain and fractures. Dual-energy x-ray absorptiometry or quantitative computerized tomography is essential for assessment. Osteoclast inhibitors such as bisphosphonates and vitamin D and calcium therapy may be useful, as well as maximizing bone deposition and strength with exercise and by avoiding smoking.

Thrombosis and Pulmonary Emboli

The mechanisms described in the pathophysiology section lead to a thrombotic state resulting increased venous thrombosis and emboli. Embolic risk is likely elevated with splenectomy.

Pulmonary Hypertension

Pulmonary emboli and hemolysis (see "Sickle Cell Disease" section above) likely both contribute to pulmonary hypertension.

Therapies and Interventions

Interventions for specific complications are described previously and in Appendix Figure 84-N. Although transfusions are the mainstay of therapy for severe thalassemics, guidelines for when to initiate transfusions and what Hgb to target vary with each individual's presentation, and among centers. In the acute setting it is essential to remain aware of the patients' recent baseline Hgb, maintain a higher Hgb (10 to 12 g/dL) for cardiac failure, and consult with hematology. Although transfusion is noncurative, HSCT, gene therapy and inducers of non-adult globin genes are actively being optimized. While all are promising, none are currently useful in the acute setting.

Hematopoietic Stem Cell Transplantation

Currently HSCT remains the only proven cure for thalassemic patients. Long transfusion histories increase the chance of graft failure, necessitating an aggressive myeloablative conditioning regimen, which in turn can lead to a high treatment-related toxicity if significant end-organ damage is present. Success is dependent on having an adequate donor, and the degree of end-organ damage. The latter is assessed using the Lucarelli staging system that factors in the degree of hepatomegaly, the degree of portal fibrosis, and the quality of the chelation treatment given before the transplant.[118] With improved pre-transplant care and increased myeloablation and immunosuppression, even the highest risk group has done well with matched-sibling donors with a 90% event-free survival, 96% overall survival, and 7% rejection rate.[119]

Gene Therapy

Three major barriers to HSCT, graft failure from rejection, the difficulty of finding a suitable donor, and graft versus host disease are all addressed by gene therapy. Though many strategies are being evaluated, the open clinical trials use retroviral or lentiviral vectors containing β-like globin genes that are used to infect patient CD34+ hematopoietic progenitors, followed by autologous transplantation. Additional approaches include adding a small-interfering RNA (siRNA) cassette to decrease α-globin, thus improving chain balance, or transducing modified transacting factors to activate δ-gene expression.

Inducers of Other β-like Genes

As expression of other β-like globin genes will ameliorate disease severity, numerous agents have been tried. Results from clinical trials vary in part by genotype, but the discussion in this chapter will be limited to a generic approach. Histone deacetylases such as the short chain fatty acid butyrate initially showed promise in increasing expression from the δ-genes, but have showed variable efficacy.[120-122] Current efforts are focused on developing related compounds such as additional histone acetylases (e.g., suberoylanilide hydroxamic acid), and additional short chain fatty acids that may induce embryonic globin genes. Hydroxyurea is less efficacious than in sickle cell, but some success has been observed in combination with erythropoietin.[123] Previously, promising results with the demethylating agent 5-aza-cytidine led to the development of the DNA methyltransferase inhibitor decitabine that results in demethylation and activation of fetal globin genes.[123,124] Early studies, and the potential to develop an oral form make decitabine an exciting future prospect for the treatment of SCD and β-thalassemia.

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References are available online at http://www.expertconsult.com.

Gastrointestinal Structure and Function

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PEARLS

- The gastrointestinal tract serves four vital roles essential to the maintenance of health: (1) digestion/absorption, (2) barrier between the external environment and internal environment, (3) synthesis and counterregulation of many substrates and hormones, and (4) excretion/elimination/detoxification of metabolic and digestive waste.
- Organization of hepatocytes into acinar/zonal structures leads to specialization of cellular function and varying susceptibility to ischemic injury depending on the distance from the vascular supply.
- Maintenance of intestinal mass and integrity is best achieved by the provision of nutrients directly into the lumen even at levels that do not support total nutritional needs for the patient.
- Common liver function tests (e.g., alanine aminotransferase/aspartate aminotransferase, γ-glutamyltransferase, alkaline phosphatase) reflect cellular injury, whereas actual functional state is reflected in maintenance of ammonia level, synthesis of clotting factors, and bilirubin elimination.

Abnormalities in gastrointestinal (GI) and hepatobiliary function occur frequently in the pediatric intensive care unit (PICU) from primary GI disease, following surgery, or from complications of systemic disease. The pediatric intensivist is called on for expertise in the preoperative and postoperative management of numerous GI tract and hepatobiliary diseases, as well as secondary dysfunction that may complicate diseases involving other organ systems. The GI tract subserves a wide range of functions beyond simple digestion that have an impact on systemic immunological, endocrinological, and microbiological functions.[1] Intact gut function beyond digestive function is of vital importance for the maintenance of health. Recent attention to alterations in GI function, interactions between liver and lung and between liver and kidneys have led to the view that the gut plays a role as an "engine" of multiple organ dysfunction.[2] Thus a practical working knowledge of the GI system and its integrated function is essential for the management of critically ill patients.

Intestinal Structure, Digestion, and Absorption of Nutrients, Water, and Electrolytes

The alimentary tract has several primary functions. These include mechanical and enzymatic degradation of nutrients, absorption of biochemical substrates, hormone regulation of substrate flow, separation of the external from internal environments, and excretion of waste. The alimentary tract essentially functions to alter nutrients to be compatible with the internal environment of the body.

The functional absorptive unit of the intestines consists of villi and crypts. The cells of the small intestine are separated from one another by specialized junctions that serve as gaskets to prevent back diffusion of material into the intestinal lumen. A mucus layer secreted by goblet cells in crypts separates enterocytes from direct contact with the luminal contents (Table 85-1).

Stem cells in crypts produce enterocytes and other specialized epithelial cells that migrate up the villous axis as they become differentiated. This migratory process takes 48 to 72 hours. Mature villous cells live 6 days. They have microvilli making up the brush border that contain digestive enzymes and membrane bound transport systems for nutrient and electrolytes. Small bowel enterocyte microvilli are estimated to increase the luminal surface area of the cell 14- to 40-fold.[3] The cells at the villous tip have a predominantly absorptive function, while crypt cells are primarily secretory. Rotavirus infections cause villous loss resulting in small intestinal mucosa composed largely of crypts and immature villi. This causes a net secretory state leading to malabsorption and osmotic diarrhea. Malabsorption of nutrients is another manifestation of villous injury.

Water and Solute Transport Across the Intestinal Epithelium

Surface area and integrity of intercellular junctions are the major determinants of water and solute flux across epithelium. The transport of solute and water across epithelium occurs either by active or passive transport or by facilitated diffusion (Table 85-2). The gut conserves large volumes of endogenously secreted material associated with digestion. The average luminal fluid input of the gut is about 9 L/day and

Table 85–1 Functional Units of the Intestine

Structure	Function
Enterocyte	Formed in crypts; migrate to villus over 2–3 days; lifespan of 6 days
Villi	Absorption
Crypts	Secretion
Microvilli	Amplify surface area; contain enzymes and transport systems

Table 85–2 Intestinal Transport Mechanisms

Active	Passive	Facilitated Diffusion
Against electrochemical gradient	Ionic specificity	Saturable kinetics
Saturable kinetics	May be associated with transport of a nonelectrolyte	Substrate specific
Requires ATP	Proceeds down electrochemical gradient	Depends on carrier molecules (glucose, amino acid)
	Steady state based on concentration differences	
	Displays first-order kinetics	
	May occur by convection via osmotic or hydrostatic gradient	

composed of oral intake and endogenous secretions. Approximately 8.8 L is absorbed, about 7 L in the small intestine and 1.8 L in the colon. Less than 0.2 L is excreted as a component of the normal stool output. When rapid changes in dietary intake or endogenous secretions occur, the intestinal mucosa can adapt transport functions in order to compensate for the changes. The loss of mucosal surface area through disease or surgical resection alters net flux of solute and water in GI tract. Furthermore, loss of specialized absorptive function may occur following loss of specific areas of gut. An example of this occurs in the setting of short bowel syndrome from resection of terminal ileum, with loss of ability to absorb bile acids and intrinsic factor.[3] Malfunction of absorptive mechanisms may lead to life threatening loss of fluid and electrolytes.

Nutrients absorbed include macronutrients such as carbohydrates, protein, and lipids; and micronutrients including minerals, electrolytes, trace elements, vitamins, and other metabolic cofactors such as biotin and carnitine. Critical illness leads to reduced intake of all nutrients and important alterations in substrate requirements and utilization.

There is a contrast between fasting in healthy persons and periods of increased physiological stress. In healthy individuals, prolonged fasting causes compensatory responses including: a decrease in overall metabolic rate, a decrease in gluconeogenesis from amino acids, increased reliance on ketone bodies for energy as the body attempts to conserve energy and protein stores, and depressed levels of insulin, cortisol, and catecholamines leading to chronic malnutrition.

In contrast, critical illness alters energy requirements. In general, the prolonged physiological stress during critical illness causes an increased metabolic rate as well as gluconeogenesis in excess of that needed to maintain serum glucose. Proteolysis and peripheral oxidation of amino acids with increased ureagenesis is also observed. This state leads rapidly to malnutrition as a result of so-called *autocannibalism,* characterized by levels of glucagon higher than insulin levels and by elevated catecholamines and cortisol that drive the relentless breakdown of peripheral tissues. These hormonal changes result in catabolism of endogenous stores of protein, carbohydrates and fat to provide metabolic substrate necessary to support the metabolic stress response.[4] Children with burn injury demonstrate extreme hypermetabolism in the initial phases of illness.[5] Children on dialysis have a negative nitrogen balance and loss of folate and selenium.[6] Use of catecholamines or neuromuscular blocking agents represent risk factors for undernutrition in critically ill children on dialysis.[7] During high physiologic stress, nutrition delivered to patients must be changed to allow for decreased reliance on fat and carbohydrate for energy production. Proteins are increasingly relied on and must be replaced with additional amino acids to support ongoing synthesis of protein including immunoglobulins by the liver and immune system. Protein requirements for various age groups are as follows: 0 to 2 years, 2 to 3 g/kg/day; 2 to 13 years, 1.5 to 2 g/kg/day; and 13 to 18 years, 1.5 g/kg/day.[8] Depressed levels of specific amino acids have been found in critically ill children.[9]

Enteral nutrition is the preferred method of feeding for critically ill children. Restriction of fluid intake seems to be the main barrier to the delivery of adequate nutrition, particularly in infants undergoing cardiac surgery.[10] Early transpyloric enteral nutrition is well tolerated in critically ill children and is not associated with an increase in incidence of complications.[11] Small-bowel feeds allow a greater amount of nutrition to be successfully delivered to critically ill children compared with gastric feeds. However, small-bowel feeds do not prevent aspiration of gastric contents.[12] The institution of a feeding protocol has been found to achieve goal feedings quickly and also improve tolerance of enteral feedings in patients admitted to the pediatric intensive care unit.[13] Enteral nutrition may also have some anti-inflammatory effects by lowering expression of specific cytokines.[14] The use of specialized formulas is not currently recommended in critically ill children. No effect from adequacy of feeding has been seen on hormone levels such as insulinlike growth factor-1 (IGF-1) and thyroid hormones.[15]

Digestion of Carbohydrates

Dietary carbohydrates may be classified in several ways (Box 85-1). Monosaccharides, such as glucose and fructose, are present in fruits, sweet corn, corn syrup, and honey. Disaccharides are simple sugars, such as sucrose (glucose + fructose), maltose (glucose + glucose), and lactose (glucose + galactose), the principal mammalian sugar. Polysaccharides, such as starch, are polymers of glucose and are abundantly present in wheat, grains, potatoes, peas, beans, and vegetables. Fiber consists of nondigestible complex polysaccharides of plant origin. This includes both water insoluble and water soluble fiber. The average American diet is 3:1 soluble to insoluble fiber. Some studies have shown that a water-soluble fiber, partially hydrolyzed guar gum can be used to decrease stool

Box 85–1 Conditions Impairing Dietary Carbohydrate Uptake

Disaccharidase deficiency (acquired or congenital)
Pancreatic insufficiency
Membrane-associated transporter defect

output in cholera.[16] Insoluble fibers affect fecal bulk, whereas soluble fibers have viscous effects in the upper GI tract including delayed gastric emptying, decreased postprandial glycemic response, and a constipating effect.

Carbohydrates are a major source of calories in healthy children. Carbohydrates are generally broken down by means of glycolysis and the Krebs cycle pathway (see Chapter 74). Carbohydrates may be stored as glycogen and lipids when ingested beyond momentary energy needs or converted to structural materials. A person's requirement for energy is highly dependent on activity level or, in hospitalized patients, the degree of hypermetabolism accompanying illness. The maximal ability to utilize carbohydrates may be limited during periods of high physiological stress as a result of the complex effects of hormonal mediators of the stress response.

Digestion of carbohydrates begins with the process of chewing that decreases the size of food particles, thereby increasing the total surface area for subsequent action by digestive juices. Salivary secretions are necessary for lubrication and also contain salivary amylase, an endoenzyme that cleaves oligosaccharides. Salivary amylase is rapidly inactivated by gastric acid, leaving the majority of starch digestion to occur in the duodenum under the action of pancreatic amylase and the intestinal brush border disaccharidase enzymes. Amylase contained in human milk facilitates starch digestion in breast-fed infants because of their low levels of endogenous salivary and pancreatic amylase.[17] Pancreatic amylase is the major enzyme of starch digestion resulting in short oligosaccharides, maltotriose, maltose, and α-limit dextrins. The amylase concentration becomes limiting in cases of pancreatic insufficiency when amylase levels become less than 10% of normal.[18]

The enterocyte is incapable of absorbing carbohydrates larger than monosaccharides. Therefore, further hydrolysis to monosaccharides is performed by intestinal *brush-border disaccharidases* of which the clinically important ones are lactase, which breaks down lactose, and sucrase, which breaks down sucrose. These enzymes are synthesized in the enterocyte and are subsequently inserted into the apical brush border membrane. With the exception of lactase and occasionally sucrase, the disaccharidases are rarely rate-limiting for complete carbohydrate digestion. Deficiencies of any of the disaccharidase enzymes, either acquired or hereditary, may result in carbohydrate malabsorption. This is characterized by osmotic diarrhea with elevated fecal reducing sugars, abdominal distension and flatulence secondary to fermentation of undigested oligosaccharides by colonic bacteria. An example of this is congenital sucrase isomaltase deficiency, an autosomal recessive disorder that is associated with absence of sucrase and maltase.[19,20]

Absorption of carbohydrates occurs in several ways. During periods of high luminal carbohydrate concentration, simple diffusion of monosaccharides may occur. Additionally, two transport mechanisms exist in the brush border for the absorption of monosaccharides.[21] First, glucose, galactose and xylitol are transported with sodium by the Na^+/glucose cotransporter. A low intracellular sodium concentration is created by the sodium-potassium-adenosine triphosphatase (Na^+-K^+ adenosine triphosphatase [ATPase]) pump located on the basolateral membrane. The resulting concentration gradient leads to movement of luminal sodium across the apical membrane, bringing with it glucose or galactose in a one-to-one molar ratio. Glucose-galactose malabsorption is a deficiency of this transport mechanism leading to neonatal onset of severe diarrhea.[22] The second mechanism is a non-energy-dependent facilitated transport system for fructose. The intestinal transport mechanisms are summarized in Table 85-2. The capacity to absorb fructose is limited, and excess ingestion has been found to cause symptoms of carbohydrate malabsorption.[23]

Clinical conditions that cause loss of the epithelium and brush border system may lead to symptoms of carbohydrate malabsorption. These conditions include: rotoviral gastroenteritis, inflammatory bowel disease, celiac disease, sprue, ischemia/hypoxia, bacterial overgrowth of the proximal gut as a result of either stasis or use of antacids, and malnutrition. Severe mucosal damage requires 7 to 10 days for recovery of brush border function. Several infant and enteral formulas rely on starch as a carbohydrate source to minimize reliance on lactase. Recent studies have observed that lactose digestive capability with lactase can be maintained despite small bowel mucosal damage.[24] Lactose absorption is primarily related to lactase activity as opposed to mucosal growth.[25]

The digestion of carbohydrates is generally very efficient, ranging from 80% to 100% of absorption from starch depending on the source of the starch. Bacterial fermentation of fiber and undigested carbohydrates produces short-chain fatty acids, used as fuel by the enterocytes, as well as gaseous hydrogen and methane, contributing to the flatulence associated with increased dietary fiber and malabsorption syndromes.

Digestion of Proteins

The GI tract has developed efficient mechanisms for processing exogenous peptides and complex proteins (Box 85-2). It is also very efficient at recycling endogenous proteins such as digestive enzymes, mucus, sloughed cells, and plasma proteins that leak into the alimentary tract.[26] The recommended dietary protein intakes in healthy children range from 2.5 to 3.5 g/kg/day in early infancy to 1.2 g/kg/day during childhood, and 0.8 to 0.9 g/kg/day in adolescence.[8] The enteral processing of proteins may be divided into digestive and transport phases.

In the digestive phase, gastric acid secretion initiates denaturation of complex proteins making them more susceptible to the actions of proteolytic enzymes. The chief cells of the stomach release pepsinogens that are converted to active pepsins under the influence of gastric acid. The pepsins are endopeptidases that release relatively large peptides and are inactivated when the pH rises above 4 as the food enters the duodenum. The completeness of gastric proteolysis depends in part on the rate of gastric emptying, the pH of intragastric contents, and the types of protein ingested.[26] It is noteworthy that patients with achlorhydria or those receiving antacids, H_2 blockers, or both agents have no evidence of impaired protein digestion ability. In addition to initiating protein digestion in the mature subject, pepsins act as milk clotting factors, which

Box 85–2 Conditions Impairing Dietary Protein Uptake

Ineffective pancreatic protease secretion
Abnormal epithelial transport (Hartnup, lysinuric protein intolerance)

are important in the neonate for curd formation and provide bulk to the infant's stools.

Luminal digestion proceeds in the small intestine mediated by five pancreatic peptidases that are secreted by the pancreatic acinar cells as proenzymes and activated by enterokinase and trypsin. Each peptidase possesses proteolytic activity at specific internal or external peptide bonds. Proteins are degraded typically into mixtures of one-third free amino acids and two-thirds peptides containing two to six amino acid residues,[27] which are suitable substrates for the brush border peptidases. The brush border peptidases convert the oligopeptides into monopeptides, dipeptides, and tripeptides suitable for transport into the enterocyte.

In the transport phase, specific membrane-associated transport mechanisms exist for the uptake of amino acids and dipeptides.[28] They involve *simple diffusion, facilitated transport,* and *carrier-mediated active transport* (Table 85-3). Na^+-coupled active transport is an energy-dependent process associated with the uptake of luminal Na^+ and an amino acid (or glucose) and exchange of the sodium and associated molecule for K^+ through the basolateral membrane on the serosal side.[29] Peptide transport may also occur using an H^+/peptide transport protein which moves according to an H^+ gradient in the acidic pH microclimate of the intestinal brush border. This microclimate is maintained by Na^+-H^+ exchange in the brush border and Na^+-K^+-ATPase in the basolateral membrane.[30] An important characteristic of these transporters is that many amino acids are absorbed more rapidly as dipeptides than as free amino acids. This fact has been capitalized on in the development of enteral nutritional formulas because oligopeptide mixtures have a lower osmolarity and are more efficiently absorbed than single amino acid solutions of equal nitrogen content. Because of the efficient gastrointestinal absorption of dipeptides, patients with specific amino acid transport defects (e.g. Hartnup disease [defective tryptophan transport] and lysinuric protein intolerance [defect in dibasic amino acid transport: lysine, arginine]) infrequently have GI symptoms related to dietary protein malabsorption and instead more commonly manifest with non-GI symptoms such as aminoaciduria.

Once inside the enterocyte, peptides are quickly degraded into their constituent amino acids by cytoplasmic peptidases that complement the activity of the brush border peptidases. Only minute quantities of intact peptide and protein gain access to the systemic circulation. The cytoplasmic amino acids derived from digested proteins are a major source of free amino acids used directly by the enterocyte. When absorbed beyond cellular needs, the free amino acids are released to the portal venous circulation for hepatic and systemic use. Only 23% of absorbed amino acid nitrogen passes to the periphery without modification.[31] Of the remaining nitrogen, 57% is converted to urea with the carbon skeleton salvaged for synthesizing other substances and 20% of the total ingested amino acids are used directly for hepatic protein synthesis.

Table 85–3 Pattern of Biochemical Tests Based on Category of Liver Disease

Biochemical Test	Hepatocellular Necrosis	Cholestasis	Infiltrative Process
ALT, AST	++ to +++	0 to +	0 to +
ALK, GGT	0 to +	++ to +++	+
Total/conjugated bilirubin	0 to +++	0 to +++	0 to +
PT	Prolonged	Prolonged; responsive to vitamin K	0
Albumin	Decreased in chronic disorders	Decreased in chronic disorders	0
Cholesterol	0	0 to +++	0
Bile acids	+ to +++	+ to +++	0

0, Normal; *+ to +++,* degrees of elevation; *PT,* prothrombin time.

During periods of fasting, the enterocyte derives the majority of its nourishment from the mesenteric arterial vascular supply, whereas during digestion, the enterocyte derives a significant part of its nutrient requirements from the luminal contents. Experience with mucosal recovery and adaptation after injury reveals that an enteral route of nutrition permits optimal recovery. In the premature infant and neonate, the small intestine is capable of absorbing intact milk proteins by pinocytosis. These proteins may include secretory immunoglobulins from breast milk as well as food antigens.[32] Peptidase inhibitors have been demonstrated in colostrum and breast milk, partially explaining the failure of normal digestive mechanisms to degrade some of these complex dietary proteins. Both antibodies and antigens ingested with maternal milk create an important part of the immune repertory developed during early infancy.[33] Although the exact time of "closure" of the intestinal mucosa to the uptake of macromolecules has not been defined in human infants, other mammals demonstrate marked intestinal impermeability to foreign proteins by the time of weaning[34] from breastfeeding.

Digestion of Lipids

Dietary fat accounts for approximately 50% to 70% of the nonprotein calories consumed by infants and approximately 30% of nonprotein calories consumed after age 2 years (Box 85-3).[35] Dietary fat is ingested principally in the form of triglycerides containing the fatty acids palmitate and oleate (C16:0 and C18:1, respectively). Dietary triglycerides of animal origin predominantly contain long-chain (i.e., longer than C14 chain length) saturated fatty acids. Polyunsaturated fatty acids are mostly of vegetable origin and include linoleic and linolenic acid, also referred to as essential fatty acids because of absent de novo synthesis in humans. Other dietary lipids include fat-soluble vitamins, cholesterol, prostaglandins, waxes, and phospholipids.

In healthy adults, digestion and absorption of fat is complete with only 5% to 7% of ingested fat escaping absorption. Under normal physiological conditions healthy infants up to age 9 to 12 months fail to absorb 15% to 35% of dietary

Box 85–3 Conditions Impairing Dietary Lipid Uptake

- Decreased bile salt pool in gut (biliary obstruction, short bowel syndrome)
- Impaired pancreatic secretions (pancreatic insufficiency, pancreatitis)
- Suboptimal pH in gut (gastric hypersecretion)
- Rapid transit time (short gut syndrome, diarrheal states)
- Mucosal diseases (celiac disease, irritable bowel disease, bacterial overgrowth)
- Impaired enterocyte function (abetalipoproteinemia)

fat. Digestion and absorption of dietary fat is generally completed by the middle third of jejunum; however, the presence of dietary fiber may reduce the rate and extent of absorption. Loss of dietary fat places children at significant risk for calorie and fat-soluble vitamin malnutrition.

Digestion of Fat

Fat digestion begins with formation of emulsions, which increase the surface area for enzyme interaction. Emulsification begins with release of fat by mastication and gastric "milling" of chyme. Bile salts and coating by phospholipid derived from the diet results in a stable emulsion droplet with a hydrophobic center consisting of triglyceride, cholesterol esters and diglyceride in a hydrophilic envelope. Mammary, lingual, and gastric lipases play an important role in direct lipolysis of long- and medium-chain triglycerides that are present in maternal milk.[36] Lingual and gastric lipases are active at pH <5 and begin digestion of fat in the stomach; however, overall only play a limited role in the digestion of lipids. Intragastric lipolysis is consistent across all age groups.[37]

Most of the enzymatic degradation of dietary lipids to fatty acids and monoglyceride is by the action of pancreatic lipase and co-lipase, and requires an alkaline environment (pH 6 to 8). This underscores the importance of secretion of bicarbonate by the pancreas and biliary tree in order to neutralize gastric acid. Co-lipase is an essential cofactor for lipase action. Co-lipase's role is to displace the bile salt-triglyceride interaction in emulsion droplets and micelles to facilitate lipase hydrolysis of the triglyceride. Triglyceride hydrolysis occurs at the interface between the emulsion droplet and aqueous phase within the lumen. This is a two-step process. The first step is the enzymatic hydrolysis of long-chain triglycerides and liberation of fatty acids from the glycerol backbone. The second step is formation of fatty acid micelles, that is most efficiently accomplished with the aid of bile salts[38] to traffic the fatty acids across the unstirred water layer to the mucosa for absorption.

Transit through the unstirred water layer adjacent to the epithelial surface is considered the rate-limiting step in lipid absorption. Intrinsic gut brush border lipase enzymes are involved as well. The milieu of the unstirred water layer is acidic (pH 5 to 6) owing to the activity of the brush border membrane sodium-hydrogen (Na^+/H^+) exchanger. The acid environment facilitates dissociation of fatty acids from micelles resulting in a high concentration of fatty acids necessary for diffusion across the mucosal membrane.[39,40]

Once inside the enterocyte, long-chain fatty acids and monoglycerides are resynthesized into triglycerides and packaged as chylomicrons. Lipoproteins (e.g., apo-A, apo-B) and cholesterol are attached to the intestinal chylomicrons and confer important properties for the subsequent systemic uptake and metabolism of the chylomicrons. This process appears to be defective in cystic fibrosis and may account for some of the fat malabsorption seen in this disease.[41] Chylomicrons are exported into the intercellular space and transported through the intestinal lacteals to become part of the intestinal lymph. On entering the bloodstream through the thoracic duct, the chylomicrons are associated with other apolipoproteins that allow them to be recognized by specific peripheral tissues.[42]

Dietary lipids containing short- and medium-chain (C6 to C12) triglycerides are handled differently from those of long-chain triglycerides. As much as 30% of medium-chain triglycerides may be absorbed intact into enterocytes by passive diffusion and enter the portal venous blood directly. Medium-chain triglycerides are hydrolyzed by pancreatic and mammary lipases to fatty acids and monoglycerides and rapidly enter the enterocytes where they emerge into the portal venous system without re-esterification as occurs with long-chain fatty acids.

Intestinal Lymphatics

The intestinal lymph, known as *chyle,* is composed of chylomicrons and lipoproteins secreted by the intestinal epithelium in the postprandial state together with nonresorbed interstitial fluid. Chyle follows the intestinal lymphatic channels along the mesentery and enters regional lymph nodes from which it flows cephalad through the thoracic duct and ultimately enters the central circulation. In the fasting state, intestinal lymph production is relatively low. It increases 20-fold during the active absorption of a typical meal. Intestinal chyle is joined by lymphatic drainage from other tissues including liver and pancreas. Protein content of chyle is 2.2 to 5.9 g/dL with a triglyceride content of 0.4 to 6.0 g/dL and 400 to 6800 lymphocytes/dL. During digestion of a meal containing long-chain fats, chyle has a typical milky white appearance because of the presence of chylomicrons. Rate of formation of chyle depends on the state of nutrient absorption, portal venous pressure, and the rate of lymphatic uptake. Factors that increase portal pressure (e.g., cirrhosis, congestive heart failure) or impair the flow of lymph back to the central circulation (e.g., increased central venous pressure, superior vena cava syndrome) predispose to the collection of chylous ascites in the abdomen.

Regulation of Electrolyte and Water Movement

Movement of water is closely linked to the movement of solute in the form of electrolytes and nutrients. Water transport is a largely passive process that occurs through paracellular routes in the intestine coupled with solute movement. Expression of transporters involved in intestinal water and electrolyte transport is regionally specific. Electrolytes are taken up by enterocytes at the apical membrane and extruded through the basolateral membrane into the paracellular space. The relatively hypertonic paracellular fluid pulls water into this space, increasing the hydrostatic pressure locally. Because the tight junction between enterocytes is more impermeable

to fluid flux than the capillary membranes, fluid and electrolytes are preferentially driven in the direction of the vascular space.[1,43,44] Tight junctions are selective and dynamic in function and are regulated by a number of signaling pathways and cellular processes that can determine the size, selectivity, and flow of molecules across this barrier.[3]

The gut responds to both systemic and local stimuli to regulate motility, transport, and digestive functions. Secretion and motility are mediated through typical agonist membrane receptor mechanisms, by local autocrine and paracrine action, or through remote endocrine and neurocrine actions. Regulation of intestinal motility is crucial for keeping the chyme in contact with the epithelial surface long enough for efficient absorption of nutrients while permitting removal of unusable material and bacteria from the alimentary tract on a regular basis. GI smooth muscle demonstrates phasic and tonic patterns of contraction. Numerous factors affecting the frequency of contractions include changes in autonomic tone, stimulation of the gut by neurohormonal peptides or pharmacologic agents, and noxious stimuli associated with infectious or inflammatory processes. Hypoxia and ischemia decrease motility, frequently leading to paralytic ileus. Neural regulation of the GI tract integrates the processes of intestinal water and electrolyte transport, motility and blood flow. The augmentation of water and electrolyte absorption after a meal in the jejunum is neurally mediated.[45] The enteric nervous system is capable of functioning independently but also may be modified by autonomic nervous system.[3]

Many other factors alter the functions of the gut. The terminal ileum and colon are particularly important in this respect. The presence of an ileostomy increases the risk of excessive sodium losses, dehydration, and electrolyte abnormalities. Terminal ileal resection or other diseases of the terminal ileum such as Crohn disease or radiation enteritis may result in bile acid malabsorption. In patients with bile acid malabsorption, bile acids reach the colon, which stimulates electrolyte and chloride secretion. Patients with mild to moderate malabsorption present with watery diarrhea and may respond to a bile acid binder such as cholestyramine.[46] Impairment of water and ion absorption in inflammatory bowel disease may occur because of numerous mechanisms including alteration of epithelial integrity, augmented secretion, and reduced absorption. In addition, intestinal inflammation is associated with defects in epithelial barrier function. It is not known what effect inflammation may have on ionic function.[47] Hyperosmolality of the ileal and colonic contents leads to an osmotic diarrhea. This state is seen when unabsorbed nutrients enter the distal alimentary tract and are broken down by enteric bacteria, resulting in increased luminal osmotic activity and osmotic diarrhea.

Electrolyte Transport

Several basic mechanisms exist for the transport of electrolytes by the epithelia. Na^+ may be transported by numerous mechanisms. The regulation of Na^+ absorption is closely regulated such that anion secretion is closely aligned with Na^+ absorption.[48] A Na^+-H^+ exchange-mechanism present throughout the intestine results in a 1:1 exchange of luminal sodium for protons. Coupled Na-Cl absorption, Na-Cl co-transport, Na-K-Cl co-transport, and movement of Na^+ down its electrochemical gradient as in Na-Glucose co-transport are other mechanisms by which Na^+ moves across the intestinal epithelium. The Na^+-H^+ exchanger plays a role in regulation of intracellular pH, regulation of cell volume, initiation of cell growth in response to various trophic factors, and metabolic response to insulin. To maintain electrical neutrality, the epithelium simultaneously exchanges Na^+ for H^+ and Cl^- for HCO_3. The presence of glucose in the lumen of the small intestine stimulates increased sodium absorption through coupled transport. Uptake of glucose is carrier mediated although the coupled transport of glucose with sodium is electrogenically driven by the Na^+ gradient across the cell membrane.[49] Absorption of glucose by Na-Glucose transport results in activation of myosin light chain kinase to regulate tight junction-permeability.[50] Backflow of sodium into the lumen is a passive process since a major task for the GI tract is sodium conservation. Systemic acidosis increases Na^+ and Cl^- absorption in the ileum and colon, whereas alkalosis has the opposite effect. As seen in other epithelial tissues, aldosterone increases ileal and colonic absorption of Na^+ and can increase absorption of water in colon three- to fourfold.[51] Spironolactone blocks this effect. Glutamine has been shown to stimulate water and electrolyte absorption in the jejunum.[52] Glucocorticoids increase sodium and water absorption in the distal colon. Opiate receptor stimulation increases active sodium and chloride absorption in the ileum, and opiate antagonists decrease basal absorption of water and electrolytes. The primary antidiarrheal effect of opiates, however, is mediated through a slowing of transit time.[1]

In the colon, active absorption and secretion of K^+ occurs in a manner consistent with K^+-H^+ exchange, is electroneutral and independent of Na^+-Cl^- exchange. After the ions have entered the enterocyte at the luminal surface, extrusion occurs through the basolateral membrane into the paracellular spaces. The process of sodium extrusion depends on Na^+-K^+-ATPase pumping function located at the basolateral membranes. Oxidative stress inhibits water and electrolyte absorption in the jejunum through inhibition of Na-K ATPase on the basolateral membrane.[53]

Extrusion of Cl^- occurs along an electrochemical potential difference.[54] The intraluminal secretion of water and other electrolytes appears to follow active secretion of Cl^- from the crypt cells of the jejunum, ileum, and colon. This is a common physiological pattern in the liver, pancreas, and kidney. Numerous substances such as muscarinic receptor agonists, serotonin, and substance P likely work through second messengers and signaling cascades to induce active chloride secretion. Vasoactive intestinal peptide mediates increased secretion of electrolytes and water by increased cyclic adenosine monophosphate production that stimulates active chloride secretion and inhibits sodium-chloride absorption. Certain arachidonic acid metabolites, especially prostaglandins (e.g., prostaglandin E_1), have been shown to increase active chloride secretion leading to increased loss of electrolytes and fluid. Many laxatives and antacids may affect fluid and electrolyte balance by stimulating active electrolyte and fluid secretion in the terminal ileum. In addition, these agents may increase mucosal permeability and stimulate motility.[1]

Disruption of normal Na^+-K^+-ATPase activity results in the net secretion of fluid and electrolytes. This mechanism is the final common pathway in a number of secretory diarrheal states such as cholera, enterotoxigenic *Escherichia coli, Salmonella* spp., *Campylobacter jejuni,* and *Clostridium perfringens*

that appear to act via second messenger pathways via their toxins.[55] Rotavirus appears to have several mechanisms of causing diarrhea. The first appears to be a mechanism of increasing chloride secretion with a resulting secretory diarrhea mediated by Ca^{++}, a different mechanism than most bacterial mediated diarrheal diseases. The second is an osmotic diarrhea caused by villus destruction and resultant malabsorption.[56] In addition, the effects of various paracrine and endocrine mediators alter intestinal adenyl cyclase activity and lead to changes in electrolyte and water balance.[54]

Zinc

Normal zinc homeostasis is required for a functional immune system, adequate antioxidant capacity, glucose homeostasis, and wound healing. In addition, zinc is a required co-factor for many enzymes, transcription factors, and replication factors. In noncritically ill patients, zinc supplementation is associated with improvement in markers of immune function. Plasma zinc concentrations are low in critically ill children, correlate with measures of inflammation and are associated with the degree of organ failure.[57] Large intestinal losses of zinc with and without complexed proteins often occur in association with high intestinal fluid losses through gastrointestinal stomas and fistulae. Although some patients with sepsis have demonstrated significantly faster recovery with zinc supplementation among other anti-oxidants.[58] there is currently inadequate evidence to recommend the routine use of high-dose zinc supplementation in the critically ill.[59]

Hydrogen Ions

Hydrochloric acid secretion by the gastric parietal cell is necessary for pepsinogen activation (pH <5.0) and to reduce bacterial colonization. H^+ and bicarbonate are produced from water and carbon dioxide by the action of carbonic anhydrase within the parietal cell. The bicarbonate is secreted into the bloodstream in exchange for chloride at the basolateral membrane. Chloride and potassium are both secreted along with H^+ across the apical membrane against a large concentration gradient. This is an active process, mainly because of the action of the proton pump, H^+/K^+-ATPase, that represents the final step in gastric acid secretion.[60]

Histamine, gastrin, and acetylcholine are the main stimulants of gastric acid secretion.[61] Gastric distension, dietary amino acids, and amines stimulate gastrin hormone secretion by G cells located in the gastric antrum. Gastrin is the most potent endogenous stimulant of gastric acid secretion and stimulates release of histamine by the enterochromaffin-like cells. Histamine then binds to histamine-2 (H_2) receptors on parietal cells leading to acid secretion. Prostaglandins and somatostatin have an inhibitory effect on gastric acid secretion via specific receptors located on the parietal cell.[62]

H_2 receptor antagonists (e.g., ranitidine, famotidine, cimetidine) block histamine-mediated gastric acid secretion found in postprandial acid secretion, Zollinger-Ellison syndrome and other disorders associated with hypergastrinemia. Proton pump inhibitors (PPIs) (e.g., omeprazole, lansoprazole, pantoprazole) block gastric acid secretion by inhibiting the parietal cell H^+/K^+-ATPase. The PPIs bind irreversibly to the enzyme and subsequent secretion of acid can occur only with the synthesis of new proton pump enzyme, a process that takes 12 to 24 hours. For these reasons, PPIs have revolutionized gastric acid suppression therapy.[61,63] H_2 receptor antagonists and PPIs are similarly effective for preventing bleeding in the upper part of the GI tract in patients receiving mechanical ventilation.[64] Recent studies have shown that some oral PPIs suppress acid in intensive care unit (ICU) patients to a greater extent than IV.[65] Patients at risk of stress ulcer–related bleeding are most likely to benefit from prophylaxis.[66]

Pancreas

The pancreas exhibits both endocrine and exocrine functions and acts in concert with the liver to regulate blood glucose levels. Endocrine-secreting cells of the pancreas are aggregated in the islets of Langerhans. There are approximately 1 million islets in the human pancreas. Four distinct cell types in the islets which serve the pancreatic endocrine function include (1) B-cells that secrete insulin (50% to 80%), (2) A-cells that secrete glucagon (5% to 20%), (3) D-cells that secrete somatostatin (5%), and (4) PP cells that secrete pancreatic polypeptide.[21,67]

Branches of the celiac, superior mesenteric and splenic arteries provide the pancreas blood supply. Venous drainage occurs via pancreaticoduodenal veins, splenic veins, and ultimately the portal vein, providing direct hormonal influence over hepatic metabolism. Both parasympathetic and sympathetic innervation of the pancreas occurs by means of the vagi and abdominal plexuses, respectively. Vagal innervation of acini, islets, and ducts facilitates secretory function, whereas sympathetic innervation occurs primarily to vascular structures. Functional ectopic pancreatic tissue may be found commonly throughout the upper gastrointestinal tract.

Pancreatic Exocrine Secretory Function

The functional unit of the exocrine pancreas consists of an acinus composed of specialized cells containing secretory granules that drain into ductules, which coalesce to form the pancreatic duct. In contrast to the pancreatic endocrine cells that demonstrate specialized function, each acinar cell is capable of secreting all the pancreatic digestive enzymes. The basolateral membrane has receptors for hormones and neurotransmitters that stimulate pancreatic secretion of the digestive enzymes stored in zymogen granules near the apical membrane of each acinar cell.[68] Ultimately, the pancreatic duct joins with the common bile duct and drains into the duodenum through the ampulla of Vater. Anatomic variation exists. 74% of people have a common channel, whereas 19% have a separate opening and 7% have an interposed septum.[69]

Pancreatic juice is an isotonic fluid, containing primarily Na^+, K^+, Cl, and HCO_3^-. The total volume of secretion is approximately 2.5 L daily. Cystic fibrosis transmembrane conductance regulator is the main channel for chloride secretion in the pancreas and may be involved in other ion transport.[70] Secretion of bicarbonate and water is mediated through the actions of the gut hormones secretin, cholecystokinin, and vasoactive intestinal peptide. Stimulation of the vagus nerves or the administration of acetylcholine induces digestive enzyme secretion. These effects may be blocked with atropine.

There are four phases of pancreatic secretion: *Basal secretion* represents approximately 2% of the potential maximum

HCO_3. The *cephalic phase* is mediated by the vagal nerves in response to the sight and smell of food. The *gastric phase* consisting of secretion of a protein-rich pancreatic juice of low volume and HCO_3 occurs following either distention of the stomach[71] or after the ingestion of food. The *intestinal phase* is characterized by marked output of digestive enzymes, fluid, and HCO_3.

Presence of bicarbonate is essential to achieve an optimal pH (>5) for pancreatic digestive enzyme activity and to ensure solubility of bile salts. In addition to bicarbonate, the primary secretory products of the exocrine pancreas are amylase, lipase, and the proteases. The secondary digestive enzymes consist of nucleases, colipase, and lecithinase. The roles of the pancreatic digestive enzymes are discussed in the sections on carbohydrate digestion (amylase), lipid digestion (lipase), and protein digestion (proteases). Cholecystokinin is the major humoral mediator of meal-stimulated enzyme secretion. It is released from the small intestinal mucosa in response to presence of fat, protein and starch. The response is related to total load rather than concentration. Cholecystokinin activates afferent neurons in duodenal mucosa that leads to secretin release via a vasovagal reflex.[72] Inhibitors of exocrine pancreatic secretion include somatostatin, pancreatic polypeptide and peptide YY.[73] Octreotide, a somatostatin analogue has been used for its antisecretory effect in clinical management of pancreatic-pseudocysts and fistulae, but its use in acute or chronic pancreatitis remains controversial.[74] Inflammation of the pancreas both from infectious and non-infectious causes can produce a dramatic systemic inflammatory response resulting in generalized permeability changes and acute lung injury.[75]

Hepatobiliary System

Examination

A complete physical examination of all children admitted to an ICU should include inspection, palpation, and auscultation of the abdomen with particular attention to hepatic or splenic enlargement, distended superficial venous channels, abdominal masses, the characteristics of the bowel sounds, and finally visual inspection of the perianal region for signs of trauma, fistulae, and venous distension.

Palpation of the liver provides information about the hepatobiliary tract as well as function of the right side of the heart. Normally, the liver is palpable roughly 1 to 3 cm below the right costal margin in the mid-clavicular line; however, assessment of liver *span*, and not palpation alone, is the only reliable non-radiological method for determining liver size. Liver span is determined by percussion, palpation, and auscultation along the right mid-clavicular line with the patient supine and breathing quietly. Dullness of the upper border is determined by percussion. Either palpation or auscultation is used to establish the lower border. The liver span increases with body weight and age in both sexes, ranging from 4.5 to 5.0 cm at 1 week of age to 7 to 8 cm in boys and 6.0 to 6.5 cm in girls by age 12 years.[76]

Examination of the liver should note consistency, contour, tenderness, the presence of any masses or bruits, and assessment of spleen size. Documentation of the presence of ascites and stigmata of chronic liver disease is important. Tenderness over the liver suggests inflammation or stretching of the fibrous capsule through rapid enlargement. Conditions associated with downward displacement of a normal liver include hyperinflated lungs, pneumothorax, retroperitoneal masses, and subdiaphragmatic abscess. End-stage liver disease and cirrhosis are associated with a reduced liver span corresponding to decreased hepatic cell mass. The spleen tip may be palpable normally in children, especially during inspiration. Enlargement of the spleen generally represents elevated portal venous pressures or invasive processes such as sequestration, malignancy, extramedullary hematopoiesis, or hyperplasia of the reticuloendothelial system.[77]

Anatomy: Microanatomy, Structure, and Function

The liver is the largest organ in the body and is composed of 60% hepatocytes, approximately 17% to 20% endothelial cells and Kupffer cells (reticuloendothelial cells), 3% to 5% bile ducts, and 1% hepatic stellate cells and oval cells. The liver has a dual vascular supply derived from the hepatic artery branches of the celiac axis providing about 30% of the blood supply and the portal vein providing approximately 70%. Innervation of the liver is by the parasympathetic branches derived from both vagi and sympathetic branches, which also carry afferent fibers deriving from thoracic segments. Denervation of the liver, such as seen after liver transplantation, does not affect function.[78]

The "liver lobule," the functional unit of the liver is composed of interconnected hepatocytes (hepatic plates) one to two cells thick and 20 to 25 cells in length separated by a venous sinusoidal space and radiating around the central vein like spokes in wheel (see Figure 85-1). The narrow tissue space between the endothelial cells and hepatic plates is called the space of Disse, which in turn connects with lymphatic vessels in the interlobular septa. Hepatic sinusoidal endothelial cells are flat cells that do not form intracellular junctions and overlap one another. They are fenestrated, allowing plasma to enter into the space of Disse and come into direct contact with the surface of hepatocytes.[79] This facilitates bidirectional exchange between the hepatocytes and the sinusoidal space. Macrophage-derived Kupffer cells line the sinusoidal space, have a phagocytic function, and mediate the hepatic inflammatory response.

Hepatic stellate sells, also known as *ito cells*, lie within the space of Disse, serve as the hepatic storage site of vitamin A, are effectors of fibrogenesis, and play a role in extracellular matrix remodeling after recovery from injury. Chronic activation and proliferation of hepatic stellate cells may lead to noncirrhotic portal hypertension, fibrosis, and cirrhosis.[80] Bile canaliculi lie between adjacent hepatocytes and drain into small terminal bile ducts, that successively drain into larger bile ductules, intralobular bile ducts and eventually the extrahepatic bile ducts. Tight junctions between the hepatocytes at the canalicular space permit unidirectional transport of substances from the hepatocytes into the canalicular space. Several different carriers, receptors and transport proteins facilitate movement of compounds across the sinusoidal, hepatocyte and canalicular membranes. ATP-binding cassette proteins are expressed in the canalicular membrane and play an important role in transportation of organic ions. Alkaline phosphatase, leucine aminopeptidase and γ-glutamyl transpeptidase are transaminase enzymes selectively localized in the bile canaliculi.

The microcirculatory "path" within the lobules leads along a declining hydrostatic pressure gradient from the terminal

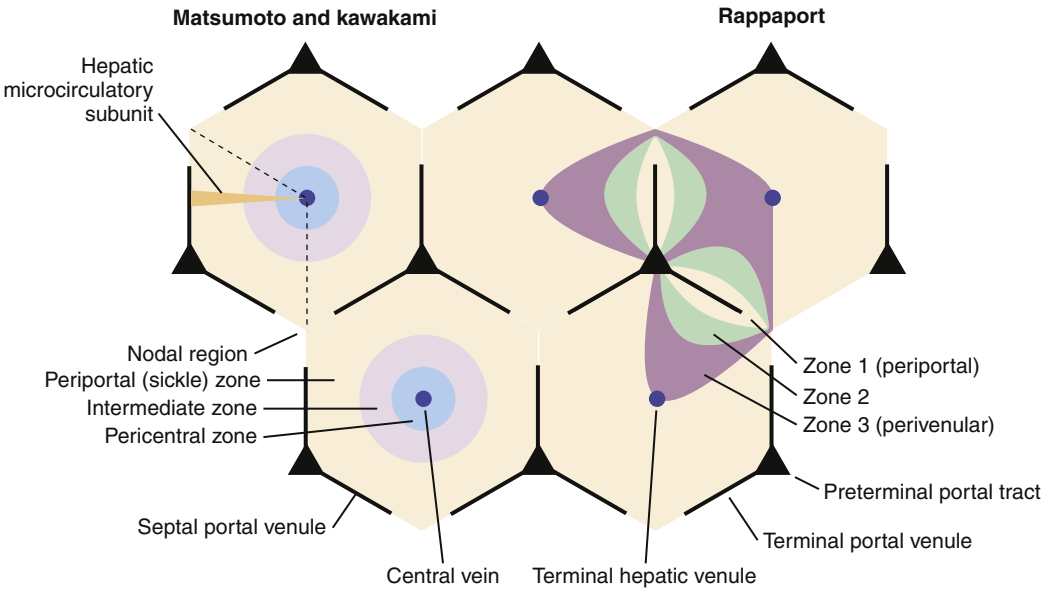

Figure 85–1. Microanatomy of the liver depicting the hepatic acinus and microcirculatory subunits. Arrangement of simple liver acinus forms zones centered about portal triads (preterminal portal tract contains terminal afferent vascular branches, bile ductules, lymph vessels, and nerves). Zone 3 forms the microcirculatory periphery because its cells are the farthest from afferent vessels. Cell damage in area surrounding the terminal hepatic venule, which extends into zone 3 produces a typical stellate pattern of fibrosis. Extensive fibrosis in zone 3 leads to bridging necrosis. *(Modified from Wanless IR: Anatomy, histology, embryology, and developmental anomalies of the liver. In Feldman M, Friedman LS, Slesinger MH, editors:* Slesinger and Fordtran's gastrointestinal and liver disease, *ed 7, Philadelphia, 2002, Saunders Elsevier.)*

hepatic arterioles and portal venules within the portal triad towards the central vein representing the terminal branch of the hepatic vein, resulting in three hepatocyte functional zones (see Figure 85-1). Zone 1 hepatocytes closest to the portal triad are exposed to sinusoidal blood containing the highest concentration of solutes and oxygen. In contrast, zones 2 and 3 represent hepatocytes more distant from the portal blood supply and are exposed to a declining oxygen and solute gradient. In addition, zone 3 hepatocytes actively participate in drug metabolism and disposition. Ischemic injury and drug hepatotoxicity impacts zone 3 hepatocytes to the greatest degree.[81]

Portal Circulation

The portal venous system drains the intestines, pancreas, and spleen with numerous collateral anastomoses to other venous beds of the abdomen. There is a mixing of portal and systemic blood circulation within the sinusoids, and all the blood eventually drains from the liver via the hepatic veins to the inferior vena cava. The liver has a high blood flow (~27% of the resting cardiac output) and low vascular resistance. The portal pressure gradient (PPG) is the pressure difference between the inferior vena cava and the portal vein and averages 0 to 5 mm Hg. Portal hypertension is defined as a PPG between 6 and 10 mm Hg. A PPG greater than 10 mm Hg carries risk for development of esophageal varices and a PPG greater than 12 mm Hg predisposes towards ascites formation.[82] Obstruction of the portal venous drainage at any level leads to portal hypertension. Portal hypertension may be classified as prehepatic, intrahepatic, or posthepatic, according to the level at which the obstruction to flow occurs. Determination of the location of obstruction is critical for instituting appropriate therapy.

Ascites formation is multifactorial. The central event in ascites formation in cirrhosis is splanchnic arterial vasodilatation secondary to portal hypertension. This creates an increase in capillary pressure because of increased blood inflow leading to leakage of fluids. Additionally, impairment of systemic hemodynamics and renal function leads to sodium and water retention with intravascular volume expansion.[83-85] Ascites may form in the absence of portal hypertension as the result of low plasma oncotic pressure associated with malnutrition, with renal or enteral protein losses, or through impaired thoracic duct lymph drainage. Rarely, arterial-portal venous malformations may lead to portal hypertension as a result of excess portal blood flow. One additional factor predisposing to ascites is an elevated central venous pressure that increases formation and impairs resorption of interstitial fluid often associated with generalized anasarca.

Hepatic Function

The function of the liver may be broadly characterized in terms of (1) production of substances uniquely made in the liver, (2) the degradation, elimination, and detoxification of biological materials, (3) the maintenance of biochemical homeostasis, and (4) storage of nutritional materials.

The liver occupies an ideal place in the scheme of digestion. Hepatocytes are exposed to large quantities of absorbed nutrients after ingestion of a meal with 20% of the total absorbed nitrogen used for hepatic protein synthesis. Of the large number of plasma proteins synthesized by the liver, several are of major significance in the ICU and deserve particular attention.

Albumin has a half-life of approximately 20 days, and is a significant contributor to colloid oncotic pressure. Decreased serum levels may predispose to edema formation and decreased binding of bilirubin, calcium, xenobiotics, and other highly protein-bound molecules. Low serum albumin levels can be secondary to impaired synthesis from protein-calorie malnutrition, chronic liver disease, cachexia,

or cytokines. Alternatively, increased losses from proteinuria, protein losing enteropathy, burns, or other iatrogenic losses including paracentesis may cause hypoalbuminemia.[86]

Prealbumin, also known as transthyretin, is a visceral protein with a short half-life of 1.9 days. Because hepatic synthesis is exquisitely sensitive to both the adequacy and levels of protein and energy intakes it may be used a nutritional marker and for monitoring short-term response to nutritional intervention.[87]

α_1-Antitrypsin is an important antiprotease with regulatory activity for elastase and other proteases. α_1-Antitrypsin can be important in regulating elastase-induced tissue injury in certain lung diseases and its absence leads to uncontrolled proteolytic activity in the lung.[88] Because α_1-Antitrypsin is an endogenous protein that is relatively resistant to hydrolysis by enteric bacteria, elevated levels detected in feces suggest protein losing enteropathy.[89]

Hepatic synthesis of transferrin facilitates iron transport in the plasma by binding two molecules of iron. Ferritin is the primary storage molecule of iron with each molecule storing up to 4500 atoms of iron. Many coagulation factors are synthesized in the liver. They include plasminogen, fibrinogen, and factors II, V, VII, IX, X, XI, XII, and XIII. Factors II, VII, IX, and X are the so-called *vitamin K–dependent* factors that require vitamin K for synthesis and secretion in active form.[90] In addition, the anticlotting proteins antithrombin III, protein C, and protein S are synthesized largely in the liver and may be vitamin K dependent. Several additional common plasma proteins are synthesized by the liver including haptoglobin, ceruloplasmin, lipoproteins, α-fetoprotein, and the C3 component of complement.

Alterations in plasma proteins frequently occur during acute and chronic liver disease. Although the levels of many of these proteins may rise as part of the systemic inflammatory response (acute phase reactants), plasma levels are generally reduced during liver disease, depending on the duration of hepatic insufficiency and the half-lives of the specific proteins. Thus a decrease in albumin with its half-life of 16 to 21 days generally represents a chronic disease state, whereas a prolonged prothrombin time may be seen within hours of acute hepatic failure because of the short half-life of factor VII (about 6 hours).[91]

Detoxification and catabolism of ammonia, bilirubin, and xenobiotics is essential to life. Ammonia arises through bacterial degradation of nitrogenous compounds in the intestine, as well as from other physiological sources including the kidneys and peripheral tissues such as skeletal muscle and the brain. Ammonia is transported to the liver via the portal vein in high concentrations and is quickly degraded in the liver to urea. High levels of ammonia are incompatible with life and during hepatic failure, hyperammonemia represents a life threatening aspect of liver disease.[92]

Bilirubin elimination is another critical excretory function of the liver. Bilirubin is mainly derived from the heme portion of hemoglobin. Smaller amounts are made through the breakdown of cytochromes and myoglobin. Heme is catabolized to bilirubin in the reticuloendothelial system and involves several steps, including transport to the hepatocyte and cellular uptake, cytosolic transport within the hepatocyte, conjugation, active cellular export, and elimination. Impairment at any juncture becomes manifest as hyperbilirubinemia and ultimately clinical jaundice.

Enterohepatic Circulation

Bile acids represent a family of steroid molecules derived from cholesterol. They act to eliminate cholesterol from the body and to solubilize dietary fats through a detergent-like action. Enterohepatic circulation acts to conserve bile acids since a minimum concentration of bile acids are required for micelle formation. Bile salts are secreted into the duodenum with 97% reuptake in the terminal ileum, undergoing recycling 4 to 12 times per day. The distal and terminal ileum have specialized transport mechanisms for absorption of bile salts and vitamin B_{12}, that are adversely affected by terminal ileal resection, jejunostomies, inflammatory bowel disease, or other acquired lesions in this anatomical region (e.g., necrotizing enterocolitis). Functional loss of the distal and terminal ileum results in malabsorption of vitamin B_{12}, bile salt deficiency, and impaired digestion and absorption of fat-soluble vitamins and long-chain fats. Furthermore, unresorbed bile acids have a detergent effect on the colonic epithelium resulting in secretory diarrhea.[1]

Hepatic insufficiency, either from immaturity or as a result of disease affects the elimination of many drugs (see Chapter 87). A large number of commonly used drugs of all classes including aminophylline preparations, narcotics, barbiturates, H_2-blockers, vasodilators, antidysrhythmics, and others demonstrate significant hepatic elimination. The hepatic P-450 system plays a central role in many of the mixed-function oxidative reactions responsible for converting lipophilic compounds into more water-soluble ones. In addition, the liver may conjugate drug metabolites to form products that can be eliminated easier in bile or through the kidney. The half-life of many drugs may be prolonged during hepatic insufficiency as a result of a decrease in the total number of functioning hepatocytes. In addition, the half-life of many drugs may be prolonged through competitive inhibition by the presence of other drugs, or may be shortened by induction of elimination reactions. For example, phenobarbital decreases the half-life of xanthines and may increase the toxicity of acetaminophen. Adjustment of medication dosage and schedule must be considered for those drugs with significant hepatic elimination when impaired liver function exists.[93]

Hepatic regulatory function involves (1) interconversion of amino acids to maintain physiological plasma levels, (2) gluconeogenesis to maintain adequate glucose serum levels for glucose-dependent tissues, and (3) regulation of numerous plasma hormones (Box 85-4).

The direct secretion of insulin and glucagon into the portal circulation exposes the liver to much higher concentrations of these hormones than peripheral tissues. This relationship amplifies the hepatic influence over carbohydrate metabolism. Approximately 50% of secreted insulin and a large portion of glucagon are degraded on a first-pass basis by the liver. Both of these hormones are known to have hepatotrophic effects and are thought to be important for differentiation and regeneration of hepatocytes. Intensive insulin therapy in the critical care setting has been shown to have a beneficial effect on liver function.[94]

The last category of hepatic function involves storage of glycogen, triglycerides, folic acid, vitamin B_{12}, and vitamins A and D. The liver uses glycogenolysis to mobilize hepatic glycogen stores and provide an almost immediate source of glucose to maintain serum levels. The liver glycogen stores contain up

Box 85–4 Hepatic Endocrine Regulation

Catabolism Primarily by Liver

Insulin
Glucagon
Growth hormone
Glucocorticoids
Estrogens
Progesterone
Parathyroid hormone
Some gut hormones

Catabolism by Liver and Other Tissues

Thyroid hormone
Luteinizing hormone
Antidiuretic hormone
Testosterone
Aldosterone
Oxytocin
Adrenocorticotropic hormone
Thyroid-stimulating hormone
Thyroid-releasing hormone

From Johnston DG, Alberti KGMM: The liver and the endocrine system. In Wright R, Millward-Sadler GH, Alberti KGMM, et al, editors: *Liver and biliary disease,* ed 2, Philadelphia, 1985, WB Saunders.

to a 2-day supply of glucose.[95] Synthesis of vitamin D_3 (cholecalciferol) occurs in the skin with subsequent accumulation of D_3 in the liver. Hydroxylation at the 25-position that occurs in the liver results in a large pool of circulating 25-(OH)D_3, the precursor of the active 1,25-(di OH)D_3. Defective storage and absorption of dietary vitamin D and 25-hydroxylation may be present in chronic liver failure.[96]

Host-Defense Mechanisms of the Gut: Immunology and Microbiology

Both the intestine and the hepatic-based macrophages can serve as a major source of nitric oxide following injury or stimulation.[97] The recently recognized role of nitric oxide on immune function further emphasizes the role of the gastrointestinal tract in systemic responses. The frequent association of hepatic dysfunction with the acute respiratory distress syndrome has led to intensive investigation of the lung-liver axis during critical illness.[98-100] A major unifying theme in these organ interactions is the regional activation of macrophages and platelets and damage to the endothelium after injury leading to both localized and remote organ function disturbance. The gut has become one of the important focuses in our evolving understanding of the syndrome of multiple organ dysfunction.[101]

Numerous mechanisms exist to maintain homeostasis within the gut. These include exclusion by mucosal barrier, phagocytosis and clearing of translocating bacteria and macromolecules, immunologic tolerance to ubiquitous antigens, and coordinated self-limited inflammatory responses leading to clearance of antigens while limiting tissue injury.

Innate mechanisms exist to prevent infection by bacterial pathogens. In the upper GI tract, action of salivary enzymes, gastric acid, pancreatic enzymes, and the detergent effect of bile acids all act to limit the amount of viable bacteria in the small intestine. The secreted mucous layer preventing attachment and adherence of bacteria combined with intestinal peristalsis continually prevents establishment of infection. In the colon, with its heavy colonization of bacteria, competitive inhibition acts to prevent infection with pathogenic species. Other innate mechanisms include tight junctions between intestinal epithelial cells that act to exclude bacteria, antigens and other macromolecules.[102] *Clostridium difficile* toxin and enteropathogenic *E. coli* act by disrupting these tight junctions.[103,104] Antibiotics profoundly reduce the number of anaerobic and coliform bacteria in the alimentary tract with particular reduction of *Bifidobacterium* and *Lactobacillus* species.[105] Routine stress ulcer prophylaxis with acid suppressing medications such as H_2 blockers and PPIs create a risk of nosocomial pneumonia due to loss of protective gastric acid. However, a recent meta-analysis and systematic review failed to show a significant association between PPI use and respiratory infections.[106] Intestinal motility is a critical factor for clearing antigens and bacteria from the gut lumen and thus reducing bacterial overgrowth with its resultant malabsorption of nutrients. Decreased motility leading to bacterial overgrowth may be seen in premature infants and may be associated with many disorders seen in older children, including the use of narcotics and some neuromuscular blockers (e.g., pancuronium bromide).

A physical barrier composed of mucin and the glycocalyx is formed over the intestinal epithelium by secretions from the goblet cells. It forms a gel that can change from a semisolid to a semifluid state under varying intraluminal conditions and thus provides either a relatively impervious barrier protecting the epithelium from osmolar forces or a fluid medium helping to propel bacteria and antigens aborally.[1]

Mucosal blood flow appears to be an important mechanism for maintaining mucosal integrity in both the stomach and the small intestine. Inadequate microcirculation in the gastric mucosa, that provides cytoprotection, appears to be a major factor contributing to stress ulceration in critically ill patients. As submucosal and mucosal blood flow diminishes, the buffering ability for acid that back diffuses into the tissues is reduced and leads to tissue necrosis. Hypoxia, hypotension, and states of high circulating catecholamines are commonly associated with altered mucosal circulation and stress ulceration.[107] Finally, the small intestine, especially the terminal ileum, of newborns and infants is more sensitive to hypoxia and ischemia than that of adults, predisposing them to mucosal injury and necrotizing enterocolitis.[108]

Bacterial translocation is defined as the migration of bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes or other extraintestinal organs, representing a disruption of the normal host flora equilibrium that leads to a self-perpetuating inflammatory response and ultimately to infection. This process is increasingly being recognized as potential source of pathogens producing bacteremia and sepsis in a variety of premorbid disease conditions such as cirrhosis and prematurity.[109,110] Translocation may occur directly through the M cells that cover the Peyer's patches or it may occur by ingestion of viable pathogenic material by the mobile phagocytic system with transport into the host bypassing the previously outlined barrier mechanisms. The three main mechanisms predisposing a host to bacterial translocation are (1) disruption of the ecological equilibrium allowing intestinal bacterial overgrowth, (2) deficiencies in the host immune

defenses, and (3) damage to the intestinal mucosa vasculature that causes increased permeability.[111] Certain aerobic enteric bacteria including *E. coli, Proteus mirabilis*, and *Klebsiella pneumoniae* appear to be more commonly associated with translocation from the gastrointestinal tract, presumably because oxygen in the blood may exert an inhibitory effect on anaerobic organisms. Intra-abdominal inflammatory foci are susceptible to invasion by translocating bacteria, suggesting one mechanism for abdominal abscess formation.[112] Some studies have demonstrated that administration of glutamine improves the prognosis of critically ill patients by maintaining the physiologic intestinal barrier and by reducing frequency of infection.[113]

Of central importance to the immune function of the gut are the gut-associated lymphoid tissues consisting of Peyer patches and single lymphoid nodules of the intestinal mucosa and appendix. In addition to mounting protective responses to invading microbial pathogens and detecting and eliminating neoplastic cells, the mucosal immune response has two unique characteristics: secretion of antibodies that complex antigen in the lumen without activating complement and induction of tolerogenic T lymphocytes that maintain controlled local responses to commensal bacteria or dietary constituents with no systemic reactions (oral tolerance).[102]

Peyer patches consist of mononuclear cells, plasma cells, macrophages and other antigen-presenting cells. B cells are the predominant lymphocyte. Peyer patches are covered by a specialized epithelium containing M cells, that transport luminal antigen into the patches. Migration of lymphocytes from one compartment to another provides communication of immunological information. In addition, migration of lymphocytes to extraintestinal tissues including the mammary gland, female genital tract, and bronchus-associated lymphoid tissue may mediate immune responses in those tissues. Penetration of the mucosal barrier by antigenic material occurs because the epithelial barrier is not totally impermeable to macromolecules. It may be accelerated by inflammation or mucosal damage. Increased permeability and tissue damage occur with such diverse disease entities as infectious enterocolitides, idiopathic inflammatory bowel diseases, hypersensitivity diseases such as celiac sprue and food allergies, and gut ischemia or hypoxia. As barrier mechanisms fail in the injured gut, bacterial penetration is more likely to occur, producing portal and systemic bacteremia. Cell-mediated cytotoxic reactions and antibody-dependent, cell-mediated cytotoxicity represent two responses of the gut-associated lymphoid tissues to encounters with antigens. These processes involve the cooperative interaction of other lymphoid cells such as killer, lymphokine-activated killer, and natural killer cells. Infected or necrotic cells and noncellular antigenic material are targeted for ultimate lysis by phagocytic cells in the circulation and reticuloendothelial system.

Kupffer cells, which account for the largest pool of mononuclear phagocytes with direct access to the blood, play a major role in clearing portal bacteria. In addition, Kupffer cells are key participants in response to tissue injury or organ invasion through the elaboration of cytokine mediators, such as tumor necrosis factor and interleukin-1, and the release of nitric oxide, leading to many of the systemic responses seen in sepsis.[97] Through their intimate proximity to the hepatocyte, Kupffer cells interact directly with hepatocytes by means of cell-cell and paracrine interactions. In response to tumor necrosis factor and interleukin-1, well-documented alterations in hepatic function occur including the inhibition of albumin synthesis, gluconeogenesis, and P-450-mediated detoxification. Acute-phase reactant synthesis is also induced by tumor necrosis factor and interleukin-1.[114]

Gastrointestinal and Hepatobiliary Testing in the Intensive Care Unit

Diagnostic testing in the ICU permits the identification of organ system injury and dysfunction and assists in monitoring the course of a disease as well as response to therapies. Laboratory testing is helpful in detecting and monitoring hepatocellular injury and dysfunction. In the ICU setting, impaired synthetic function is the hallmark of liver failure. This is of more immediate concern than hepatocellular injury alone. Decreased synthesis of the liver dependent clotting factors I (fibrinogen), II (prothrombin), V, VII, IX and X, results in a prolonged prothrombin time. In the absence of vitamin K deficiency or related inhibitors, this represents liver failure. Because factor VII has the shortest half-life shortest half-life (2 to 6 hours) compared to the other factors, it acts as the rate-limiting step for conversion of prothrombin to thrombin. The use of recombinant activated factor VII in acute liver failure remains under debate.[91] Other less specific measures of liver dysfunction include increased bilirubin, decreased serum albumin and decreased prealbumin.

Liver failure may also be associated with life-threatening hypoglycemia from a variety of mechanisms including decreased hepatic glycogenolysis, gluconeogenesis and release of glucose, hyperinsulinemia from impaired hepatic degradation, and increased glucose utilization secondary to anaerobic metabolism. A frequent finding in advanced liver failure is elevated serum ammonia reflecting impaired ureagenesis and/or other ammonia clearance mechanisms. Ammonia elevation results from urea cycle defects, portal systemic shunting, and events such as large gastrointestinal bleeds that generate substrate for increased ammonia production by enteric bacteria. In the setting of impaired liver function, this leads to hyperammonemia.[115]

Liver disease can be broadly categorized into hepatocellular, cholestatic, and infiltrative processes. The biochemical tests commonly used to detect cholestasis, which is impaired bile flow, and hepatocellular injury are serum bilirubin and aminotransferase activities (alanine transaminase [ALT], aspartate transaminase [AST]). Cholestasis, reduced bile excretion or transport, and biliary obstruction in the bile canaliculi or large ducts are represented by elevations in serum conjugated bilirubin, bile acids, alkaline phosphatase (ALK), γ-glutamyltransferase (GGT), or 5′-nucleotidase.

The van den Bergh reaction assesses conjugated (direct fraction) bilirubin levels. The unconjugated (indirect) fraction represents the difference between the total bilirubin and the direct fraction. Elevated levels of predominantly indirect bilirubin result from (1) increased bilirubin load to the liver (e.g., hemolysis); (2) diminished uptake and intracellular transport; and (3) reduced conjugation (e.g., immaturity, fulminant necrosis).

In children, elevations in ALK may be seen with rickets or during periods of rapid skeletal growth. Isoenzymes may distinguish between liver or bony sources. ALT and AST are

hepatic cytosolic enzymes that catalyze the reversible transfer of the α-amino group of the amino acids alanine and glutamate producing pyruvic and oxaloacetic acids respectively. Elevations in serum activities of ALT and AST suggest hepatocellular injury (see Table 85-3). AST is also present in myocardial tissue, skeletal muscle, kidney, pancreas and erythrocytes. Therefore increased serum AST is not specific for hepatocellular injury. Alanine transaminase is present in only relatively low concentrations in tissues other than liver, thus providing greater specificity for hepatocellular injury than AST. Falling levels of AST and ALT in the setting of rising levels of conjugated bilirubin represent worsening destruction of hepatocytes suggesting liver dysfunction rather than recovery. Elevated serum lactate dehydrogenase activity lacks specificity and may be seen in association with hepatocellular injury, hemolysis and myopathy; however, when in association with elevated serum creatinine phosphokinase or aldolase indicates myopathy or a rhabdomyolysis injury.

Imaging of the hepatobiliary system has become easier, safer, and more reliable in the last decade. Ultrasonography is particularly useful in the ICU and allows rapid, safe, bedside evaluation of (1) hepatic vascular structures and patterns of blood flow; (2) structural abnormalities such as tumors, abscess, hematoma, or dilated intrahepatic bile ducts; (3) the gallbladder, extrahepatic, pancreatic and common biliary system; (4) the pancreas; (5) the genitourinary system; and (6) the abdomen and retroperitoneum. In addition, ultrasound can provide guidance for therapeutic interventions such as drainage of abscesses.

Computed tomographic scan with and without contrast and magnetic resonance imaging provide additional methods for evaluating the abdominal and retroperitoneal organs for masses, abscesses, and fluid collections. A downside to both modalities is that they usually require a prolonged period away from the ICU, which may lead to instability in a tenuous, critically ill patient.

Many of the radioisotope studies can be performed in the ICU and provide a wide range of diagnostic possibilities in critically ill patients. Technetium-99m (^{99m}Tc) iminodiacetic acid compounds are handled by the hepatobiliary system much like bilirubin and provide a qualitative and semiquantitative image of function and structure. These compounds may be used diagnostically to evaluate infants with persistent jaundice and also used in follow-up after Kasai procedure or liver transplantation.

Of the available biochemical markers of pancreatic disease, serum amylase and lipase determinations are the most widely available. Serum lipase is elevated in about 87% of patients with acute pancreatitis and demonstrates fewer false-positive results than amylase testing. Transient hypocalcemia

Table 85–4 Diagnosis of Selected Hepatobiliary Disorders

Form of Liver Injury	Supportive History/Laboratory Data
PREDOMINANTLY HEPATOCELLULAR	
Viral hepatitis	Viral serologies: hepatitis A, B, C, E; Epstein-Barr virus; cytomegalovirus, varicella zoster virus, herpes simplex virus
Drug-induced hepatitis	History of toxic/excess ingestion ± elevated eosinophil count
Ischemia	Shock, status post–cardiac surgery
Autoimmune hepatitis	Increased globulin ratio, antinuclear antibody, anti–smooth muscle antibody, anti-liver kidney microsomal antibody
Wilson disease	Serum ceruloplasmin, 24-hour urine copper
α-Antitrypsin deficiency	α_1 antitrypsin phenotyping
CHOLESTATIC	
Bacterial sepsis	*Proteus*, *E. coli* urinary tract infection
Galactosemia	Urine-reducing substances, *E. coli* sepsis, red blood cell galactose-1-phosphate uridyltransferase
Tyrosinemia	Urine succinylacetone
Biliary atresia	Intraoperative cholangiogram
Anatomic anomalies: choledochal cysts, biliary stricture, cholelithiasis, congenital hepatic fibrosis, Caroli disease	Ultrasonography, cholangiogram
Alagille syndrome	Butterfly vertebrae, posterior embryotoxon on eye exam, echocardiogram
Cystic fibrosis	Sweat test, genetic testing
Graft-versus-host disease, venoocclusive disease	History of bone marrow transplant, high-dose busulfan
Ischemia	Extracorporeal membrane oxygenation
INFILTRATIVE	
Hepatocellular carcinoma, hepatoblastoma	α-Feto protein
PREDOMINANTLY COAGULOPATHIC	
Neonatal hematochromatosis	Serum iron and ferritin

(<8.0 mg/dL) occurs in about 30% of patients with pancreatitis. Mild to moderate hyperglycemia as a result of islet cell damage is seen in up to 25% of cases, often necessitating the administration of exogenous insulin.

Evaluation of the alimentary tract consists of examining gastric aspirates and stool samples for gross bleeding or occult blood with the guaiac test (Hemoccult). A positive result mandates further evaluation and surveillance to determine the source and severity of gastrointestinal tract blood loss. Nasogastric lavage may be used to distinguish a source of bleeding as being proximal or distal to the pylorus. ^{99m}Tc sulfur colloid or red blood cells labeled with ^{99m}Tc may provide information regarding the site of active mucosal bleeding and are less invasive than arteriography.

Esophageal pH monitoring is useful for evaluating the efficacy of antisecretory therapy. It may be useful to correlate symptoms (e.g., cough, chest pain) with acid reflux episodes and to select those infants and children with wheezing or respiratory symptoms in whom gastroesophageal reflux is an aggravating factor. The sensitivity, specificity, and clinical utility of pH monitoring for diagnosis and management of possible extraesophageal complications of gastroesophageal reflux are not well established.[116]

Imaging studies are of primary importance in acutely ill patients in a number of circumstances. Plain radiographs can be reliably used to locate radiopaque objects, to diagnose intestinal ileus, mechanical obstruction and perforated viscus. Contrast studies are required to diagnose organ and soft-tissue inflammation including appendicitis, pancreatitis and its complications, mesenteric and retroperitoneal masses, abscesses/fluid collections, intussusceptions, and anatomical anomalies.

GI bleeding from sites distal to the ligament of Treitz and proximal to the terminal ileum that are inaccessible to video endoscopy (e.g., Meckel diverticulum, vascular malformations, altered anatomy post-GI surgery) are best assessed using radio nuclide scans and angiography. Because of the need to perform the more sophisticated imaging studies away from the controlled environment of the ICU, the studies must be tailored to the patient's diagnostic needs according to the priorities of the initial stabilization of life-threatening illness and subsequent treatment of the underlying pathologic condition.

Video and or fiberoptic endoscopy in the hands of operators skilled in managing small children has found a place in ICU management to (1) diagnose the source of upper gastrointestinal tract bleeding, (2) to control and sclerose bleeding varices, (3) to place percutaneous gastrostomy tubes for feeding, and (4) for the placement of stents to maintain patency of the distal biliary and pancreatic tract.

See Table 85-4 for suggested diagnosis tests for selected hepatobiliary disorders.

References are available online at http://www.expertconsult.com.

Disorders and Diseases of the Gastrointestinal Tract and Liver

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PEARLS

- So much reliance is placed on electronic monitoring of patients that physicians are often tempted to perform only a cursory examination or go days without laying hands on the patient. Regrettably, adopting such an approach deprives the clinician of an adequate perspective on the patient's day-to-day condition and deprives the patient of optimal care.
- When compared with a scintiscan of the lungs after administration of a radiolabeled meal or with the discovery of lipid-laden macrophages after bronchoalveolar lavage, the use of colorants is notoriously inaccurate.
- Several antireflux barriers exist in the region of the lower esophageal sphincter. Beyond intrinsic myogenic tone, barriers such as the cardioesophageal angle, the abdominal esophagus (which acts as flutter valve), the mucosal rosette of the sphincter (which acts as a choke valve), and the diaphragmatic crura themselves act to prevent reflux of gastric contents.
- The association between *Helicobacter pylori* infection and both chronic gastritis and duodenal ulcer is well established, but the role of *H. pylori* in the pathogenesis of gastric ulceration remains somewhat speculative.
- Intravenous administration of somatostatin or its synthetic analogue, the active octreotide moiety, has been effective in stemming variceal hemorrhage and may work for other causes of bleeding. In addition to their hemodynamic effects, they inhibit gastric acid production.
- Crohn's disease and ulcerative colitis are chronic, relapsing disorders without known causes. The transmural inflammation of Crohn's disease may affect any portion of the alimentary tract in a patchy distribution, whereas the inflammation of ulcerative colitis is confined to the mucosa of the colon.
- The diagnosis of necrotizing enterocolitis may be confirmed by an abdominal plain film showing pneumatosis intestinalis, hepatic portal air, or both. A random breath hydrogen/carbon dioxide ratio greater than 8 ppm/mm Hg strongly suggests the diagnosis. Because the pathogenesis is unknown, treatment must be symptomatic. In most centers, feedings are discontinued for 48 hours to 2 weeks depending on the severity of symptoms. Fluid resuscitation and broad-spectrum parenteral antibiotics are the basis of medical therapy. Surgical resection is reserved for severe cases when medical management fails and gangrenous bowel develops.
- Abdominal compartment hypertension and sydrome are two distinct entities becoming increasingly recognized in the intensive care setting. Prompt recognition of clinical symptoms and signs may prevent vital organ compromise.

Gastrointestinal Evaluation of the Critically Ill Child

Dramatic advances in pediatric critical care have resulted in improved outcomes for children admitted to pediatric intensive care units (PICUs). Indeed, the improved technology available today has resulted in improved management strategies for a variety of conditions. So much reliance is placed on electronic monitoring of patients that physicians are often tempted to perform only a cursory examination or go days without laying hands on the patient. Regrettably, adopting such an approach deprives the clinician of an adequate perspective on the patient's day-to-day condition and deprives the patient of optimal care. Daily physical examination is of paramount importance in the assessment of children with either life-threatening gastrointestinal disease or gastrointestinal manifestations of multisystem disease. The current approach to gastroenterologic diagnosis and therapy as well as principles of gastroenterologic physical examination are therefore reviewed in this chapter.

Abdominal Examination

Astute clinicians recognize that the abdomen extends from "the neck to the knees." A thorough examination of the head, neck, and chest is essential when patients with abdominal symptoms are evaluated. For example, pneumonia may be discovered by chest auscultation in the child who has abdominal pain. All too often, a child whose abdominal symptoms are due to pneumonia undergoes exploratory laparotomy for a purportedly "surgical" abdomen.

The abdominal examination, which can be difficult to perform on young children without life-threatening illness, is made more difficult in the ICU setting. Pain and fear limit cooperation. Patients who are obtunded by narcotics, sedatives, or an underlying central nervous system (CNS) disorder display inconsistent responses to abdominal palpation. Neuromuscular blockade abolishes abdominal guarding. Children

with multisystem trauma may not localize pain. These impediments notwithstanding, the observant clinician can glean a great deal of information from a carefully performed examination. Simple inspection of the child's abdomen can reveal generalized distention; abnormally prominent abdominal wall veins (which signify portal hypertension); or anterior and lateral abdominal wall ecchymoses, such as Cullen's sign or Grey Turner's sign (which herald acute pancreatitis). In addition, because of the child's relatively undeveloped abdominal musculature, visceromegaly or abdominal masses may be apparent on inspection.

Auscultation will ascertain the frequency and quality of peristaltic sounds. They normally occur every 10 to 30 seconds and are low pitched. High-pitched, frequent bowel sounds suggest enteritis or obstruction. In obstruction, bowel sounds characteristically reverberate and seem to originate "from a deep well." Bowel sounds are absent in paralytic ileus or peritonitis. Ancillary findings include venous hums, which suggest portal obstruction, or bruits that may denote arteriovenous malformations.

In pediatric patients, palpation should generally precede percussion because it is less threatening. The child should be in the supine position, and when possible the hips and knees should be comfortably flexed to enhance abdominal wall relaxation. The abdomen should be palpated through all phases of respiration in all four quadrants. The examiner should lightly palpate to judge guarding and tenderness and should use gentle ballottement. Deeper palpation better localizes organomegaly or masses.

Percussion permits estimation of visceral size and helps to diagnose obstruction, peritonitis, or ascites. Excessive tympany implies that bowel loops are distended with air, whereas dullness suggests that excessive fluid or a solid mass is present. Shifting dullness is relatively easy to detect in cooperative children with percussion of the abdomen with the child in the supine, left lateral, and right lateral positions. When the child with ascites is in the supine position, dullness is found primarily over the flanks. The dullness moves to a new level nearer the midline when the child is moved to each lateral position. It is essential to perform a digital examination of the rectum in children with gastrointestinal dysfunction. Inspection of the perineum may reveal perianal or perirectal abscesses, which may be the first sign of acute leukemia, chronic granulomatous disease of childhood, or Crohn's disease. Similarly, deep fissures or sentinel piles suggest ulcerative colitis or Crohn's disease, and hemorrhoids can be found in portal hypertension. The digital examination should be performed in the alert, older child only after its purpose is explained. Any material that returns on the examining finger should be evaluated for occult blood. Absence of stool in the vault can corroborate Hirschsprung's disease in an infant with abdominal distention and a history of obstipation. Rectal masses related to pelvic abscesses or tumors may be digitally palpated. Rectal tenderness signifies mural or extramural inflammation or infection.

Gastrointestinal Endoscopy

The development of flexible fiberoptic endoscopes appropriately sized for use in infants and children has greatly expanded the value of endoscopy in diagnosing and treating a variety of gastroenterologic disorders in critically ill pediatric patients. For example, pediatric endoscopes with an outside diameter of 5 mm can now be used for diagnostic purposes in newborn infants. Electrocautery, injection therapy, or variceal banding of gastrointestinal bleeding sites can also be performed with devices that now fit within the biopsy channels of a standard 9.4-mm pediatric endoscope. Upper gastrointestinal endoscopy (esophagogastroduodenoscopy [EGD]) is performed most often with the child under deep sedation or general anesthesia, although some clinicians report successful unsedated upper endoscopy in very young infants. Many pediatric endoscopists in North America use a combination of narcotic sedative and benzodiazepine to achieve acceptable sedation analgesia.[1] Other agents commonly used for sedation are propofol and ketamine. General anesthesia with endotracheal intubation is appropriate when the side effects of sedation or the endoscopy pose an undue risk of respiratory compromise (e.g., when underlying pulmonary disease, upper airway disease, or disorders of respiratory control are present) or if the patient is at risk for aspiration of gastric contents (e.g., when massive upper gastrointestinal hemorrhage is present or when an emergency foreign body extraction is performed on a child with a full stomach). In an ICU setting, patients supported by ventilators should receive additional sedation and neuromuscular blockade if the endoscopist anticipates that the procedure will be lengthy or excessively difficult.

Advantages of elective endotracheal intubation for EGD also include control of both the airway and ventilation during the procedure. In very small patients, the relatively large endoscope may partially obstruct the glottis. Distention of the gut with air may interfere with diaphragmatic movement. The risk of inadvertent extubation during EGD, however, mandates careful fixation of the endotracheal tube and careful monitoring of ventilation during the procedure by a physician from the critical care team.

Because bacteremia may occur during both upper and lower gastrointestinal endoscopy, some endoscopists routinely use perioperative antibiotics for endoscopy in patients with a central venous line or ventriculoperitoneal shunt. In recent years, therapeutic endoscopy has complemented diagnostic endoscopy. Gastrointestinal tract hemorrhage from varices, peptic ulceration, and angiodysplasia may be controlled by injection therapy or photocoagulation, electrocoagulation, and thermocoagulation. Band ligation of esophageal varices is also a proven therapy for variceal hemorrhage. Percutaneous endoscopic gastrostomy has become a popular alternative to surgical gastrostomy for patients in the ICU who cannot take oral alimentation on a long-term basis.

The diagnosis and treatment of oropharyngeal dysphagia can be difficult but is improved with the use of fiberoptic endoscopic evaluation of swallowing (FEES). The endoscope can be passed transnasally to visualize both laryngeal and pharyngeal structures. Both the structure and functioning of the pharyngeal phase of swallowing can be evaluated by giving the patients food and liquid boluses. Sensory testing can also be conducted to elicit the laryngeal adductor reflex. Some studies have suggested a good correlation between FEES and videofluoroscopy.

Wireless video endoscopy or video capsule endoscopy (VCE) is a noninvasive technology used to provide imaging of the small intestine, an anatomic site often difficult to visualize. The images acquired are of excellent resolution and the procedure uses the principle of physiologic endoscopy via passive movement and does not inflate the bowel, so images of

the mucosa are captured in a collapsed state. Primary indications include the diagnosis of obscure gastrointestinal bleeding, small bowel tumors, or Crohn's disease. There is growing experience in the use of this technology for children older than 6 years. Advantages include its noninvasive nature and the ability to examine the small bowel mucosa, which is not possible with push enteroscopy. Disadvantages include the impossibility of any tissue sampling or therapeutic intervention. However, studies have suggested that the overall yield of VCE is superior to push enteroscopy and barium studies.[2-4]

Gastroesophageal Reflux Monitoring

Like gastrointestinal endoscopy, esophageal reflux monitoring has benefited from technical advances that permit insertion of miniature, flexible electrodes into the esophagus of the smallest children.

Esophageal pH monitoring has been in use since the late 1970s. Esophageal pH is continuously recorded for 24 hours, and the duration of esophageal acidification, defined as decreases in pH less than 4, is quantified. Additional variables including the quantity of reflux in the 2 hours after a feeding and during fasting are determined. Detection of alkaline reflux episodes, which commonly occur in the postprandial period when food buffers gastric acid, is not possible with this technique. The administration of apple juice (pH < 4) rather than formula for feedings during the monitored period has been proposed to circumvent this limitation; however, it is an imperfect strategy insofar as normative data are scarce for older children whose esophageal pH is measured during apple juice feedings. Furthermore, the technique is unreliable for children who have been maintained with histamine-2 (H_2) antagonists or proton pump inhibitors. For reliable pH monitoring of such children, proton pump inhibitors must have been discontinued for at least 72 hours and H_2 antagonists for at least 48 hours. Critical care physicians may not have the luxury of stopping these agents temporarily in critically ill patients who are at risk for stress ulceration of the gastrointestinal tract.

Esophageal impedance monitoring[5] is the preferred means of measuring gastroesophageal reflux among patients who are receiving acid suppression or in whom alkaline reflux is suspected. The intraesophageal impedance device measures total opposition to current flow between two electrodes and expresses the value in ohms. Because air and fluid have different conductivities, the contents of the esophagus can be differentiated at any point in time. Thus when the esophagus is devoid of fluid, a baseline impedance is measured. When a bolus of fluid enters the esophagus from refluxed material or from a swallowed bolus, the impedance changes. These changes in intraluminal impedance thus permit the continuous monitoring of pH neutral or alkaline reflux episodes.

In addition to detecting pathologic quantities of reflux in children who have symptoms suggestive of reflux disease, reflux monitoring is also useful in determining whether a temporal correlation exists between gastroesophageal reflux and pathologic events such as cough, bronchospasm, or apnea. Because it does not determine the cause of vomiting, reflux monitoring adds little to the evaluation of vomiting children.

For the ambulatory child capable of undergoing an endoscopy, a small pH transducer capsule can be deployed and attached to the esophagus, being left in place to monitor esophageal acidification for up to 48 hours with an external sensor before being naturally sloughed. The advantage of this device is that nasoesophageal intubation need not be performed, thereby creating a more "natural" environment. For the critically ill, intubated patient, this device is impractical to place and offers no advantage over traditional reflux monitoring.[6,7]

Use of Colorants to Identify Aspiration in the Intensive Care Unit

Patients who are obtunded or who have been ventilator dependent for an extended time are at significant risk of pulmonary aspiration. A deceptively simple way of documenting aspiration in patients receiving gavage or gastrostomy feedings in the past has been to add a coloring agent such as blue dye No. 1 or methylene blue to formula. The rationale for this strategy was that quantities sufficient to tint formula should be readily apparent when suctioned from the lungs. The fallacy of the technique is that when compared with scintiscanning of the lungs after administration of a radiolabeled meal or with the discovery of lipid-laden macrophages after bronchoalveolar lavage, the use of colorants is notoriously inaccurate. Furthermore, all colorants are dangerous when instilled into the gastrointestinal tract. They are customarily absorbed in minimal quantities, but among critically ill patients, the gastrointestinal tract becomes porous to all macromolecules and appreciable quantities of dye are absorbed. Once absorbed, even minimal quantities function as metabolic poisons, uncoupling oxidative metabolism, thereby resulting in life-threatening metabolic acidosis among susceptible patients.[8]

Radiologic Procedures

Plain Films

The abdominal x-ray film provides valuable assistance to the clinician evaluating children with abdominal distention, guarding, or tenderness. Dilated, gas-filled bowel loops, with or without air-fluid levels, can signify obstruction or ileus. Air-fluid levels in a "stepladder" configuration along the length of small bowel suggest obstruction, whereas levels that appear in a parallel configuration suggest ileus. Pneumatosis intestinalis and mucosal "thumbprinting" are signs of bowel wall ischemia and can often be appreciated on the plain film. Pneumoperitoneum can be evaluated with the inspection for air in the lesser sack, air between bowel loops, or a visible falciform ligament. Even though an upright film is optimal for visualizing peritoneal air, lateral decubitus or cross-table lateral films are acceptable substitutes in bedridden patients. Air in an abscess cavity or air in liver parenchyma, biliary tree, or portal venous system should be acknowledged as signs of serious intraabdominal infection.

Abnormal densities such as abdominal masses, ascites, or calcifications can often be identified on plain films. Calcifications in the region of the gallbladder, pancreas, or appendix suggest cholelithiasis, pancreatitis, or appendicitis, respectively. The abdominal contour and the contour of extraperitoneal structures such as lung bases, pelvic organs, and kidneys should always be assessed.

Contrast Radiography

Although endoscopy is more sensitive than single-contrast radiography for identifying mucosal ulceration, contrast radiography remains a valuable procedure in the critical care

setting. In general, the upper gastrointestinal tract series and small bowel series are indicated when partial small bowel obstruction is suspected. A contrast enema will document (and possibly treat) intussusception and document Hirschsprung's disease. The type of contrast agent for a particular examination depends on the clinical condition of the patient undergoing the examination. Although barium sulfate is superior to water-soluble contrast agents for outlining mucosa, its use in typical patients in the ICU is riskier because barium may form a concretion in a patient with ileus and because barium leaking into the peritoneum from a perforated hollow viscus can cause serious peritoneal injury. Hyperosmolar, water-soluble contrast agents are usually not favored because they pose the risk of dehydration. Currently, isosmolar agents are more commonly used for studies on the critically ill patient.

Ultrasonography, Computed Tomographic Scanning, and Magnetic Resonance Scanning

Ultrasonography, computed tomographic (CT) scanning, and magnetic resonance imaging (MRI) each have advantages and disadvantages. For example, in the slim child with little mesenteric fat, ultrasonography is sometimes better than CT scanning of abdominal viscera. Conversely, CT scanning is superior for abdominal imaging of obese individuals.[9] MRI is limited by its inability to distinguish bowel loops from adjacent structures and by blurring caused by motion. It is helpful, though, in identifying vascular tumors, which are seen as low-intensity masses on T1-weighted images and high-intensity masses on T2-weighted images. Ultrasonography or CT is used when an intraabdominal abscess, cystic lesion, hepatobiliary disease, tumor, ascites, or pancreatitis is suspected. In the identification of pancreatic lesions, dynamic CT scanning is a most imaging technique. CT also best identifies enlarged periaortic nodes. CT or MR enterography are other modalities used in the detection of small bowel inflammatory disease. Oral hyperhydration can achieve adequate luminal distension often not requiring nasoenteric intubation. Unlike routine CT or MRI, enterography can display mural changes along with perienteric inflammatory changes with much better resolution. These studies are more accurate than the standard small bowel follow-through or enteroclysis.[10-13]

Ultrasonography of the liver and biliary tract identifies hepatic parenchymal disease, biliary stones, or congenital abnormalities such as choledochal cyst. Intussusception, pyloric stenosis, and acute appendicitis are particularly amenable to ultrasonographic diagnosis. In addition, Doppler flow analysis has significantly aided the preoperative and postoperative evaluation of liver transplant recipients by identifying congenital vascular anomalies and postoperative vascular thromboses.

Radionuclide Scanning

Radionuclide scanning is helpful when patients in the ICU have pulmonary aspiration, gastrointestinal bleeding, intraabdominal abscesses, or cholestasis.

Gastroesophageal reflux and the rate of gastric emptying can be measured with liquid-phase gastroesophageal scintigraphy.[14] Technetium-99 sulfur colloid is mixed with formula or another enterally administered liquid. When there is a scan above and below the diaphragm in 30- to 60-second windows during the first postprandial hour after isotope administration, the number of reflux episodes, the height of the reflux column, and the rate of gastric emptying are quantitated. A 4- to 6-hour delayed scan of the lungs determines whether pulmonary aspiration of that meal has occurred.[15]

Three techniques are used to aid in the diagnosis of gastrointestinal bleeding. ^{99}Tc sulfur colloid and ^{99}Tc-labeled red cells are used in patients with continuous or intermittent bleeding. The advantage of sulfur colloid is that less than 0.1 mL of blood per minute will be shown. Bleeding in a spot near the liver or spleen, however, may be obscured by high levels of activity in those organs. Tagged red blood cell scans detect intermittent bleeding by means of delayed scans, but migration of blood down the gastrointestinal tract over time may preclude exact localization. ^{99}Tc pertechnetate scanning does not require active bleeding to localize a Meckel's diverticulum. Isotope is concentrated by gastric mucosa, and if a scan reveals an ectopic focus a Meckel's diverticulum can be suspected. Scan results are negative in the 15% of diverticula not containing gastric mucosa. A variety of non-Meckel's lesions (most of which require surgical correction) cause false-positive results on pertechnetate scans. The sensitivity of the scan can be increased when acid suppression is given prior to scanning.

Resolution of hepatobiliary scans has improved dramatically since the introduction of derivatives of ^{99}Tc iminodiacetic acid. Scanning can now document cholecystitis when there is no gallbladder uptake or biliary obstruction when there is no excretion into the bowel. Other entities such as biliary leaks or cystic lesions of the biliary tree can also be documented. Furthermore, delayed or reduced hepatocyte uptake can confirm impaired hepatocellular function.

Intraabdominal abscesses and inflammatory intestinal lesions can be localized with radioscintigraphy.[16] Leukocytes are extracted from the patient, tagged with a radioisotope in vitro, and are reinjected. Scanning of the area in question is then performed. Technetium hexamethyl propyleneamine oxime (HMPAO) has replaced indium because of improved resolution of HMPAO scans and because HMPAO scans can be completed within 4 hours rather than 72 hours.

Testing for Occult Blood Loss

Occult blood loss is generally determined with the Hemoccult or Gastroccult test; these are modifications of the guaiac test.[17,18] They work because hemoglobin oxidizes the reagent to a blue product. The recently marketed Hemoccult Sensa (Beckman Coulter, Inc., Brea, Calif.) slide detects as little as 2 to 3 mL of blood loss per day. This slide is virtually 100% sensitive when blood loss equals 10 mL/day.[8]

In the stomach, blood can be denatured, and this can lead to false-negative results. Gastroccult, which contains borate-buffered reagent, significantly improves the sensitivity for testing gastric contents. (Urine test tapes should never be used for gastrointestinal occult blood testing because they are too sensitive.) Therefore even physiologic quantities of enteric blood loss (<1 mL of blood per day) will yield positive results.

Stool pH and Reducing Substances

Excessive enteral carbohydrate loads may worsen preexisting diarrhea in critically ill children. Carbohydrate malabsorption can be assessed with the measurement of reducing sugars

and pH of stool. The two tests should always be used in conjunction because colonic transit time and quantity or type of colonic flora affect either of these tests. Malabsorbed sugars appear in feces when colonic transit is sufficiently rapid and are detected by Clinitest tablets or reagent strips; more than 0.5 mg of sugar per 100 mL of stool water suggests malabsorption. If the malabsorbed dietary sugar is primarily sucrose, a nonreducing sugar, the Clinitest result is negative unless the stool is first hydrolyzed with hydrochloric acid. Stools can be negative for reducing sugars despite carbohydrate malabsorption if colonic transit is slow enough to permit complete bacterial fermentation. In such an event, pH of fresh stool (measured by nitrazine paper) is consistently below 5.5. The pH of samples not tested for several hours, however, tends to rise over time as short-chain fatty acids generated from sugar fermentation are further metabolized.

The Intensive Care Unit as a Satellite Laboratory Facility

Regulations of the Joint Commission on Hospital Accreditation prohibit testing for occult blood loss or stool testing by anyone other than an individual certified in accordance with the Clinical Laboratory Improvement Act (CLIA). Thus for many pediatric critical care units, "bedside" testing has moved from the bedside to the clinical laboratory. Turnaround time for measuring occult blood in stool has risen from seconds to hours. Furthermore, when fecal samples are sent to the clinical laboratory for measurement of reducing sugars and pH, results are meaningless insofar as bacterial metabolism of sugars continues ex vivo in these samples between the times of collection to the time of testing. Critical care units wishing to perform reliable fecal testing on site must train a cohort of staff in common bedside tests and obtain CLIA certification for each staff member. Furthermore, just as many ICUs have chosen to comply with CLIA regulations and have established approved satellite laboratory facilities, to measure blood gases or serum electrolytes, they can extend the scope of their laboratory activities to include bedside gastroenterologic testing.

Breath Hydrogen Testing

Breath hydrogen testing confirms monosaccharide or disaccharide malabsorption and small bowel bacterial overgrowth. The technique documents intestinal bacterial fermentation of carbohydrates; their byproduct is hydrogen gas. Fasting alveolar hydrogen concentrations greater than 40 ppm suggest bacterial overgrowth. A rise in concentration of 20 ppm occurring beyond 90 minutes after an enteral carbohydrate challenge suggests carbohydrate malabsorption. A peak less than 60 minutes after the challenge is consistent with bacterial overgrowth.

Because of difficulties in consistent alveolar air sampling, some investigators internally standardize by measuring both H_2 and carbon dioxide (CO_2) and expressing their results as a ratio.

Perhaps breath hydrogen testing is most valuable in the ICU as a screening test for neonatal necrotizing enterocolitis. Cheu et al.[19] showed that randomly obtained breath H_2/CO_2 ratios greater than 8 ppm/mm Hg strongly suggest necrotizing enterocolitis.

Life-Threatening Complications of Gastrointestinal Disorders

Esophagus

Congenital Esophageal Anomalies

Esophageal atresia and tracheoesophageal fistula are true neonatal emergencies. With an incidence of 1 in 3000 live births, they are among the most common congenital anomalies of the esophagus. Five anatomic varieties exist in the following descending order of frequency: (1) blind proximal esophageal pouch with distal esophagus originating at the tracheobronchial junction (80%), (2) blind proximal esophageal pouch with blind distal esophageal pouch (8%), (3) uninterrupted esophagus with H-type tracheoesophageal fistula (4%), (4) proximal esophagus fistulizing into trachea with blind distal esophageal pouch (2%), and (5) interrupted esophagus with both proximal and distal esophagus communicating with trachea (1%).

The embryogenesis of this disorder is unknown, but other cardiovascular, gastrointestinal, skeletal, or urogenital anomalies are present in 50% of cases.

Infants with a blind proximal esophagus have excessive salivation, respiratory distress, and cyanosis. Diagnosis of blind proximal esophagus can be made by the failure to pass a nasogastric tube into the stomach. Complete atresia leads to a gasless lower gastrointestinal tract. An H-type fistula is sometimes seen on contrast radiography or esophagoscopy, but bronchoscopy is usually the most sensitive diagnostic tool.

Treatment is surgical. A simple fistula can be ligated, and a short atresia can be repaired primarily. Long atresia, however, may require staged treatment with initial esophagostomy and gastrostomy and subsequent definitive repair after internal or external traction is applied. Circular myotomy of the esophagus reduces anastomotic tension. Occasionally a "gastric tube" procedure or colonic interposition is required.

Caustic Injury to the Esophagus

Despite widespread efforts by poison control centers to publicize the dangers of household caustics, thousands of inadvertent ingestions occur annually; most occur in children younger than 5 years. Crystalline products produce greater damage to the hypopharynx and upper airway because of prolonged mouth contact and a smaller volume reaching the esophagus. In recent years most household cleaners have been reformulated to contain less lye, but pure liquid lye can be purchased if desired. Its resemblance to milk leads to numerous inadvertent ingestions by children (see Chapter 106).

Tissue damage can be caused by either strong alkali or acid. Deep esophageal burns are more common after alkali ingestion. Alkalis produce rapid liquefaction of esophageal tissue, and burns can range from first to third degree in depth.[20] An intense inflammatory infiltrate develops, and blood vessels thrombose to produce ischemic necrosis. Perforation may occur within hours or days. Strictures can occur weeks to years after ingestion.[21] Esophageal burns occur infrequently after acid ingestion, but gastric or duodenal erosions have been reported.

Symptoms that predominate are chest pain and the inability to swallow secretions. Children with upper airway damage often exhibit stridor. When mouth burns are present, the chances of esophageal injury are 75%.[10] Conversely, 25% of patients with significant esophageal burns have no pharyngeal or mouth involvement.[20]

Treatment of severe stridor should be directed toward establishing an airway, and emergency tracheostomy should be contemplated. Upper endoscopy within 24 hours is advisable. If burns are minor, no further therapy is necessary, and patients are at low risk of sequelae. Third-degree burns require ongoing intensive care, though. The role of antibiotics and steroids remains controversial.[12] Although steroids reduce tissue damage when given before experimental injury, recent double-blind clinical trials show no efficacy of steroids in preventing sequelae.[22] When third-degree burns are endoscopically evident, a nasogastric tube should be positioned with endoscopic guidance. This tube will enable early feeding and serve as a guide for future dilations if they become necessary. Some surgeons have advocated early placement of gastrostomies and esophageal stents in patients with third-degree burns.[23]

Esophageal Foreign Bodies

A variety of metallic, wooden, or plastic foreign bodies in a myriad of shapes and sizes can be swallowed by children. All that are lodged in the esophagus require urgent removal (within 24 hours). Even more urgent endoscopic retrieval is required for button batteries or pennies minted after 1983 that are lodged in the esophagus because both are caustic to esophageal mucosa and may cause damage within 1 to 4 hours. The preponderance of evidence suggests that once a battery has escaped the esophagus, complications from an unretrieved battery are rare.[24]

Similarly, pennies minted after 1983 are predominantly zinc based and can be nearly as caustic within the esophagus as button batteries. No published epidemiologic studies are available on which to base the approach to zinc-based pennies within the stomach or small intestine.

Gastroesophageal Reflux

Several antireflux barriers exist in the region of the lower esophageal sphincter. Beyond intrinsic myogenic tone, barriers such as the cardioesophageal angle, the abdominal esophagus (that acts as flutter valve), the mucosal rosette of the sphincter (that acts as a choke valve), and the diaphragmatic crura themselves act to prevent reflux of gastric contents. A complex set of factors, including hormonal changes, anatomic relationships, increased or decreased sensitivity to neurotransmitters, and CNS derangements, act to produce inappropriate sphincter relaxation (usually transient), which leads to most episodes of gastroesophageal reflux. With the advent of more sophisticated otolaryngolocal procedures such as the laryngotracheoplasty and slide tracheoplasty, prevention of gastroesophageal reflux is of utmost importance to facilitate surgical healing. Some surgeons advocate the use of aggressive acid suppression postoperatively because acid-induced damage can result in significant cicatrix formation at the site of laryngotracheal surgery.

Life-threatening events such as apnea and pulmonary aspiration are sometimes attributed to reflux. The relationship between infantile apnea and reflux remains in question,[25] but both human and animal data suggest that reflux can occasionally be associated with obstructive breathing patterns. Severe pulmonary aspiration of refluxed material can also take place. A number of protective mechanisms such as an active gag reflex, cough reflex, and laryngospasm protect against aspiration,[26] but these reflexes may be lost under special circumstances such as obtundation. Symptoms of obstructive apnea often include a brief episode of stridor accompanied by a struggle to breathe, a change in skin color to red or purple, and finally cyanosis and cessation of respiratory effort. Patients who have aspirated massive amounts of fluid become tachypneic and dyspneic shortly after the meal. Food or formula is often found in the nares or mouth. Cough may occur. The diagnostic modality most helpful in documenting a temporal relationship between apnea and acid reflux is 24-hour esophageal reflux monitoring combined with simultaneous electrocardiography, pneumography by chest wall impedance, pneumography by nasal thermistor, pulse oximetry, and endtidal CO_2 measurement. Aspiration is often difficult to document, but the presence of a new infiltrate on chest x-ray films and a consistent clinical history provide strong circumstantial evidence. If repeated aspiration is suspected, an upper gastrointestinal tract series may reveal gastroesophageal reflux and immediate aspiration of barium; however, aspiration of gastroesophageal refluxate that occurs minutes or hours after a feeding may be missed with contrast radiography. A milk scan may be more sensitive than radiography for documenting this type of aspiration. Children who are not fed orally may nevertheless aspirate oral secretions. The scintigraphic "salivagram" is performed with the placement of a drop of saline containing ^{99m}Tc sulfur colloid on the tongue.[27] Subsequent imaging permits observation of its handling. Appearance of isotope in the trachea and bronchi confirms aspiration.

When recurrent aspiration is suspected but not confirmed noninvasively, bronchoscopy with bronchoalveolar lavage may support the diagnosis by returning fluid-containing lipid-laden alveolar macrophages.[28] Aspiration during swallowing and aspiration of refluxed gastric contents cannot be distinguished by this method in patients who are fed orally.

Although some clinicians view one episode of reflux-induced aspiration or apnea as an absolute indication for fundoplication, the decision to perform fundoplication should be based on the severity of the initial episode, underlying conditions that predisposed the child to the episode, risk for recurrence, and the expected natural history of reflux for a particular patient. In other words, some patients may be successfully managed with pharmacotherapy (a proton pump inhibitor with or without a prokinetic agent such as metoclopramide or erythromycin).

Stomach and Duodenum

Gastric Volvulus

Acute gastric volvulus may be of two types. When the whole stomach revolves about its long axis, organoaxial volvulus has occurred. When the fundus and pylorus exchange positions, the volvulus is mesenteroaxial. Predisposing factors include paraesophageal hernias or eventration of the diaphragm.

Because a closed obstruction has occurred, the patient is unable to vomit despite severe pain, distention, and retching. Plain radiographs reveal a markedly distended stomach with air-fluid levels, and contrast radiography may reveal cardioesophageal junction obstruction. An immediate operation is indicated.

Gastric Ulcer

Whereas some authors suggest that duodenal ulcers outnumber gastric ulcers in childhood,[1] others have reported that young children are more likely to have gastric ulcers. Most

gastric ulcers lie at the junction of gastric fundus and body. Those high in the fundus are usually related to stress. Antral ulcers are often the result of use of nonsteroidal antiinflammatory drugs (NSAIDs).

A well-recognized complication of severe illness requiring admission to the ICU is stress ulceration of the stomach. Bleeding becomes an important source of morbidity and mortality in patients with burns and trauma, as well as in those who have undergone major operations or have systemic disease. Prophylaxis against bleeding is common in the ICU setting. Antacids, H_2-receptor antagonists (H_2RA), proton pump inhibitors such as lansoprazole and pantoprozole, and sucralfate are most often used. Unfortunately, elevation of gastric pH by antacids and H_2RA removes one barrier against bacterial colonization and may increase the risk of pneumonia with organisms colonizing the stomach.[29] Large controlled trials, however, have failed to confirm this concern. Sucralfate is equally effective as prophylaxis against bleeding but does not affect gastric pH. If sucralfate is given concurrently with antacids or acid-suppressing medications, its efficacy will be reduced because it requires an acidic environment for optimal effect. Furthermore, sucralfate administered in close temporal proximity to other enterally administered medications may reduce their bioavailability by binding with them within the intestinal lumen.

Most patients with gastric ulcers are hypochlorhydric rather than hyperchlorhydric because exposure to detergents or toxins such as NSAIDs, pepsin, bile salts, or ethanol erodes the gastric barrier to back-diffusion. A second consistent finding among patients with gastric ulcers is delayed gastric emptying, which may be an epiphenomenon or central to the pathogenesis of ulcers. The association between *Helicobacter pylori* infection and both chronic gastritis and duodenal ulcer is well established, but the role of *H. pylori* in the pathogenesis of gastric ulceration remains somewhat speculative.[30]

Clinical features of gastric ulcer resemble those of duodenal ulcer. Pain predominates and is epigastric in location but usually follows eating more closely. Nausea and vomiting may occur. Milk or antacids relieve the pain. The two complications of gastric or duodenal ulceration most commonly requiring intensive care are perforation and bleeding. Perforation, requiring immediate surgical intervention, produces exquisite pain and rapid development of peritoneal signs in patients without immunosuppression.

Hematemesis heralds gastric ulcer bleeding and may be as massive as that of duodenal ulcer. Careful, repeated assessment of vital signs and prompt restoration of circulating blood volume by large-bore venous catheters are essential. Saline solution or epinephrine gastric lavage through a large sump tube is mandatory. "Iced" saline lavage offers no advantage and excessively depresses core temperature.

Efforts should also focus on reducing gastric acid production with a parenteral proton pump inhibitor.[31] Continuous intravenous vasopressin infusion, commonly used for control of variceal hemorrhage, reduces arterial flow through the splanchnic bed. Selective intraarterial infusion appears to be unnecessary. Intravenous administration of somatostatin or its synthetic, active octreotide moiety, has been effective in stemming variceal hemorrhage and may work for other causes of bleeding. In addition to their hemodynamic effects, they inhibit gastric acid production.

When the patient's condition is stable, endoscopy may be performed to localize the ulcer. Endoscopic therapy may then be performed on actively bleeding ulcers or those with visible vessels (which tend to rebleed). Ulcer beds may be photocoagulated, electrocoagulated, or thermocoagulated. They may also be injected with hemostatic agents such as epinephrine. If nonsurgical techniques fail to stop the bleeding, one of several surgical options (that include ulcer oversewing or resection, variations of gastric drainage procedures, and vagotomy) must be performed. Fortunately, successful pharmacologic and endoscopic therapies have precluded the need for these surgical therapies in all but the rarest circumstances.

Duodenal Ulcers

The incidence of duodenal ulcer in childhood is unknown. A large series completed before the popularization of endoscopy suggested an incidence of 4.4 cases per 10,000 pediatric patients per year, which is, no doubt, an underestimation.[32] The male predominance seen among adults is present only among postpubertile children. The risk for patients with blood group O is 1.3 times that expected.

A number of factors have been implicated in the pathogenesis of duodenal ulcers. Unquestionably, excessive acid production plays a major role. Some factors leading to hypersecretion include excessive gastrin or histamine production and increased vagal tone. Approximately half of patients with ulcers are also hyperpepsinogenemic, and their mucosal integrity may therefore be suboptimal.[33] Infection with *H. pylori* reduces the ulcer healing rate and increases the recurrence rate.[34] Although approximately 90% of adult duodenal ulcers are associated with *H. pylori* infection, only about 50% of pediatric duodenal ulcers are related to *H. pylori*.[35] The effects of diet and stress have been minimized in the recent literature.

Symptoms are similar to those of adults. Epigastric pain occurs after meals and often awakens the child from sleep. Vomiting occurs in 40% of patients.

The major life-threatening complications are perforation and hemorrhage, which lead to a "surgical" abdomen and shock, respectively. Abdominal plain films reveal free air if perforation has occurred. Hemorrhage presents as hematemesis, hematochezia, or melena. Endoscopy is the most sensitive tool to localize the ulcer and to characterize the risk for rebleeding. Ulcers with visible vessels in the crater are at greatest risk of recurrent hemorrhage and may require endoscopic coagulation. Principles of management are identical to those for gastric ulcer. Obviously, antibiotics such as clarithromycin, amoxicillin, and metronidazole should be used for the first 14 days of a 1-month course of acid suppression when ulcers are associated with infections.

Small Intestine and Colon

Malrotation

In embryonic life the cecum and ascending colon are located on the left side of the abdomen and the small bowel is on the right. During gestation, the midgut transiently protrudes into the umbilicus and rotates 270 degrees, and the cecum is moved to the right lower quadrant and the duodenojejunal junction to the left upper quadrant. Incomplete rotation is of little consequence unless midgut volvulus, which can be a catastrophic event, occurs.

Some patients with malrotation experience partial duodenal obstruction because of extrinsic compression by mesenteric

bands. Chronic diarrhea and protein-losing enteropathy may be seen, among others, without complete obstruction.

Clinical features of obstructing volvulus include severe abdominal pain, bilious vomiting, and abdominal distention. Surgical treatment requires a Ladd procedure, in which mesenteric bands are divided and the bowel is returned to its fetal position. Failure to promptly relieve the volvulus leads to ischemic necrosis of all of the gut supplied by the superior mesenteric artery (proximal jejunum to midtransverse colon). Short gut syndrome results from resection of the affected intestine.

Necrotizing Enterocolitis

Necrotizing enterocolitis is primarily a disorder of premature infants, affecting 2.5% of neonatal patients in the ICU but only 0.2% of all infants. The most common areas involved are the ileum and proximal colon, but any part of the intestinal tract may be affected. Its pathogenesis is unknown, but bowel ischemia, feeding of hyperosmolar formula, rapid advancement of feeding,[36] reduced immune surveillance, and population of the bowel by excessive quantities of enterotoxin-producing bacteria[37] may all play a role.

The classic clinical features are abdominal distention, bilious vomiting, and bloody stools, but symptoms are more subtle in some infants. If left unrecognized, necrotizing enterocolitis may become fulminant, leading to shock, disseminated intravascular coagulation, and apnea.

The diagnosis of necrotizing enterocolitis may be confirmed by an abdominal plain film showing pneumatosis intestinalis, hepatic portal air, or both. A random breath H_2/CO_2 ratio greater than 8 ppm/mm Hg strongly suggests the diagnosis.[19] Because the pathogenesis is unknown, treatment must be symptomatic. In most centers, feedings are discontinued for 48 hours to 2 weeks depending on the severity of symptoms. Fluid resuscitation and broad-spectrum parenteral antibiotics are the basis of medical therapy. Surgical resection is reserved for severe cases when medical management fails and gangrenous bowel develops. Perforation may sometimes be managed successfully in infants with very low birth weight with simple peritoneal drainage performed with the infant under local anesthesia,[38] and a multicenter study is currently being conducted to compare the outcomes of simple drainage and resection in such high-risk infants.

Low Cardiac Output Syndrome

Over the past decades, advancements in surgical techniques have led to significant improvement in morbidity and mortality after pediatric heart surgery. However, patients remain at risk for decreased cardiac ouput and impaired systemic oxygen delivery, especially in the early postopertaive period. The drop in cardiac ouput after cardiac surgery is characterized as low cardiac ouput syndrome (LCOS). LCOS is defined as an inability of the heart to provide adequate oxygen delivery to meet the body's metabolic demand. It is primarily due to transient myocardial dysfunction compounded by acute changes in myocardial loading. Cardiopulmonary bypass, along with residual cardiac abnormalities, may further aggravate the underlying low cardiac output state.[39,40] Although there are several manifestations of this clinical constellation beyond the scope of this chapter, it is important to recognize its clinical signs and symptoms (see Chapter 31). Systemic venous congestion may be observed in the gastrointestinal tract. Manifestations include hepatomegaly, ascites, and peripheral edema. Hypoperfusion to the liver can result in hepatic insufficiency and may lead to coagulopathy if severe enough. Furthermore, intolerance to enteral feeding may be evident in these patients with LCOS and central venous hypertension. Feeding difficulties may be further compounded by high-dose inotropes and narcotic infusions. These patients often require parenteral nutrition. Complications such as mesenteric ischemia or necrotizing enterocolitis may be observed in rare cases and are often fatal.[41,42]

Food Allergy

Food allergy can be defined as a reproducible, immunologically mediated reaction to an ingested food protein. Pathogenic events can be classified according to the schema of Gell and Coombs as type I (reagenic, immediate hypersensitivity reaction), type II (cytotoxic reaction), type III (immune-complex reaction), or type IV (delayed hypersensitivity reaction).

Manifestations may be systemic[43] or confined to the gastrointestinal tract.[44] Life-threatening systemic manifestations include acute urticaria and anaphylaxis.[43] Gastrointestinal reactions, which are sometimes severe, include allergic enteritis, allergic colitis, and celiac crisis.[44]

Acute urticaria is usually easily recognized by the classic wheal and flare cutaneous lesions often accompanied by laryngeal edema and angioedema. Anaphylaxis is an antigen-triggered immune reaction that leads to vascular collapse and bronchospasm.[45]

Food protein–induced enteropathy is characteristically a disorder of the infant and toddler. The small bowel develops patchy villous atrophy. Symptoms and signs range from those of malabsorption and enteric protein loss to those of profound diarrhea and shock. Colitis caused by food protein sensitivity is seen most commonly among infants younger than 6 months.[44] Bloody, mucoid diarrhea develops several days or weeks after their first oral antigen challenge. Even though this colitis usually takes a benign course, it may be severe enough to mimic necrotizing enterocolitis.

Although some do not categorize gluten enteropathy as true food allergy, it shares enough features with allergy to justify inclusion with this category of disorders.[44] Celiac crisis is a rare, life-threatening complication that may occur among untreated patients with a large gluten load or in treated patients as a result of dietary indiscretion. Massive fluid and electrolyte loss leads to shock.

The cornerstone of long-term therapy is elimination of the offending food, but emergency measures are also required. Immediate administration of epinephrine and corticosteroids is essential in the treatment of anaphylaxis. Urticaria may require the administration of antihistamines, corticosteroids, and epinephrine.[45] Steroid use also seems to benefit patients in celiac crisis. Rapid administration of crystalloid or colloid is crucial in the management of any of these reactions.

Hemolytic-Uremic Syndrome

The hemolytic-uremic syndrome may occur in epidemic or sporadic forms (see Chapter 71) . It is frequently preceded by enteric infection with bacterial[46] or viral pathogens. Infection with *Escherichia coli* O157:H7 has preceded an inordinately high number of cases.[47,48] Some instigating factors, such as bacterial verotoxin, cause endothelial damage in the kidney, liver, heart, brain, adrenal glands, and gastrointestinal tract.

Clinical features include a prodrome of abdominal pain, vomiting, and diarrhea, which may be bloody. Patients may have endoscopic, radiographic, or histologic evidence of ischemic bowel disease. As gastrointestinal symptoms improve, anemia and thrombocytopenia rapidly appear and produce pallor, petechiae, and ecchymoses. Subsequently, patients become oliguric, hypertensive, and azotemic. The clinical course may be complicated further by pancreatitis. Seizures may occur.

The intensivist caring for children with acute, hemorrhagic colitis must pay exceptional attention to fluid balance, hemogram, and renal function tests. Any sudden change in hemoglobin, platelet count, blood urea nitrogen, or urine output should be considered a potential sign of the hemolytic-uremic syndrome. In the absence of hypovolemic shock, fluid intake should be curtailed if hemolytic-uremic syndrome is documented. In the event of severe renal insufficiency, dialysis is necessary. Plasma exchange and anticoagulants are probably not beneficial.[49] High-dose vitamin E has been suggested as a nonspecific adjunct to therapy.

Inflammatory Bowel Disease

Crohn disease and ulcerative colitis are chronic, relapsing disorders without known causes. The transmural inflammation of Crohn disease may affect any portion of the alimentary tract in a patchy distribution, whereas the inflammation of ulcerative colitis is confined to the mucosa of the colon. The latter always involves distal colon, and its contiguous inflammation extends for varying distances from the rectum. The two entities are different enough to usually permit accurate categorization, but there is sufficient overlap in symptoms and distribution that the diagnosis is indeterminate in 15% of cases. Table 86-1 summarizes the clinical, radiographic, endoscopic, and histologic differences between the two.

The cause of these disorders remains speculative. Clearly, genetic factors predispose patients to one or the other, but environmental factors also appear to play a role.[50] Etiologic factors considered important over the years have included psychogenic predisposition, food allergies, infectious processes, immunologic deficiency, and immunologic hyperreactivity.

Presenting signs and symptoms include abdominal pain; bloody or nonbloody diarrhea; anorexia; abdominal mass; and extraintestinal manifestations, such as weight loss, fever, arthritis, or erythema nodosum. Patients are often anemic and hypoproteinemic, and they may show hematologic or biochemical signs of acute-phase response. The radiographic and histologic features are typical (see Table 86-1).

The cornerstone of medical management has long been the use of corticosteroids, but 5-aminosalicylic acid (5-ASA) is effective for mild to moderate ulcerative colitis and Crohn's colitis. Evidence is less compelling that 5-ASA is effective in small intestinal Crohn disease. Immunosuppressants, such as 6-mercaptopurine (6-MP) and methotrexate, have been used for Crohn disease, and 6-mercaptopurine also seems effective in the treatment of ulcerative colitis. Biologic therapy has revolutionized the therapy of Crohn disease.[51] Infliximab, a monoclonal antibody against tumor necrosis factor, has shown dramatic efficacy against Crohn disease in up to 75% of patients. A second anti-TNF agent, adalimumab, can be given subcutaenously but appears to be less efficacious than infliximab. Other biologic agents such as antibodies against proinflammatory cytokines and antisense molecules blocking white cell adhesion molecules are currently in development.

Table 86–1 Differential Diagnosis Between Ulcerative Colitis and Crohn Disease

Feature	Ulcerative Colitis	Crohn Disease
RELATIVE INCIDENCE OF SYMPTOMS		
Rectal bleeding (gross)	Common	Rare
Diarrhea	Often severe	Moderate or even absent
Pain	Less frequent	Almost always
Anorexia	Mild or moderate	Can be severe
Weight loss	Moderate	Severe
Growth retardation	Usually mild	Often pronounced
Extraintestinal manifestations	Common	Common
INVOLVEMENT		
Small Bowel Involvement		
Extensive	—	10%
Lower ileum	5%–10%	90%
Colon	100%	75%
Rectum	95%	50%
Anus	5%	85%
DISTRIBUTION OF LESIONS	Continuous	Segmental
RADIOLOGIC FEATURES	Superficial ulcers, loss of haustration, no skip areas, shortening	Serpiginous ulcers, thumbprinting, skip areas, string sign
PATHOLOGIC CHANGES	Diffuse mucosal disease	Focal transmural disease, granulomas
RESPONSE TO TREATMENT		
Steroids and sulfasalazine	75%	25%–75%
Parenteral nutrition and elemental diets	Poor	Very good for small bowel
Azathioprine and 6-mercaptopurine	Good in selected cases	Good in selected cases
Surgery	Excellent	Fair or poor
COURSE		
Remissions	Common	Common
Relapse after surgery	Rare	5%–100%
Cancer risk	High in pancolitis	Slight

Modified from Silverman A, Roy CC, editors: *Pediatric clinical gastroenterology*, ed 3, St Louis, 1983, Mosby, p 354.

Probiotics, such as nonpathogenic helminths and anaerobic lactobacillus species, are also under study.

Severe complications may also be directly attributed to therapy. Pancreatitis has been associated with 5-ASA and 6-MP. In addition, bone marrow suppression as well as hepatitis has been observed with 6-MP. Infliximab has been associated with lymphoid malignancies and the concomitant use of 6-MP with infliximab may syngergistically heighten the risk

of lymphoma. Patients who take infliximab should also be observed for possible anaphylaxis.

Complications most likely to require an intensivist's attention are perforation, toxic dilation of the colon, and fulminant colitis. A patient whose bowel has perforated exhibits decreased bowel sounds and abdominal rigidity. Point and rebound tenderness may be present. Abdominal x-ray films may reveal free intraperitoneal air. Most perforations in Crohn disease produce intra-abdominal abscesses, but peritonitis does not. Some abscesses, however, can contaminate the peritoneum. Free colonic perforation tends to occur among patients with ulcerative colitis. Toxic dilation and fulminant colitis are also more common with ulcerative colitis but may occasionally occur in Crohn colitis. Because management of severe inflammatory bowel disease frequently includes immunosuppression with high-dose corticosteroids, cyclosporine, or azathioprine, some of the signs and symptoms of perforation may be masked in the population most likely to have such complications. Factors such as patient immobility, antiperistaltic drugs, rigorous cathartic use, and electrolyte imbalance are frequently associated with toxic dilation of the colon. Patients initially have massive abdominal distention and pain. X-ray films reveal an increased transverse colonic diameter. The patient's status is observed through careful monitoring of vital signs, physical examination, and repeated abdominal radiographs. Management includes giving nothing by mouth during nasogastric tube suction and inserting a rectal tube for decompression. Frequent position changes may aid in redistributing air distally. Fluid and electrolyte balance is aggressively maintained, and broad-spectrum parenteral antibiotics are given. Efforts at medical management should not exceed a few hours because of the extreme risk of perforation. Clinical decompensation or perforation is an indication for urgent surgical resection of the colon.

Fulminant colitis is characterized by fever, shock, severe abdominal pain, 10 or more bloody stools per day, and abdominal tenderness. Broad-spectrum antibiotics, intravenous steroids, immunosuppressants such as cyclosporine,[52] red blood cell transfusion, and fluid replacement are the mainstays of treatment for fulminant colitis. Small, uncontrolled series have also suggested that infliximab may be beneficial for fulminant colitis.[53] Failure to respond within a few days, however, warrants colectomy.

Hirschsprung Disease

Hirschsprung disease occurs in 1 in 5000 live births. It may be the result of incomplete craniocaudal migration of neural crest elements, but some investigators believe that ganglion cells degenerate after migration. Aganglionosis may involve as little as a few centimeters or the entire colon and small bowel (in rare cases). Total colonic Hirschsprung disease occurs in clusters in some families with the risk being 21% in those families.[54] The inheritance of familial Hirschsprung disease appears to be polygenic, with mutations in several loci of the RET proto-oncogene being associated with autosomal dominant Hirschsprung disease that is most commonly the short-segment type. Mutations of the endothelin receptor type B gene are more likely to be observed in long-segment, autosomal recessively transmitted Hirschsprung disease. Other gene mutations may also modify the expression of the disease.[54]

The most common feature of Hirschsprung disease is the failure to pass meconium in a timely fashion after birth; 94% of infants with Hirschsprung disease pass their first stool beyond 24 hours of life. Most patients with Hirschsprung disease are constipated but cannot pass flatus. If their condition is undiagnosed during the first months of life, they may fail to thrive.

Physical findings include abdominal distention and an empty rectum on digital examination. Barium enema often reveals a narrow-caliber aganglionic distal colon; a transition zone; and a dilated, ganglionic proximal colon. It is essential that the barium enema be performed without prior enema preparation to preserve the transition zone. Absence of the anal-inhibitory reflex on anorectal manometry is suggestive. The diagnosis is confirmed histologically by rectal biopsy of the distal rectal mucosa where hypertrophic nerve trunks but no ganglion cells are found. Acetylcholinesterase staining of the specimen improves the diagnostic yield by enhancement of the abnormal nerve trunks.

In some children the course of Hirschsprung disease is punctuated by episodic, severe enterocolitis, which leads to copious, bloody diarrhea, fever, and shock. The intensive care of patients with enterocolitis should emphasize reconstitution of circulating blood volume with crystalloid, colloid, and red blood cells. Broad-spectrum parenteral antibiotics are advisable. After the patient's condition is stabilized, urgent decompressive enterostomy is indicated. Pull-through operations are usually performed after several months. Enterocolitis in the remaining ganglionated intestine may occur even in some patients who have undergone a pull-through operation.[55]

Acute Colonic Pseudo-obstruction

First described by Oglivie,[56] acute colonic pseudo-obstruction is occasionally observed among critically ill adults and children who are immobilized in an ICU setting. It is characterized by massive cecal dilation of 5 to 10 cm on abdominal plain film. The mechanism is uncertain, but it appears to occur among patients given neuromuscular blockade and antimotility drugs such as narcotics. If left untreated, it may result in colonic perforation at the cecal level. Therapy should involve decompression of the gastrointestinal tract by nasogastric and rectal intubation and suction. Placing the patient in the prone position also seems to be effective initial therapy. None of these measures, though, seem to be as effective as is parenteral administration of neostigmine.[40] Adverse effects of neostigmine, such as excessive salivation or abdominal cramping are self-limiting, but bradycardia that occasionally occurs must be managed with atropine.

Abdominal Compartment Syndrome

Abdominal compartment sydrome (ACS) is defined as organ dysfunction caused by intraabdominal hypertension. The organ dysfunction observed with abdominal compartment syndrome may go under-recognized because it affects patients who are critically ill and their organ dysfunction may erroneously be ascribed to their underlying illness. If untreated, ACS can lead to crucial organ failure and death. The clinician must take great care in children to be familiar with this clinical entity as timely recognition and intervention can be life saving.

The standard method for measuring intraabdominal pressure is through the assessment of bladder pressure. A three-way stopcock is placed between the catheter and pressure tubing. The bladder is emptied and sterile isotonic sailne is

injected in the distal stopcock and into the bladder to allow for a continuous fluid column. There is some variability in the amount of fluid administered based on tubing and patient size. The pressure transducer is zeroed at the level of the mid-axillary line and the pressure is measured at end-expiration while supine.

Intra-abdominal hypertension (IAH) and ACS are distinct clinical entites. The intra-abdominal pressure is a steady pressure wtihin the abdominal cavity. The normal range is variable based upon individual patient differences. Much of the variability is due to the body habitus of the patient. IAH is defined as a sustained pressure of 12 mm Hg or greater.[57] ACS is defined as sustained pressure greater than 20 mm Hg associated with organ dysfunction. Although recording of pressure is important for research purposes, the clinical presentation is the most important component in defining ACS. ACS can be classified as primary or secondary. Primary ACS is due to injury or disease in the abdominal region, such as trauma or organ transplantation, and often requires early surgical decompression. Secondary ACS is due to conditions requiring extensive fluid resuscitation, such as sepsis, burns, or other capillary leak syndromes.

IAH can impair practically every organ system resulting in ACS. It can impaire cardiac function by reducing venous return as well as impairing cardiac function directly via diaphragmatic pressure. In mechanically ventillated patients, peak inspiratory and mean airway pressures will be significantly increased resulting in barotrauma. In addition, chest wall compliance is markedly reduced. Renal impairment may be attributed to several mechanisms in patients with ACS. Venous drainage can be impaired by renal vein compression. The subsequent cardiac output fall can lead to renal artery vasoconstriction via the renin-angiotensin systems. The urine sodium and chloride concentrations will typically be decreased while the renin, aldosterone and antidiuretic hormone may be markedly increased.[58,59] The most sensitive organ to changes in intra-abdominal pressure is the gut. Both human and animal studies have shown decreased intestinal mucosal perfusion at intra-abdominal pressures of 20 mm Hg. Impaired mesenteric venous drainage results in intestinal edema which can increase intra-abdominal pressure and result in worse hypoperfusion and possible bowel ischemia.[60] Finally, intracranial pressure (ICP) can be elevated leading to a decrease in cerebral perfusion.[61]

The management of IAH and ACS is requires both supportive care and, in some instances, surgical decompression. In general, surgical decompression is indicated for ACS. There is increasing evidence that surgical decompression prior to development of ACS may be beneficial.[62] Following decompression, the abdomen is left open and typically covered with a Dacron mesh or humanized regenerative tissue matrix. Early recognition and timing of decompression of ACS may be crucial in the preservation of organ function (see Chapter 89).

Acute Pancreatitis

Even though gallstone pancreatitis and ethanolic pancreatitis are uncommon in children, numerous structural, toxic metabolic, and infectious diseases are associated with acute childhood pancreatitis. Appropriate radiographic or biochemical evaluation for pancreatitis should be performed on all children admitted to the ICU with acute abdomen.

Acute pancreatitis is preceded by intrapancreatic activation of proteases. The triggering mechanism remains obscure, but once protease inhibitors are overcome and trypsinogen is converted to trypsin, a cascade of steps produces active proteases, lipase, and amylase. The enzymes induce local and distant organ damage, which includes edema, increased vascular permeability, cytolysis, and fat necrosis.

The clinical hallmark of acute pancreatitis is severe, boring epigastric or left upper quadrant pain that radiates through to the back. Serum amylase and lipase levels are greatly elevated, and radiographic imaging studies reveal pancreatic enlargement, sonolucency, or irregularity of the margin. Ultrasonography is a satisfactory screening technique, but CT scanning should be used when the course is severe. If CT scanning is performed with a dynamic, contrast-enhanced technique, interstitial pancreatitis can be differentiated from the more ominous necrotic pancreatitis, which often requires surgical debridement.

Because serum lipase is almost exclusively pancreatic in origin and amylase comes from a number of organs, the serum lipase concentration may be a better indicator of pancreatitis. Use of both measures to follow the course of pancreatitis is preferable to using either one alone.

Several nonspecific laboratory derangements such as anemia, hypoglycemia, hypocalcemia, and hypoproteinemia may occur. Intensive support may be required for severe, acute attacks. Severe, hemorrhagic necrosis of the pancreas carries a poor prognosis. Extraordinarily large third-space fluid and electrolyte losses must be replaced. If significant hyperglycemia occurs, insulin must be given. Calcium infusions may also be necessary. Physicians should be able to minimize pancreatic stimulation by giving the patient nothing by mouth and using nasogastric suction, although the efficacy of suction has been questioned for patients without ileus. Use of protease inhibitors, H_2 antagonists, somatostatin, 5-fluorouracil, and glucagon has not found much support in the literature. Antibiotics are not indicated unless an abscess is suspected. Some studies support the use of free-radical scavengers such as selenium, methionine, vitamin E, and vitamin C.[63]

Several complications may be catastrophic. Rupture of a pancreatic duct or leakage of a pseudocyst must be suspected if ascites develops. Gastrointestinal hemorrhage during pancreatitis may originate from a variety of sources. Discovery of gastric varices suggests splenic vein thrombosis. Gastritis may also appear. Pseudoaneurysms of the hepatic or splenic artery may bleed into the pancreas. Small bowel or colonic ischemia caused by fat necrosis may produce gastrointestinal hemorrhage. Infected pancreatic necrosis is uniformly fatal unless the patient undergoes an emergency operation to debride the necrotic tissue.

Time to recovery from pancreatitis is variable and may be prolonged (weeks to months). Nutritional management during that interval is affected by the desire to avoid stimulation of the pancreas by enteral administration of nutrients. Although total parenteral nutrition (TPN) is indicated during the initial phase of severe pancreatitis,[64] enteral administration of elemental formulas by nasojejunal tube phase has been successfully implemented[65] early in the course of the illness. If such a nutritional strategy does not exacerbate the pancreatitis, it is preferable to using TPN because of its relative safety when compared with TPN.

Acute and Chronic Liver Failure

The term *liver failure* refers to the constellation of symptoms, signs, and biochemical aberrations that appear when hepatic synthetic capacity is severely compromised. Liver failure is categorized as fulminant when encephalopathy appears within the first 2 months of the illness, as late onset when it appears within 6 months, and as chronic when it appears beyond the sixth month of liver dysfunction. Infectious, metabolic, and toxic liver diseases, as well as biliary obstruction, may lead to liver failure (Table 86-2). Obviously, it is advisable to establish a cause of liver disease before the onset of liver failure. It is beyond the scope of this chapter to outline a diagnostic approach to childhood liver disease, but several reviews are available (see Chapter 88).[66,67]

Elucidating the cause of fulminant hepatic failure is often made more difficult by the rapid development of coagulopathy and ascites, which preclude percutaneous liver biopsy. Laparotomy with surgical wedge biopsy may be necessary. More recently, techniques for transjugular liver biopsy have been developed.[68, 69] A core of liver tissue is obtained by passing the biopsy forceps retrograde through the superior vena cava and hepatic vein after introduction via the jugular vein. The biopsy site then bleeds directly into the liver parenchyma, minimizing extravasation.

Hepatic encephalopathy is a consistent finding in adult liver failure, although it occurs inconsistently and relatively late in pediatric cases.[70]

Progressive hepatic encephalopathy culminates in coma. When patients have entered coma, CNS resuscitation becomes necessary. Patients should undergo elective endotracheal intubation, and they should be hyperventilated. Administration of narcotics and benzodiazepines should be avoided. Benzodiazepine antagonists provide temporary improvement in consciousness among patients with hepatic encephalopathy.[71] Beyond CNS metabolic derangements, cytotoxic cerebral edema often complicates hepatic failure. Placement of an intracranial monitoring device should be contemplated; the risk of instrumentation in patients with coagulopathy should be weighed against the benefit of continuous CNS pressure monitoring (see Chapter 59).

Plasmapheresis or plasma exchange remove circulating mediators and toxins from patients with liver failure. This temporary effect may be due to removal of neuroinhibitory factors.

A variety of bioartificial liver support devices have been formulated as a bridge to liver transplant. Since most of these patients go onto liver transplantation, it will be difficult to ever demonstrate superiority of these devices over conventional plasmapheresis.[72,73]

The non-CNS manifestations of liver failure are protean. Hepatosplenomegaly is common in the early stages of fulminant failure, but the liver may shrink rapidly. In end-stage liver disease caused by cirrhosis, the liver is shrunken, firm, and nodular. Most patients with liver failure have jaundice. Spider angiomas, palmar erythema, ascites, and peripheral edema are common features of chronic liver disease. Fetor hepaticus (mercaptan breath) may be present.The biochemical features of liver failure are variable depending on its cause, duration, and severity. Hypoglycemia should be corrected when present. Serum bilirubin levels may be elevated or normal. Liver aminotransferase concentrations are increased in acute liver disease but decrease as hepatocytes are lost and therefore may be only mildly elevated or normal in cirrhosis and in the terminal stages of failure. Decreasing aminotransferase levels and albumin in the face of rising bilirubin, prothrombin time, and partial thromboplastin time denotes a failing liver. Serum globulin and ammonia levels are usually elevated. The serum aminogram reveals an elevated aromatic/branched-chain amino acid ratio.

Renal insufficiency may appear because of prerenal azotemia, acute tubular necrosis, or hepatorenal syndrome.[50] Patients with both acute and chronic liver failure frequently have renal failure. Hepatorenal syndrome (HRS) is the most common cause of acute renal failure in this population. From 40% to 80% of patients with hepatic failure develop HRS. The onset often occurs following an acute change in intravascular volume. The development of HRS is precipitated commonly by hemorrhage, excessive diuresis, or sepsis. HRS is a diagnosis of exclusion once other causes of renal failure and absent diuretic response are further explored. Although certain clinical characteristics may or may not exist in the description of HRS, almost all patients have hyponatremia prior to the development of renal insuffiency.[74] The treatment is nonspecific but includes volume administration and maintenance of adequate systemic perfusion. This is achieved by overcoming the sphlanchnic vasodilation and increasing renal perfusion and filtration (see Chapter 88).[75]

Patients with late-onset or chronic liver failure are likely to have portal hypertension. Ascites may develop as plasma oncotic pressure decreases or portal pressure increases. Patients who are hyponatremic usually have total-body sodium overload,[76] and they should be treated with moderate salt restriction but vigorous fluid restriction, colloid

Table 86–2 Diseases that Cause Liver Failure

Viral	Hepatitis (A, B, C, D, E), CMV, HSV, EBV, VZV, HHV-6, parvovirus B19, parainfluenza, yellow fever
Idiosyncratic	Halogenated hydrocarbons, coumadin, methyldopa, phenytoin, carbamazepin, valproic acid, rifampicin, penicillin, sulfonamides, quinolones
Toxic dose–dependent	Acetaminophen (Paracetamol), isoniazid, tetracycline, methotrexate, carbon tetrachloride, amphetamines, amanita phalloides toxin
Toxic synergistic	Ethanol + acetaminophen, barbiturate + acetaminophen, isoniazid + rifampicin
Metabolic	Wilson disease, alpha-1-AT-deficiency, galactosemia, tyrosinemia, Reye syndrome, NASH
Associated with pregnancy	Acute fatty liver of pregnancy, HELLP syndrome
Vascular	Budd-Chiari syndrome, veno-occlusive disease, shock, heart failure
Miscellaneous	Autoimmune hepatitis, malignant infiltration, hyperthermia, sepsis

CMV, Cytomegalovirus; *HSV,* herpes simplex virus; *EBV,* Epstein-Barr virus; *VZV,* varicella zoster virus; *HHV,* human herpesvirus; *NASH,* nonalcoholic steatohepatitis; *HELLP,* hemolysis, elevated liver enzymes, and low platelet count.

Data from Gotthardt D, et al: Fulminant hepatic failure: etiology and indications for liver transplantation, *Nephrol Dialysis Transplant* 22(suppl 8):viii5-viii8, 2007.

administration, and diuretic therapy are the cornerstones of therapy. High-volume abdominal paracentesis is proven to be safe in both adults and children who have ascites compromising ventilation.

Spontaneous engorgement of esophageal, gastric, and rectal veins leads to varices. Similar prominent veins in the abdominal wall and around the umbilicus (caput medusa) may develop. Splenic congestion from impaired venous flow into the portal system results in splenomegaly and hypersplenism so that patients are classically anemic or pancytopenic. Less commonly, unknown factors lead to intrapulmonary arteriovenous shunting, which characteristically causes hypoxemia.

Coagulopathy and bleeding are frequent in patients with liver failure. Thrombocytopenia, which may be profound, is a common component of hypersplenism. Fat-soluble vitamin malabsorption in patients with cholestasis leads to vitamin K deficiency, which prevents hepatic production of clotting factors II, VII, IX, and X. Ultimately, failed synthesis of all liver-dependent clotting factors results in prolonged prothrombin time (unresponsive to vitamin K administration) and partial thromboplastin time.

The sites of bleeding are predictable. Bleeding from incisions, needle puncture sites, nose, and gingiva are common but are usually not life threatening. Persistent bleeding may require packed red blood cell transfusion. In contrast, intracranial and variceal bleeding may be fatal and demand immediate attention. Esophageal varices bleed because of acute changes in variceal pressure or because of gastric hyperacidity. Platelets should be given to patients with thrombocytopenia. Patients with coagulopathy may receive fresh frozen plasma if their coagulopathy is mild; however, those whose prothrombin time is markedly deranged (international normalized ratio [INR] >2) may have pulmonary edema if attempts are made to correct the coagulopathy by administration of plasma alone. Acceptable alternatives include plasmapheresis[77] or the administration of recombinant factor VII concentrate[78] as bridges to transplantation.

Mechanical means of hemorrhage control include direct compression, creation of portosystemic shunts, and surgical transection/reanastomosis of the esophagus. Endoscopic control of bleeding from varices involves sclerotherapy in infants too small to tolerate a banding device or endoscopic banding in toddlers and older children.[79] Balloon tamponade by Sengstaken-Blakemore tube carries substantial risk and has largely been abandoned. It should not be used to manage persistent bleeding after sclerotherapy because of the risk of esophageal perforation.

Complications of portal hypertension can be managed with surgical shunting procedures that decompress the portal system by creating a venous anastomosis between the portal and systemic circulations. Several surgical varieties exist. Central vascular shunts, such as portocaval or mesocaval shunts, carry substantial risk. Transjugular intrahepatic portosystemic shunts are frequently used in children who weigh more than 10 kg as a bridge to transplantation.[80] In the past, shunt thrombosis was sometimes treated with surgical esophageal transaction, but urgent liver transplantation with either a cadaveric or living related donor is the preferred therapeutic strategy under such conditions (see Chapter 88).

Other extracorporeal liver assist devices, analogous to dialysis for renal failure, remain investigational a decade after their inception.[72,73,82] In any event, the basic principles of therapy must be directed toward CNS resuscitation, minimization of gastrointestinal bleeding, normalization of metabolic state, and correction of coagulation profile. Ultimately, orthotopic transplantation holds the greatest promise for saving patients with end-stage liver disease.[83,84]

References are available online at http://www.expertconsult.com.

V

Chapter 87

Gastrointestinal Pharmacology

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PEARLS

- Antiemetic management in both chemotherapy induced nausea and vomiting and postoperative nausea and vomiting is rooted in a multiple-drug approach with distinct targets of action.
- Risk of nausea and vomiting should be assessed for individual patients before optimal, guideline-driven, medical management is determined.
- H_2-receptor blockers and proton pump inhibitors remain the preferred agents over prokinetic agents in the treatment of gastroesophageal reflux disease.
- Risk factors for clinically significant gastrointestinal hemorrhage include mechanical ventilation, coagulopathy, and Pediatric Risk of Mortality score >10.
- Proton pump inhibitors are the preferred agent for treatment of gastrointestinal hemorrhage due to acid suppression; however, combination therapy may be necessary.
- Liver injury in children may result from autoimmune disease, metabolic disease, infectious causes, acute hepatitis, ischemia, irradiation damage, and exposure to toxins or medications.
- In a pediatric critical care environment, rectal administration of medication may be most beneficial when intravenous access issues are present, either because of an inability to maintain or achieve intravenous access or in situations when placement of an intravenous line is otherwise not necessary.
- Consideration of the activity of the CYP450 isoenzymes, with specific focus on age differences, may aid in accurate drug dosing.

Nausea and Vomiting

Introduction and Definitions

Uncontrolled nausea and vomiting in the pediatric intensive care unit may result in consequences that range from minor patient discomfort to life-threatening infection or electrolyte imbalance. To the patient this can mean wound dehiscence, gastrointestinal (GI) bleeding, malnutrition, dehydration, pulmonary aspiration, and increased anxiety with future medical interventions.[1] Indeed, nausea and vomiting has been referred to as the "big little problem" with the capacity to delay discharge, monopolize nursing care, and impact financial resources.[2] These costs can be limited with a focus on prophylactic treatment, employing recent drug developments and guideline-driven therapy when possible. The data that drive these guidelines are, particularly in pediatrics, largely based on studies that look at vomiting more specifically than nausea.[3] Because nausea is an unpleasant, largely subjective sensation in the epigastrium that may be associated with vomiting, it is more difficult to quantify objectively.[3,4] Vomiting, defined as the forceful expulsion of gastric contents from the mouth, can be more easily measured for medication assessment purposes. Although distinct, when vomiting is discussed here, it can be inferred to also pertain to managing nausea (unless otherwise noted).

The causes of nausea and vomiting in intensive care are as diverse as their consequences and include radiation, increased intracranial pressure, meningitis, diabetic ketoacidosis, hypercalcemia, hyponatremia, hepatitis, pancreatitis, bowel obstruction, GI bleeding, and surgery. Common medications that can trigger vomiting include antineoplastics, anesthetics, antibiotics, contrast media, and opiates. This section's focus, and on which the majority of research has focused, considers chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). Before moving on to these topics specifically, the mechanism mediating nausea and vomiting will be explored.

Pathophysiology

The vomiting center or emetic center or "central pattern generator," located in the medulla oblongata, is a collection of neurons that may trigger vomiting after receiving input from the chemoreceptor trigger zone, abdominal vagal afferents or cerebral cortex.[1,5-7] The chemoreceptor trigger zone, located in the area postrema region near the fourth ventricle, is not fully protected by the blood-brain barrier; and is therefore vulnerable to antineoplastic agents, or other stimuli in the blood or cerebral spinal fluid.[5-7] The vagus nerve provides important stimuli to both the chemoreceptor trigger zone and vomiting center, and appears to have the largest role in CINV.[5,7] This occurs when cells within the GI tract are exposed to chemotherapy and release mediators, including 5-hydroxytryptamine (5-HT), substance P, and cholecystokinin, that stimulate the vagus nerve.[5,7] Finally, the role of the cerebral cortex is less well defined, but is thought to play a role in anticipatory nausea and vomiting.[1]

The mechanism described is most dependent upon the neurotransmitter receptors for dopamine, serotonin (5-hydroxytryptamine type 3), and substance P.[1,5-7] Additional receptors that are thought to play a supporting role

include corticosteroid, histamine, cannabinoid, acetylcholine, opiate, neurokinin-1, and gamma-aminobutyric acid.[1,6,8] The intricate cascade briefly described here and multiple neurotransmitter involvement, foreshadow treatment guidelines that will often be rooted in multiple agents that target various pathways.

Chemotherapy-Induced Nausea and Vomiting: Types of Emesis

Emesis that occurs from chemotherapy is divided into three distinct categories. Anticipatory CINV occurs before chemotherapy administration and occurs as a conditioned response in patients that have had significant past CINV. Acute CINV occurs within 24 hours of chemotherapy administration and is the most widely studied. Delayed nausea and vomiting occur after 24 hours and may persist for 7 days. Pediatric patients that have well-controlled acute nausea and vomiting are less likely to have delayed nausea and vomiting.[8] This highlights the importance of "staying ahead" of symptoms with prophylactic treatment.

Treatment Guidelines

The advent of 5-HT_3 receptor antagonists in the early 1990s provided a new cornerstone in how acute nausea and vomiting is managed in patients receiving highly or moderately emetogenic chemotherapy. The first-generation 5-HT_3 receptor antagonists of dolasetron, granisetron, and ondansetron have been established in pediatrics to be equally effective, and equally toxic, with the most common side effects including headache, constipation, and dizziness.[3,9-13] It should be noted that the approved pediatric dose of granisetron of 10 ug/kg once daily is likely ineffective, and a dose of 40 ug/kg once daily is more appropriate.[3,13,14,20] The 5-HT_3 receptor antagonists have been established, at the appropriate doses, to be as effective when given orally as when given intravenously, and that single daily dose schedules are as effective as multiple-dose schedules.[15-20] These agents are most useful for CINV occurring within the first 24 hours after administration of chemotherapy.[21]

In 2003, what may be considered a "second-generation" 5-HT_3 receptor antagonist, palonosetron, gained Food and Drug Administration approval for both acute and delayed CINV. It is unique from other 5-HT_3 antagonists because of its long half-life (21 to 37 hours in children and 40 hours in adults) and greater affinity for 5-HT_3 receptors.[14,22] Three phase III trials have established palonosetron as not inferior to older 5-HT_3 antagonists.[23-25] A trial comparing palonosetron with ondansetron in pediatric patients found a significant reduction in emesis on the first 3 days after treatment, and in nausea intensity the first 4 days after treatment favoring the palonosetron group.[26] Further prospective study is needed before palonosetron can be established as superior to other 5-HT_3 receptor antagonists. To date, CINV guidelines have not stated any one 5-HT_3 receptor antagonist to be superior to another.[20]

Corticosteroids, most commonly dexamethasone or methylprednisolone, are potent antiemetics and have a critical role in managing acute and delayed CINV in pediatrics. Their exact mechanism of action is unclear, but may involve decreasing 5-HT_3 release in the periphery.[27] However, corticosteroids also have the potential to decrease the effect of antineoplastic drugs on brain tumors, osteosarcomas and carcinomas.[27] Dexamethasone may augment the ability of a number of carcinomas to resist both radiation and chemotherapy.[3] Interferon or interleukin-2 may be less effective when used along with steroids.[1] Corticosteroids may also impact the quality of brain tumor images generated by computed tomography or magnetic resonance imaging by altering the distribution of contrast media.[3] In addition to these concerns, the usual side effects of steroids must be kept in mind, including: hyperglycemia, hypokalemia, anxiety, euphoria, and insomnia. It would be prudent to consult a patient's chemotherapy protocol or an oncologist before initiating corticosteroids in a pediatric patient with a malignancy to verify the appropriateness of this approach.

The neurokinin-1 receptor antagonist is the most recent antiemetic class. These are effective for both acute and delayed nausea and vomiting in moderately and highly emetogenic chemotherapy. Such agents are approved in CINV only when used in conjunction with a 5-HT_3 antagonist and a corticosteroid. Currently the only medications that represent this class on the market are oral aprepitant and intravenous fosaprepitant. They are generally well tolerated with diarrhea, fatigue, headache, and hiccups being common side effects.[28-30] Both aprepitant and fosaprepitant are substrates, inhibitors and inducers of the cytochrome P450 enzymes 3A4 and 2C9.[14] A thorough review of potential interactions for individual patients is merited. Most notable of these cytochrome interactions are: The effect of Coumadin (brand name form of the generic warfarin) on coagulation pathway (altered prothrombin time, International Normalized Ratio) may be reduced, the concentration of corticosteroids will be increased with a dose reduction needed when used for CINV with aprepitant, and a backup contraception method should be used for patients taking oral contraceptives.[30] This class of medication does not have approval for patients younger than 18 years, nor are suggested dose modifications available.[14] One study examined aprepitant dosed for young adults in patients ages 11 to 19 years weighing 43 to 105 kg.[31] Aprepitant containing regimens performed comparably to non-aprepitant-containing regimens, but an increase in the number of cases of febrile neutropenia was noted in the aprepitant patients.[31] Further prospective study is necessary before neurokinin-1 receptor antagonists are prescribed in pediatric patients.

Other agents commonly seen in pediatrics for CINV include benzodiazepines, most often lorazepam, which is routinely employed for anticipatory nausea and vomiting at a dose of 0.04 to 0.08 mg/kg/dose (maximum dose, 4 mg).[14] Diphenhydramine is anecdotally used in pediatric patients despite its absence from guidelines and reviews of CINV.[3,20] Dopamine receptor antagonists, including phenothiazines (e.g., prochlorperazine), butyrophenones (e.g., droperidol), and benzamides (e.g., metoclopramide), cause a high incidence of dystonic reactions when used at high doses for several days and potentially oculogyric crisis.[20,32] Cannabinoids (i.e., dronabinol) are limited by their lack of pediatric data, and their side effects, which include euphoria, sedation, depression, and hallucinations.[14] A scopolamine patch may have some utility in patients older than 12 years that are able to wait up to 12 hours for relief.[3] Generally speaking, these agents should only be considered for pediatric patients who do not tolerate first-line therapy alone.

Determining appropriate antiemetic therapy requires one to first evaluate the likelihood that a particular chemotherapy

Table 87–1 Antiemetic Selection for Chemotherapy Based on Emetogenicity of Frequently Encountered Single-Day Pediatric Chemotherapy

Emetic Risk (Incidence of Emesis with no Prophylaxis)	Antineoplastic Agent*	Recommended Antiemetic
High (>90%)	Cisplatin Cyclophosphamide >1.5 g/m^2 Dactinomycin Methotrexate >5 g/m^2	Children: day 1: 5-HT$_3$ antagonist + dexamethasone Adults: Day 1: 5-HT$_3$ antagonist + dexamethasone + NK-1 antagonist Day 2, 3: dexamethasone + NK-1 antagonist Day 4: dexamethasone
Moderate (30%-90%)	Carboplatin Cyclophosphamide <1.5 g/m^2 or oral Cytarabine >1 g/m^2 Daunorubicin Doxorubicin Etoposide (oral) Ifosfamide Irinotecan Methotrexate >1 g/m^2	Children: day 1: 5-HT$_3$ antagonist + dexamethasone Adults: For anthracycline and cyclophosphamide combination: Day 1: 5-HT$_3$ antagonist + dexamethasone + NK-1 antagonist Day 2, 3: NK-1 antagonist (dexamethasone if NK-1 antagonist contraindicated) All other regimens: Day 1: 5-HT$_3$ antagonist + dexamethasone Day 2, 3: dexamethasone or 5-HT$_3$ antagonist
Low (10%-30%)	5-Fluorouracil Asparaginase Cytarabine <1 g/m^2 Etoposide Methotrexate >100 to <1000 mg/m^2 Topotecan	Children: day 1: 5-HT$_3$ antagonist or dexamethasone Adults: day 1: dexamethasone
Minimal (<10%)	6-Thioguanine (oral) Hydroxyurea (oral) Methotrexate <100 mg/m^2 or oral Rituximab Vinblastine Vincristine	Children and adults: 5-HT$_3$ antagonist or dexamethasone only if needed

5-HT$_3$, 5-Hydroxytryptamine-3; *NK-1,* neurokinin-1.
*Table focuses on more common pediatric chemotherapy (see references 20 and 33 through 38 for complete list). Medication is parental unless otherwise stated.

regimen will produce nausea or vomiting.[20,33-35] This has been accomplished with literature and expert opinion and is summarized in Table 87-1, with subsequent dosing information provided in Table 87-2.[14,20,33-40] This categorization is largely based on adult data, so it is vital to take individual patient parameters and CINV history into account. If a chemotherapy regimen is close to the next highest emetic risk category, it is better to be aggressive with antiemetic management.

Table 87-1 includes aprepitant and dexamethasone that may be contraindicated for multiple reasons in children as discussed previously. In such patients, medications that are less-well supported for delayed CINV, such as diphenhydramine or 5HT$_3$ receptor antagonists, may be employed based on individual practitioner preference. Other areas of future research include breakthrough emesis that occurs despite adequate prophylaxis in a single cycle, and refractory emesis that occurs despite adequate prophylaxis over multiple cycles.[8] Additional areas that require further investigation in pediatric CINV include multiple-day chemotherapy, high-dose chemotherapy with stem cell rescue, and intractable symptoms in terminal patients.[41-43] Finally, each institution would be well advised to conduct a pharmacoeconomic review to aid in antiemetic selection of pharmacologically equivalent products.

Postoperative Nausea and Vomiting

Assessing the risk of the pediatric surgical candidate is the first step in determining PONV prophylaxis. Strabismus repair, tonsillectomy, hernia repair, orchiopexy, penile surgery, or any procedure where anesthesia time is 30 minutes or longer have an increased likelihood of PONV.[4,40,44] Children aged 3 years and older continue to increase their risk of PONV until they become pubescent.[40,44] Patients who have a history of PONV, motion sickness, or patients with first-degree relatives with such histories are more prone to have PONV.[40,44] Prophylaxis is recommended only for children thought to be at moderate or high risk of PONV.[4] Regional anesthesia is optimal in such patients.[4] However, if general anesthesia is necessary, the following may reduce the risk of PONV: using intraoperative supplemental oxygen, adequate hydration, minimizing opioid or neostigmine exposure, and avoiding nitrous oxide or volatile anesthetics when possible.[40]

Individual institutions should determine which patients are at moderate or high risk. These patients should receive a combination of two or three agents with distinct mechanisms of action for PONV prophylaxis.[4,40] A 5HT$_3$ receptor antagonist and dexamethasone combination is a reasonable first choice.[4] Other options include dimenhydrinate, perphenazine, or droperidol.[4,40,44] Because of potential for QT prolongation and *torsades des pointes*, droperidol should be reserved for patients who have failed first-line therapy and are hospital inpatients.[4] Droperidol should be dosed once for prophylaxis at 0.05 mg/kg (maximum, 1.25 mg), or at 0.01 to 0.03 mg/kg/dose for PONV treatment.[14,40] Finally, NK-1 receptor antagonists have been established as potent agents for PONV in adult patients, but even if approved in pediatrics it seems likely a multiple agent approach to PONV as described above will remain the standard of care.[45-48]

Table 87–2 Antiemetic Dosing in Chemotherapy-Induced and Postoperative Nausea and Vomiting[14,36,39,40]

Medication	CINV (IV)	CINV (PO)	PONV (IV)	PONV (PO)
Dolasetron	First dose 30 min before chemo: ≥2 y: 1.8 mg/kg (max*: 100 mg)	First dose 1 h before chemo: ≥2 y: 1.8 mg/kg (max, 100 mg)	15 min before anesthesia cessation: ≥2 y: 0.35 mg/kg (max, 12.5 mg)	2 h before surgery: ≥2 y: 1.2 mg/kg (max, 100 mg)
Granisetron	First dose 30 min before chemo: ≥2 y: 10 μg/kg/day per manufacturer *or* 20–40 μg/kg/day divided in 1–2 doses (max, 3 mg/dose)	First dose 1 hr before chemo: Adults: 2 mg q24h or 1 mg q12h	Before anesthesia induction or after reversal: ≥4 y: 20–40 μg/kg (max, 1 mg)	N/A
Ondansetron	First dose 30 min before chemo: ≥6 months: 0.15 mg/kg (max, 12 mg), then at 4 and 8 h Adults: may consider once-daily dose of 32 mg	First dose 30 min before chemo: 4–11 y: 4 mg q8h >11 y: 8 mg q8h or 24 mg q24h	Before anesthesia induction: ≥2 y and <40 kg: 0.1 mg/kg >40 kg: 4 mg	1 h before anesthesia: adults: 16 mg
Palonosetron	First dose 30 min before chemo: ≥2 y: 0.25 mg	First dose 1 hr before chemo: Adults: 0.5 mg	Immediately before anesthesia: adults: 0.075 mg	N/A
Dexamethasone	First dose before chemo: Children†: 10 mg/m^2 (max, 20 mg), then 5 mg/m^2 q6h or 10 mg/m^2 q12h	First dose before chemo: Children†: 10 mg/m^2 (max, 20 mg), then 5 mg/m^2 q6h or 10 mg/m^2 q12h	Before induction of anesthesia: children: 0.15 mg/kg (max, 8 mg)	N/A
Fosaprepitant (IV)/Aprepitant (PO)	30 min before chemo: adults: 115 mg (follow with PO aprepitant next 2 days)	1 hr before chemo: adults: 125 mg, then 80 mg q24h for the next 2 days	N/A	Within 3 h before anesthesia: adults: 40 mg

CINV, Chemotherapy-induced nausea and vomiting; *PONV,* postoperative nausea and vomiting; *IV,* intravenous; *PO,* oral; *max,* maximum dose; *N/A,* not applicable.
*Maximum dose is recommended adult dose unless otherwise stated; see appropriate adult reference for complete dosing.
†Dosing is only intended for pediatric patients not receiving aprepitant; see appropriate adult reference because dosing varies based on emetogenicity of therapy, type of CINV (e.g., acute, delayed), and aprepitant interaction.

Diarrhea

Introduction and Definition

It is estimated that in the United States, diarrhea-based illnesses result in approximately 200,000 hospital admissions and 400 deaths per year.[49] The majority of acute diarrhea episodes stem from infections to the GI tract and it is estimated that 20% to 40% of children treated with broad-spectrum antibiotics will develop diarrhea.[50,51] Infectious causes include viruses (e.g., Rotavirus), bacteria (e.g., *Escherichia coli*, *Shigella*, *Clostridium difficile*), and parasites (e.g., *Cryptosporidium parvum*, *Giardia lamblia*). Noninfectious causes include appendicitis, intussusception, food allergies, irritable bowel syndrome, and ulcerative colitis. Diarrhea may be defined for practical purposes as a decrease in stool consistency, along with an increase in frequency to more than three bowel movements in 24 hours.[49] After diarrhea is identified, rehydration is paramount. Identifying the underlying cause will guide specific treatment.

Treatment

If *C. difficile* is identified, any potentially contributing broad-spectrum antibiotics should be discontinued, or streamlined to more a specific agent if possible. Oral metronidazole for 10 days is first line therapy in mild to moderate disease.[51,52] Cases that require protracted courses of metronidazole should include monitoring for peripheral neuropathy. Oral vancomycin should be considered for patients with severe symptoms, intolerance to metronidazole, or metronidazole failure.[51-53] Indeed, there is growing evidence in the adult population of superior outcomes when vancomycin is used first line for severe disease.[52,53] Probiotics, bile-acid sequestrants, intravenous immunoglobulin, or tapering doses of vancomycin may be considered for recurrent cases. The impact of *C. difficile* can be minimized with prevention that includes good hand hygiene, infection control, and appropriate antibiotic usage. It would be prudent to limit acid suppressing agents (e.g., proton pump inhibitors, histamine H_2 antagonists) to legitimate indications, as a positive association has been identified in adult populations between acid suppression and *C. difficile* disease.[54,55]

Probiotics are widely defined as live microorganisms that offer health benefits. These agents have been studied in pediatric patients in terms of potential reduction in antibiotic-associated diarrhea. One meta-analysis found that for every seven pediatric patients administered probiotics, one fewer would develop antibiotic-associated diarrhea. Positive risk reduction was identified, in decreasing strength, for those treated with *Lactobacillus* GG, *Saccharomyces boulardii*, and the combination of *Bifidobacterium lactis* and *Streptococcus thermophilus*.[56] Significant reductions were not found with *L. acidophilus/Bifidobacterium infantis* or *L. acidophilus/L. bulgaricus*.[56] A second meta-analysis reviewing *Lactobacillus* GG, *L. sporogenes*, and *Saccharomyces boulardii* found a significant decrease in antibiotic-associated diarrhea but nonsignificant overall results in intent-to-treat analysis.[57] Such agents require further study from an efficacy and pharmacoeconomic standpoint before

they become the standard of care. If these agents are used, sufficient live organism content should be verified. These agents should be used cautiously, if at all, in premature infants and in patients with any of the following: short bowel syndrome, central catheters, cardiac valve disease, and immune compromise.[58,59]

Other important treatments for diarrhea include the antimotility agents loperamide and diphenoxylate. Both inhibit excessive GI peristalsis and increase GI transit time.[14] Neither medication should be used in diarrhea resulting from pseudomembranous enterocolitis or any infectious cause, because it is critical that toxins produced are cleared from the GI tract.[14,49] Underlying electrolyte imbalances and dehydration should be addressed before these antimotility agents are initiated, because the potential exists that intestinal fluid retention may exacerbate such underlying conditions. Side effects to be mindful of include: sedation, confusion, ileus, and respiratory depression (with younger children at increased risk).[14]

Constipation

Introduction and Definition

Constipation is defined as a reduction in the number of bowel movements. This number varies significantly based on the infant or child's age and breastfeeding status with exclusively breast-fed infants having an increased frequency of bowel movements.[60,61] The differential diagnosis underlying constipation in a pediatric intensive care unit is extensive and includes: anatomical (e.g., anal stricture, rectal abscess), metabolic (e.g., hypothyroidism, cystic fibrosis), neurologic (e.g., Hirschsprung disease, cerebral palsy), and connective tissue disorder (e.g., systemic lupus erythematosus).[61] Medications such as opiates, phenobarbital, antacids, antihypertensives, anticholinergics, and antidepressants, and lead may all contribute to a child's constipation.[61]

Treatment

Any underlying disease state or anatomical anomaly should be managed individually. If medication related, the offending agent should be discontinued if possible; or the minimal effective dose should be targeted. Constipation itself is addressed as a two-step process of disimpaction lasting 3 to 5 days, followed by maintenance. The duration of the latter stage is determined by symptom recurrence when treatment is withdrawn.[60,62]

Disimpaction may be accomplished with oral or rectal medication administration. The oral route is less invasive and may give a sense of empowerment to the child, but the rectal route is quicker and may be necessary if the child has abdominal pain. Oral options include mineral oil, oral electrolyte solutions, lactulose, sorbitol, magnesium hydroxide, magnesium citrate, senna, and bisacodyl. Mineral oil may result in lipoid pneumonia if aspirated and is not recommended in children younger than 1 year or any patient on aspiration precautions. Options for rectal disimpaction include phosphate soda, saline, or mineral oil enemas followed by a phosphate enema. Also effective are glycerin suppositories in infants, and bisacodyl suppositories in older children. Soapsuds, tap water, and magnesium enemas are discouraged because of their potential toxicity.[60] Enemas are to be avoided in children younger than 3 years and in young children with severe neurologic deficiencies as they are more likely to be retained with subsequent resulting toxicities.[62]

Maintenance therapy with polyethylene glycol 3350 without electrolytes (MiraLax) has demonstrated superior palatability in children, and although not yet recommended by guidelines in infants, there is growing evidence of its safe use in this population.[60,62] Other maintenance therapies include mineral oil, magnesium hydroxide, lactulose, and sorbitol. Bisacodyl or senna may be necessary as a stimulant laxative as rescue therapy, but should be avoided for extended use.[60]

Gastroesophageal Reflux Disease

Treatment of gastroesophageal reflux disease (GERD) should alleviate symptoms and prevent or heal esophageal damage. Although researchers conducting multiple pediatric studies have used varying doses, multiple drug therapies, and nonpharmacologic therapies, guidelines do exist for the treatment of GERD in infants and children.[63] Many patients who may be admitted to the intensive care unit for other conditions are likely to have preexisting gastroesophageal reflux conditions and corresponding surgical and pharmacologic therapies. These populations include patients with reactive airway disease, recurrent pneumonia, neurologic impairment, premature infants, and genetic syndromes including Down syndrome.

Histamine-2 Receptor Antagonists

Histamine-2 (H_2) receptor antagonists inhibit gastric acid secretion by means of competitive inhibition of H_2 receptors of the gastric parietal cells. H_2 receptor antagonists are generally well tolerated. Common adverse effects include nausea and headache. Although thrombocytopenia may occur, it is often difficult to determine the sole cause in critically ill patients. Ranitidine should be avoided in patients with acute porphyria. Tachyphylaxis is well documented for intravenous and oral H_2 receptor blockers in adult and pediatric populations. Infants may suffer from irritability, headache, and somnolence, which when mistaken for GERD symptoms, may lead to an unwarranted increase in dose.[63] All of the currently available H_2 receptor blockers require dosage adjustment for renal impairment. Although fewer pediatric studies exist for ranitidine and famotidine, these agents are frequently used and may be preferred over cimetidine because of fewer drug interactions and central nervous system adverse effects. Availability of both oral and intravenous formulations allow for easy continuation of therapy when patients are admitted to the intensive care unit.

Proton Pump Inhibitors

By covalently bonding to the hydrogen-potassium-adenosine triphosphatase (ATP) of parietal cells, proton pump inhibitors (PPIs) suppress gastric acid secretion for the life of the parietal cell. Ideally, therapy should be given 30 minutes before feeding so that peak plasma concentrations coincide with parietal cell stimulation. Administration with food reduces bioavailability by fifty percent. Although their serum half-lives are relatively short; the pharmacological effect persists until new parietal cells are generated.[64] Omeprazole, esomeprazole, and lansoprazole have been approved for use in pediatrics. Extemporaneously compounded suspensions of omeprazole and lansoprazole are frequently used, even in patients with various

types of feeding tubes. Intravenous lansoprazole is no longer available. Neither intravenous pantoprazole nor esomeprazole is Food and Drug Administration (FDA)–approved for use in pediatric patients. Until sufficient pediatric dosing information becomes available, intravenous PPIs are likely to be reserved for patients with active GI bleeding or contraindication to alternative therapies. Although PPIs are generally thought of as well tolerated, both long- and short-term adverse effects are gaining more attention. Reactions include idiosyncratic reactions, drug-drug interactions, drug-induced hypergastrinemia, and drug-induced hypochlorhydria.[63] The most common side effects are headache, diarrhea, constipation, and nausea.[14] Case reports of biopsy proven interstitial nephritis associated with PPI use have emerged. Thus far no pediatric cases have been reported.[63] The FDA and Health Canada are currently investigating potential links between PPIs and decreased effectiveness of clopidogrel. Although the data are primarily from adult reports, the potential interaction may be relevant in pediatrics as well. PPIs should not be discontinued abruptly because a hypersecretory phase results.[63,65] Acid suppression, whether from H_2 receptor antagonists or PPIs, may increase the rates of community-acquired pneumonia, gastroenteritis, candidemia, and necrotizing enterocolitis.[63,66-68]

Antacids

Both aluminum hydroxide and magnesium hydroxide are effective treatments of GERD. In infants, however, aluminum hydroxide formulations can increase plasma levels of aluminum to those reported to cause osteopenia, microcytic anemia, and neurotoxicity. Aluminum-based antacids should be avoided in patients with renal impairment. Efficacy of calcium carbonate antacids has not been demonstrated in pediatric patients. Depending on the antacid formulation chosen, adverse effects may include electrolyte disturbances, nausea, flatulence, diarrhea, or constipation. Because alternative therapies are available and generally well tolerated, antacids should be reserved for intermittent symptom management rather than chronic treatment of GERD.[63]

Surface Agents

Sucralfate, an aluminum salt of sulfated sucrose, forms a protective barrier by binding to damaged mucosa in an acidic environment. Although it has demonstrated effectiveness in the treatment of esophagitis, it is not recommended for long-term treatment of GERD in children because of a lack of efficacy data and safety concerns associated with aluminum toxicity.[63]

Prokinetic Therapy

Prokinetic agents are of interest in GERD because of their ability to enhance esophageal peristalsis and accelerate gastric emptying. Cisapride is a prokinetic agent that at one time was widely used not only for GERD, but also for a variety of adult and pediatric motility disorders, including constipation and gastroparesis. It was prescribed more frequently than metoclopramide in children most likely because of its broader range of action and decreased risk of neurological side effects. Prolongation of the QTc interval with potential life-threatening ventricular arrhythmias was reported when cisapride was used concomitantly with drugs that inhibit the hepatic cytochrome P450-3A4 system. This uncommon, yet potentially fatal, adverse effect led the manufacturer to place it under a limited access protocol requiring close supervision by a pediatric gastroenterologist.

Erythromycin is a macrolide antibiotic and motilin agonist. It increases motility in the proximal GI tract. The most frequent adverse effects include abdominal cramping, nausea, vomiting, diarrhea, cardiac dysrhythmias with interacting medications, and risk of bacterial overgrowth. Metoclopramide promotes gastric emptying by acting as an antagonist to the inhibitory actions of dopamine in the gut. It also sensitizes the gut to acetylcholine and increases lower esophageal sphincter tone.[69] Metoclopramide blocks dopamine receptors in the chemoreceptor trigger zone and accelerates gastric emptying and intestinal transit time without stimulating gastric, biliary, or pancreatic secretions.[14] Adverse effects are common; are dose dependent; and can include extrapyramidal effects, seizures, and Parkinsonian reactions, which may be irreversible.[14,63] The FDA required the addition of a boxed warning to metoclopramide drug labels regarding the risks of long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia, which may include involuntary and repetitive movements of the body, even after drug discontinuation. It is noted that these adverse effects are more prevalent in elderly populations.[70] Extrapyramidal reactions in children and younger adults are more likely after intravenous administration of high doses, particularly within 24 to 48 hours after starting therapy.[14] Prescribers are urged to carefully consider legitimate indications for initiating drug therapy. Current GERD guidelines recommend against use of prokinetic agents.

Gastroesophageal Reflux Disease and Acute Life-Threatening Event

An acute life-threatening event (ALTE) is an episode of combined apnea, color change (cyanosis, pallor, plethora), abnormal muscle tone (limpness and stiffness), choking, and gagging that requires intervention. Some patients have succumbed to sudden infant death syndrome who have had a history of ALTE with documented GER. This combination is rare and assigning the timing and causality of the event is extremely difficult. Neither pharmacotherapy nor surgical intervention has been adequately studied in secondary prevention of ALTE. Those patients who may benefit from pharmacologic intervention may include those whose ALTEs were obviously associated with vomiting, regurgitation, or obstructive apnea.[63]

Stress-Induced Mucosal Damage: Ulcer Prophylaxis

Prospective studies reveal similar incidence of GI hemorrhage between adult and pediatric intensive care units. Of 1006 patients admitted to a pediatric intensive care unit, 10.2% had upper GI hemorrhage; however, only 1.6% of the admissions were viewed as clinically significant. Respiratory failure, coagulopathy, and a Pediatric Risk of Mortality score greater than or equal to 10 were identified as independent risk factors for GI hemorrhage.[71,72] Other studies also identified pneumonia, multitrauma, a surgical operation longer than 3 hours,

and circulatory shock in patients as high-risk factors.[73,74] One subsequent pediatric study demonstrated mechanical ventilation as the only statistically significant risk factor for clinically significant bleeds after multivariate analysis.[75] Children ventilated for greater than 48 hours were at additional risk of hemorrhage if thrombocytopenia, coagulopathy, organ failure, high pressure ventilator settings (>25 cm H_2O), or Pediatric Risk of Mortality score greater than 10 were present.[76] Mechanical ventilation and coagulopathy are recognized as independent risk factors in adult patients.[72] Because of the low incidence of clinically significant hemorrhage, prophylaxis may only be warranted in those patients with risk factors.[77]

Sucralfate, H_2 receptor antagonists, antacids, and PPIs have been used for prophylaxis of stress-induced mucosal damage in pediatric critical care patients. Individual trials including comparative studies and case series have shown each agent to be effective. With the low incidence of clinically significant bleeds, studies intending to demonstrate superiority of one drug class or agent over another would require an extremely large sample size. Therefore pediatric studies use a surrogate endpoint of gastric pH 4 or greater to evaluate efficacy of various dosing regimens.[78-80]

One study included 165 patients treated with ranitidine, antacid, sucralfate, or placebo. There were no differences among the treatment groups and all treatment groups had a lower incidence of bleeding than the placebo group.[81] Another study compared ranitidine, omeprazole, sucralfate, or placebo for stress ulcer prophylaxis and also compared adverse events. No differences were found among groups with regard to macroscopic stress ulcer bleeding, mortality, or ventilator-associated pneumonia.[82] Because multiple agents appear to be effective for stress ulcer prophylaxis, selecting an appropriate agent may be patient specific. However, when prescribing prophylaxis to adult patients, the inadequacy of sucralfate it is widely recognized after the landmark trial by Cook et al.[83] published in 1998 that demonstrated significantly lower rates of clinically relevant bleeding in the ranitidine treatment group. In addition there was no significant difference in pneumonia rates in this 1200-patient trial. Critical care patients do present challenges with regard to drug administration for antacids and sucralfate. Both agents require multiple doses per day, lack intravenous formulations, and may chelate or inhibit absorption of other drugs. In addition, aluminum toxicity may be of greater concern in critical care patients because of the potential for renal impairment. H_2 receptor antagonists are commonly used because of the availability of intravenous formulations. Adverse effects of the central nervous system, particularly in patients with renal impairment who have not been dose adjusted; thrombocytopenia; and drug interactions remain a concern. Most of these adverse events, however, can be prevented or at least monitored for early detection. PPIs may also be used orally, intravenously, or off-label through feeding tubes.

Stress ulcer prophylaxis is recommended, along with other supportive therapies, for acute lung injury and acute respiratory distress syndrome in children.[84] Stress ulcer prophylaxis is also recommended as supportive care for patients with sepsis in the 2008 Surviving Sepsis Campaign. H_2 receptor antagonists use was recommended with a stronger level of evidence than PPIs.[85] Some experts believe that although greater acid suppression is achieved with PPIs over H_2 receptor antagonists, PPIs should be used as second-line agents for stress ulcer prophylaxis because of the greater association with adverse effects such as community-acquired pneumonia, ventilator acquired pneumonia, and *C. difficile* infection.[86]

Gastrointestinal Hemorrhage

Clinical guidelines for treatment of nonvariceal upper GI bleeding in adults include recommendations for pharmacotherapy.[87] Unfortunately, this body of evidence does not exist in the pediatric population. H_2 receptor antagonist use is discouraged as primary treatment for patients with acute bleeding. Although octreotide and somatostatin are more effective than H_2 receptor antagonists, these agents are also not recommended for routine management. PPIs are cited as the drugs of choice for treatment of acute nonvariceal upper GI bleeding.[87] High-dose intravenous proton pump inhibitor therapy (80 mg pantoprazole bolus followed by 8 mg/hr for 72 hours after endoscopic therapy[39]) is preferred over H_2 receptor antagonists alone, or in combination with octreotide, to prevent rebleeding in adult patients. As more data become available regarding the use of intravenous proton pump inhibitors in pediatric patients, parallels may be seen between the treatments of adult and pediatric nonvariceal upper GI bleeding.

Proton Pump Inhibitors

Multiple oral proton pump inhibitors are approved for pediatric use. Pantoprazole and esomeprazole are available intravenously in the United States; however, neither product's intravenous formulation has been well studied in children. Doses have been extrapolated from the adult high-dose intravenous pantoprazole recommendations for use in clinical practice in pediatric patients with nonvariceal upper GI bleeding. Although it is not yet specified in the literature, many pediatric sites reportedly use a pantoprazole loading dose of 2 mg/kg IV, followed by 0.2 mg/kg/hr for 72 hours (neither the loading dose nor continuous infusion should exceed the adult dose).

Octreotide and Somatostatin

Octreotide is a somatostatin analogue. Its pharmacologic actions include inhibition of gastric acid secretion and decreased splanchnic blood flow. Although its 1.7-hour half-life is approximately 30 times longer than that of somatostatin, octreotide is usually administered through continuous infusion for GI hemorrhage. Adverse effects include abdominal pain, sinus bradycardia, nausea, pain at the site of injection, elevation of liver enzymes, chest pain, emesis, headache, dizziness, fatigue, flushing, and diarrhea. Long-term use (longer than 1 month) has been associated with changes in thyroid function, gallstone formation, and cholecystitis.[88]

In adults, octreotide has been shown to decrease the duration of hemorrhage and prevent recurrence of peptic disease more so than cimetidine or ranitidine. A Cochrane Review cited improved initial hemostasis and decreased transfusion requirements; however, no change was evident in rebleeding or secondary outcomes when octreotide was used to treat variceal bleeding.[88] Few researchers have evaluated octreotide for GI hemorrhage in children. In one study, continuous infusion of octreotide in seven patients was evaluated. Bleeding ceased in six of the seven patients. The duration of infusion ranged

from 24 to 234 hours. Although bleeding stopped within 24 hours in nearly half of the patients, on average, bleeding stopped after 40 hours. The most notable adverse effect was hyperglycemia.[89] Subcutaneous octreotide has also been used for severe chronic GI hemorrhage for periods of 24 to 50 months.[90]

Vasopressin

Generally vasopressin has been used for treatment of variceal bleeding more frequently than for nonvariceal upper GI bleeding. In fact, adult guidelines do not address the use of vasopressin for non-variceal bleeding.[87] Vasopressin acts by mechanisms similar to octreotide; however, its effects on blood pressure make it a less desirable option in many patients.[91] From a medication safety perspective, vasopressin prescribing can be confusing given the wide range of accepted dosing conventions and variety of indications in pediatric patients (e.g., diabetes insipidus, GI hemorrhage, shock). Dosing recommendations that require units per kg per unit time require careful decimal place checks. Intensive care units should decide on the accepted dosing convention and dose range for vasopressin for each indication and use infusion pumps with safety software that can accommodate the predetermined limits to prevent 10-fold dosing errors.

Helicobacter Pylori Infection

Patients who have GI bleeding of unknown etiology should be tested for *Helicobacter pylori*. At minimum, therapy requires three different medications administered twice daily for 1 to 2 weeks. Three different regimens are recommended for first-line treatment in pediatrics. Each consists of a proton pump inhibitor in combination with amoxicillin and clarithromycin, amoxicillin and metronidazole, or metronidazole and clarithromycin. Second-line options incorporate bismuth subsalicylate or ranitidine, and tetracycline as one of the antibiotic choices.[92] Tetracycline is contraindicated in patients younger than 8 years because of permanent discoloration of teeth, enamel hypoplasia, and retardation of skeletal development and bone growth.[14] Noncompliance with *H. pylori* regimens is the most commonly cited reason for treatment failure.[92] Pediatric *H. pylori* treatment guidelines are currently under revision.[93]

Drug-Induced Liver Injury

Cause

Liver injury in children may result from autoimmune disease, metabolic disease, infectious causes, acute hepatitis, ischemia, irradiation damage, and exposure to toxins or medications.[94,95] Drug-induced liver injury (DILI) has been noted to account for more than 50% of cases of acute liver failure in adults and approximately 20% in children, with acetaminophen as the agent most cited in the United States.[96,97] Most cases of DILI in children are mild, and many correct after the offending medication is discontinued.[97] However, some still progress to chronic liver injury.[98,99] Diagnosis of DILI is largely a diagnosis of exclusion. DILI patients typically present within 12 months of starting the suspected medication.[98] The Pediatric Acute Liver Failure (PALF) Study Group, a multinational, multisite consortium, was formed to prospectively study acute liver failure in children from birth through 18 years of age.[94,97] The 24 sites in the PALF study group hope to improve understanding of the pathogenesis, treatment, and outcomes of acute liver failure in children.[95] The PALF study group found that of the first 348 children enrolled through 2005, 14% had acute liver failure caused by acetaminophen, 5% caused by a drug or toxin other than acetaminophen, 10% caused by metabolic disease, 6% caused by autoimmune liver disease, 5% was idiosyncratic DILI, and 49% of unknown cause.[95,97,98] Younger children were more likely to develop ascites, require ventilator support, and require red blood cell and plasma infusions than older children.[95]

Various clinical scoring systems, including the Roussel Uclaf Causality Assessment Method (RUCAM) and the Naranjo Probability Scale, have been developed as a means to increase the specificity of diagnosis of drug hepatotoxicity. These scales consider the postexposure interval, biochemical pattern, exclusion of alternative causes, extrahepatic manifestations, rechallenge attempts, and previously reported cases. Their routine use has been limited in pediatrics and is not routinely recommended.[97] Table 87-3 summarizes the pharmacologic agents most cited as causing DILI in adult and pediatric patients. The corresponding references provide a more thorough discussion of the individual agents and/or case reports.

Treatment

Various pharmacological agents may be started to manage the wide-ranging adverse effects that arise from liver failure.

Cerebral Edema and Hepatic Encephalopathy

Protein restriction to 2 to 3 g/kg/day may help lessen excessive ammonia production,[100] whereas fluid restriction to 75% of maintenance may prevent cerebral edema and reduce encephalopathy.[101] Intravenous mannitol, continuous furosemide infusions, and tight glucose control have also been used for treatment of cerebral edema.[101] Oral antibiotics, in particular neomycin, have been effective in reducing ammonia production in adults with hepatic encephalopathy by suppressing ammonia-forming bacteria in the gut.[94,100] However, neomycin should be used cautiously in children because of potential renal toxicity and deafness. Synthetic disaccharides such as lactulose are metabolized by bacteria in the colon to form organic acids that lower the colonic stool pH and trap diffusible ammonia, thus decreasing serum ammonia levels. Lactulose forms the basis of therapy in children with hepatic encephalopathy and elevated serum ammonia levels, although the bulk of research surrounding its use is in adults.[100] Levocarnitine may offer another option for reduction of ammonia levels in the brain, whereas albumin infusions have been used to reduce plasma ammonia levels.[101] Sodium benzoate has been used in adults with cirrhosis, and may provide an alternative option in children.[94,101,103]

Ascites

Ascites is the accumulation of fluid in the peritoneal cavity. Although liver transplantation is the only definitive treatment for refractory ascites, many pharmacologic and nonpharmacologic options exist for acute management of ascites. Diagnostic abdominal paracentesis can help in directing therapy. Traditionally, bed rest has been recommended, however a lack of scientific evidence and difficulty enforcing in children may limit its

Table 87–3 Common Agents Cited in Drug-Induced Liver Injury[94,96-99,103,117,145-147]

Drug Class or Group	Specific Agents and Reaction	Comments
Analgesics	Acetaminophen: necrosis	
	Aspirin: Reye syndrome, necrosis	
	Bromfenac*: acute liver failure	
	Celecoxib: hepatocellular	
	Diclofenac: hepatitis, cholestasis	
	Etodolac: fulminant hepatic failure	
	Ibuprofen (rare): hepatitis, vanishing bile duct syndrome	
	Indomethacin: cholestasis, necrosis	
	Meloxicam: hepatitis	
	Naproxen: cholestasis	
	Oxaprozin: hepatocellular, hepatitis	
	Piroxicam: hepatocellular, cholestasis, necrosis	
	Sulindac: hepatitis, cholestasis	
Cardiovascular agents	Amiodarone: steatohepatitis, acute liver failure	
	Angiotensin-converting enzyme inhibitors (captopril, enalapril, fosinopril): hepatitis, cholestasis	
	Angiotensin II receptor inhibitors (irbesartan, candesartan, losartan): cholestasis, hepatocellular	
	β-Adrenergic receptor blockers (propranolol, metoprolol, acebutolol, atenolol, labetalol): hepatocellular, cholestasis	
	Calcium channel antagonists (diltiazem, nifedipine, verapamil): hepatitis, cholestasis	
	Hydralazine: hepatitis, necrosis, granulomas, cholestasis	
	Labetalol: necrosis, hepatitis	Labetalol: most hepatotoxic β-blocker
	Methyldopa: hepatitis, cholestasis, steatosis, cirrhosis, granulomas	
	Thiazide diuretics (hydrochlorothiazide, chlorothiazide, chlorthalidone): cholestasis	
Drugs used to treat diabetes mellitus	Glucosidase inhibitors (acarbose): hepatitis, cholestasis	Thiazolidinediones: monitor baseline liver tests and every 2 months after during first year of therapy
	Human insulin: hepatitis	
	Metformin: hepatitis, cholestasis	
	Sulfonylureas (chlorpropamide, gliclazide, glipizide, glimepiride, tolazamide, tolbutamide): hepatitis, cholestasis, vanishing bile duct syndrome	
	Thiazolidinediones (troglitazone,* rosiglitazone, pioglitazone): liver failure, hepatotoxicity, fibrosis	
Lipid-lowering agents	Ezetimibe: elevated serum transaminases	
	Fibrates (fenofibrate, gemfibrozil, nicotinic acid): hepatitis, acute liver failure, cholestasis, necrosis	
	HMG-CoA reductase inhibitors (statins) (atorvastatin, cerivastatin,* fluvastatin, lovastatin, pravastatin, simvastatin): cholestasis, hepatitis, acute liver failure	Statins: monitor liver function at baseline, within 12 weeks, and then every 6 months
Anticonvulsants	Carbamazepine, oxcarbazepine: cholestasis, hepatitis, vanishing bile duct syndrome, acute liver failure	
	Felbamate: hepatitis, acute liver failure (reserve use to drug-refractory epilepsy and Lennox-Gastaut syndrome)	Felbamate: discontinue immediately if aminotransferase is elevated

Continued

Table 87–3 Common Agents Cited in Drug-Induced Liver Injury—cont'd

Drug Class or Group	Specific Agents and Reaction	Comments
	Lamotrigine: hepatitis	
	Phenobarbital: acute hepatitis, cholestasis	
	Phenytoin: hepatitis (rare), cholestasis, granulomas, focal necrosis	
	Topiramate: acute liver failure, hepatocellular	
	Valproic acid: steatosis, necrosis, increase in aminotransferases; greatest risk in first 2 years of life; progression to liver failure most common in patients with underlying mitochondrial disorders	
Psychotropic and antidepressant medications	Atomoxetine: hepatobiliary	
	Chlorpromazine: cholestasis	
	Clozapine: hepatocellular, fulminant hepatic failure	
	Haloperidol: cholestasis	
	Nefazodone: liver failure	
	Olanzapine: hepatitis	
	Paroxetine: hepatitis	
	Pemoline: hepatitis, acute liver failure	
	Prochlorperazine: cholestasis	
	Risperidone: hepatocellular	
	Thiazide diuretics (hydrochlorothiazide, chlorothiazide, chlorthalidone): cholestasis	
	Trazodone: hepatocellular, cholestasis	
	Tricyclic antidepressants (amitriptyline, imipramine): cholestasis	
Chemotherapy and immunosuppressants	Azathioprine: hepatitis, hepatic veno-occlusive disease	
	Busulfan: hepatic veno-occlusive disease	
	Chlorambucil: cirrhosis, fibrosis, (rare)	
	Cyclosporine: cholestasis	
	Dacarbazine: acute hepatic failure	
	Dactinomycin (in combination with radiotherapy): hepatitis	
	Erlotinib: hepatitis, hepatorenal syndrome	
	Fluorouracil (when given intra-arterially): hepatitis, sclerosing cholangitis	
	Flutamide: cholestasis	
	Gemcitabine: hepatitis	
	Interleukin-2: hepatitis	
	L-asparaginase, pegaspargase: liver steatosis, hepatitis, necrosis, fibrosis	
	Megestrol acetate: cholestasis	
	Mercaptopurine, azathioprine: hepatitis, cholangitis	
	Methotrexate: cirrhosis, fibrosis, steatosis	
	Natalizumab: hyperbili	
	Nitrosoureas (carmustine, lomustine, streptozotocin): hepatitis, hepatic veno-occlusive disease	
	Paclitaxel, docetaxel: hepatitis	
	Plicamycin: hepatitis, necrosis	Plicamycin: most hepatotoxic chemotherapy agent commercially available
	Recombinant α-interferon: hepatitis	
	Tamoxifen: cholestasis	
	Thioguanine: hepatic veno-occlusive disease	

Continued

Table 87–3 Common Agents Cited in Drug-Induced Liver Injury—cont'd

Drug Class or Group	Specific Agents and Reaction	Comments
Anesthetics	Halothane: hepatitis, necrosis	
Anti-infectives	**ANTIBIOTICS**	
	Amoxicillin and amoxicillin/clavulanic acid: cholestasis, hepatitis	
	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin: cholestasis	
	Erythromycin: cholestasis, necrosis, hepatitis	
	Tetracycline, minocycline: microvesicular steatosis, hepatitis	
	FLUOROQUINOLONES	
	Ciprofloxacin, ofloxacin, levofloxacin, norfloxacin: hepatitis	
	Rifampin: hepatitis	
	SULFONAMIDES	
	Sulfamethoxazole and trimethoprim, sulfamethoxazole: hepatitis, cholestasis, granulomas	
	Nitrofurantoin: cholestasis, granulomas, chronic hepatitis	
	ANTIFUNGALS	
	Fluconazole, itraconazole, ketoconazole, flucytosine, terbinafine: cholestasis, hepatitis, necrosis	
	ANTIRETROVIRALS	
	Nucleoside analogue reverse transcriptase inhibitors (didanosine, stavudine): hepatic steatosis and lactic acidosis	
	Nevirapine: hepatitis	Nevirapine: monitor liver enzymes for first 18 weeks of therapy
	PROTEASE INHIBITORS	
	Ritonavir, tipranavir: acute liver failure, hepatitis, cholestasis	
	ANTITUBERCULOUS AGENTS	
	Isoniazid: hepatocellular necrosis	
	Pyrazinamide + rifampin or isoniazid	Rifampin + pyrazinamide combination use is discouraged by the CDC and ISDA because of severe liver injury
Miscellaneous	Allopurinol: hepatitis, fulminant hepatic failure	
	Amatoxin, found in wild mushrooms: acute liver failure	
	Cocaine: ischemic liver necrosis	
	Designer drugs of amphetamine (ecstasy): resemble acute viral hepatitis, acute liver failure requiring transplant	
	Estrogens: cholestasis	
	Marijuana and hashish: alterations in liver enzymes	
	Ondansetron: hepatitis	
	Propylthiouracil: hepatitis	
	Tolcapone: acute liver failure	
	Vitamin A (dose dependent): fibrosis, portal hypertension	
	Zafirlukast: hepatitis, necrosis	
Herbals	Camphor: necrolytic hepatitis	
	Cascara sagrada: cholestasis	
	Chaparral leaf, germander: acute and chronic hepatitis, cholestasis, cirrhosis, fulminant liver failure	
	Greater celandine: chronic hepatitis, cholestasis, fibrosis	

Continued

Table 87–3 Common Agents Cited in Drug-Induced Liver Injury—cont'd

Drug Class or Group	Specific Agents and Reaction	Comments
	Kava kava: acute and chronic hepatitis, fulminant liver failure	
	Ma huang: acute hepatitis, autoimmune hepatitis	
	Mistletoe: chronic hepatitis	
	Pyrrolizidine alkaloids (found in herbal and bush teas): veno-occlusive disease, dose-dependent hepatotoxicity	
	Sassafras: hepatocarcinogen	
	Saw palmetto: mild hepatitis	
	Usnic acid (lichen alkaloid): fulminant liver failure	
	Valerian: mild hepatitis	

*Withdrawn from market.
HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; *CDC,* Centers for Disease Control and Prevention; *ISDA*, Infectious Disease Society of America.

role.[104] Dietary restriction of sodium, such as restriction to 1 to 2 mEq/kg/day for infants and children and 1 to 2 g/day in adolescents, may help increase diuresis.[104,105] Diuretics are used to increase urinary sodium excretion, leading to a negative fluid balance and weight loss. The target negative fluid balance in children of approximately 10 ml/kg/day is often used.[104] Conflicting approaches to initiation of diuretics exist. Spironolactone typically is added first, with thiazide and loop diuretics (mainly furosemide in children) added if maximal doses of spironolactone are insufficient. Spironolactone acts to inhibit aldosterone at the distal renal tubule, thus inhibiting reabsorption of sodium, whereas furosemide inhibits sodium reabsorption in the ascending limb of the loop of Henle. Initial doses can be given once or twice daily, and titrated upwards as necessary.[94,101,104] Another approach is to initiate both spironolactone and furosemide upfront in a ratio of 5:2, with subsequent change to spironolactone monotherapy once a desired diuresis occurs.[105] Monitoring of serum electrolytes, acid base status, urine output and serum creatinine is necessary with all diuretic use, especially when using spironolactone and furosemide in combination. Potassium supplementation may be necessary. In patients with hypoalbuminemia, albumin infusion followed by furosemide may offer a brief, brisk diuresis.[101, 104] Fluid restriction is typically not necessary in children. In refractory ascites, other options may include large volume paracentesis, transjugular intrahepatic shunts, although unlike with adults have limited use in children, peritoneovenous shunts, and ultimately liver transplantation.[104] The most significant complication of ascites is spontaneous bacterial peritonitis.[105] *E. coli* and *Klebsiella pneumoniae* are the most common causes, hence an intravenous, third-generation cephalosporin such as cefotaxime is often used for empiric therapy as it covers 95% of the associated flora.[100,105] A β-lactam and β-lactamase combination agent, such as ampicillin/sulbactam, may offer an alternative,[104] as well as once-daily norfloxacin in cirrhotic patients with ascites for prevention of spontaneous bacterial peritonitis.[105] Trimethoprim-sulfamethoxazole has been considered a therapeutic alternative to fluoroquinolones given safety concerns in pediatrics.[100]

Coagulopathy and Hemorrhagic Complications

As both procoagulant and anticoagulant proteins are reduced in acute liver failure, clinically relevant bleeding rarely occurs. Intravenous vitamin K can be used to control coagulopathy, whereas severe cases may be treated with fresh frozen plasma and cryoprecipitate.[101] Recombinant factor VII offers another alternative for correction of prothrombin time/INR abnormalities when active bleeding is present, although its high cost may preclude its use.[94] Prophylaxis with H_2 receptor blockers, PPIs, or sucralfate is started to prevent any GI bleeding.[94,101] Infection may precipitate bleeding in this population; thus initiation of antibiotics should be considered if bleeding develops.[94] The use of nonselective β-blockers in children, while successfully used in both primary and secondary prevention of variceal hemorrhage in adults with portal hypertension, is controversial. Insufficient data exist to demonstrate its use in this population; however, use may be considered as related to a risk reduction in bleeding. Both endoscopic injection sclerotherapy and endoscopic variceal ligation for variceal bleeding have been shown to be effective in treating varices in children and preventing future bleeding, thus these options are considered first-line, with beta blocker use adjunctive therapy.[100] For emergent treatment of variceal bleeding in children, intravenous octreotide or continuous vasopressin is often initiated in an attempt to lower splanchnic vascular tone, thus decreasing portal venous pressure.[100,101] However, approximately 30% of children treated with octreotide will still have a persistent hemorrhage despite conservative management and octreotide.[100]

Pruritus

Pruritus may be a result of prolonged cholestasis or noncholestatic liver disease. Treatment of underlying cholestatic disease should improve pruritus. Cholestyramine, an anion exchange resin, is widely used.[106] Other agents that have been used and may offer benefit include ursodiol, opioid antagonists such as naloxone and naltrexone, rifampin, antihistamines, dexamethasone, and ondansetron.[98,106] Trials have also evaluated prednisolone, cyclosporine, methotrexate, exposure to ultraviolet light, s-adenosyl methionine, antioxidants, macrolide antibiotics, and plasmapheresis with varying results.[106]

Cholangitis

Primary care consists of fasting, adequate intravenous hydration and broad spectrum antibiotics such as a third-generation cephalosporin and/or aminoglycoside to cover gram-negative bacilli, mainly *Enterobacter* spp.[107]

Miscellaneous

Acetaminophen is a widely used over the counter medication and the most common cause of DILI in children in the United States. DILI can occur after ingestion of therapeutic doses of acetaminophen over several days to treat clinical symptoms or a single overdose. Interventions for toxic acetaminophen ingestion include inhibiting drug absorption (i.e., gastric lavage), dialysis,[108] prevention of the conversion to the toxic intermediate metabolite *N*-acetyl-p-benoquin imine (i.e., through use of cimetidine), replenishment of glutathione stores to prevent hepatotoxicity, and liver transplant. Methionine, cysteamine and *N*-acetylcysteine (NAC) are available agents to detoxify *N*-acetyl-p-benoquin imine.[109] NAC is available either oral or intravenously in the United States and is the antidote of choice with fewer GI and central nervous system adverse effects compared with these other agents.[109,110]

It has been proposed that NAC may be useful therapy in other types of liver failure because of its ability to enhance hepatosplanchnic perfusion, to improve oxygen supply and demand, and its presumed cytoprotective and antioxidant effects. NAC may offer benefit in this patient population; however, many unanswered questions regarding dose, duration, and timing still remain.[111,112]

Dose Adjustments for Hepatic Dysfunction

Drugs absorbed via the GI tract undergo hepatic metabolism via a Phase I reaction (i.e., oxidation, reduction or hydrolysis) mediated be the CYP450 family of enzymes. These enzymes are found primarily in the liver.[96,105] These reactions cause the biotransformation of the parent compound to a more polar compound, that is more readily excreted.[99,113] Many adverse drug reactions and therapeutic failures can be attributed to genetically based differences in drug metabolism and elimination. Individuals can be divided into three groups: poor metabolizers, intermediate metabolizers, and extensive metabolizers. Average doses of medications given to poor metabolizers leads to higher drug exposure and greater risks of adverse drug reactions and drug toxicity.[99] The CYP3A subfamily makes up the largest group of CYP enzymes in the liver, with CYP3A4 the most important for post natal metabolism.[103,114-116] Consideration of the activity of the CYP450 isoenzymes, with specific focus on age differences, may aide in accurate drug dosing. For example, children require doses 50% to 100% higher than adults of drugs metabolized primarily by CYP2C9, whereas CYP3A4 activity is low at birth and reaches 72% of adult values at 1 year of age.[115] However, age-related changes in the pharmacokinetics of various drugs may be difficult to separate from altered enzyme activity due to altered liver mass, liver blood flow, and changes in plasma drug binding.[113]

There are no specific diagnostic tests or pathological findings to diagnose liver dysfunction. Routine laboratory tests to assess liver function are helpful in identifying a hepatic insult; however, these findings are not specific to viral, autoimmune, metabolic disorders or drug-related causes, nor do they identify the extent that hepatic metabolism may be impaired.[117] When hepatotoxicity is attributed to a dose-dependent hepatotoxin such as acetaminophen, blood levels of the suspected agent should be drawn.

Table 87–4 The Child-Pugh Score

Points	1	2	3
Encephalopathy	None	Minimal (stage I–II)	Advanced (coma) (stage III–IV)
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time	<4	4–6	>6
Child-Pugh class A: 5–6 points	Child-Pugh class B: 7–9 points		Child-Pugh class C: 10–15 points

Modified from Pugh RN, Murray-Lyon IM, Dawson JL, et al: Transection of the oesophagus for bleeding oesophageal varices, *Br J Surg* 60:646-649, 1973.

The Child-Pugh score, adapted from the original Child score proposed in 1964, has been extensively used in adults as a user-friendly classification system for liver disease. This score is used as a prognosis of liver disease and as an indicator of a patient's ability to metabolize drugs eliminated by the liver.[118] However, this tool does not have the ability to predict the liver's ability to metabolize individual drugs.[116] Although various recent tools exist to classify liver disease, such as the Model for End-Stage Liver Disease (i.e., MELD) score widely used in adult liver transplantation ranking, the Child-Pugh score is the classic standard.[116,119] Patients are divided into three risk groups, based on their degree of liver dysfunction. Class A is low risk/mild disease, class B is intermediate risk/moderate disease, and class C is high risk hepatic dysfunction/severe disease (Table 87-4). Even with the wide acceptance and use of the Child-Pugh score, there are a limited number of medications containing specific recommendations for dosage adjustment based on hepatic function as categorized by the Child-Pugh score.[116] In 2005, a review of all Food and Drug Administration-approved medications found that only 23 included guidance for dosage adjustment based on Child-Pugh. Dose adjustments were typically recommended starting with Class B liver dysfunction, with many agents suggesting nonuse in patients with Class C rankings.[120]

Rectal Administration of Medication

Many drugs otherwise approved for oral and/or intravenous use have been administered rectally, in both adults and children. Rationale for using the rectal route varies. Rectal administration allows for avoidance of the orogastric route when necessary or avoidance of the intravenous route when access is an issue or when parenteral dosage forms are not available. The rectal route allows for a higher local concentration of drug in situations where limited systemic absorption is desired. Administration via this route may afford a less-costly alternative to a considerably more expensive parenteral product, and may offer an alternative when a parenteral product is unavailable. Although generally well accepted amongst patients and their families[121,122] clinicians may need to overcome resistance to rectal administration from patients and families because of personal perceptions.

Interpatient variability surrounding rectal administration is a key factor for clinicians to consider. Drug absorption may be accelerated or delayed. The rate of rectal transmucosal

absorption is affected by various factors. First, the formulation of the product itself varies, causing differences in the time to liquefaction with suppositories, the volume of liquid administered and the concentration of the drug. The length of the rectal catheter helps determine the site of absorption. Drugs administered high in the rectum, which is drained by the superior rectal veins, typically are carried to the liver via the portal vein, thus subject to first-pass hepatic metabolism. Drugs administered low in the rectum are delivered into the venous circulation by the inferior and middle rectal veins before passing through the liver. Presence of stool in the rectum and rectal pH can alter drug absorption. Rectal pH affects absorption by ionizing varying amounts of drug. The rectal mucosa in children typically has a more alkaline pH.[123] Nonionized drugs have greater lipid solubility, causing enhanced absorption across biological membranes. The rectal retention of the drug administered also affects absorption.[124]

The rectal route has been commonly studied with the use of rectal diazepam gel (Diastat). This commercially available product is used for prolonged or repetitive seizures in children and has approval by the FDA for at-home administration by a trained nonprofessional caregiver. Clinical trials and postmarketing data have reported a low rate of serious respiratory adverse events,[125] a major concern of many clinicians surrounding at-home use; however, cases have been reported in chronic, high-dose users of fluctuating effects of rectal diazepam, including reappearance of seizure activity.[126] This product may offer an alternative to other oral and intravenous benzodiazepine options available in a critical care setting, especially in emergent situations if access cannot be readily achieved. The controlled environment of a critical care unit can easily recognize adverse effects as opposed to home administration.

Clinically, successful rectal administration of medication in children has dealt mainly with anticonvulsants such as diazepam, lorazepam, and oxcarbazepine for status epilepticus[127]; sedatives such as diazepam, midazolam, and ketamine in varying uses[124,128]; localized treatment for irritable bowel disease using mesalamine[129-131]; vancomycin for pseudomembranous colitis[132]; antibacterial agents such as erythromycin[133]; antiemetics[134]; cardiovascular agents such as nifedipine and metoprolol[135-138]; and analgesics, specifically acetaminophen, nonsteroidal antiinflammatory drugs, and tramadol, for temperature reduction and postoperative pain control.[121,122,139,140] Although the American Academy of Pediatrics dissuades the rectal use of acetaminophen without consultation with a health care provider,[141] it has been widely used and studied.[139,140,142,143] In addition, rectally administered nonsteroidal anti-inflammatory medications, opioid analgesics, antiseizure medications, antiemetics, anticholinergic medications, antidepressants, psychostimulants, and antibiotics have been used with success in the hospice and palliative care settings.[144]

In a pediatric critical care environment, rectal administration of medication may be most beneficial when intravenous access issues are present, either because of an inability to maintain or achieve intravenous access or in situations when placement of an intravenous line is otherwise not necessary. Rectal administration in children is relatively painless, and comparable to rectal temperature monitoring, a common practice. Practical considerations for prescribers include knowledge of available dosage forms for rectal use, either commercial or those approved for orogastric use, interpatient variability of absorption, varying amounts of immeasurable drug expelled by the patient, thus altering dosage, and social considerations including patient and/or family perceptions of rectal medications, especially in older children and adolescents.

References are available online at http://www.expertconsult.com.

V

Chapter 88

Acute Liver Failure, Liver Transplantation, and Extracorporeal Liver Support

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PEARLS

- Pediatric liver failure represents a large number of heterogenous etiologies, although the management of acute failure is similar in most situations.
- Although orthotopic transplantation is definitive for irreversible hepatic failure, many cases of acquired acute failure may experience complete, recovery making the *timing* of transplantation a critical decision best undertaken in a transplant center.
- Extracorporeal support provided as continual renal replacement therapy can contribute to stabilization by optimizing (1) fluid balance, (2) electrolyte status, (3) nutritional support, and (4) coagulation status.
- The best outcomes following transplantation are seen in patients who are managed by a knowledgeable team pre- and postoperatively including hepatologists, transplant surgeons, and a meticulous intensive care unit team.

Acute liver failure (ALF) is a relatively rare and potentially fatal disease. It represents a heterogeneous condition with numerous etiologies in which the pathophysiology is diverse and frequently unclear, preventing substantial advances in specific therapy. Recognized etiologies include infections, toxins, metabolic disorders, infiltrative diseases, autoimmune hepatitis, ischemic, or irradiation damage, although a proportion of cases are unable to be diagnosed and fall into the cryptogenic group.[1-4] For the pediatric intensivist, the mainstay of therapy consists of *meticulous* supportive measures, with a focus on anticipation and prevention or treatment of complications and early consideration for liver transplantation.[5-10] With the onset of cerebral edema in children with acute liver failure, the risk for permanent disability increases dramatically.[11-13] Thus the timely intervention to prevent the metabolic derangements associated with acute liver failure is pivotal in preventing progression and the morbidity associated with this condition.[14-16] The rewards of bridging children with end-stage liver failure are reflected in the recent publication of the Pediatric Acute Liver Failure (PALF) Study Group, in which 53% of patients survived with medical therapy alone and an additional 30% survived with the aid of liver transplantation.[3]

Definition

Liver failure is defined as the loss of vital functions of the normal liver that entails synthesis of serum proteins including clotting factors and albumin, bile production and excretion, detoxification of organic anions, metabolism and storage of glucose and fatty acids and elimination of ammonia and other byproducts of energy utilization and protein metabolism. The significant compromise of these functions implies loss of a critical mass of hepatocytes, and the clinical manifestations of liver failure are dependent on the extent and time course of liver cell death.

The clinical syndrome of acute or "fulminant" liver failure is defined as the onset of hepatic encephalopathy and coagulopathy within 8 weeks of the onset of liver disease in the absence of preexisting liver disease in any form.[1,17] This narrow definition does not adequately address children with new-onset liver disease who develop encephalopathy more than 8 weeks after presentation or children with subclinical chronic liver disease such as autoimmune hepatitis or Wilson disease who present initially with liver failure. Although the management principles of children are similar for most etiologies of liver failure,[15,16] it is important for the intensivist to recognize that the prognosis can be remarkably different for the different underlying causes.

Epidemiology

The cause of ALF in children continues to be age dependent[2,3,18] with viral hepatitis probably the most common cause of ALF in all age groups overall. Severe hepatitis from echovirus and adenovirus is seen almost exclusively in the neonatal population. Liver failure can be one of the manifestations of overwhelming herpes infection in the newborn or immunocompromised patient. Metabolic liver disease and familial erythrophagocytosis are most commonly found in infants. Acute hepatitis A and B infections are rare causes of ALF in North America, but are a common cause of ALF in school-aged

Box 88–1 Investigations in Fulminant Hepatic Failure

Baseline essential investigations
Biochemistry
- Bilirubin, transaminases
- Alkaline phosphatase
- Albumin
- Urea and electrolytes
- Creatinine
- Calcium, phosphate
- Ammonia
- Acid-base, lactate
- Glucose

Hematology
- Full blood count, platelets
- PT, PTT
- Factors V or VII
- Blood group cross-match

Septic screen
Omitting lumbar puncture
- Radiology
- Chest radiograph
- Abdominal ultrasound
- Head CT scan or MRI

Neurophysiology
- EEG

Diagnostic investigations
Serum
- Acetaminophen levels
- Cu, ceruloplasmin (>3 years)
- Autoantibodies
- Immunoglobulins
- Amino acids
- Lactate
- Pyruvate
- Hepatitis A, B, C, E
- EBV, CMV, HSV
- Other viruses

Urine
- Toxic metabolites
- Amino acids, succinylacetone
- Organic acids
- Reducing sugars

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

children in developing countries.[19] Drug-induced liver disease is more common in older children especially that secondary to intentional acetaminophen overdose.[20] Acute liver failure of indeterminant cause is common in all age groups, accounting for 40% of ALF among patients younger than age 3 years and 60% in those age 3 years and older.[20]

The incidence of ALF in childhood is not well described but has been estimated to be 2000 cases per year in adults in the United States. A recently established multicenter database (PALF) including 24 pediatric liver centers in the United States, Canada, and England, has collected demographics and outcome data from 348 pediatric cases of acute liver failure over a 6-year period.[20] A specific etiology could not be determined in 49% of the cases. Overall survival in this group was 84% at 3 weeks after presentation with 36% of the survivors receiving liver transplantation.[3,20] Considering the infrequency of this diagnosis and the frequent associated morbidity and mortality it is not unexpected that few pediatric subspecialists are comfortable managing patients with this diagnosis.

Clinical Presentation by Etiology

The clinical presentation varies with etiology but, in most cases admitted to the pediatric intensive care unit (PICU), there is hepatic dysfunction with hypoglycemia, coagulopathy and encephalopathy. Jaundice may be a late feature, particularly in metabolic disease. The clinical onset may be within hours or weeks. Most pediatric patients who develop ALF are previously healthy, with no history of major medical problems and no clear exposure to hepatitis or toxins.

Beyond the acute stabilization and attempts at detoxification of children with ALF, subsequent diagnosis and management of these patients must occur at a center familiar with the needs of this subset of critically ill children and with the resources (e.g., blood banking, continuous renal replacement therapy) necessary to provide optimal care until either recovery or transplantation occurs. The decision to transfer a patient with evolving signs of progressive liver failure must be made in a timely manner, because the risks of transporting patients in a deteriorating condition with advanced hepatic encephalopathy or uncontrolled bleeding can be monumental. When liver transplantation is not possible due to geography or other considerations, such transfer to a distant center may be a futile effort and a very disruptive experience for the terminal patient (and family) with advanced liver failure.

Family Support

Families of children with acute liver failure are naturally devastated by the development of potentially fatal, acute organ failure in their child. Such families require a considerable amount of psychological support and counseling, particularly as many families will not be able to grasp the seriousness of their child's condition and the implications of liver transplantation. Living donor transplantation is a reasonable option for families who are able to quickly assimilate the broad implications of ALF. The family's ability to comply with long-term care and medication regimens, should liver transplantation be necessary, is critical to the ultimate success of the process. The particular problems of suicide attempts and gestures in adolescents may require additional psychiatric help.

Management

Initial Assessment and Care

There is no specific therapy for acute and end-stage liver failure except hepatic replacement. Management therefore is directed toward early consideration for liver transplantation, hepatic support, treatment of acquired infections, and prevention and treatment of complications while awaiting recovery or a suitable donor for liver transplantation.[15,16,22-36] The key elements in managing patients before transplantation are meticulous medical support in the setting of an intensive care unit and rapid referral to a transplant center. It is essential to take a full history from the parents; this would include establishing appropriate risk factors such as information on intravenous injections, infusions of blood products, foreign travel or contact with individual exhibiting jaundice. It is important

Table 88–1 Clinical Stages of Hepatic Encephalopathy[3]

Stage	Asterixis	EEG Changes	Clinical Manifestations
I (prodrome)	Slight	Minimal	Mild intellectual impairment, disturbed sleep-wake cycle
II (impending)	Easily elicited	Usually generalized	Drowsiness, confusion, coma/inappropriate behavior, disorientation, mood swings
III (stupor)	Present if patient cooperative	Grossly abnormal slowing of rhythm	Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign
IV (coma)	Usually absent	Appearance of delta waves, decreased amplitudes	Unconscious, decerebrate or decorticate response to pain present (stage IVA) or absent (stage IVB)

to establish what medications the child has taken, including over-the-counter preparations, folk remedies and herbal supplements, what medications might be in the household, and in adolescents to inquire about the use of illicit drugs and sexual contact. Folk remedies, some Chinese herbs, and herbal supplements (e.g., pennyroyal) in particular are often overlooked by parents giving a medical history but may be vital information in establishing an etiology.[27] Until a diagnosis is made (Box 88-1), it is assumed that all children are infectious and that all blood, excretions and secretions are potentially capable of transmitting viral hepatitis. Enteric isolation procedures must be enforced (http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf) until an infectious etiology has been ruled out.

The initial physical examination should determine the status of major organ systems including hepatic, cerebral, cardiovascular, respiratory, renal, and acid–base balance. The patient's level of consciousness and degree of hepatic encephalopathy (Table 88-1) should be established using a reliable scale[3,28,29] and a complete central nervous system examination performed including examination of reflexes and mental status. Progression of coma may be assessed by serial examinations. Evidence of chronic liver disease or other signs which may suggest an etiology, such as Kayser-Fleischer rings, caput succedaneum, cataracts, and needle marks, should be established. Liver size and consistency should be determined and documented. The presence of impaired central nervous system function with acute liver disease is an indication for immediate hospitalization independent of any other clinical or biochemical findings. Observation in a suitable facility to intervene immediately with mechanical ventilation, intracranial pressure monitoring, if deemed beneficial, rapid availability of blood products and the ability to maintain acid-balance/fluid and electrolyte balance is critical. Typically, this level of support warrants referral to a transplant center where greater experience and availability of emergency transplantation may prove lifesaving.

A central venous catheter is useful for assessment of right heart function and volume status, but must be placed with care in patients with significant coagulopathy or thrombocytopenia. Use of a multilumen catheter, which enables simultaneous administration of blood products, dextrose solutions to maintain normal serum glucose levels, intravenous fluids and drugs, is helpful and may be replaced if needed to facilitate exchange blood transfusions or renal replacement therapy when required. An indwelling arterial line for continuous measurement of blood pressure and for biochemical and acid-base monitoring is frequently helpful especially in patients with evolving cardiopulmonary instability or in whom intracranial pressure monitoring is planned.[30] A nasogastric tube is passed and placed to gravity, with regular gentle saline lavage to detect upper gastrointestinal hemorrhage. The urinary bladder is catheterized and strict output measured to help in the evaluation of fluid status and renal function. Ideally, the patient is placed on a bed that permits the body weight to be recorded frequently.

Baseline biochemical and other investigations should be performed and management initiated as in Box 88-2. Frequency of biochemical monitoring will depend on the severity of illness, ranging from daily in mild cases to every 4 to 6 hours in patients in stage III and IV coma, and should include complete blood count, blood gases, electrolytes, aminotransferases, and prothrombin time, plus daily monitoring of plasma creatinine, bilirubin, and ammonia. A baseline chest radiograph is useful to diagnose cardiac dysfunction or aspiration.

Box 88–2 Management of Fulminant Hepatic Failure

No sedation except for procedures
Minimal handling
Enteric precautions until infection ruled out
Monitor:
- Heart and respiratory rate
- Arterial BP, CVP
- Core/toe temperature
- Neurological observations
- Gastric pH (>5.0)
- Blood glucose (>4 mmol/L)
- Acid-base
- Electrolytes
- PT, PTT

Fluid balance
- 75% maintenance
- Dextrose 10%–50% (provide 6–10 mg/kg/min)
- Sodium (0.5–1 mmol/L)
- Potassium (2–4 mmol/L)

Maintain circulating volume with colloid/FFP
Coagulation support only if required
Drugs
- Vitamin K
- H_2 antagonist
- Antacids
- Lactulose
- *N*-acetylcysteine for acetaminophen toxicity
- Broad-spectrum antibiotics
- Antifungals

Nutrition
- Enteral feeding (1–2 g protein/kg/day)
- PN if ventilated

BP, Blood pressure; *CVP,* central venous pressure; *FFP,* fresh frozen plasma; *PN,* parenteral nutrition; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

An abdominal ultrasound may indicate liver size and patency of hepatic and portal veins, particularly if liver transplantation is being considered.

Fluid Balance

The aim of fluid balance is to maintain hydration and renal function while not provoking cerebral edema. Maintenance fluids consist of 10% dextrose in 0.25 normal saline, and intake should be 75% of normal maintenance requirements unless cerebral edema develops. A total sodium intake of 0.5 to 1.0 mmol/kg/day is usually adequate. Potassium requirements may be large, 3 to 6 mmol/kg/day, as guided by the serum concentration. As patients may become hypophosphatemic, intravenous phosphate may be given as potassium phosphate. Maintenance of euglycemia is critical and may require 3 to 6 mg/kg/min of dextrose infusion or greater.

Attempts should be made to maintain urinary output using loop diuretics in large doses (furosemide at 1 to 3 mg/kg dosed intravenously every 6 hours), vasoactive-inotropic agents and colloid/fresh frozen plasma (FFP) to maintain adequate preload and renal perfusion. Should profound oliguria occur, early consideration should be given to hemofiltration or dialysis prior to the development of hemodynamic instability (see section below on hemofiltration).

Anemia should be corrected, maintaining the hemoglobin concentration above 10 g/dL to provide acceptable oxygen delivery to tissues. Coagulopathy should be managed conservatively; the massive requirements for fresh frozen plasma may result in fluid overload requiring the institution of renal replacement therapy. In addition, the use of frequent FFP when not essential to control bleeding may confuse the signs of clinical recovery, which is often best reflected in an improving prothrombin time.

Nonspecific Adjunctive Therapy

It is usual to administer a single dose of vitamin K (2 to 10 mg intravenously) although it is frequently not effective. Proton pump inhibitors and antacids (see below) should be administered prophylactically to minimize the risk of gastrointestinal hemorrhage from stress erosions. The role of *N*-acetylcysteine in the management of ALF other than acetaminophen poisoning has been investigated with promising results. A multicenter, randomized trial of a continuous infusion of *N*-acetylcysteine over the first 72 hours after presentation in adult patients with ALF suggests that *N*-acetylcysteine may improve spontaneous survival in patients with early stages of encephalopathy.[31,32]

Antibiotic Therapy

The results of surveillance cultures can be used to guide antibiotic therapy in the event of suspected infection, but broad-spectrum antibiotics (amoxicillin, cefuroxime, metronidazole, and prophylactic fluconazole) are only prescribed if sepsis is suspected or liver transplantation is anticipated.

Nutritional Support

The role of parenteral nutrition in the management of patients with acute liver failure is controversial. The main aims of therapy are the following:

1. To maintain blood glucose (>40 mg/dL) and ensure sufficient carbohydrates for energy metabolism
2. To reduce protein intake to 1 to 2 g/kg/day, either enterally or parenterally
3. To provide sufficient energy intake to reverse catabolism, either enterally or parenterally

Children who are mechanically ventilated should receive parenteral nutrition to minimize negative nitrogen balance because it may be 7 to 10 days before full normal diet is resumed after transplantation.

Central Nervous System Monitoring

A baseline electroencephalogram may be helpful to stage coma; however, the findings are typically nonspecific. Computed tomography scans may be useful early in encephalopathy as a baseline examination to be compared with subsequent imaging to evaluate for signs of progressive, cerebral edema later in the disease. Frequent evaluation of neurological function with serial examinations and blood ammonia is essential to follow the progress of hepatic encephalopathy. Continuous or frequent electroencephalography may demonstrate abnormal electrical activity as a heralding sign of progressive hepatic encephalopathy or subclinical seizure activity. The role of intracranial pressure monitoring remains controversial (see Cerebral Encephalopathy and Edema sections in the following sections). The choice of intracranial pressure monitoring system is dependent on the standards of the individual institution and neurosurgeon consulting on the case (see also Chapter 59). All forms of intracranial monitoring are potentially hazardous in patients with severe coagulopathy, but they may provide helpful information on changes in intracranial pressure and improve selection for liver transplantation.[30]

Prevention and Management of Complications

The clinical course before transplantation of patients with advanced hepatic failure is dominated by the myriad complications affecting a wide range of organ systems. Monitoring for evidence of those complications and their skillful and timely management should be the focus of the intensivist in the preoperative period. The following discussion covers the most common organ system dysfunctions seen in this critically ill patient population.

Hypoglycemia

Hypoglycemia (blood glucose <40 mg/L) develops in the majority of children. It may contribute to central nervous system impairment and other organ dysfunction. Factors contributing to hypoglycemia include (1) failure of hepatic glucose synthesis and release, (2) hyperinsulinemia (due to diminished of hepatic degradation), (3) increased glucose utilization (due to anaerobic metabolism), and (4) secondary bacterial infection.[33-36]

Frequent bedside monitoring of blood glucose concentrations (every 2 to 4 hours) and the intravenous administration of glucose (10% to 50% dextrose) are required to prevent this complication. Patients may typically require 5 to 8 mg/kg/min of dextrose infused to meet these goals; however, clinicians should avoid excessively high rates of glucose infusion and the resulting hyperglycemia. Increased insulin production, secondary to excess glucose infusion, leads to increased glucose need and net lipogenesis that can be avoided by permitting the blood glucose to remain between 40 and 60 mg/L. Profound *refractory* hypoglycemia carries a grave prognostic implication and often heralds the imminent death of the patient.

Coagulopathy and Hemorrhage

The management of coagulopathy and hemorrhage is a major challenge in the overall care of the child with acute liver failure. Profound disturbances in hemostasis develop secondary to failure of hepatic synthesis of clotting factors and fibrinolytic factors, reduction in platelet numbers and function, and/or intravascular coagulation.[37,38] The coagulation factors synthesized by hepatocytes include factors I (fibrinogen), II (prothrombin), V, VII, IX, and X, and a reduction in synthesis leads to the prolongation of prothrombin and partial thromboplastin time

The prothrombin time is the most clinically useful measure of hepatic synthesis of clotting factors. Prolongation of the prothrombin time often precedes other clinical evidence of hepatic failure, such as encephalopathy, and may alert the clinician to the severity of acute hepatitis; it is a guide to the urgency of liver transplantation. Administering vitamin K parenterally (2 to 10 mg intravenously) assures the sufficiency of this essential cofactor, but rarely improves coagulation in ALF.

The prothrombin time depends on the availability of factor VII, which has the shortest half-life (approximately 4 to 7 hours) of the clotting factors and decreases more rapidly than other liver-derived clotting factors when production does not keep up with its utilization. As a result, measurement of factor VII is be a more sensitive indicator than the prothrombin time but is typically not as readily available. Fibrinogen concentrations are usually normal unless there is increased consumption such as in disseminated intravascular coagulation (DIC). The level of factor VIII may help differentiate between DIC and ALF because factor VIII is synthesized by vascular endothelium and therefore is normal or increased in ALF as an acute-phase response or from decreased utilization. Decreased levels of factor XIII may contribute to poor clot stabilization.

A reduction in platelet numbers ($80 \times 10^3/\mu L$) occurs in up to half of adult patients, although thrombocytopenia is less of a problem in pediatric experience. Severe thrombocytopenia, requiring platelet transfusion, suggests hypersplenism, intravascular coagulation, or aplastic anaemia. Use of extracorporeal support devices may also contribute to abnormally low platelet numbers.

Intravascular coagulation as detected by abnormal concentrations of fibrin degradation products is present in almost all ALF patients, indicating ongoing clot deposition and dissolution, most probably as a consequence of tissue necrosis in the liver. Rarely significant in ALF, DIC can contribute to organ damage. Sepsis may also be present as an additional cause of DIC. With the ready availability of activated Factor VIIa concentrate, the intensivist should recognize that the administration of commercial concentrates containing activated clotting factors may itself precipitate DIC.

Oozing from needle puncture sites and line insertion is common, whereas pulmonary or intracranial hemorrhage may be terminal events. Petechiae reflect decreased platelet function, disturbed vascular integrity, or DIC.

Although in the early stages of assessment prolongation of prothrombin time is a sensitive guide to prognosis and the need for liver transplantation, coagulopathy resulting in significant bleeding should be treated with FFP infusion at a rate of 15 to 20 mL/kg FFP every 6 hours, or by continuous infusion at a rate of 3 to 5 mL/kg/h, with the addition of cryoprecipitate and platelets as needed. Treatment to improve coagulation status should also be attempted prior to invasive procedures. In the very small infant, recombinant Factor VIIa may provide significant hemostasis with less volume loading.

Administration of recombinant factor VIIa (40 μg/kg) reliably corrects the coagulation defect in patients with acute liver failure for a period of 6 to 12 hours and may be useful in preparation for invasive procedures.[39] Double-volume exchange transfusion may also temporarily improve coagulation to control life-threatening hemorrhage, especially in patients with DIC. Hemofiltration may be necessary to control fluid balance and provide fluid "space" if large amounts of coagulation support are required. Platelet counts should be maintained above $50 \times 10^3/\mu L$ by infusion of platelets. DIC is rarely severe enough to warrant the risks of heparin infusion to break the vicious cycle.

Prevention of Gastrointestinal Hemorrhage

Gastrointestinal tract hemorrhage may be life-threatening and secondary to gastritis or stress ulceration. PPIs (pantoprazole 0.5 to 1.0 mg/kg/day up to 20 mg for children <40 kg) or high-dose H_2 antagonists (ranitidine 1 to 3 mg/kg dosed every 8 hours) should be administered intravenously to reduce the risk of upper gastrointestinal tract bleeding. Prevention of gastrointestinal hemorrhage may also prevent further hyperammonemia by eliminating the large protein load to the intestines.

Encephalopathy

Clinically, acute hepatic encephalopathy is defined as any brain dysfunction that occurs as a result of acute hepatic dysfunction[40] and may be exacerbated by sepsis, gastrointestinal bleeding, electrolyte disturbances, or sedation, particularly benzodiazepine administration. Clinical manifestations and progression are highly variable, but acute hepatic encephalopathy usually evolves over days through definable stages. In rare cases, it may progress rapidly with coma and fatal cerebral edema developing within hours of the earliest detectable signs.

A scale for grading clinical encephalopathy is presented in Table 88-1. This scale is useful for assessing encephalopathy in older patients and the table includes guidelines for assessing infants, particularly in the early stages of encephalopathy.

The earliest abnormalities may not be detectable by clinical assessment, but are apparent to family members. Personality changes, reflective of forebrain dysfunction, include regression, irritability, apathy and occasionally euphoria. Younger children are more likely to be irritable and apathetic. Sleep disturbances, such as insomnia or sleep inversion, are often observed.

Intellectual deterioration, observed in stage I of chronic hepatic encephalopathy, is usually not evident in acute encephalopathy. Constructional apraxia related to disturbed spatial recognition may be present. Simple age-related tasks may be clinically useful tools for the day-to-day assessment of inattentiveness and apraxia. Subtraction of serial 7s (in older children and adults), recall of events (such as recently viewed videos), handwriting, and figure-drawing are appropriate tasks that older children can be asked to repeat daily in order to assess early encephalopathy. Younger children when asked to color a figure in a simple coloring book may not complete the task (inattentiveness), or scribble far outside the lines (constructional apraxia).

As the patient progresses into stage II hepatic encephalopathy, drowsiness and lethargy are readily apparent. Mental deterioration is clearly eviden—the personality changes and

behavior becomes inappropriate, with outbursts of anger or crying. Infants exhibit increasing irritability and often produce high-pitched screams. They may refuse to take feedings. Asterixis develops and is a useful sign, but it cannot be elicited with regularity in children less than 8 to 10 years of age. Motor impairment becomes evident, including ataxia, dysarthria and apraxia. Other neuromotor disturbances that can be detected at this stage include hyperreflexia, sustained clonus, rigidity, extensor posturing, and bizarre facial expressions. Electroencephalogram abnormalities are detectable at this stage.

Stage III hepatic encephalopathy is characterized by deepening somnolence and stupor. The patient is arousable by vigorous physical stimuli, but does not respond to commands. Patients are disoriented and often do not recognize family members. School-aged children and teenagers in deepening stage II and stage III coma often exhibit extreme agitation and rage. Biting and aggressive behavior may be a problem, and individuals caring for such children must be aware of the potential health risks involved. Seizures may develop. Neurological findings are more profound (see Table 88-1).[3]

Progression into stage IV hepatic encephalopathy is heralded by the onset of coma. The patient responds only to painful stimuli. At first, the patient is flaccid, but in deeper stage IV the patient will assume decerebrate posturing, and brainstem reflexes are lost. Respirations may become ineffective requiring mechanical support to prevent death.

Acute hepatic encephalopathy is completely reversible after resolution of the hepatic dysfunction as long as neuronal death has not developed due to the consequences of cerebral edema.

Management of Hepatic Encephalopathy

Although the role played by ammonia in the development of encephalopathy is controversial, traditional therapy to reduce ammonia production or accumulation is indicated. The essential components of therapy are (1) restriction of dietary protein, (2) enteral antibiotics, (3) enteral lactulose, (4) continuous hemofiltration in patients with renal insufficiency, and (5) controlling the complications of acute liver failure that contribute to ammonia accumulation.

In the early stages of hepatic encephalopathy, conventional measures are taken to minimize the formation of nitrogenous substances by the intestine. A cathartic, such as sodium-free magnesium sulphate and/or a nonabsorbable disaccharide (lactulose 1 to 2 mL/kg every 4 to 6 hours) may be administered orally or via the nasogastric tube. Enteral neomycin (50 to 100 mg/kg/day) may also be used to reduce ammonia production by colonic bacteria if diarrhea secondary to lactulose is a problem. Protein intake should be limited to 0.5 to 1.0 g/kg/day in this phase and may be administered enterally or parenterally to limit the production of ammonia. Caloric intake is maintained in the early stages with glucose polymers and supplemented by infusion of 10% dextrose solution or greater as needed while frequently monitoring blood glucose.

The older patient with aggressive delirium is a particular risk to care providers. Sedation is not usually needed, except in violent patients to prevent self-injury. Elective ventilation should be considered if the encephalopathy progresses compromising the airway or if respiratory distress occurs. If sedation is required, either for restraint or during procedures, short-acting barbiturates or opiates can be safely used, but benzodiazepines should be avoided. There are potential therapeutic implications related to the γ-aminobutyric acid (GABA) receptor, which has been implicated in encephalopathy. Flumazenil (a benzodiazepine antagonist) may produce temporary reversal of hepatic encephalopathy.[41,42] Administration is followed within minutes by a clinical response, which may last for several hours, and it has been suggested that a lack of response to flumazenil may indicate a poor prognosis.

Cerebral Edema

Cerebral edema may develop between stage III and stage IV encephalopathy and present within hours of the onset of coma. Brain death associated with cerebral edema is the most frequent cause of death in acute liver failure and contributes to reduced survival after liver transplantation.[13,43-46] Every effort should be made to prevent this complication since the prognosis is poor once it has become manifest.

The diagnosis and management of cerebral edema associated with hepatic failure is analogous to that utilized for other forms of cytotoxic cerebral edema.[13,30,45]

Renal Dysfunction

Renal insufficiency complicates the course in 75% of children with ALF[47,48] and may be due to prerenal azotemia, acute tubular necrosis and functional renal failure.

Prerenal azotemia may be due to dehydration or gastrointestinal bleeding because of absorption of nitrogenous substances from the gut. A marked increase in blood creatinine concentration may develop from decreased glomerular filtration and/or increased muscle breakdown.

Acute tubular necrosis is seen in the minority of patients and may occur because of hypovolemia or dehydration and may be induced after mannitol infusion or diuretic therapy. Features include: abnormal urinary sediment; urinary sodium concentration greater than 20 mmol/L, reduction in creatinine clearance (urine/plasma creatinine ratio <10), and oliguria (urine output <0.5 mL/kg/h).

Functional renal failure (hepatorenal syndrome) is the most common cause of renal insufficiency. Features include sodium retention (urinary sodium concentration <20 mmol/L), normal urinary sediment, and reduced urinary output (<1 mL/kg/h). The etiology is multifactorial, and electrolyte imbalance, sepsis, and hypovolemia all play a part. Endotoxemia may contribute to renal injury.[49]

The aim of management is to maintain circulating volume to prevent hypovolemia and ensure that urine output is greater than 0.5 mL/kg/h. A fluid challenge with isotonic volume expander (10 mL/kg) may be successful unless central venous pressure indicates fluid overload (>8 to 10 cm H_2O), in which case the use of furosemide (1 to 2 mg/kg intravenously) or (0.25 mg/kg/h by infusion) may be effective. Established renal failure requires hemodialysis or continuous renal replacement therapy as detailed in the following section (see Chapter 72).

Although functional renal failure recovers quickly after liver transplantation, acute tubular necrosis may severely complicate the postoperative management.[49,50] Although 50% of patients require hemodialysis or continuous renal replacement therapy, renal function returns to normal after successful liver transplantation.

Ascites

Use of ultrasound in the pretransplant assessment has demonstrated excessive peritoneal fluid in most ALF patients, probably from acute portal hypertension, from lobular collapse,

vasodilatation, poor vascular integrity, and reduced oncotic pressure. Clinically evident ascites occurs in less than half the patients but may be a site for secondary bacterial or fungal infection, indicating the necessity for paracentesis in septic patients without an obvious focus of infection. Therapy for ascites is not indicated, other than the correction of oncotic pressure with albumin infusion and general fluid management. Paracentesis may be indicated if peritonitis is suspected or if the intra-abdominal pressure leads to impaired renal perfusion or intractable embarrassment of diaphragmatic movement.

Secondary Bacterial and Fungal Infections

The majority of adults and 50% of children will develop significant infection[51,52] that may be related to impairment of cellular and humoral immune systems.[53] The organisms most often implicated are gram positive (*Staphylococcus aureus, S. epidermidis*, and streptococci), presumably of skin origin. Gram-negative bacteria or a fungal infection is occasionally observed. Urinary tract infections from indwelling catheter, and pulmonary infection, particularly in ventilated children, are common.

Management includes surveillance cultures from the endotracheal tube, indwelling catheters, and urine. Broad-spectrum antibiotics should be started at the first suspicion of sepsis, as the signs may be subtle and fever may be absent as part of the immune paralysis seen with advanced liver failure. Cefuroxime (75 to 150 mg/kg/day divided every 8 hours), piperacillin/tazobactam (240 mg/kg/day; piperacillin component divided every 8 hours), and/or metronidazole (30 mg/kg/day divided every 6 hours), if there is a suspicion of anaerobic infection, are reasonable first-line medications. When fungal infection is suspected, antifungals such as amphotericin (1.5 mg/kg/day) or fluconazole (3 to 6 mg/kg/day) should be included, although are potentially nephrotoxic. Positive cultures in the absence of clinical infection should result in removal or replacement of the infected catheter and administration of the appropriate antimicrobials, with close attention to the possibility of additional, perhaps opportunistic infection. Aminoglycoside antibiotics should be avoided, if possible, because they can contribute to renal failure.

Hemofiltration for Hepatic Support

Although the definitive therapy for *irreversible* hepatic failure is organ transplantation, because of limited organ availability, transplantation may not be available in short enough time to prevent irreversible complications (e.g., cerebral edema, fatal hemorrhage). Therefore therapies have been developed over the last decade intended to temporize and support adult patients suffering from acute fulminant hepatic failure or so-called *acute-on-chronic hepatic failure* have been used in the adult population. They use a single vascular access with a clearance of toxins resulting from hepatic failure using a charcoal filter.[54] Such techniques have been used less frequently in pediatrics and to date there is very limited pediatric literature to support this therapy.[55,56] Attempts to create extracorporeal artificial liver systems using living hepatocytes in various configurations have shown promise[57-59]; however, as yet unsolved technical problems have limited the utility and widespread availability of this approach to research centers only.[58,60]

As an alternative to extracorporeal hepatic systems, many programs have used continuous hemofiltration as a way to support electrolyte status and ammonia clearance as well as to permit the administration of large quantities of FFP in patients with hepatic failure (see Chapter 72). This has been used in primarily in patients with concurrent renal insufficiency. Such therapy is continued until either the patient recovers or progresses on to irreversible loss of hepatic function with subsequent hepatic transplant or death. The specific techniques of continuous hemofiltration will depend upon the capability of the PICU, but all such approaches depend on optimizing clearance of medium and small molecular weight compounds as well as maximizing nutritional and anticoagulation support.

Data have shown that small molecular weight solutes (e.g., urea) can be cleared equally effectively with convective (continuous venovenous hemofiltration [CVVH]) or diffusive (continual venovenous hemodiafiltration [CVVHD]) approaches.[61] Personal experience has also demonstrated that ammonia, which is not effectively cleared during acute hepatic failure, can be equally cleared by CVVH and CVVHD. In addition, exogenous amino acids delivered via total parenteral nutrition can be equally cleared with both the modalities with a slightly greater clearance in convective methods.

Therefore the choice of CVVH versus CVVHD is based on the preferences, capabilities, and experience of each center. Using this therapy requires controlled anticoagulation in spite of the prolonged clotting times associated with liver failure. Because of the underlying coagulopathy, such patients may require little to no anticoagulation.[62] It should be remembered that the prolonged clotting times resulting from liver failure are due to decreased factor levels rather than to direct antagonism of clotting mechanisms (i.e., anticoagulation). Thus, some patients may have a paradoxical coagulation status in which they appear "anticoagulated" based on clotting times but yet have a tendency to be hypercoagulable partially due to depressed levels of anticlotting factors and intravascular coagulation as well. Most programs have used citrate or no therapy for this population for anticoagulation.[63-65] Citrate is intended to bind calcium within the hemofiltration circuit decreasing its availability as a cofactor in the clotting cascade. Calcium then is infused back to the patient distal to the hemofiltration circuit to rescue the patient from potential risk of hypocalcemia. Citrate is cleared both via the dialysis membrane as well as the residual hepatic function. Hepatic citrate metabolism results in bicarbonate production, which typically results in metabolic alkalosis. However, in patients with hepatic failure, citrate may be poorly metabolized and may accumulate over time. This condition may result in so-called *citrate lock* that represents residual citrate in the patient as the delivery of citrate exceeds its hepatic clearance. This can be accentuated if the patient receives banked blood products containing citrate such as FFP, although this is becoming less common in contemporary blood bank practice. Citrate can be used nonetheless in this population by minimizing citrate infusion and watching closely for the signs and symptoms of citrate lock (i.e., clinical hypocalcemia). Laboratory evidence for citrate lock is a rising total of calcium with a falling ionized calcium level when measured in the patient's blood rather than a sample drawn from the hemofiltration circuit. The decision to use no anticoagulation, heparin anticoagulation, or citrate anticoagulation is based on local experience and preference. In the hands of an experienced hemofiltration program, any of these approaches can be successfully used.

In undertaking either CVVH or CVVHD, one must use an appropriate solution to provide for either convective or diffusive clearance. Since the mid 2000s, the Food and Drug Administration–approved the use of dialysis solutions as drugs, paving the way for commercially produced solutions to be used for convective clearance in the mode of CVVH. This has allowed programs to replace "custom" mixed solutions in the hospital's own pharmacy that have been associated with significant complications due to errors in mixing.[66]

For diffusive methods (CVVHD), multiple solutions are available that commonly are bicarbonate based, some with calcium and some without. The calcium free solutions are more commonly used in a citrate anticoagulation protocol. Use of Normocarb HF as a replacement solution creates options of bicarbonate-based solutions for either convective or diffusive clearance.[67] Lactate is normally hepatically metabolized but in this population lactate from the dialysis solution may rise due to the diminished hepatic clearance. Whereas lactate is not thought to be directly toxic except at exceedingly high levels, rising lactate levels may prompt the clinician to undertake unwarranted investigation for sepsis, bowel necrosis, etc. It is well recognized that patients with lactate-based solutions will exhibit lactate concentrations that are detectable[68] using conventional clinical lactate assays. One can discriminate between patient and dialysis solution derived lactate by measuring the dextro- and levo- portion of lactate. Unfortunately, this test is not widely available and often will take an average of 4 to 6 weeks for an answer. Data by Barenbrock et al.[69] have demonstrated that bicarbonate-based convective solutions result in improved hemodynamics when compared to lactate-based solutions. Therefore many programs prefer bicarbonate-based solution. Clinicians can choose solutions compounded by the hospital pharmacy or the Food and Drug Administration-approved solution Normocarb that is now available for dialysis and continuous therapy. The latter eliminates the risk for pharmacy error and is less expensive.[70]

Once continuous hemofiltration has been initiated, the goals for hepatic support are several: The first goal is fluid management of the patient. An edematous patient at the time of liver transplant will have difficulty with closure of the abdomen as well as subsequent wound healing. Therefore preoperative maintenance of euvolemia and minimizing tissue edema is desirable. The second goal is the correction of electrolyte disturbances. Often patients with fulminant hepatic failure develop sodium perturbations, metabolic acidemia as well as other electrolyte disturbances. CVVHD with bicarbonate-based solutions can maintain normal electrolytes and minimize the adverse effects of electrolyte changes on the central nervous system. The third goal is to optimize nutrition and minimize the loss of visceral and somatic protein pools. Because liver failure often represents a catabolic state, the provision of nutrition in these patients benefits not only their postoperative care, but also helps support them during the period of organ failure before transplantation. Providing excess protein ammonia and may worsen hepatic encephalopathy, but modest amounts (0.75 to 1.50 g/kg/day) of high bioavailable protein or amino acids with suitable nonprotein calorie source will enhance wound healing, antibody synthesis and support body protein pools until transplantation can be performed. By balancing nutrition with the clearance of amino acids and ammonia through continuous hemofiltration, one optimizes the nutritional status that will benefit both the pretransplant and posttransplant status of the patient. The fourth goal is to maintain a balanced state of anticoagulation while noting the predisposition of the patient to bleeding. Many programs use frequent or continuous FFP therapy to reduce the risk of spontaneous bleeding from the underlying coagulopathy as well as to improve the response to anticoagulation therapy. The last benefit of continuous therapy is for control of ammonia levels and removal of potentially toxic substances not eliminated by the failed liver. Although hyperammonemia is not the sole cause of hepatic encephalopathy, the use of continuous hemofiltration is an effective adjunct in controlling the ammonia level in patients with hepatic failure.

If the condition of the patient necessitates ongoing continuous hemofiltration preoperatively, one may need to consider its intraoperative use as well. Intraoperative fluid flux with blood products, as well as other fluid management may need to be addressed during the operation. Blood transfusion can expose the patient to large potassium loads that may not be tolerated well by oliguric patients. Experience has shown that the use of intraoperative hemofiltration during liver transplantation can be safely and effectively undertaken.[71] The use of hemofiltration without anticoagulation provides optimal intraoperative support, whereas continuing to infuse calcium to offset the risk of hypocalcemia associated with intraoperative FFP and blood administration.

Continuous hemofiltration represents an important adjunctive support modality for patients with advanced hepatic failure and multiorgan dysfunction. By virtue of its ability to provide both a modicum detoxification as well as create a more desirable fluid balance, continuous hemofiltration may be a life-sustaining bridge to transplant for patients.

Extracorporeal Hepatic Support

Extracorporeal hepatic support has been under development for over two decades.[55,59] In general such systems are composed of immobilized living hepatocytes or multiphase dialytic and plasma exchange/absorber systems. There have been obstacles with each of these approaches and both systems have been used in clinical trials in adults and children with mixed results. Given the complexity of each system neither approach has gained widespread adoption although in Europe, there appears to be greater acceptance in particular for supporting adults with hepatic failure.[72] Because of the limitations in availability, expertise, and adaptation to smaller pediatric patients, extracorporeal support cannot be considered a standard of care at this time, although in centers where it is available for use, it may be a valuable bridge to either recovery or transplant. In lieu of specific extracorporeal liver support systems, the use of continuous renal replacement therapy as described above in conjunction with continuous FFP infusion can achieve many of the goals of support in the patient with advanced liver failure.

Liver Transplantation

Liver transplantation should be considered in all children who develop a stage III or IV hepatic coma, as spontaneous survival in this group is only 40%.[20,73,74] Transplantation is indicated for all forms of ALF, namely viral hepatitis (including of hepatitis B), drug-induced live injury including acetaminophen overdose and halothane hepatitis and liver injury of indeterminant

cause. It is also appropriate for certain forms of inborn errors of metabolism, for example Wilson disease and tyrosinemia type I, although contraindicated for some children with multisystem disease or mitochondrial DNA deletions.[75] Because the certainty of a successful outcome after liver transplantation is less likely than with other forms of liver disease[76,77] selection is critical[78] and is based on previous experience of mortality in the pretransplant era.[73] Transplantation using a living donor can accelerate the process and is associated with better outcome in the setting of acute liver failure.[19,79,80]

Etiology of ALF is an important factor in determining whether transplantation is appropriate. The highest mortality is seen in children with indeterminate hepatitis, particularly those with a rapid onset of coma and progression to stage III or IV hepatic coma, a shrinking liver, falling transaminases associated with an increase in bilirubin, and coagulopathy. Such children should be immediately considered for transplantation. Children with fulminant Wilson disease are unlikely to recover with medical treatment and require transplantation.

In contrast, children with hepatitis A and children with drug-induced liver disease, particularly acetaminophen poisoning, may make a complete recovery with intensive medical therapy. Thus, careful monitoring for poor prognostic factors is required before selection.

In practical terms, it is appropriate to list for emergency liver transplantation all children who have reached stage III hepatic coma as the shortage of donor organs may mean a considerable wait for transplantation, or death on the waiting list.

As the development of irreversible brain damage is a major contraindication to transplantation, it is essential to be certain that brain damage has not occurred before the operation. Current techniques are inadequate, but include intracranial pressure monitoring, the identification of cerebral infarction or intracranial hemorrhage by cerebral computed tomography or magnetic resonance imaging scans and establishing evidence of mid-brain herniation, such as fixed, dilated pupils.[30]

Auxiliary transplantation, in which the recipient liver is left in situ to regenerate, is controversial treatment for acute liver failure, but may have the benefit that the graft may be removed if the original liver regenerates.[81] It is not suitable for transplantation for acute liver failure secondary to metabolic liver disease because there is no potential for these livers to recover and there may be a risk of hepatoma in the cirrhotic liver.

Relative contraindications for transplantation include untreated sepsis, HIV infection, and the presence of vascular thrombosis.[82] Absolute contraindications for isolated hepatic transplantation include progressive terminal extrahepatic disease, irreversible or rapidly degenerative central nervous system disease, intestinal failure, or untreatable metastatic diseases.

Technical Aspects of Liver Transplantation

A detailed discussion of the techniques of liver transplantation is beyond the scope of this chapter. Several aspects of intraoperative management, however, are pertinent to the intensivist in managing the patient postoperatively.

First and foremost in reducing intraoperative and postoperative morbidity is to send the patient for transplantation in the best condition possible. This means that (1) infections have been treated, (2) excess edema has been avoided, (3) cardiopulmonary and renal systems are functioning well, and (4) the brain has been spared irreversible damage.

Limited availability of donor organs has led to the development of techniques for using "technical variant grafts" (reduced size, living donors, and split liver) to expand the donor pool and reduce waiting time.[83] The ability to provide a reduced segment allows smaller children to receive grafts from larger donors, increasing the availability of organs for younger patients. Although technical variant grafts may reduce waiting list mortality in the setting of acute liver failure, they are associated with a higher rate of postoperative complications. However, patient survival for recipients of technical variant grafts is similar to that seen with whole liver transplants, thus leading to a favorable risk/benefit ratio for selection of these types of grafts. Intraoperative issues affecting the postoperative course are listed in Table 88-2. In general, these issues can be managed with conventional approaches while adhering to two critical, postoperative principles: (1) maintain patency of vascular anastomoses, and (2) maintain normal to slightly supraphysiologic arterial pressure to provide adequate perfusion of the graft. Avoidance of excessive hemoconcentration and rapidly correcting all clotting parameters is key to successful care.

Immune Suppression

Currently, calcineurin inhibitors (e.g., cyclosporine [Neoral], tacrolimus [Prograf]), comprise the initial approach to immunosuppression. Tacrolimus is usually combined with low-dose steroids. Cyclosporine-based protocols may incorporate steroids and a third agent (e.g., azathioprine or mycophenolate [CellCept]).[74]

Most centers have tended to reduce the use of corticosteroids because of the poor growth and infectious risks associated with their use. The practice of steroid withdrawal varies between centers with weaning often started at 3 to 12 months posttransplant. The exception to this rule pertains to children who were transplanted for autoimmune hepatitis who have a high incidence of recurrence.

Postoperative Management Issues of Concern to the Intensivist

The postoperative period is critical due to the need to anticipate predictable complications and to detect unexpected issues as early as possible. The intensivist must be aware of the

Table 88–2 Common Postoperative Issues After Liver Transplantation

Postoperative Condition	Intraoperative Cause
Fluid overload	Intraoperative crystalloid, fluid shifts
Capillary leak syndrome	Altered perfusion state, multiple blood products, venous congestion
Hypoxemia	Atelectasis, edema, mucus plugging
	Distended abdomen impairing ventilation
Renal dysfunction	Altered perfusion, impaired venous return, renal vasoconstriction secondary to calcineurin inhibitor exposure
Coagulopathy	Inadequate fresh frozen plasma/platelets transfusion
	Small for size graft
	Primary poor graft function

risk for early complications including primary nonfunction, bleeding, hepatic artery or portal vein thrombosis, and bile leak. Later complications include infections, rejection, hypertension, renal dysfunction and lymphoproliferative disease.

As in all other organs, prolonged ischemia because of vascular compromise will potentially lead to the loss of graft function. It is impossible to overly stress the need for close and rapid communication between the PICU team caring for the postoperative transplant patient and the surgical and hepatology teams responsible for the operative interventions and managing the immunosuppression following transplantation. Joint rounding in the immediate postoperative period of *at least* once a day with all teams caring for the patient will facilitate the best communication during the critical postoperative period.

Primary Nonfunction

Primary nonfunction of the graft is a disastrous complication necessitating immediate retransplantation. Of children with graft failure within 30 days, primary graft dysfunction accounted for 25.6%.[74] Evidence of primary nonfunction includes worsening coagulopathy, acidemia, rising liver enzymes, and cholestasis. All measures used to support a patient with minimal liver function must be considered and instituted since the condition will become rapidly fatal in the absence of retransplantation.[82]

Bleeding

Postoperative bleeding occurs due to the profound coagulopathy and thrombocytopenia that many patients have going into liver transplantation as well as the dilutional coagulopathy and thrombocytopenia that can occur intraoperatively. Bleeding should abate as the function of the graft returns postoperatively. In addition, patients may return to the pediatric intensive care unit on heparin infusions in an attempt to maintain patency of the hepatic artery and portal vein anastomoses. Monitoring drainage devices for trends in the amount and the characteristics of the drainage is critical to detect postoperative bleeding at the surgical site. Additionally, monitoring of the hemoglobin is important as an indirect sign of bleeding and to assure adequate oxygen carrying capacity, optimally 8 to 10 g/dL. Platelet count should be followed and maintained in a suitable postoperative range as agreed on by both surgical and medical teams. Attempts to achieve perfect clotting function are generally avoided due to the high potential to promote thrombosis of the vascular anastomoses. Worsening coagulopathy suggests hepatic dysfunction, sepsis with DIC, or unrecognized internal bleeding and requires rapid, aggressive diagnosis with treatment of the underlying cause.

Monitoring Vascular Anastomotic Patency

Progress in microsurgical techniques has led to improvements in maintaining vascular patency. During the first 30 days after transplant, vascular complications are a major cause of graft failure. Forty-three percent of liver graft loss in children is directly attributable to either hepatic arterial or portal vein thrombosis.[74] Of the vascular complications, hepatic artery thrombosis occurs most commonly, 10% overall and is probably the most important, because it can lead to biliary leaks, strictures, and intra-abdominal infection.[84] Routine assessment of hepatic artery patency using color Doppler ultrasonography at the bedside is critical during this period. Magnetic resonance angiography or computed tomography angiography can be helpful in defining the status of vascular structures but can be technically difficult to perform in critically patients. Attempts at revascularization may be successful, if performed early. The intensivist should work closely with the surgical and radiology team to detect early signs of vascular occlusion. Avoidance of excess hemoglobin (hyperviscosity) and overzealous transfusion of platelets and clotting factor replacement in the immediate postoperative period is essential. Once again, detailed discussion with the other members of the transplant team will achieve consensus and minimize risks.

Infection

Sepsis continues to be the most frequent final pathway leading to death in liver transplant recipients.[85] The presence of arterial thrombosis or biliary leak significantly increases the risk of infection as well as abscess formation. Patients having undergone previous abdominal surgery and those who have received pretransplant steroid therapy are at increased risk for postoperative infection. Percutaneously drainage of intra-abdominal abscesses can be an effective method to treat these infections provided there is no evidence of an enteric leak. A high index of suspicion for postoperative infection in the immunosuppressed patient must be maintained with early culture and institution of antibiotic treatment including antifungal and anti-cytomegalovirus as indicated by the patient and donor status. Children are at particular risk for cytomegalovirus and Epstein-Barr virus infections because many are naive to these viruses at the time of transplantation. Passenger donor lymphocytes in the graft are a frequent source of primary infection. Prophylactic therapy with antiviral medication can delay infection and monitoring active viral replication by polymerase chain reaction can be a useful tool to assist in adjustment of immunosuppressive medications in patients with early, acute infection.[85]

Biliary Complications

Biliary complications include biliary anastomosis dehiscence and bile leaks from the cut surface of the liver. Approximately 15% of patients experience biliary complications within the first 30 days and 25% or more will experience this complication in long-term follow-up.[74] Early bile leaks may be diagnosed by the appearance of bile in the abdominal cavity drains, by nuclear scan or transhepatic contrast studies. Cut surface leaks from minor biliary radicals may resolve spontaneously, but leaks from the biliary anastomosis or from larger cut surface ducts require operative management. Bile duct ischemia secondary to hepatic artery thrombosis that results in a stricture or leak will likely require retransplantation. Bile leaks increase the risk of postoperative infections that require aggressive attempts to diagnose and treat with targeted antibiotic therapy when possible.

Rejection

The median time to first rejection after transplant in one series was 16 days with 40% to 70% of children experiencing a first episode of rejection 7 to 10 days after successful transplantation.[85] Laboratory findings including elevation in AST and γ-GTP followed by elevations in bilirubin. Liver biopsy is important to confirm the diagnosis of acute rejection and distinguish patients with viral infection, biliary obstruction, or graft ischemia who may have a similar clinical presentation. Early detection of rejection is critical to allow the initiation

of intensified immunosuppression to reverse the process and minimize graft loss.

Complications of Immune Suppressive Medications

Each of the immune suppressant agents in common use has potential undesirable side effects.[86] The most common issues are listed in Table 88-3. The majority of patients will receive a calcineurin inhibitor and corticosteroids setting the stage for postoperative hypertension with or without deterioration in biochemical renal function. Hypertension is treated with conventional pharmacologic agents and may remain a persistent problem. Diabetes is also relatively common in patients receiving tacrolimus with a prevalence of 25% at 3 months posttransplant. Hyperglycemia in the immediate postoperative period can be controlled by insulin drip and should not limit the clinician's ability to deliver adequate caloric intake.[87] Cyclosporin and tacrolimus-related encephalopathy and seizures occur in 11% and 8% of patients, respectively, with the most common onset in the first 2 weeks after transplantation. Both can be managed by reduction or elimination of the calcineurin inhibitor exposure. Seizure control will frequently require short-term treatment with antiepileptic medications.[88]

Table 88–3 Adverse Effects of Immunosuppressants

Agent	Adverse Effect
Tacrolimus	Hypertension, headache, infection, seizures, hyperglycemia, insulin resistance/diabetes, renal failure, PTLD, cardiomyopathy
Cyclosporine	Hypertension, infection, seizures, hyperglycemia, renal failure, hirsutism, gingival hyperplasia, PTLD
Sirolimus	Hypercholesterolemia, infection, edema, poor wound healing, PTLD
Corticosteroids	Hypertension, increased appetite, Cushing syndrome, acne, gastritis, poor wound healing, osteoporosis, poor linear growth
Mycophenolate	Intestinal hypermotility, cramping, diarrhea, infection, leucopenia, depressed WBC/plt counts

PTLD, Posttransplant lymphoproliferative disorder; *WBC,* white blood cell; *plt,* platelet.

References are available online at http://www.expertconsult.com.

Acute Abdomen

Robert Sawin

PEARLS

- Observation of a child's vital signs, position, and demeanor can be as valuable as palpation in assessing the abdomen.
- Decisions about imaging tests to assess the abdomen must consider the differential diagnosis, risks, and whether the results of the study will change therapy.
- Abdominal compartment syndrome cannot be defined by absolute intra-abdominal pressure alone.

The abdomen is both the primary source of disease conditions that require care in the intensive care unit (ICU), and frequently, is a secondary source of additional pathophysiology for children in the ICU being treated for other conditions. In either case, the early recognition of these conditions and the judicious use of surgical intervention can be key to the successful outcome in the ICU population.

Anatomic and Physiologic Considerations

The Peritoneum

The peritoneum provides a protective environment for the intra-abdominal organs, and, because of its marked sensitivity, a valuable "window" for the examining health care provider. It is composed of a single layer of mesothelial cells lining the abdominal cavity along the abdominal wall (the parietal peritoneum) and the intra-abdominal viscera (the visceral peritoneum). The space between these is the peritoneal cavity. Beneath the mesothelium is a submesothelial layer of extracellular matrix, capillaries, and lymphatics.[1] The peritoneum's sensitivity to inflammation, ischemia, and necrosis is mediated by the fluid in the peritoneum that contains macrophages and other leukocytes.[2] Thus, with a focus of inflammation anywhere in the peritoneal cavity, inflammatory mediators are released by these leukocytes, often resulting initially in poorly localized, generalized pain. With irritation of the peritoneum associated with early appendicitis, for example, the patient interprets the inflammation as periumbilical pain. This is related to the embryologic development along dermatomes. As more inflammatory cytokines are secreted throughout the peritoneal cavity, the pain becomes more generalized and will eventually result in spasm of the overlying muscles of the abdominal wall, interpreted by the examiner as guarding.

Pain in the gastrointestinal tract is mainly limited to conditions that result in distention of the organ. Inflammation or irritation of the mucosa is generally not the cause of pain, except in the stomach. Disease states that result in full-thickness inflammation of the bowel wall, however, can stimulate the visceral peritoneum, inciting the release of leukocytic and tissue macrophage derived inflammatory mediators that results in pain. Patients who are receiving drugs such as steroids, which blunt the immune response, have reduced production of these peritoneal inflammatory mediators, and consequently can have deceptively little pain despite a significant intra-abdominal disease. Just as in other parts of the body, ischemia associated with any abdominal condition results in severe pain, often out of proportion to what is detected on physical examination.

Visceral Blood Flow

The regulation of visceral blood flow is a tightly controlled balance of neural, humoral, paracrine, and metabolic factors.[3] In the gut, enteral feeding increases the blood flow and the metabolic demands on the intestinal mucosa. Some of these effects are directly related to the nutrients in the intestinal lumen, whereas others are dependent on the enteric nervous system and the associated refexes, on gastrointestinal hormones, and on gastrointestinal vasoactive mediators such as adenosine, endothelin-1, and nitric oxide.[4] In pathologic states such as sepsis alone or shock, whether from sepsis, hemorrhage, or cardiac failure, visceral blood flow is reduced, which can lead to ischemia of the intestinal mucosa and submuscosa. Even with restoration of blood pressure and cardiac output after treatment of shock, microvascular perfusion of the intestine may remain impaired resulting in mucosal ischemia and persistent lactate production.

Such ischemia can lead to altered integrity of the mucosal barriers to bacteria and other pathogens, thus increasing the entry of endotoxins into the splanchnic venous and lymphatic systems. These pathogens can fuel the inflammatory response. This finding has fostered the theory of "the gut as a central organ of sepsis or multisystem organ failure."[5] Whether the translocation of bacteria or endotoxin from gut lumen to splanchnic drainage is the chicken or egg can be debated; regardless, this perturbation of intestinal blood flow contributes to the pathophysiology of shock and sepsis.

Other conditions in the ICU can affect splanchnic blood flow, especially mechanical ventilation with high inspiratory

pressures, high positive end-expiratory pressure, or high tidal volumes.[6,7]

Physical Exam of the Abdomen

The examination of the child's abdomen requires keen observation, patience, and sensitivity to the patient's fears and their parents' anxiety. One should first notice the child's position and demeanor. Children with peritonitis do not move or writhe about the bed because this only worsens their pain, whereas a child with visceral ischemia that has not progressed to peritonitis may be actively seeking a more comfortable position. As mentioned earlier, pain out of proportion to the findings on physical exam in an ICU patient is suggestive of ischemia, independent of the location in the body. Tachycardia is a very sensitive marker for significant intra-abdominal disease and therefore its absence should prompt the examiner to look for other explanations of the reported pain. Observation of the patient's facial expressions is important throughout the physical exam, especially in nonverbal children.

The exam of a child with abdominal pain should begin by avoiding palpation of the abdomen. Testing for rebound tenderness is only valuable in older children and should be avoided in children younger than adolescence as it is too startling, and thus has a high false-positive rate. Shaking the bed, asking the child to cough, or gently grabbing the hips and moving them from side to side will cause a painful response in conditions with peritonitis and is much less threatening to younger children. Once the manual examination is to begin, the examiners should make certain that their hands and stethoscopes are warm. For the verbal child who has localized the pain to a specific portion of the abdomen, the examiners should start the palpation in the opposite quadrant. In generalized peritonitis, spasm of the rectus abdominis can be detected regardless of where the source of the inflammation is located. When rectus spasm is detected on one side of the abdomen, a comparison to the rectus on the other side is helpful; when both are in spasm, it could be a manifestation of guarding by an anxious child, and therefore distraction should be employed. Distraction can often be created by engaging in conversation with the verbal child, or by using the warmed stethoscope to listen with light pressure over the area of the abdomen in question, followed by gradually increasing the pressure to elicit a response. Asking the child to take a deep breath and "blow it all the way out" while feeling the rectus can overcome the spasm if it is due to voluntary guarding, whereas a child with peritonitis will fail to relax the rectus spasm. Bowel sounds are highly variable and their assessment is not usually useful in the ICU patient.

If palpation in one area causes referred pain in a different location (Rosvig sign), that is suggestive of localized peritonitis in the area of pain, classically seen in appendicitis, but also can be seen in other localized abdominal conditions.

In addition to steroids, other medications can interfere with the reliability of the physical exam of the abdomen. Although patients receiving opiates may have a blunted response to painful stimuli, significant intraperitoneal pathology can still be ascertained by careful observation. Those patients who are receiving paralytic drugs are particularly challenging because the rectus abdominis spasm that is associated with peritonitis may be substantially blunted. Observation of the face, heart rate, or blood pressure can still be valuable, especially by comparing these findings during examination to other areas of the body. Just as in the nonsedated, non-ICU patient, beginning the exam on another portion of the body gives the examiner a baseline for comparison.

Laboratory Tests

Assessment of possible intra-abdominal conditions should include blood and serum tests that measure inflammation, acid-base abnormalities, possible coagulopathy, and those focused on suspected involved organs. The leukocyte count and differential, hematocrit, and platelet count should always be checked for patients with suspected abdominal disease. Leukocytosis, especially with an increased percentage of neutrophils or immature forms should raise one's concern about an infectious process. Neutropenia suggests a more severe infection or a suppression of the patient's bone marrow from medications or from the infection; such a situation might make clearance of a bacterial infection more difficult. Similarly, both an increased and decreased platelet count can indicate an intra-abdominal infection. Serial declines in the platelet count are particularly suggestive of a continuing inflammatory consumption seen in conditions such a necrotizing enterocolitis. Hematocrit levels must be followed in any child in the ICU because they can demonstrate intra-abdominal bleeding or hemolysis related to disseminated intravascular coagulopathy. Other coagulation tests should be considered, especially in children with severe infections or those with liver dysfunction. In such situations the prothrombin time, partial thromboplastin time, d-dimers, and fibrin split products are helpful to characterize and monitor the coagulopathy.

Abnormalities of acid-base balance should be monitored regularly in a child hospitalized in the ICU with an abdominal disease process. The source of increased acid can either be an overproduction, such as ongoing lactate generation by ischemic bowel, or decreased acid clearance by the liver or kidneys in conditions associated with shock and decreased visceral blood flow. Lactate is a very sensitive measure of intestinal ischemia, especially when monitored serially for trends. Arterial blood samples are more reliable than venous samples in that measurement. Hyperlactemia is not specific to intestinal ischemia and can be associated with any tissue necrosis or underperfusion of organs.

Liver function test, more accurately termed liver injury tests, include transaminases (ALT and AST), bilirubin, and gamma glutamine transferase. These can be elevated with trauma to the liver, active hepatic inflammation, hepatic ischemia, or obstruction of the hepatic venous outflow, known as Budd Chiari syndrome. The latter can result in extremely elevated transaminase levels. Elevation of the gamma glutamine transferase without a significant rise in the transaminase suggests a biliary condition such as common bile duct obstruction or cholecystitis.

Amylase is a valuable diagnostic test for children with abdominal pain or unexplained intra-abdominal sepsis as hyperamylasemia can indicate pancreatitis. Elevated amylase is not specific to pancreatic insults and can be elevated with head trauma, decreased renal clearance, and intestinal obstruction. Serum lipase can be an additive test to the

assessment of the pancreas. It tends to be more specific to the pancreas, but can be mildly elevated in intestinal obstruction as well. When both amylase and lipase are markedly elevated, pancreatitis is most likely. Children with a history of severe or chronic pancreatitis might not have marked elevations, so the level of the enzyme does not always correlate with the severity of the disease.

Imaging Options

The reliability of abdominal exam is subjective and highly variable, and may be dependent on the experience of the observer, the fluctuating status of the patient and his or her medications, the patient's level of anxiety, and many other factors. Consequently, most ICU providers have developed a dependency on imaging studies to ascertain whether intra-abdominal pathology warrants intervention. For reasons of resource efficiency as well as considerations about the potential risks of ionizing radiation, prudence needs to be exercised before ordering expensive, potentially obfuscating data from imaging studies. The following factors should always be evaluated before performing each study:

1. Specifically, what is one looking for (i.e. what is the differential diagnosis)?
2. How reliably will this study rule-in or rule-out those diagnoses (i.e. what is the specificity and sensitivity of the study)?
3. Will the results of this study change the management (i.e. will a negative result prompt the termination of a drug regimen or life-supporting technology, and will a positive study necessitate surgical intervention or initiation of a new therapy)?
4. Are the risks, such as ionizing radiation, transportation of a heavily medicated or unstable patient from the ICU to the radiology suite, the administration of intravenous contrast, or other factors offset by the value of the study?

Ultrasonography

Ultrasonography has several advantages over other imaging studies, most notably its portability, which obviates the need for moving the patient and its lack of ionizing radiation exposure. In addition, the use of Doppler modality permits assessment of visceral blood flow to kidneys, pelvic organs, and the gastrointestinal tract. When the relative positions of the mesenteric vein and artery can be accurately determined, an abnormal orientation suggests an increased risk of malrotation, even without midgut volvulus.[9] The presence of a "whirlpool sign" can be diagnostic of malrotation with midgut volvulus.[10] Neither finding is sensitive enough to exclude the diagnosis of malrotation. Thus, if suspected, malrotation requires an upper gastrointestinal contrast study to assess the position of the duodenal-jejunal junction.[11] Assessment of gall bladder wall thickening suggestive of acalculous cholecystitis or biliary tree dilation are particularly accurate. Intra-abdominal and pelvic fluid collections can be identified and characterized well with ultrasonography, suggesting collections that would be suitable for drainage, either surgical or percutaneous, via ultrasound guidance. In the patient with bowel obstruction or severe paralytic ileus, the resultant intestinal distention creates ultrasonic distortion, minimizing the value of this imaging modality.

Abdominal Plain Radiographs

Plain radiographs of the abdomen can be revealing and also are portable, relatively inexpensive, involve small amounts of radiation, and require minimal patient movement. To be of greatest value, however, the abdominal radiograph should be done with the patient in at least two different positions, such as supine and upright, and ideally as lateral decubitus as well. Cross-table laterals can also add value. These different views facilitate the identification of air-fluid levels suggestive of small bowel obstruction, and the presence of pneumoperitoneum indicating likely visceral perforation. Pneumoperitoneum in a patient with high inspiratory pressures on a mechanical ventilator can sometimes be unrelated to abdominal pathology, but rather a consequence of air dissecting through mediastinal and diaphragmatic tissue planes. Other plain radiograph findings suggestive of intestinal disease include "thumb printing," pneumatosis intestinalis, and portal venous gas.

Computed Tomography

Abdominal computed tomography (CT) scans are accurate, fairly rapid, and can be used to guide interventional procedures such as percutaneous biopsies or drainage of intra-abdominal fluid collections. Except in institutions where CT scans are located in the ICU or those that have mobile CT units, patients must be transported to access imaging with this modality. That requirement can be a significant challenge with children who are ventilated or hemodynamically unstable. In addition to the transport challenges, the radiation exposure of a CT scan may pose a risk for developing malignancies later in life, especially for those children who receive serial radiographs.[12] That risk can be reduced by using directed scans (i.e., limiting the scan to the portion of the abdomen in question). Other risks include the administration of intravenous contrast material that can cause anaphylaxis in those who are allergic, or renal injury, especially in those who might already be hypovolemic or receiving nephrotoxic drugs.[13] That risk can be minimized as well, by using non-ionic contrast materials, or with the administration of sodium bicarbonate and N-acetylcysteine before the administration of the intravenous contrast. Administration of enteral contrast can result in aspiration if there is intestinal obstruction or delayed gastric emptying with vomiting or gastroesophageal reflux.

The abdominal CT scan can be very effective at identifying the condition of all the intra-abdominal organs, and the retroperitoneal spaces. It is being used with increasing success to assess for bowel obstruction. Identification of fluid collections and their characteristics can help ascertain whether blood, bile, or pus is present and whether it can be drained percutaneously. To make certain that nonopacification of fluid-filled loops of bowel is not misconstrued for pathologic collections of fluid, enteral contrast should be given as long as no contraindications exist. With intravenous contrast and carefully timed image capture, conclusions about organ perfusion can be assessed as well. Colonic and intestinal ischemia, necrotizing pancreatitis, and decreased renal perfusion can all be seen reliably.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the abdomen can be valuable, especially because the risks of radiation can be obviated, but the logistical challenges of moving an ICU patient

to the MRI suite are similar to those mentioned previously for CT scans. The added challenges posed by MRI include the slower speed of the image capture that interferes with accessing the unstable patient for interventions, as well as the restrictions for certain MRI-incompatible ICU equipment to be in the MRI scanning room. Despite this, MRI enterography and cholangiography are now capable of generating very revealing images of the gastrointestinal and hepatobiliary tracts.[14] Thus, if the value of the images can offset the risks of transporting a sick child to the MRI suite, it should be considered.

Abdominal Conditions Requiring Intensive Care Unit Care

Perforated Viscera

Children with perforation of the gastrointestinal tract will frequently require either preoperative resuscitation or postoperative stabilization in the ICU. The most common condition resulting in perforation is appendicitis. Although perforated appendicitis is common, occurring in 30% to 50% of children who present to children's hospitals with appendicitis,[15] it is unusual for it to result in serious intra-abdominal sepsis. Nevertheless, deaths do still occur in such children, related most often to septic shock with cardiovascular collapse or severe acute respiratory distress syndrome.

Other sites of perforation in the gastrointestinal tract include gastric perforation from either severe gastritis, gastric ischemia, or after manipulations such as insertion of gastric tubes or transpyloric feeding tubes. In children with chronic gastrostomies, accidental dislodgements or manipulations of the gastrostomy site can result in separation of the stomach from the abdominal wall, leading to spillage of gastric contents into the peritoneal cavity. Because the acidic gastric pH results in lower bacterial counts, such perforations do not usually result in serious intra-abdominal sepsis. However, chronically hospitalized children, or children with gastroesophageal reflux on chronic acid suppression therapies may be colonized with resistant bacterial or fungal organisms such as Candida species that can lead to serious septic consequences.

Ingested foreign bodies can lead to perforation anywhere in the gastrointestinal tract, with common items being sharp materials such as pins or nails, fish bones, disc batteries, and magnets.[16] Trauma can also result in perforation, notably in lap seat belt injuries from motor vehicle accidents, or in cases of nonaccidental trauma where a punch or kick can compress the small bowel against the vertebral column causing a jejunal perforation. Therefore, characteristic in this mechanism is that the intraoperative finding of a jejunal perforation in the absence of a known trauma history should prompt an evaluation by the hospital's child abuse team.[17]

Ischemia

Volvulus of a loop of small intestine can occur when a segment of bowel, typically distal ileum, becomes entrapped beneath an omphalomesenteric remnant. This particular lesion can be very difficult to diagnose as neither contrast enema radiographs nor antegrade upper gastrointestinal contrast studies are likely to reach the involved area of volvulus. In addition, such children will often not have impressive physical exam findings until the bowel has become ischemic. At that point, systemic sepsis can occur rapidly. Similar pathophysiology can develop from a twist of bowel within an internal hernia.

In children with intestinal malrotation, the entire intestine supplied by the superior mesenteric artery (i.e., from jejunum to right transverse colon) can twist, resulting in midgut volvulus. In a somewhat similar manner, the colon alone can twist when there is sufficient redundancy in the mesocolon, typically in the cecum or the sigmoid colon. In any of these situations with intestinal and mesenteric twisting, the resultant venous congestion can compromise the capillary inflow to the bowel wall, ultimately leading to irreversible ischemia if the bowel is not untwisted promptly.

In the pediatric ICU, another cause of intestinal ischemia is low cardiac output or hypoxemia. Children with congenital heart disease, particularly those with single ventricle physiology or severe cyanotic heart disease, can develop mucosal ischemia after cardiac surgery, manifested as pneumatosis intestinalis on radiographs, bloody stool, metabolic acidosis with elevated serum lactate, and sepsis. Children on potent vasoactive pressors such as epinephrine or norepinephrine, and those receiving extracorporeal support, can develop ischemia as well. This is a variant of necrotizing enterocolitis and can involve the entire small intestine, and less commonly the colon. If the diminished cardiac output or hypoxemia is corrected and the ischemia is limited to the mucosa, surgical treatment may be avoided. Resection is necessary if the acidosis or systemic perturbations are refractory or if perforation results. Unfortunately, because this disease can involve the entire gut, the utility of resection may be limited.

Other causes of intestinal ischemia include small bowel obstruction, usually from adhesions after previous laparotomies, or, less commonly, related to incarcerated inguinal hernias. If the bowel becomes sufficiently distended, the intraluminal pressure can exceed the intramural perfusion pressure of the microcirculation, resulting in ischemia. Other, less common causes of intestinal ischemia include conditions that alter the microcirculation of the bowel wall such as vasculitis or hemolytic uremic syndrome.

The systemic physiologic insult of intestinal ischemia is usually proportional to the degree of ischemic tissue. Thus, midgut volvulus or total intestinal involvement with necrotizing enterocolitis can be the most catastrophic of these disease states acutely, and can have the most devastating long-term consequences, with short bowel syndrome and intestinal failure a common consequence if the ischemia is irreversible.

Neutropenic Enterocolitis

Children who have significant neutropenia, whether drug-induced from chemotherapy for malignant diseases or as a primary disease, may develop inflammation of the intestinal tract. The most common location is the right colon. Historically, this has been termed typhlitis, but more accurately is labeled neutropenic enterocolitis, because it can affect other portions of the intestinal tract as well. It may be preceded by mucositis that permits the intestinal bacteria to invade the bowel wall. Affected children exhibit fever, abdominal pain and tenderness, abdominal distention, ileus or diarrhea, radiographic signs of inflammation, and sometimes hemodynamic instability. The diagnosis is made best by CT scan or ultrasound.[18] Surgical treatment is reserved for those patients

with peritonitis or hemodynamic instability after appropriate resuscitation.

Pancreatitis

Severe pancreatitis can require intensive care in children. Etiologies for the pancreatitis are most often idiopathic in children, but anatomic causes such as gallstones, pancreatic trauma, or pancreas divisum can also be responsible. Drugs and hemolytic uremic syndrome can be unusual causes of severe pancreatitis. In severe cases, pancreatitis can lead to significant third-space fluid losses, pleural effusions, retroperitoneal hemorrhage, abscess formation, and hypocalcemia. Necrotizing pancreatitis, although rare in children, can require repeated surgical debridement to eradicate the ongoing source of sepsis.

Hemorrhage

Intra-abdominal hemorrhage can result from trauma or surgical procedures or manipulations. In blunt trauma, the spleen is the most commonly injured abdominal organ. To avoid the risk of overwhelming postsplenectomy infection, nonoperative management is attempted as long as hemodynamic stability can be maintained. Hospitalization in the pediatric ICU with strict bed rest is indicated when the splenic injury is Grade IV or V, or if there are other significant injuries. The risk of delayed splenic rupture after nonoperative management is extremely low. If surgery is necessary, attempts to salvage the spleen with splenorrhaphy are important. Before surgery, if time permits, the child should be immunized for encapsulated bacterial organisms including *Hemophalus influenza*, *Streptococcus pneumoniae*, and meningococcus.

The liver is also a commonly injured organ in blunt abdominal trauma, and it too can usually be managed nonoperatively. The development of hemobilia several weeks after nonoperative management of hepatic laceration is uncommon, but when it occurs it can result in significant gastrointestinal bleeding. This can usually be managed with arteriographic embolization or endoscopic biliary stent placement,[19] but sometimes requires resection of the involved hepatic segment or lobe.

Other Specific Conditions

Cholecystitis

Gall stones are increasingly common in children, perhaps because of the increased use of parenteral nutrition with its associated risk of cholestasis. Gall stones can result in cholecystitis, biliary obstruction, or pancreatitis that can complicate an ICU course for a child. Acalculous cholecystitis can be seen in children who are hospitalized in the ICU, particularly those who are receiving large does of opiates that leads to biliary dyskinesia, or those who have decreased perfusion of the abdominal organs because of hypotension. Acalculous cholecystitis can be associated with a significant systemic inflammatory response, and should be considered as a source of unexplained sepsis in a child. Ultrasonographic and CT scan findings of a dilated gall bladder with a thickened gall bladder wall and pericholecystic fluid are diagnostic, although a radionuclide study such as a hepatobiliary iminodiacetic acid scan is the most accurate functional imaging study.

Empiric antibiotic coverage for common biliary pathogens such as Gram negative organisms like klebsiella, pseudomonas, or *Escherichia coli* should be started immediately. Cholecystectomy would be definitive therapy. In critically ill children who might not tolerate a trip to the operating room, percutaneous drainage of the gall bladder done by ultrasound guidance in the ICU can be an effective temporizing procedure.

Abdominal Compartment Syndrome

Intra-abdominal hypertension (IAH) is defined as intra-abdominal pressure (IAP) that is >12 mm Hg. Although this is relatively uncommon in pediatric ICU patients, it can be associated with a high morbidity and mortality. If the IAP reaches a point where perfusion to intra-abdominal organs is compromised, a constellation of organ dysfunctions may occur including renal insufficiency, intestinal ischemia, hepatic dysfunction, elevated diaphragms, and respiratory insufficiency.[20-22] This constellation is termed abdominal compartment syndrome (ACS). Risk factors for ACS include massive fluid resuscitation for any illness, intra-abdominal hemorrhage, intra-abdominal inflammation or infection from any cause, obesity, and tight abdominal wall closures following laparotomy. As with compartment syndrome in extremities, there is no absolute pressure to define the presence of ACS; the intravascular volume status, blood pressure, and systemic vascular resistance are all factors that can impact the perfusion pressure of the abdominal organs and minimize the effect of the IAP. An abdominal perfusion pressure can be calculated as the mean arterial pressure minus the IAP. If abdominal perfusion pressure is > 60 mm Hg, a higher survival rate has been reported. The diagnosis of ACS is made when there is a sustained increased IAP in combination with signs of organ dysfunction such as decreased cardiac output, oliguria, and respiratory insufficiency. Other organ systems that can be affected by IAH include the reduction of portal and mesenteric venous flow, potentially leading to hepatic dysfunction and intestinal edema and ischemia. In addition, the increased intrathoracic pressure that can result from the elevated diaphragms can raise intracranial pressure.

When signs of IAH are evident in the setting of abdominal distention, pressure measurements can be made using nasogastric tubes, rectal catheters, bladder catheters, and peritoneal drainage tubes such as peritoneal dialysis catheters. The most reliable and easily practical measurement can be obtained using a closed system of a Foley bladder catheter connected to a fluid column and a pressure measuring device such as a tube manometer or a pressure transducer. Ultrasound evaluation, including Doppler imaging of renal, portal, and mesenteric blood flow can be helpful in the assessment of end-organ perfusion, as well as estimating the intra-abdominal venous pressure by assessing the caliber of the inferior vena cava. CT scan can also reveal poor perfusion of these organs and a flattened inferior vena cava, as well as increased abdominal girth, especially in the anterior to posterior dimension.

If the diagnosis of ACS is suspected, efforts to augment perfusion must be initiated. Avoid the reverse Trendelenburg or prone positions because these can increase IAP. Effective decompression of the gastrointestinal tract is important and can be optimized by effective nasogastric tube drainage, administration of prokinetic medications, and colonic decompression by either enemas or colonoscopy. Supporting

renal function is also important and includes liberal use of diuretics along with volume resuscitation. If these maneuvers have not improved the organ function, temporary decompression by insertion of an abdominal drain to decrease the amount of fluid in the abdomen may be necessary. If this does not adequately decompress the IAH, laparotomy is necessary with placement of a sterile patch or silo that may provide sufficient compliance to reverse the ACS.

The morbidity of ACS is significant, with mortality rates of >50% reported, especially if treatment is delayed until multisystem organ failure develops. After decompression, and after resolution of any end-organ dysfunction occurs, and after the underlying causes of the IAH have abated, delayed closure of the abdomen can be considered. Sometimes that closure will require abdominal wall reconstruction techniques such as skin flap closure without fascial repair or skin grafts. Primary or delayed primary fascial repair may be feasible, sometimes requiring separation and release of the muscle groups, or insertion of prosthetic patches such as synthetic mesh, Goretex, or biologic sheet materials made from human dermal grafts or porcine intestinal submucosa.

The Intestine as a Source of Sepsis

The intestine is an organ endowed with large quantities of both lymphatic tissue and bacteria. Consequently, it can be a central organ in the systemic inflammatory response in children hospitalized in the ICU. The role of the gut's immune system is not fully understood, but may play a key role in some intestinal inflammatory diseases such as Crohn disease. In addition, the interplay between the gut-associated lymphoid tissue and the bacteria present in the bowel lumen is important in critical illness. The sick child with decreased visceral blood flow and under severe stress likely has alterations in the mucosal integrity of the intestine. That loss of integrity can lead to bacterial invasion of the bowel wall with subsequent entry of the bacteria/toxins into the lymphatic or portal venous circulation. Once in the circulation, such bacteria/toxins can trigger a severe systemic inflammatory response, even if the bacteria are not detectable as a blood stream infection. Use of enteral antibiotics to decrease potentially pathologic gut bacteria has proven effective in reducing intestinal sources of sepsis in some settings, while replacement of gut flora using probiotics or synbiotics has been employed with some success in others.

Surgical Intervention

The decision to perform a laparotomy or laparoscopy in a pediatric ICU patient can be very challenging. There are indeed times when a patient can be "too sick" to go to the operating room and other times when the patient is so sick that only an immediate operation will provide a chance for successful treatment.

With the possible exception of patients with continued intra-abdominal hemorrhage or abdominal compartment syndrome, delaying operative treatment with time spent on preoperative resuscitation is usually valuable. Induction of general anesthesia in a hypovolemic, or acidotic patient with cardiogenic or septic shock can be dangerous. An understanding of the differential diagnosis can be most helpful in planning the appropriate antibiotic coverage and the timing of the surgical treatment. Most of the conditions that require laparotomy in ICU patients have an infectious component and thus empiric broad spectrum antibiotics should be administered early in the resuscitation. Depending on the disease, resuscitation and antibiotics alone may obviate the need for emergent laparotomy. Effective communication between the surgical team and ICU team is therefore essential. To optimize the timing of the operation, the surgical team should be ready to go immediately, once the preoperative resuscitation is sufficient. In situations where physical exam or radiographs do not provide localization, bedside imaging can help localize the disease.

References are available online at http://www.expertconsult.com.

The Innate Immune System

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PEARLS

- Innate immunity provides the front-line "ready-made" response to pathogen invasion.
- These same pathways are activated in response to other critical insults including trauma, hypoxic/ischemic injury, and bypass.
- Pattern recognition molecules recognize exogenous as well as endogenous molecular patterns.
- Genetic changes may have functional sequelae in the immune response.

The immune response aims to ward off pathogens and mitigate injury. Traditionally a distinction is made between adaptive and innate immune responses. The adaptive immune system has been studied in the greater detail and is essentially a *specific* response to individual pathogens. Adaptive immunity is a highly sophisticated process with many safety mechanisms to target responses at pathogens (or pathogen-infected cells) while leaving normal tissues alone. This sophistication and specificity takes time to develop (days to weeks) and has many effector cells and molecules to deliver a coordinated response (T and B lymphocytes, immunoglobulins). Although the adaptive response is essential for health and in particular for the phenomenon of immunological memory, it is not sufficient to address a sudden major bacteremia or widespread tissue injury—or even the thousands of minor bacterial inoculums all individuals experience during their lifetimes—for example, during teeth brushing. Bacterial growth is exponential under optimal conditions—*Neisseria meningitides* counts can double in 20 minutes. Given these threats, there is a need for a "ready-made" system that can act swiftly to neutralize external threats. This is called the *innate immune system*.

In humans, the innate immune system is largely present at birth (in contrast to the years it takes to build an adaptive immune repertoire). Innate immunity is phylogenetically conserved and found in nearly all multicellular organisms; again, this contrasts with the adaptive immune system that is found in vertebrates only. Its hallmarks are immediacy, promiscuousness, redundancy, and generality. Given that the adaptive immune system evolved in the presence of innate immunity, these systems do not operate in isolation from each other; rather the innate immune system presents to and instructs the adaptive part of immunity.

Innate immunity encompasses immune cells, such as tissue macrophages, neutrophils, and monocytes, but also cells that are primarily known for other functions: platelets and endothelial cells. Complex networks of circulating mediators including the complement cascade, collectins, defensins, and the coagulation cascade are integral parts of innate immunity. Recent work has highlighted apparent contributions from neurohumoral and autonomic nervous systems.

No critically ill child is admitted to intensive care without activation of its innate immune system. No intensivist can function adequately without a good working knowledge of innate immunity, because it is central to many of the clinical entities he or she faces on a day-to-day basis. Infection, trauma, ischemia-reperfusion, acute respiratory distress syndrome, and cardiopulmonary bypass sequelae are all largely mediated by the innate immune system.

The immune system can be considered as a complex tool to distinguish tissues that are "infectious non-self" from "non-infectious self."[1] More recently a distinction between "dangerous" and "nondangerous" matter has been proposed as a better description for innate immunity.[2]

This chapter provides a framework and outline of concepts in innate immunity that will help understand some of the pathophysiological processes central to pediatric critical care.

Components of the Innate Immune System

An ideal first-line response to invading microbes would readily recognize and promptly neutralize infectious agents without widespread collateral tissue injury. The innate immune system achieves these objectives to some degree by a combination of circulating molecules that either cause direct pathogen lysis or prime pathogens for phagocytosis and by phagocytic cells themselves.

Complement, lectins, and defensins are important humoral defenses. The main cellular components are neutrophils, monocytes, macrophages, and dendritic cells. Platelets and endothelial cells are now understood to have innate immune functions also. There are complex interactions between these components as well as with the coagulation, endocrine, and the autonomic nervous systems.

The afferent, or "sensing," limb of the innate immune system consists of pattern recognition molecules that recognize typical molecular structures on pathogenic micro-organisms. Gram-negative lipopolysaccharide and Gram-positive lipoteichoic acid are obvious targets, but pattern recognition

molecules are also directed against characteristic non-human patterns of sugars involving mannose, glucose, fructose, *N*-acetyl-D-glucosamine, and *N*-acetyl-mannosamine. Mannose-binding lectin (MBL) binds to all of these and thus recognizes a wide variety of bacteria, viruses, yeasts, fungi and protozoa, but also endogenous ligands.[3]

The importance of these danger signals is illustrated by the number of names competing in the literature to describe them: pathogen-associated molecular patterns, danger associated molecular patterns, and most recently *alarmins*.[4] Whatever name used, the importance is that when such patterns encounter pattern recognition molecules of the innate immune system, they initiate and/or potentiate a cascade of events that is aimed at rapid killing of invading pathogens or reestablishing immune homeostasis.

Circulating Pattern Recognition Receptors: Complement, Lectins, and Defensins

Pattern recognition molecules also circulate in the bloodstream. The lectin-complement pathway facilitates pathogen removal via carbohydrate recognition mediated phagocytosis. The alternative complement pathway is a continuously activated bactericidal humoral mechanism.

Sugar-recognizing *collectins*, molecules that contain collagenous structures and C-type carbohydrate recognizing domains (CRD) include MBLs and surfactant proteins A and D (SP-A and SP-D). Mannose binding lectin is a liver derived acute phase reactant whereas SP-A and SP-D are synthesized in the lung. The main determinant of MBL levels is genotype, whereas SP-A and SP-D do increase significantly with inflammatory stress. Collectins bind to many microbes: viruses, bacteria, fungi, and protozoa and prepare organisms for phagocytosis (opsonization) and activate complement pathways. The ficolins, L-ficolin, M-ficolin, H-ficolin, are similar but they have different structures with a fibrinogen-like domain. Both MBL and the ficolins initiate the lectin pathway of complement activation via associated serine proteases.[5]

Similarly, antimicrobial proteins such as bactericidal/permeability increasing protein and lactoferrin have pathogen killing properties. Notably, these factors do not induce a downstream cytokine response.

Alarmins, such as α and β defensins, and cathelicidins are expressed in neutrophils, intestinal Paneth cells, and epithelial cells in the respiratory tract. Defensin synthesis and release occurs constitutively but increases with cellular activation. Defensins exert a dose-dependent direct bactericidal activity and function as chemo-attractants for phagocytes. They also act generally to increase phagocytic function by increasing production of reactive oxygen species, binding to C1q to activate the classical complement pathway and inhibiting the production of immunosuppressive adrenal glucocorticoids.[6]

Neutrophils

Neutrophils are a key element in the rapid clearance of bacterial and fungal invasion. They are equipped to sense pathogens, to migrate toward them, and subsequently to ingest and kill them. Neutrophils typically circulate for only of 6 to 8 hours after release from the bone marrow. They "scan" the vascular endothelium for signs of local inflammation by rolling on weak adhesion molecules (selectins). When the endothelium displays signs of local inflammation or injury—such as a high local concentration of interleukin-8 (IL-8), neutrophils alter the structure of their main adhesion molecules (β_2-integrins) and firmly adhere to the site of trouble. They then pass through the endothelium and hunt pathogens (or injured tissue) in need of removal. They may digest pathogens or tissue with a combination of enzymes such as elastase and they eat their fill through phagocytosis. Organisms that are phagocytosed into neutrophil vacuoles are then subjected to protease activity and changes in charge conditions—that disrupt the bacterial membranes by ion shifts. Ideally, once spent, the full neutrophil quietly undergoes apoptosis—the debris of which is phagocytosed in due course.

The degree of local (and subsequently systemic) inflammation is determined to some degree by the balance between the numbers of infective organisms and the extent of neutrophil recruitment and activation. An inadequate neutrophil response means the infection is unlikely to be controlled as a minor local problem—hence, the very high frequency of bacterial blood stream infections that occur in patients who are neutropenic after chemotherapy or bone marrow transplantation. Patients who are unable to localize neutrophils to the endothelium and hence the tissue (via congenital failures of firm adhesion: "leukocyte adhesion deficiencies") typically fail to heal normally minor wounds—but bacteremias are less common. Finally, in the most severe forms of *purpura fulminans* associated with overwhelming bacterial infection, typically circulating neutrophil counts are low, reflecting the very widespread endothelial activation and injury. This means the whole circulating neutrophil pool is depleted by adhesion to multiple sites of infection and damage. Neutropenia in this scenario is a very powerful predictor of poor outcome and reflects a severe infection that has outstripped the host's early control mechanisms.

Cellular Pattern Recognition Receptors

The archetypal pathogen-associated molecular pattern is the gram-negative cell wall component lipopolysaccharide (LPS), to which humans are exquisitely sensitive. Endotoxin or LPS is recognized by the humoral factor LPS binding protein and the cell membrane receptor toll-like receptor 4 (TLR4). LPS binding protein, a liver-derived glycoprotein, binds to LPS and shuttles it to an immune cell surface (e.g., a monocyte). The monocyte receives the LPS binding protein/LPS compound on a complex consisting of TLR4, CD14, and MD2. On binding, the transmembrane receptor TLR4 signals to intracellular components, that in turn, activate nuclear factor κB (NFκB)-mediated downstream gene expression cytokine activation (Figure 90-1). Thus a gram-negative infection such as meningococcemia gives rise to a rapid nonspecific response that aims to kill the inoculum and contain the infection.

TLR4 is only one of a family of related molecules. There are at least 10 related receptors in humans (Table 90-1). These TLRs are evolutionary preserved from the worm *Caenorhabditis elegans* and strikingly homologous to Toll, a gene product essential to *Drosophila* immunity. These TLRs are transmembrane glycoproteins that are characterized by an extracellular binding domain with varying numbers of leucine-rich-repeat motifs

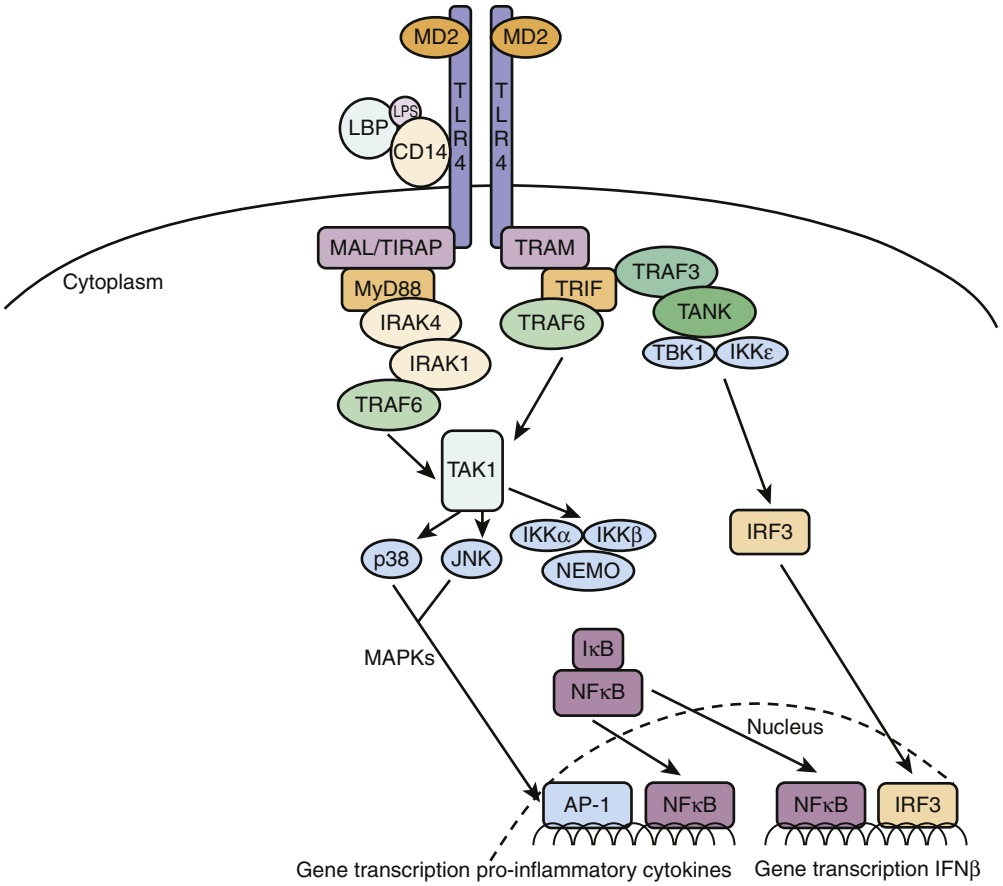

Figure 90–1. LBP shepherds LPS to the TLR4 complex. On ligation, TLR4 dimerizes and activates the two distinct MyD88- and MyD88-independent TRIF-dependent pathways. The early inflammatory phase is characterized by the MyD88-dependent pathway. This pathway activates MAPKinase and NFκB mediated pro-inflammatory gene induction. The TRIF-dependent pathway will activate late-phase NFκB and IRF3 mediated gene expression resulting in a more endotoxin tolerant response.[38-40] LBP, Lipopolysaccharide binding protein; LPS, lipopolysaccharide (endotoxin); CD14, cluster of differentiation 14; MD2, myeloid differentiation protein 2; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary-response protein 88; MAL/TIRAP, MyD88 adaptor like/Toll-interleukin 1 receptor (TIR) domain containing adaptor protein; IRAK4, interleukin 1 receptor associated kinase 4; IRAK1, Interleukin 1 receptor associated kinase 1; TAK1, transforming growth factor β-associated kinase 1; TRIF, TIR domain-containing adaptor protein inducing interferon β; TRAM, TRIF-related adaptor molecule; TRAF6, tumor necrosis factor receptor–associated factor 6; TRAF3, tumor necrosis factor receptor–associated factor 3; TANK, TRAF family member–associated NFκB activator; TBK1, TANK binding kinase 1; IKKε, inhibitor of nuclear factor κB kinase ε; IKKα, inhibitor of nuclear factor κB kinase α; IKKβ, inhibitor of nuclear factor κB kinase β; p38, p38 kinase; JNK, c-Jun N-terminal kinase; MAPKs, mitogen activated protein kinases; NEMO, nuclear factor κB essential modulator; IRF3, interferon regulatory factor 3; IκB, inhibitor κB; NFκB, nuclear factor κB; AP-1, activator protein 1.

and an intracellular cytoplasmic signaling domain homologous to that of the interleukin-1 receptor (IL-1R). This Toll/IL-1R homology (TIR) domain sits beneath the plasma membrane and interfaces primarily with the key signaling adaptor myeloid differentiation primary response gene 88 (MyD88).[7]

TLR2 recognizes cell wall component lipoteichoic acid and peptidoglycan of Gram-positive bacteria, whereas TLR5 recognizes flagellin on *Salmonella enterica*. Viral matter is recognized by TLR3, TLR7, and TLR8. TLRs also combine in heterodimers and thus generate wider ligand specificity, for instance TLR6/TLR2 recognizes the fungal cell wall component zymosan. TLR9 recognizes bacterial DNA, which is distinct from mammal DNA by way of the presence of unmethylated CpG dinucleotides.

One TLR may also recognize different pathogen components; TLR4 not only binds LPS, but also the structurally unrelated fusion protein of respiratory syncytial virus and *Plasmodium falciparum* glycosylphosphatidylinositol. Recently, TLR4 has been observed to ligate endogenous molecules such as heat shock proteins and fibrinogen. These interesting observations suggest that these pathways contribute to the ongoing immune response from other insults such as trauma rather than being specific to individual pathogens. This fits with a danger model of immunity, rather than a strict pathogen non-self and non–pathogen self model.

TLRs are expressed on many immune and nonimmune cells, including macrophages, platelets, and cardiac myocytes. This expression is modulated rapidly in response to pathogens and cytokines. Many of these TLRs (e.g., TLR1, -2, -4, -5), are expressed on the cell wall, others are found intracellularly (e.g., TLR3, -7, -9).

A different type of pattern recognition receptors recognize pathogens after invasion in the cytosol. RIG-I-like receptors (RLRs) respond to viral RNA. Activation induces NFκB-mediated gene transcription and production of type I interferon (INF). Of particular relevance to the intensivist are the nucleotide binding oligomerization domain and leucine rich repeat containing molecules (NLRs). The best studied of these

Table 90–1 Human Toll-like Receptors

PRR	PAMP	Organism	Endogenous Ligand	Location
TLR1-TLR2	Triacyl lipopolypeptide	Gram-positive bacteria		Cell surface
TLR2-TLR6	Diacyl lipopeptide LTA Zymosan	Mycoplasma Gram-positive bacteria Fungus		Cell surface
TLR2	Porins Peptidoglycan Hemagglutinin protein	*Neisseria* Gram-positive bacteria Measles	Hyaluronic acid HSP HMGB1	Cell surface
TLR3	dsDNA	Virus		Intracellular vesicles
TLR4	LPS Envelope proteins	Gram-negative bacteria RSV	Fibrinogen HSP ROS Hyaluronic acid Heme HMGB1	Cell surface
TLR5	Flagellin	*Salmonella*		Cell surface
TLR6				Cell surface
TLR7	ssRNA	RNA virus		Intracellular vesicles
TLR8	ssRNA	RNA virus		Intracellular vesicles
TLR9	CpG DNA DNA Malaria hemozoin	Bacteria DNA virus Parasites		Lysosomes
TLR10	Unknown	Unknown		B lymphocytes

PRP, Pattern recognition receptor; *PAMP,* pathogen-associated molecular pattern; *LPS,* lipopolysaccharide; *HSP,* heat shock protein; *ROS,* reactive oxygen species; *HMGB1,* high mobility group protein B1; *RSV,* respiratory syncytial virus; *dsDNA,* double-stranded deoxyribonucleic acid; *ssRNA,* single-stranded ribonucleic acid; *CpG DNA,* cytosine phosphodiester bond guanine deoxyribonucleic acid.

proteins, NOD1 and NOD2, both contain N-terminal CARD domains and are specialized in detection of bacterial peptidoglycan components. Two types of activation occur: NOD1 and NOD2 ligation causes their oligomerization, that in turn induces downstream gene expression via NFκB activation. Alternatively, NLRs activate caspase-1 activating complexes, also known as inflammasomes, that in turn mature cytokines IL1-β and IL-18.[8] Inflammasomes may be seen as sensors for danger. For instance, loss of cell integrity activates the inflammasome and hence the potent pro-inflammatory cytokine IL-1β. The significance of this pathway is increasingly recognized. Recent data show the inflammasome to be integral to the pathogenesis of severe *Staphylococcus aureus* infections.[9]

Signaling

Ligation of a cell surface TLR will activate a cascade of events, ultimately leading to gene transcription of proteins. These proteins, in turn, activate and dampen processes to allow for an appropriate host defense. Figure 90-1 provides an example of downstream signaling in response to LPS binding to the TLR4 complex. Toll-like receptors dimerize and change in conformation; this allows for recruitment of adaptor molecules to the TIR domain of the receptor. Four adapter molecules exist: MyD88, Mal (TIRAP), TICAM1, and TRAM. Different TLR ligands induce selected recruitment of these adaptor molecules explaining some of the distinct responses after TLR ligation.

Myeloid differentiation primary response gene 88 is essential for all downstream signaling via TLRs (except for TLR3). In addition, Mal is essential for TLR2 and TLR4 signaling, arguably the most important TLRs in critical care.

After activation of these adaptor molecules, IL-1 receptor–associated kinase 4 (IRAK4) and IRAK1 are recruited. These, in turn catalyze a cytoplasmic cascade that ultimately leads to mitogen-activated protein kinases (MAP kinases) p38, ERK1, ERK2, and consequently NFκB-mediated gene transcription in the cell nucleus. A MyD88 independent pathway exists, that has a role in dendritic cell maturation and INF-α/β production.[10]

Crosstalk

The innate and adaptive immune systems interact continuously. Considering them as separate systems reflects an enormous simplification. Even more so, now newer data indicate the complexity of the interactions between immunity and other complex body systems. Coagulation, neuroendocrine, cardiovascular, and autonomic nervous systems all influence, and are influenced by, immune responses. At the simplest level, this is shown by many molecules having important properties in multiple systems (e.g., acetylcholine is a neurotransmitter as well as a paracrine regulator of lymphocytes, or epinephrine stimulates the bone marrow to release neutrophils into the circulation). High plasma glucose levels arising from the stress response and insulin resistance during critical illness may inhibit complement binding to and killing of microorganisms.

Two examples of well-characterized "crosstalk" between these systems are discussed in the following section. Plasminogen activator inhibitor 1 (PAI-1) is a potent inhibitor of fibrinolysis. It achieves this response by inhibiting both tissue and urinary type plasminogen activator. Levels are increased after

trauma and sepsis, especially so in severe meningococcal sepsis. Inflammatory mediators tumor necrosis factor (TNF)-α, IL-1, and IL-6, complement 5a, and LPS all act to increase PAI-1 production. In turn, PAI-1 contributes to a procoagulant state and inhibits neutrophil apoptosis. Although this may help to contain inflammation at the site of infection, genotypes associated with high levels of PAI-1 production are associated with worse outcome in septic shock. The PAI-1 4G/5G insertion deletion promoter polymorphism influences PAI-1 plasma concentration (4G is associated with higher concentration). So there is a direct link between how readily the immune system triggers an increased clotting tendency in critical illness and poor outcome.

Similarly, the inflammatory mediator IL-6 stimulates release of the potent coagulation activator tissue factor from activated endothelial cells, monocytes, and macrophages. This promotes thrombin formation that, in turn, converts fibrinogen to fibrin. Thrombin and fibrin generation are increased in inflammation, in part, because fibrinolysis is impaired from increased activity of PAI-1, but also secondary to diminished activated protein C and tissue factor pathway inhibitor.[11] These processes have been the targets for numerous clinical trials of drugs with anticoagulant/pro-fibrinolytic actions—all aiming to achieve anti-inflammatory effects by targeting coagulation systems.

A recent example of a novel interaction between the coagulation and immune systems is that TLR4-activated platelets interact with neutrophils to trap and kill bacteria in so-called neutrophil extracellular traps. In vitro studies showed that LPS as well as plasma from septic adults could induce this phenomenon.[12]

The nervous system is an integral part of inflammation. At a local level inflammatory responses induce pain—one of the defining elements of inflammation. Regionally, sympathetic and parasympathetic activation will, in general, inhibit inflammation. Centrally, the hypothalamic-pituitary-adrenal axis has an overarching immunomodulatory role by activating many neuroendocrine responses.

Importantly, immune cells carry the receptors for neurotransmitters, neuropeptides, and neurohormones, including adrenergic and cholinergic receptors. These receptors may respond in an autocrine or paracrine manner. Alternatively, the autonomic nervous system and innate immunity may be directly linked by the "cholinergic anti-inflammatory reflex." In vivo sepsis models suggest that vagal stimulation may directly dampen TNF-α production via NACHR7 receptors on macrophages.[13]

The sympathetic-immune interface is another area of growing interest. At a local level sympathetic activation may have pro- as well as antiinflammatory effects. Based on current understanding, the most prominent general effect is inhibition of inflammation.[14]

Because this is a new field and many questions remain unanswered, it should be little surprise that there exists debate about the clinical significance of neural modulation of the immune response.[15]

Similarly, the hypothalamic-pituitary-adrenal axis will release stress hormones CRF, cortisol, epinephrine, and α-melanocyte-stimulating hormone that regulate gene transcription and translation of cytokines.[16] The neuroendocrine fine tuning of inflammation warrants a discussion that is beyond the scope of this chapter.

Hypoxic-ischemic injury

The primary function of intensive care is to maintain tissue oxygenation. When this is inadequate, tissue injury occurs. Mechanisms of hypoxic injury are reviewed elsewhere in this text, but an intensivist should appreciate that failed perfusion also initiates an inflammatory cascade[17] and that hypoxia is itself is a regulator of the immune response.

Acute inflammation commonly occurs under local hypoxic circumstances—neutrophils and macrophages function well in these conditions, indeed they are activated by them. In part this effect is mediated by cytosolic hypoxia–inducible factors (HIFs). Constitutive and inducible HIF subunits bind to DNA and induce upregulation of genes for neutrophil adhesion, activation of phagocytosis, and inhibition of apoptosis. Pro-inflammatory cytokine production is also enhanced.

This cascade sounds very similar to that described after bacterial invasion. This is exactly the point—acute inflammation has many common responses to a variety of insults. Indeed, the overlap is greater still because these same HIF proteins can be robustly stabilized in an active configuration by some bacteria, and some TLR genes also upregulate HIFs. So infection causes tissue hypoxia with inflammatory consequences, but pure hypoxia activates many similar pathways.[18]

Complex System

The complexity of the early response to infection or insult is difficult to overestimate. A single injection of LPS to human volunteers has been shown to induce differential expression of nearly 4000 genes in leukocytes. These gene products join hundreds of inter- and intracellular protein and lipid mediators of inflammation—many with multiple effects. The immune response evolves rapid with time and differs between different organs or body compartments.

Complex systems such as this have a number of typical characteristics. They can appear to be unpredictable because they can produce vastly different end results with only apparently small differences in starting conditions. They also exhibit "robustness" wherein major changes (such as therapeutic inhibition of a proinflammatory mediator such as TNF) have surprisingly little measurable effects because other mediators carry the same information at times of crisis. Failure to appreciate these characteristics of the immune response has in part contributed to the very limited success of therapies for severe sepsis.[19]

Predisposition to an (in)Appropriate Response

Premature death from infectious disease is attributable to genetic influences to a higher extent than cardiovascular disease or cancer.[20] With the advent of methods to identify subtle changes in genes coding for components in the innate immune system it became possible to search for specific genetic predisposition to an inappropriate innate immune response.

Gene variations occur as single nucleotide polymorphisms, insertion or deletion or copy number variation. Early work on genetic polymorphisms showed that a high TNF-α and low IL-10 pattern, suggesting a vigorous pro-inflammatory potential, was associated with better outcome in meningococcal

disease.[21] Conversely, recent work suggested that a polymorphism associated with high TLR1-mediated inflammatory cytokine production was strongly associated with increased mortality and organ dysfunction in sepsis.[22]

There are many studies of genetic variability in critical illness, but very few provide compelling evidence of genetic variation influencing outcome. One reason may be the complexity of the clinical phenotype: i.e. heterogeneity in patients, grouped as "SIRS," "sepsis," or "acute respiratory distress syndrome." These definitions may be insufficiently precise in clinical critical illness where patient differ widely in, for example, the contribution of chronic disease to the acute state.[19]

Genetic association studies in areas with more uniformity in disease definition and better understanding of the pathophysiology of disease have isolated some effects of polymorphisms. For instance, a TNF-α receptor mutation in a standardized mouse model of sepsis improves survival but worsens localized control of infection.[23,24]

The innate immune system is complex with many redundancies. It may be unrealistic to identify those parts that have a discernible effect on outcome in the complex outcome called critical illness by analyzing variance in individual mediators. This is effectively the same issue that has confound randomized clinical trials in severe sepsis as recently highlighted.[25] Design and execution of genetic association studies need to be held against robust and reproducible end-points and rigorous quality markers.[26,27]

Despite all these difficulties, there are some observations that contribute to our understanding of innate immune variability in critical illness. The following is a sample of studies that illustrate some of these issues.

A recent systematic review and meta-analysis showed susceptibility to pneumococcal disease with MBL deficiency (odds ratio, 2.57 [95% confidence interval, 1.38 to 4.8]) but not for the single TLR2 polymorphism Arg753Gln. It may be that complement activation is a more important part of innate immunity than TLR2 or that this specific TLR2 polymorphism does not exert a strong enough difference in response.

Similarly, no evidence was found for a susceptibility to meningococcal disease for TLR4 Arg299Gly or the PAI-1 4G/5G insertion deletion promoter polymorphism.[27] However, the PAI-1 4G/5G polymorphism was shown to influence the *severity* of disease in meningococcal septic shock: children who were homozygous for the high-producing 4G were more likely to have vascular complications or to die.[28] Interestingly, a recent study shows that critically ill children with a genotype associated with high complement activation were less likely to develop systemic inflammation.[29] It may be more interesting to study the influence of genetic differences on specific patterns of disease severity rather than overall outcome that reflects the sum of so many pathophysiology processes.

Another example is variability in the adaptor molecule Mal (TIRAP). This molecule is an essential part of TLR2 and TLR4 downstream signaling. In a large multiethnic cohort (n = 6106) the effect of Mal polymorphism S180L was studied with respect to invasive pneumococcal disease, malaria, and tuberculosis.[30] Heterozygosity was associated with reduced disease severity. The authors postulated that this was due to reduced NFκB medicated cytokine response. Homozygous variant allele carriers would thus mount an inadequate antimicrobial response and wild-type carriers would mount an excessive response.

A better-known heterozygote protection against infectious disease is sickle cell trait that protects against malaria. Homozygous sickle cell anemia however predisposes to increased susceptibility to infectious disease. Children with sickle cell anemia were 25 times more likely to present with bacteremia than controls in a recent study from sub-Saharan Africa.[31]

Cytokines

Cytokines are polypeptide intercellular messengers. Because they were first described as agents that contribute to the severity of the immune response in sepsis with direct or indirect cytotoxic properties, they have often been considered to be harmful mediators and potential targets for therapeutic blockade. The reality is much more complex. Cytokines have actions stimulating or inhibiting the immune response. Pro-inflammatory cytokines include TNF-α, INFγ, IL-1β, IL-6, and IL-8, whereas IL-10 and IL-4 are thought to have predominantly anti-inflammatory properties. However, the distinction of pro- and anti-inflammatory cytokines also does not do justice to the pleiotropic functions of these proteins. For instance, dependent on timing and location, the prototypical pro-inflammatory cytokine TNF-α may have a function in pro-inflammation or in resolution of inflammation. One key issue is the appropriateness of the TNF-α action—an injection of TNF-α to a healthy volunteer causes temperature and signs of systemic inflammatory (and perhaps shock if the dose is high). This is the *cost* of TNF-α without the potential *benefit* of immune activation to kill an invading microorganism. The cost-benefit of a cytokine such as TNF-α is dependent on the scale of the infective insult it is facing. Meta-analysis of animal models and human trials with agents that block TNF-α or its receptor suggest that TNF-α is useful when the insult is mild; but harmful when the insult is very severe.[32] This dose-dependent complexity is typical of cytokine responses.

A good but extreme example of the potential harm that an acute pro-inflammatory cytokine excess can cause, in the absence of a pathogen needing killing, occurred in North West London in 2006. A phase I trial of the anti-CD28 monoclonal antibody TGN1412 in healthy adults was stopped because of a massive rapid onset of a systemic inflammatory response with multiple organ dysfunction syndrome and concomitant lymphopenia, monocytopenia, thrombocytopenia, and peripheral gangrene. This antibody caused direct T-cell activation independently of T-cell receptor ligation (in a similar manner to toxic shock toxins). Serum cytokine levels rose very rapidly with high levels of TNF-α, INFγ, and IL-6, followed by IL-8, IL-2, IL-1β, IL-10, IL-4, and IL12p70.[33]

Another, perhaps more familiar, example is secondary hemophagocytic lymphohistiocytosis. This multisystem disease results from a persistence of the inflammatory response to a systemic viral infection beyond its useful phase. The bone marrow and liver fail as they are infiltrated by activated cells derived from monocytes/macrophages. This typically occurs in patients with a congenital predisposition in which lymphocyte apoptosis is abnormal. The resultant abnormal persistence of the inflammatory response induces excessive monocyte/macrophage activation. The disease is treated by steroid immunosuppression—even though the original trigger was viral infection.[34]

Therapeutic Interventions

Numerous attempts have been made to intervene in the acute response to infection either with agents that block elements of the acute response or which top-up infusions of endogenous or innate immune or anticoagulant molecules (e.g., recombinant bactericidal/permeability increasing protein,[35] activated protein C).[36] None has shown convincing evidence of benefit in children (or adults). There are powerful arguments that even very effective agents would have failed in the methodology of inclusive randomized clinical trials because of wide variability in inclusion severity criteria and control group mortality between centers.[32,37] It may be that it is just not feasible to intervene with a single agent in the complex system with the redundancy we have discussed above. Or it may be that anti-inflammatory drugs cause harm to many patients who were already at very low risk of bad outcomes. One way forward would be to characterize the inflammatory and coagulation responses in individual patients and target intervention to the specific needs of that patient. The other approach is to recognize that the majority of poor outcome from sepsis worldwide could be averted with attention to excellent early recognition and prompt resuscitation. This should be the priority, at least in the short term.

References are available online at http://www.expertconsult.com.

VI

Chapter 91

Infection and Host Response

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PEARLS

- Innate and acquired immunity are closely interrelated, defects in one path will likely affect others.
- Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns use "same" pattern recognition receptors, and may result in similar immune response.
- Local immunity against an invading pathogen is robust and complex. Uncontrolled infection locally results in a systemic immune response.
- Cellular and soluble elements on the hemostatic system are intricately related to the immune response.
- Acquired immunity depends both on pathogen and host's response to PAMP.

Historical Perspectives

"*Rubror et tumor cum calore et dolore*," or redness and swelling with heat and pain, were recognized as the four cardinal signs of inflammation by Cornelius Celsus (30 BCE to 38 CE). It was not established until the late 1800s to early 1900s that the body used both cellular and humoral components to identify and destroy microbes. Through the work of such pioneers as Elie Metchnikoff, Paul Ehrlich, and Almoth Roth, it was demonstrated that certain humoral factors called *opsonins,* later identified as antibodies and complement products, rendered bacteria more susceptible to ingestion and killing by phagocytic cells. Antibodies together with complement could also kill bacteria directly.

Traditionally, the immune system has been divided into innate and adaptive components. Clonal expansion of lymphocytes in response to infection is absolutely critical to the development of the immune response. However, it takes 3 to 5 days for clonal expansion to produce sufficient numbers of "effector" cells. Clearly, this is more than enough time for a pathogen to damage the host. The innate immune system is fundamental in eliminating the infection, and if not, then controlling it, until the adaptive immune responses eliminate it. If the innate and adaptive immune responses are "adequate," the infection remains localized. If not, then the systemic response to infection, or "sepsis" results (see Chapters 90 and 103). What has become increasingly clear is that the adaptive and innate immune systems can each affect the functioning of the other.[1]

In the past 25 years, new concepts that are fundamental to the care of critically ill patient have arisen directly from our understanding of the host's response to infection. (1) Inflammatory reactions first characterized as a response to infection are the foundation of a number of other pathogenic mechanisms, such as ischemia/reperfusion injury, direct trauma, drug-induced injury, inhalational injury, and multiple-system organ dysfunction. (2) The response to infection may lead to further injury of the host. Alternatively, an exuberant antiinflammatory response may likewise be deleterious, resulting in immune suppression and fibrosis (see Chapter 104). (3) There is a direct interaction between the neuroendocrine axis and inflammation (see Chapter 102). (4) There is a fundamental interrelationship among endothelium, inflammation, and coagulation, and efforts to intervene in one will likely have effects in others (see Chapter 101).

Innate Immune Versus Adaptive Immune Response

The innate immune system is phylogenetically ancient. Innate immune recognition is genetically predetermined (i.e., by germline-encoded receptors). Thus these receptors have evolved by natural selection, and have defined specificities for infectious organisms. In contrast, in the adaptive immune system, the T-cell and B-cell receptors are somatically generated in a way that gives each lymphocyte a unique structural receptor. Because the T- and B-cell receptors are not encoded in a germline, they are not predetermined to recognize any particular antigen. No matter how useful these "receptors" become, they cannot be passed down to the next generation. Although there are potentially a large number of variants of germline-encoded receptors (perhaps in the hundreds), there are 10^{14} and 10^{18} different somatically generated immunoglobulin receptors and T-cell receptors, respectively.[1] Microbes are heterogenous and can mutate at very high rates. This can be handled appropriately by the adaptive immune system. This heterogeneity, however, represents more of a challenge for the innate immune system. As such, a different strategy, phylogenetically older than the adaptive system, evolved. The innate immune system has developed receptors that recognize "pathogen-associated molecular patterns" (PAMPs). PAMPs are highly conserved structures present in a large group of microorganisms. The common features of PAMPs are (1) PAMPs are only produced by microbial pathogens, not hosts; (2) structures recognized by the innate immune system are usually essential for survival or pathogenicity of the

microorganism; and (3) PAMPs are usually invariant structures shared by an entire class of pathogen. The best known examples of PAMPs are bacterial lipopolysaccharide (LPS), peptidoglycan, lipoteichoic acid (LTA), mannans, bacterial DNA, double-stranded RNA, and glucans.[2]

Pattern Recognition Receptors

In the innate immune system, pathogen recognition molecules are called *pattern recognition receptors* (PRRs) and belong structurally to several families of proteins: leucine-rich repeat domains, calcium-dependent lectin domains, and scavenger receptor domains. Functionally, PRRs can be divided into three classes: secreted, endocytic, and signaling. Secreted PRRs function as "opsonins." They bind to microbial cell walls, flagging them for recognition by the complement system and by phagocytes. Members of the secreted PRRS include C-reactive protein (CRP), mannose binding lectin, and the ficolins.[3-5] These molecules recognize sugar residues that are rich on microbial surfaces and can function directly as opsonins, promoting phagocytosis. Alternatively, they can also function indirectly by activating the classical complement pathway (CRP) or the lectin-dependent pathway (ficolin and mannose-binding lectin).[4]

Endocytic pattern-recognition receptors occur on phagocytes and can mediate the uptake and delivery of pathogens into lysosomes. Once in the lysosomes, the microbe can be destroyed. The macrophage mannose receptor recognizes carbohydrates with large numbers of mannoses (characteristic of microorganisms) and mediates their phagocytosis by macrophages. The macrophage scavenger receptor binds to bacterial cell walls and effectively clears them from the circulation. Complement receptor 3 (also known as Mac-1 and CD11b/CD18), in addition to recognizing microbes opsonized with complement, can function by binding mannose molecules directly, thus also functioning as an endocytic pattern-recognition receptor.[2] Dectin-1 present on macrophages is the endogenous receptor for β-glucan, a major cell wall component of budding yeast. Mutations in dectin 1 lead to mucocutaneous fungal disease, though fungal phagocytosis and killing is normal in affected individuals.[6]

Toll-Like Receptors

Work done by Janeway and Medzhitov revolutionized understanding of the critical role of the innate immune system as the first step in adaptive immunity.[7] They identified the human counterpart of a protein found in fruit flies (*Drosophila melanogaster*) known as Toll. The Toll protein in fruit flies is responsible for infectious susceptibility to fungi. This protein in humans, human Toll-like receptor 4 (TLR4), recognizes LPS, and is located on antigen-presenting cells (APC) such as dendritic cells, macrophages, and monocytes. Through a complex signaling cascade TLR-4 results in activation of cytoplasmic nuclear factor-κB (NF-κB). NF-κB can then translocate into the nucleus and induce the transcriptional activation of a wide variety of inflammatory and immune responses.[2] These responses include the induction of cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-12, and the induction of costimulatory molecules such as CD80 and CD86. The presentation of antigen by the major histocompatibility complex (MHC) II molecule on the APC is insufficient to induce the activation of the T-cell receptor, and thus the T cell. There must also be expression of CD80 or CD86 by the APC that is required for full T-cell receptor activation. Thus normally pathogen-specific T cells should only be activated and not self-antigen.

At present there are nine human TLR receptors.[8] The TLRs recognize molecules common to pathogens ranging from protozoa to bacteria to fungi and to viruses. The TLRs that recognize bacterial cell wall components (TLR1, -2, -4, and -6) are located on the cell surface, forming homodimers and heterodimers. Once ligated, they then translocate to the endosome for signaling (see Chapter 103).[9] TLR3, TLR7, and TLR9 reside in the endosome, recognize nucleic acids produced by viruses and bacteria, and thus are available for activity against intracellular viruses.[10]

Endogenous proteins such as heat shock proteins, surfactant protein A, high mobility group 1 (HMGB1), uric acid, and fibrinogen among many others may also function as ligands for TLRs and other PRRs. These endogenous proteins are termed *damage-associated molecular patters* (DAMPs).[11,12] The immune system has critical roles in normal physiologic processes, such as tissue remodeling after injury and development and scavenging of apoptotic cells; it is thought that the DAMPs participate in "alerting" the immune system. Mitochondria have evolved from an endosymbiont alphaproteobacterium. They have their own DNA, enriched in hypomethylated CpG-containing sequences. Zhang et al.[13] detected mitochondrial DNA in the blood of patients with systemic inflammatory response after major trauma at levels that would active TLR9 and phosphorylate signaling molecules downstream of TLR9. Accordingly, TLR9 could be signaled by mitochondrial DNA. Mitochondrial proteins from human tissues injected into animals activated formyl-peptide receptors on neutrophils, resulting in neutrophil activation and acute organ injury. As mitochondria are released from injured and dying cells (necrosis, not apoptosis), this may be the "signal" for systemic inflammation in these disease states.

There are several other classes of PRRs in addition to TLRs: RIG-I–like receptors (RLRs), Nod-like receptors (NLRs), and C-type lectin receptors (CLRs) (previously described). RLRs, an intracellular receptor, recognize single- and double-stranded viral RNA and transmit their signal through a common adaptor protein, interferon promoter stimulator-1 (IPS-1) and NF-κB, to induce type I interferon production and antiviral responses.[10] Double-stranded RNA-dependent protein kinase (PKR) is a unique PRR in that it can turn off protein translation directly; its effect does not seem to be modulated by downstream effectors.[14] Nod1 and Nod2 are NLRs that recognize PAMPs derived from the bacterial cell wall. Nod1 and Nod2 are localized to the cytoplasm and can elicit TLR-independent antibacterial responses. Other NLRs, such as NALP1, NALP3, IPAF, and NAIP5, are components of a molecular complex called the *inflammasome*. The inflammasome complex comprises one or some of the NLR proteins and caspase-1. Caspase is activated in this complex and cleaves critical inflammatory molecules such as pro-IL-1β and pro-IL-18 to produce mature proteins.[10] The NALP3 inflammasome is activated by stimuli such as uric acid crystal, silica, and asbestos; thus NALP3 appears to be a receptor for danger-associated molecular patterns. Infections with the malaria parasite or the fungus *Candida albicans* were also reported to activate the NALP3 inflammasome.

What follows is a focus on the pathogen ligands of the PRRs, in particular TLR4. It had been recognized for a number of years that CD14, present on monocytes and blood-derived macrophages, and lipopolysaccharide binding protein (LBP), found in plasma, were critical for an LPS response. However, CD14 is a glycosylphosphatidylinositol-anchored protein lacking transmembrane and intracellular domains and would be unable to signal intracellular processes. CD14 is also present to a limited extent on neutrophils.[15] In addition, a soluble form of CD14 could substitute for membrane-bound form of CD14 in LPS-mediated signaling. Thus it was clear that at least one other molecule present on the cell surface would be needed to elicit an LPS-dependent response. TLR4 knockout mice and human TLR4 mutations conferred such a role for this receptor for LPS-induced responses in humans and mice. TLR4 requires an additional molecule, MD-2, that is part of the complex on the cell surface. LPB is an acute phase reactant.[2,16] It catalyzes the transfer of LPS to CD14, which is then able to interact with TLR-4 and MD-2, resulting in intracellular signaling through the Toll/IL-1 receptor homologous region (TIR) adaptor molecules.[9] Downstream signaling events result in release of transcriptional activating factors including NF-κB, that guide gene transcription of many genes, including TNF and interferon-β (IFN-β), a type I interferon. TNF is discussed at greater length later in this chapter; however, it is a central mediator in innate immune response pathway. IFN-β is critical in adaptive and antiviral immunity (see Chapter 103 for a description of other TLRs).

Endogenous Antimicrobials

The epithelial surface of the skin, gastrointestinal tract, and bronchial tree produce a number of antibacterial peptides.[17] Leukocytes are also a rich source of these or similar proteins that can be secreted into the phagolysosome or alternatively secreted into biofilms protecting the mouth and gastrointestinal tract.[18,19] These antimicrobial proteins include the defensins, cathelicidin, lactoferrin, and bacterial permeability increasing factor (BPI).[20] Because the antimicrobial peptides are heavily positively charged (due to cationic amino acids), they specifically target bacterial cell membranes whose outermost leaflet of lipid bilayer is heavily populated with negatively charged phospholipid head groups.[17] Thus they also act as pattern recognition receptors. It is still unclear exactly how these antimicrobial peptides actually kill microbes. Possibilities include the creation of physical holes that cause cell contents to "leak out," disturbances of cell membrane function by "scrambling" the lipid bilayer, or fatal depolarization of the normally energized bacterial membrane.[21]

The α defensins are stored in the granules of neutrophils, monocytes, and macrophages, and are released extracellularly. The β defensins are produced by Paneth cells, reproductive tissues, epithelial cells, and keratinocytes; some are produced constitutively, some in response to LPS and proinflammatory products such as TNF and IL-1. Cathelicidin/LL37 is stored in neutrophil granules but is also produced by keratinocytes and epithelial cells in response to inflammatory stimuli. In addition to the antimicrobial effects of the defensins and cathelicidin, both are chemotactic for CD4 and CD8 T cells, phagocytes, and immature dendritic cells. They also enhance antigen-specific immunity and regulate complement activation.[20]

Lactoferrin and BPI are found in secondary and primary granules of the neutrophils, respectively, but they are also secreted or presented on epithelial surfaces. Lactoferrin is found in milk, tears, saliva, and other secretions such as bile, pancreatic juice, and small intestinal secretions. Lactoferrin is structurally similar to transferrin, though its affinity for iron is about 300 times higher, allowing it to retain iron at low pH.[22] Both lactoferrin and BPI have cationic-rich regions that are critical to binding and neutralizing LPS. Lactoferrin also has direct antimicrobial actions. Lactoferrin can potentiate the cytotoxic effects of monocytes and T cells.[22] BPI was initially identified in neutrophil primary granules. Because of its high affinity for the lipid A region of LPS, it is particularly cytotoxic for gram-negative bacteria, and its antibacterial activities are synergistically enhanced by defensins and cathelicidin.[23] In addition, BPI can function as an opsonin, enhancing phagocytosis.

Antimicrobial peptides have been used in a number of conditions and, though initially promising, their potential has not been completely realized. In the largest study to date, recombinant fragment of BPI, $rBPI_{21}$, was trialed in 400 children with severe meningococcal sepsis.[24] Although $rBPI_{21}$ had no effect on survival, fewer patients had multiple severe amputations, and by day 60 had a more functional outcome compared with those who did not receive $rBPI_{21}$.[24] A mammalian cathelicidin, protegrin, had no effect on the development or reduction of mucositis among patients who received stomatotoxic chemotherapy.[25]

Soluble Components of Immunity

C-Reactive Protein

CRP is phylogenetically ancient and is highly conserved in evolution. It is a member of the pentraxin family of calcium-dependent ligand-binding plasma proteins, the only other member of which is serum amyloid P (SAP). Although CRP is an acute-phase reactant in humans, SAP is not. In mice the major acute-phase reactant is SAP, with a minor fraction being CRP. In humans, plasma CRP is produced only by hepatocytes and is predominantly under the transcriptional control of IL-6. It is greatly elevated in infections, allergic complications of infection, inflammatory diseases, necrosis, trauma, and malignancy. It is modestly elevated or absent in systemic lupus erythematosus, scleroderma, dermatomyositis, ulcerative colitis, leukemia, and graft-versus-host disease. CRP binds to glycan and phospholipids of bacteria, fungi, and parasites. When aggregated or bound to macromolecular ligands, CRP is recognized by C1q and activates the classic complement pathway; thus it initiates direct microbial toxicity. Because it also recognizes phospholipids, in particular phosphocholine, it may be involved in handling apoptotic and necrotic cells.[3]

Complement System

The complement system is critically positioned to participate in both the innate and adaptive immune response.[26] However, it is also critical for the disposal of immune complexes from tissues and clearance of apoptotic cells.[4] The three pathways in which complement may become activated are the classic, alternative, and mannose-binding lectin pathway. Although complement activation initiates differently in each, all three

converge at the cleavage of C3 (Figure 91-1). The classic pathway is initiated by the binding of the C1 complex (consisting of C1q, C1r, and C1s) to antibodies bound to antigen on the cell wall. The mannose-binding lectin pathway is initiated by binding of the complex of mannose-binding lectin and the mannose-binding lectin-associate proteases 1 and 2 (MASP1 and MASP2) to arrays of mannose groups on the surface of the bacterial cell wall. Both MASP2 and C1q then function similarly in forming the C4bC2a complex, representing the convertase for C3. Bacterial products, LPS, yeast cell wall particles, and aggregated antibody, including immunoglobulin (Ig)A and IgE, are all capable of activating the alternative pathway. The alternative pathway is initiated via low-grade cleavage of C3 in plasma to C3b. C3b binds to the hydroxyl groups on cell surface carbohydrates. C3b binds factor B to form a C3bB complex, which is activated by factor D, forming C3bBb and stabilized with properdin. C3bBb then functions as an alternative convertase for C3, that cleaves many molecules of C3 to C3b. C3b binds to hydroxyl groups on the microorganism around the area of complement activation. C3a, an anaphylatoxin, is released by the C3 convertase. C3b can also bind to the C3 convertase to form C5 convertase. The C5 convertase releases the anaphylatoxin C5a and initiates the formation of the membrane attack complex (MAC), C5b6789.[4] The membrane attack complex created inserts into the cell membrane, creates large pores, and leads to osmotic lysis of the target.

Thus the complement system amplifies the initial response to the organism. In addition to lysing the target organism, opsonization with complement fragments C3b/C4b and C3bi (fragment C3b) occurs, resulting in phagocytosis by neutrophils, monocytes, and macrophages. Binding occurs through specific complement receptors, CR1 for C3b/C4b (CD35) and CR3 for C3bi (CD11b/CD18, also known as *Mac-1* and $\alpha_M\beta 2$). The anaphylatoxins C3a, C4a, and C5a produced are low molecular weight, biologically active peptides defined by their actions on small blood vessels, smooth muscle, mast cells, and peripheral blood leukocytes. Blood vessels, smooth muscle cells, basophils, and mast cells respond to all three anaphylatoxins. Neutrophils, monocytes, and macrophages respond to C5a. The anaphylatoxins promote edema and increase vascular permeability through the release of histamine from mast cells and through the local production of vasodilatory prostaglandins such as prostaglandin E_2 (PGE_2) and edemogenic leukotrienes (LT) C_4, D_4, and E_4. C5a is a powerful activator of granulocyte function including chemotaxis, degranulation, and increased oxidative metabolism. C5a actions occur through its seven-transmembrane–spanning, G protein–coupled receptor, C5aR.[27] In animal models, C5a/C5aR is critical to the development of sepsis and multiple organ failure, and potentiates many early response cytokines and coagulation. C5aR is present not only on leukocytes, but also other tissue, including the brain, kidney, gastrointestinal tract.[27,28]

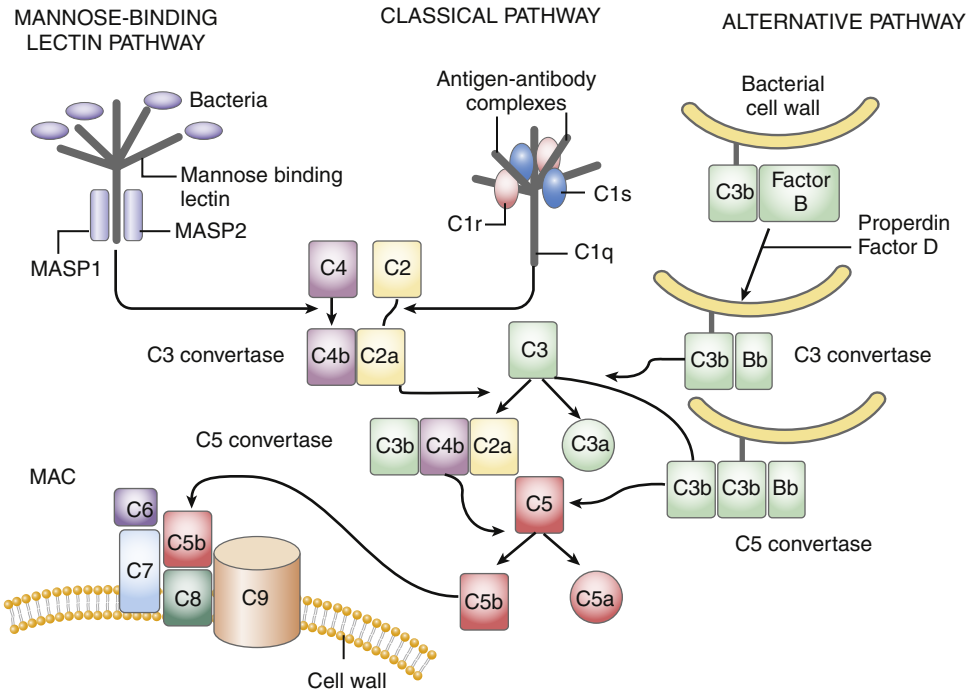

Figure 91–1. The three activation pathways of complement: the mannose-binding lectin, the classic, and alternative pathways. The three pathways converge at the point of cleavage of C3. The mannose-binding lectin (MBL) pathway is initiated by binding of the complex of the MBL and MBL-associated proteases 1 and 2 *(MASP1, MASP2)* to arrays of mannose on the bacterial cell wall. MASP2 then activates first C4, then C2 to form the C3 convertase, C4b2a. The classic pathway is initiated by the binding of the C1 complex (which consists of C1q, two molecules of C1r, and two molecules of C1s) to antibodies bound to antigen on the surface of the bacterial cell wall. C1s, similar to MASP2, then activates C4 followed by C2 to form C4b2a (the C3 convertase). The alternative pathway is initiated by covalent binding of a small amount of C3b to hydroxyl groups on the cell surface carbohydrates and is activated by low-grade C3 in plasma. This C3b binds factor B to form C3bB, which is then activated by factor D to then form C3bBb, the alternative pathways C3 convertase. Properdin stabilizes this activation step. The C3 convertase then cleaves many molecules of C3 to C3b and C3a (an anaphylatoxin). C3b binds covalently around the site of complement activation, some of which binds to the C4b and C3b of the classic and alternative pathway C3 convertase, respectively, to form the C5 convertase. The C5 convertase cleaves C5 to C5a (an anaphylatoxin) and C5b, which initiates the formation of the membrane attack complex (MAC). *(Modified from Walport MJ: Complement. First of two parts,* N Engl J Med *344:1058, 2001.)*

Complement activation also occurs after oxidative stress such as occurs with ischemia/reperfusion. Complement activation is an early event after injury and the inhibition of complement activation or its components offer tissue protection after reperfusion.[29] Finally, complement proteins transduce various cell signals. Complement can activate B and T cells. It can regulate apoptosis of various cell types (see Chapter 100).[20,26]

Immunoglobulin

The different immunoglobulins (Igs) secreted by B cells (IgG, IgA, IgM, IgD, and IgE) are known as *isotopes*. IgD plays little role, if any, in containment of microorganisms. Ig isotypes can be divided into subclasses, variants that show slight structural differences but are sufficiently alike structurally to be essentially identical to other members of the isotype class. There are four IgG subclasses: IgG1, IgG2, IgG3, and IgG4. As seen in Table 91-1, isotype subclasses have specialized roles in the immune response. For example, IgG2 has a major role in the formation of carbohydrate antibodies, but has poor complement fixation characteristics. The antibody system consists of Ig present in serum, protecting the blood and tissue spaces, and that present in the secretory system, lining the gastrointestinal and respiratory tracts and present in tears. The serum component is mostly IgG (85%), with lesser amounts of IgA and IgM. The secretory system consists mostly of secretory IgA (85%), which is structurally different than serum IgA, and lesser amounts of IgG and IgM. All Igs have a basic four-chain structure composed of an identical pair of heavy (H) and light (L) chains. The H-L pairs are held together by interchain disulfide bonds and noncovalent forces. The binding site for antigen is formed by one H and one L chain. IgM is a polymer of five four-chain units, and secretory IgA is a dimer. Polymeric forms (Figure 91-2) possess a J chain that is synthesized with the H and L chains and serves to stabilize the sulfhydryl groups during polymerization. At regular intervals along the peptide chain a disulfide bond forms an intrachain loop, known as the *Ig domain*. This motif is repeated among immunoglobulins, T-cell receptors, adhesion proteins, and histocompatibility antigens. Proteins with these Ig domains share close homology structurally and functionally and suggest a common evolutionary origin. They are termed *members of the Ig superfamily* (IgSF), and all are involved in cell interaction processes associated with recognition.

The Ig molecule is divided into regions, the amino acid sequence of which is similar, such as regions needed for complement fixation or attachment to receptors on leukocytes. However, other regions are highly variable; those that bind

Table 91–1 Biologic Properties of Ig Classes and IgG Subclasses

Property	IgG1	IgG2	IgG3	IgG4	IgM	IgA	IgE	Secretory IgA
First detectable antibody	–	–	–	–	+	–	–	–
Major part of secondary response	+	+	+	+	–	–	–	–
Placental transport	++	+	++	++	–	–	–	–
Complement activation								
Classic pathway	++	+	++	–	–	–	–	–
Alternate pathway	–	–	–	–	–	++	+	+
Agglutination	+	+	+	+	++	–	–	–
Opsonization	+	+	+	+	++	–	–	–
Virus neutralization	+	+	+	+	+	–	–	–
Anaphylaxis	–	–	–	–	–	–	++	–
Present in exocrine secretions (gastrointestinal system and lung)	+	+	+	+	+	+	+	++
Binds to receptors on:								
Macrophages	++	±	++	±	–	–	+	–
Lymphocytes	+	±	+	±	–	–	–	–
Neutrophils	+	+	+	+	+	+	±	+
Platelets	+	+	+	+	–	–	–	–
Mast cells	–	–	–	–	–	–	+	–
Binding to Fc receptors:								
FcγRI (CD64)	++	±	++	+	–	–	–	–
FcγRII (CD 32)	++	+	++	±	–	–	–	–
FcγRIII (CD 16)	++	±	++	±	–	–	–	+
FcαR	–	–	–	–	–	+	–	+
FcμR	–	–	–	–	+	–	–	–
FcεRI and FcεRII	–	–	–	–	–	–	+	–

++, Very strong; +, strong; ±, equivocal; –, absent.

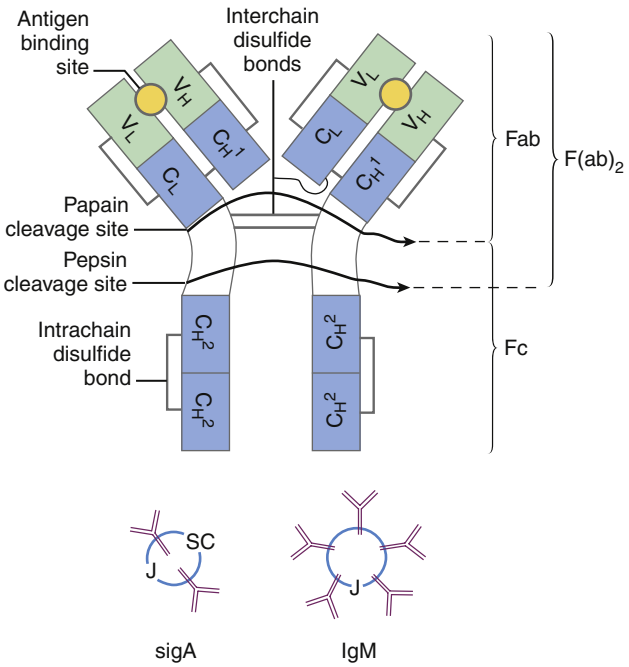

Figure 91–2. Basic immunoglobulin (Ig) structure. Sites of cleavage for papain or pepsin are shown with resulting fragments. The intrachain disulfide bond forms the region of the Ig domain. *Insets* show polymeric immunoglobulins, secretory IgA (*left*) and IgM (*right*). J chain is common to all polymeric forms; SC is the secretory component. V_L, Variable domain of light chain; C_L, constant domain of light chain; V_H, variable domain of heavy chain; C_H, constant domains of heavy chain.

to antigen have the highest divergency and are collectively known as the *hypervariable region*. Thus each Ig chain can be divided into constant and variable regions. The H chain has three constant regions and one variable region; the L chain has one variable region and one constant region. The hypervariable region of the L and H chain is tightly apposed and forms the combining site for antigen (see Figure 91-2). The digestion of Ig with papain and pepsin generates fragments with varying biologic capability. The Fc region of the Ig molecule accounts for its isotypic biologic capability. This is the region critical for complement fixation and recognition by Fc receptors on the leukocytes. The Fab region provides for specific unique antigen-antibody interactions. The F(ab′)2 fragment is formed with pepsin cleavage; the affinity for antigen is twice as great as Fab alone.

Contact Activation System

There are four major plasma protein systems that contribute to the host's defense and participate in the development of inflammatory tissue injury: the complement system (previously discussed), the contact activation system (also known as *Hageman factor* or *intrinsic coagulation system*), the extrinsic coagulation cascade, and the fibrinolytic system (see Chapter 80). The contact activation system is critical to host defense and control of local blood flow at sites of injury. Hageman factor (Factor XII) is activated spontaneously (XIIa) on contact with negatively charged surfaces, such as lipid A of LPS and vascular basement membranes (Figure 91-3). High-molecular-weight kininogen (HMWK), prekallikrein, and factor XI circulate in the plasma as complexes. Factor XIIa will activate factor XI and cleave prekallikrein to kallikrein. Kallikrein will then cleave HMWK to bradykinin. The kallikrein-kinin system also encompasses the tissue (or glandular) kallikrein-kinin system (see Figure 91-3). Tissue kallikrein is immunologically distinct from plasma kallikrein and present throughout the body as an inactive "pro-" substance. In the presence of intracellular enzymes, plasmin, or plasma kallikrein, tissue kallikrein is produced, secreted, and active in the tissue where it is made. Tissue kallikrein can then cleave HMWK to bradykinin directly, or it can cleave low-molecular-weight kininogen (LMWK) or tissue kininogen (T-kininogen) to kallidin that is then directly converted to bradykinin. In the plasma, 80% of kininogen is low molecular weight.

Bradykinin is an exceedingly potent vasoactive peptide.[31] It can cause venous dilation, increased vascular permeability, hypotension, bronchoconstriction, and activation of phospholipase A_2. Phospholipase A_2 releases arachidonic acid from cell membrane and initiates the production of both proinflammatory and antiinflammatory phospholipids-derived products (see subsequent section and Figure 91-3). Bradykinin is metabolized by angiotensin-converting enzyme (ACE) to inactive peptides. Bradykinin, along with prostanoids, stimulates the pain response through polymodal receptors and C-fibers (capsaicin sensitive).[32] Bradykinin has been shown to be responsible for the four signs of inflammation: heat, redness, swelling, and pain. The bradykinin effect is enhanced by simultaneous production of prostanoids. Prostanoids, particularly along with the low pH of exudates, inhibit the activity of kininases such as ACE.

Lipid-Derived Mediators of Inflammation

Although these products per se are not "soluble" components of immunity, their production nonetheless has both proinflammatory and antiinflammatory effects. They are discussed here because of their production as a result of the contact activation syndrome. These mediators are not stored preformed, but are rapidly generated after cell stimulation. Arachidonic acid (AA, or eicosatetranoic acid) is a 20-carbon fatty acid. Its metabolites are termed *eicosanoids*. The eicosanoids are produced by a variety of cell type–, tissue-, and species-specific biosynthetic pathways. Prostanoids are a specific class of mediators generated via initial actions of cyclooxygenase. The eicosanoid family includes the thromboxanes, prostacyclins, leukotrienes, hydroeicosotetranoic acids (HETES), epoxyeicosatrienoic acids (EETs), lipoxins, and isoprostanes. Release of AA and the 1-alkyl-2-acetyl analogs of phosphatidyl choline (platelet activating factor [PAF]) occurs through the action of phospholipase A_2 and phospholipase C on cell membrane phospholipids. Phospholipases can be stored in lysozymes or exist in the cytoplasm. Through cell activation, they translocate to the inner cell membrane, where they can hydrolyze cell membrane phospholipids. The major routes of AA metabolism for proinflammatory effects are the 5-lipoxygenase pathway (production of the leukotrienes, LT) and the cyclooxygenase pathway (production of prostaglandins and thromboxane, i.e., prostanoids). Of particular interest are newly recognized classes of prostanoids derived from polyunsaturated fatty acids (omega-3 fatty acids) that mediate antiinflammatory effects, the resolvins and protectin.[14]

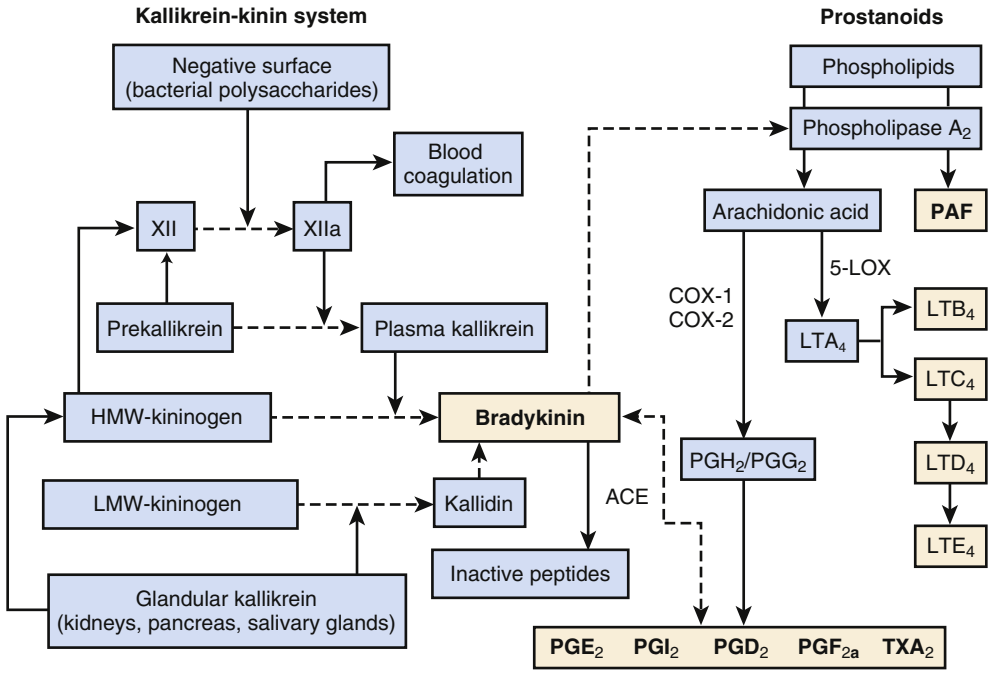

Figure 91–3. Contact activation system and prostanoid production. Bradykinin can be produced by either the plasma kallikrein (*top left*) or tissue (glandular) kallikrein system (*bottom left*). Once formed, bradykinin can activate phospholipase A_2, and thus drive prostanoid production. In addition, it can potentiate the affects of the prostaglandins and vice versa. Bradykinin is metabolized into inactive peptides via several steps, the last of which is enzymatically driven by angiotensin-converting enzyme *(ACE). HMW,* High molecular weight; *LMW,* low molecular weight; *PAF,* platelet activating factor; *COX-1,* cyclooxgenase-1; *COX-2,* cyclooxygenase-2; *5LOX,* 5-lipoxygenase; *LT,* leukotriene; *TXA_2,* thromboxane A_2; *PG,* prostaglandin. *(Modified from Ueno A, Oh-ishi S: Roles for the kallikrein-kinin system in inflammatory exudation and pain: lessons from studies on kininogen-deficient rats,* J Pharmacol Sci *93:1, 2003.)*

The 5-lipoxygenase pathway is prominent in leukocytes and mast cells. Leukotrienes C_4, D_4, and E_4 are potent vasoconstrictors and bronchoconstrictors with specific effects on the peripheral airways. LTB_4 is produced by neutrophils, monocytes, and macrophages within minutes of cell activation. LTB_4 is a powerful chemoattractant and activator of other leukocytes, resulting in enhanced leukocyte-endothelial cell interactions, sequestration of leukocytes in the pulmonary vasculature, and induction of permeability at the endothelial interface.

Thromboxane A_2 is principally produced by platelets but also by neutrophils and macrophages. Thromboxane induces platelet aggregation and is also a potent vasoconstrictor of vascular beds, especially pulmonary, coronary, splanchnic, and renal. It induces bronchoconstriction and increases microvascular permeability. The major prostaglandin produced by the endothelium is prostaglandin I_2 (PGI_2). PGI_2 is important in the control of hemostasis and is a potent inhibitor of platelet aggregation. It is four to eight times more potent that PGE_2 in its vasodilatory action. Unlike PGE_2, however, it is not metabolized by the pulmonary endothelium. PGE_2 is produced by neutrophils, platelets, macrophages, and endothelium. Both PGE_2 and PGI_2 inhibit adhesion of neutrophils to endothelium. The production of PGE_2 by hypothalamic microvessels in response to pyrogens such as LPS initiates fever.

Platelet activating factors (PAFs) are implicated in a diverse range of human pathophysiologic conditions, including shock, ischemia/reperfusion injury, asthma, anaphylaxis, necrotizing enterocolitis, and a number of other inflammatory states. Though historically PAF was first described as a potent platelet activating substance, it has diverse biologic effects, many of which are platelet independent. PAF, through its G protein–linked receptor, induces microvascular permeability, transformation of the endothelium from an anticoagulant to a procoagulant state, and vasoconstriction. Produced in very small amounts, it can be presented at the endothelial surface and serve as an activating agent for neutrophils as they are tethered and roll on the endothelium (see further description of leukocyte localization). Increased levels of PAF have been demonstrated in animal models and clinical studies of septic shock, acute lung injury, and necrotizing enterocolitis. Although isolated effects of PAF can be demonstrated, there is a complex interaction among PAF, prostaglandins, and cytokines in the pathophysiologic changes associated with sepsis, shock, trauma, and ischemia/reperfusion injury.[33,34]

Cytokines

Cytokines are signaling proteins secreted by cells that affect the functional properties of other cells of the same organism. The cytokine family includes lymphokines, chemokines, interleukins, and interferons. Unlike circulating hormones, cytokines travel short extracellular distances before interacting with target cell surface receptors in a paracrine or autocrine manner. Cytokines can be detected in serum samples, particularly during times of maximal production, as occurs in sepsis. Cytokines as a group are low-molecular-weight (<80 kDa) proteins. They interact with high-affinity cell surface receptors specific for each cytokine. Their cell surface binding ultimately leads to changes in the pattern of protein synthesis and/or altered cell behavior. They often have multiple-overlapping cell regulatory functions. Many cytokines are

produced early in infection, whereas others are produced at later stages.

Interleukin-1 and Tumor Necrosis Factor

IL-1 is a phylogenetically old molecule that predates the evolution of lymphocytes and immunoglobulin. Its activity extends beyond immune function. IL-1 is produced by a wide variety of cells, including macrophages, endothelial cells, epithelial cells, and vascular smooth muscle cells. There are two separate forms of IL-1, IL-1α, and IL-1β. In contrast, TNF-α is produced by cells primarily of the innate immune system, including monocytes/macrophages, NK cells, mast cells, and neutrophils under specific conditions. TNF is also produced by other cell types under conditions of stress. For example, TNF is produced by cardiac myocytes and is implicated in both acute and chronic congestive heart failure as well as in the cardiomyopathy associated with sepsis. TNF-β (also known as *lymphokine*) is produced by T lymphocytes, but occasionally antigen-activated T cells may also produce TNF-α. Both TNF and IL-1 are produced as small precursor molecules or "pro" molecules that are cleaved by IL-1β converting enzyme in the inflammasome (by caspase 1) and TNF-α converting enzyme, ADAM17 (***a d***isintegrin ***a***nd ***m***etalloproteinase), respectively. Once cleaved, these proteins are then excreted. It should be noted that caspase-1 (in the inflammasome) and ADAM17 are multifunctional proteinases and have activity on other interleukins and inflammatory molecules. IL-1 is the only cytokine with a natural inhibitor, IL-1 receptor antagonist (IL-1RA) produced by the same cells that produce IL-1. IL-1RA functions to downregulate the proinflammatory effects of IL-1. IL-1 and TNF-α are the early major mediators of gram-negative endotoxin shock (see Chapter 103). As outlined earlier in this chapter, signaling of cells by TNF and IL-1 occurs at least in part through NF-κB, and consequently share a similarity in receptor function and signaling molecules.

For routine infection and injury, IL-1β and TNF-α are transiently expressed and secreted. Their activities are modulated by coproduction of naturally occurring antiinflammatory cytokines, such as IL-10 and IL-1RA. The levels of these cytokines fall off rapidly; thus production is tightly regulated. Dysregulated cytokine production, such as occurs in chronic diseases such as rheumatoid arthritis and inflammatory bowel disease, has lead to the development of anticytokine therapy such as human recombinant IL-1RA (Anakinra), human/murine chimeric monoclonal antibody against TNF-α (Infliximab), and recombinant fusion protein composed of the extracellular binding domain of TNF receptor II and human IgG1 (Etanercept). With the development of these products, there is increasing evidence that neutralization of TNF-α is associated with increased risk of opportunistic infections, including mycobacterial diseases. Blockade of IL-1 using IL-1RA appears at present to be safe.[35] Using such blocking agents in animal models it appears that neutralization or gene deletion of TNF-α is associated with reduction of host defense in models of live gram-positive or gram-negative infections as well as infection by intracellular microbes such as *Salmonella* and *Listeria.* Absence of IL-1RA can also result in decreased resistance to *Listeria* or gram-positive bacteria. TNF and IFN-γ (discussed in the following paragraphs) are required for defense against infection caused by *Mycobacterium tuberculosis.*[35]

Il-17 is produced by an effector helper T cell, Th17, as well as natural killer (NK) cells and NK-T cells (combined properties of both NK and T cells). Th17-driven inflammation is typified by neutrophils predominating the inflammatory response. A number of pathogens induce Th17 response, including *Citrobacter, Klebsiella pneumonia, Mycobacterial tuberculosis,* and fungi such as *Candida albicans.*[36] To eliminate the body of fungi and certain extracellular pathogens requires inflammation driven by Th17. Most cell types have IL-17 receptors, and signaling through this receptor produces IL-6, TNF, IL-8, antimicrobial peptides, and matrix metalloproteinases. IL-17 is also implicated in several inflammatory conditions, including rheumatoid arthritis, psoriasis, multiple sclerosis, and inflammatory bowel disease.[36]

IL-18 is a member of the IL-1 family of ligands. It has unique characteristics in that only in conjunction with IL-12 is IFN-γ produced by activated T cells and by LPS-stimulated macrophages. IL-18 is implicated in the development of endotoxic shock and in the myocardial depression that occurs in these models.[37] As a key mediator of IFN-γ production, IL-18 serves an important role in controlling infections from *Salmonella, Cryptococcus,* toxoplasma, *Candida*, and *Mycobacterium* organisms, often through its modulation of the production of nitric oxide.[37,38]

IL-12 is produced by monocytes, macrophages, dendritic cells, neutrophils, and to a lesser extent B cells. IL-12 effects are primarily on T and NK cells. The responses by T cells and NK cells include increased proliferation, increased IFN-γ production, increased cytotoxic activity (cytotoxic T lymphocytes and NK cells), and for T cells, polarization toward a Th1 phenotype (see following discussion). Patients with defects in IL-12 or IL-12 receptor have increased susceptibility to mycobacterial and salmonella infections. Neonates have diminished IL-18 and IL-12 production contributing to inadequate IFN-γ production and increased susceptibility to infections.[39,40]

IL-6 is one member of the IL-6 family of cytokines. It is produced by many cell types including the cardiac and skeletal myocytes, but mainly by macrophages and monocytes, adipose cells, endothelial cells, T lymphocytes, mast cells, and osteoclasts. Many cell types respond to IL-6, including hepatocytes. IL-6 is the factor most directly responsible for the production of acute phase reactants. Its production is somewhat delayed compared to IL-1 and TNF, IL-6 levels remain elevated longer than the other two. IL-6 deficient animals have an increased susceptibility to *Listeria monocytogenes, Streptococcus pneumoniae, Escherichia coli, Candida albicans,* and mycobacterial infections.[35,41]

IL-10, like IL-6, is a pleiotropic cytokine that exerts both immunosuppressive and immunostimulatory effects. It is produced primarily by $CD4^+$ T cells, B cells, and other cell types. Its predominant suppressive effect is to inhibit Th1 (IFN-γ and IL-2) cytokine production. It downregulates MHC II expression, thus limiting its interaction with T cells and NK cells. It also inhibits cytokines involved in inflammatory responses, including prostaglandin E_2, TNF-α, IL-1, IL-6, and IL-8. IL-10 induces the production of IL-1RA. IL-10 can upregulate FCRγI on monocytes, macrophages, and NK cells, enhancing antibody-mediated cellular cytotoxicity.

IL-2 is produced by CD4 T cells when they encounter foreign peptide-MHC complex on antigen-presenting cells. This cytokine is critical for adaptive immune response in that it has both an autocrine and paracrine function, triggering T cells to undergo multiple rounds of proliferation and differentiate into effector T cells.

Interferons and Other Soluble Products

IFN-α and IFN-β are known as type I interferons. IFN-α is produced by monocytes and macrophages, whereas IFN-β is produced by fibroblasts and other cell types. The major stimuli for type I interferon are viral infections; they also respond to T-cell–derived factors in adaptive immune responses. Type I IFNs inhibit viral replication, and patients with insufficient production suffer from severe progressive or fulminant viral disease. These IFNs inhibit cell proliferation, enhance the lytic potential of NK cells, and increase class I HLA while decreasing class II HLA. IFN-γ is a type II IFN and is produced primarily by $CD4^+$, $CD8^+$, and NK cells (Figure 91-4). IFN-γ has antiviral and antiproliferative activity. It upregulates class I and II HLA expression, thus enhancing cellular toxicity and antigen presentation, respectively. IFN-γ activates monocytes and macrophages as well as neutrophils, resulting in enhanced killing of intracellular organisms, including mycobacteria and listeria. In addition, IFN-γ induces inducible nitric oxide synthase in macrophages, resulting in the generation of nitric oxide, a critical component for bactericidal function. Animals with a deficiency of IFN-γ have decreased survival in response to salmonella and mycobacterial infections. Patients with complete loss of IFNγ receptors have severe, early life infections with salmonella and viral infections (including respiratory syncytial virus, parainfluenza, herpes simplex virus, and cytomegalovirus) with a high mortality rate.[35,40,42] IFN-γ is a critical cytokine at the interface of the adaptive and innate immune system because of its function on NK cells and ultimately monocytes/macrophages.

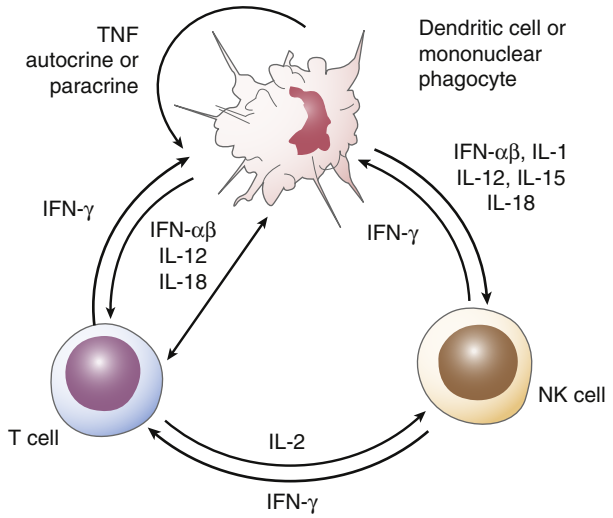

Figure 91–4. Secreted cytokines and effects on adaptive (T cell) and innate (dendritic cell/mononuclear phagocyte) and NK cells. NK cells activate mononuclear phagocytes and dendritic cells via IFN-γ secretion. With activation, mononuclear phagocytes demonstrate increased phagocytic and antimicrobial actions against intracellular pathogens. The phagocytes secrete cytokines which activate the NK cells, inducing IFN-γ production. IFN-γ from NK cells, and IFN αβ, IL-12, IL-18 from the mononuclear phagocytes/dendritic cells in turn activate the T cell along the TH-1 pathway. Activation of the T cell produces IL-2 and IFN-γ, which affects the mononuclear phagocyte/dendritic cell, NK cell, other T cells. Activation of the mononuclear phagocyte/dendritic cell results in production of TNF that has both autocrine and paracrine effects. (*Modified from Douglas S, Kapur R, Merrill JD, et al: In Stiehm ER, Ochs HD, Winkelstein JA, editors:* Immunologic disorders of infants and children, Philadelphia, *2004, Saunders Elsevier.*

Macrophage migration inhibitory factor (MIF) has been identified for more than 40 years, though its function has only been well defined in the past 15 years with the cloning of human MIF cDNA. Although T cells were initially believed to be the main source, monocytes, eosinophils, basophils, dendritic cells, B cells, mast cells, and neutrophils all express MIF. In contrast to other cytokines, MIF is secreted and stored in intracellular pools and therefore does not require de novo protein synthesis before secretion. MIF has a very broad tissue distribution and is expressed by cells and tissues that are in direct contact with the host's natural environment as well as organs involved in the stress response (hypothalamus, pituitary, and adrenal glands). MIF is implicated in both gram-negative and gram-positive infections. MIF-deficient animals have increased susceptibility to low-dose inoculum of salmonella and *Escherichia coli.* In contrast, blockade of MIF results in improved survival in animals treated with high doses of *E. coli*, after cecal ligation and puncture, or after bacterial superantigen challenge. Recent work supports that MIF also has isomerase activity and contributes to chronic inflammation seen in inflammatory bowel disease and cancer.[43,44]

High mobility group box 1 (HMGB1) has been identified as a late mediator of sepsis. Like MIF, antibodies to HMGB1 can be given many hours after the induction of sepsis and improve survival in animal models.[43,45] Also similar to MIF, HMGB1 is released from the cytoplasmic pool. Intracellular HMGB1 has diverse functions, including nucleosomal structure and function, as well as binding of transcription factors to their cognate DNA sequences. However, in systemic concentrations it has diverse proinflammatory responses mirroring the "late" effects of systemic inflammation and as such is often grouped with DAMPS (reviewed elsewhere[45]). Macrophages and neutrophils, when stimulated with LPS and C5a, respectively, release large amounts of HMGB1 into the culture medium. Systemic HMGB1 accumulation occurs in mice 8 hours after LPS administration, long after TNF and IL-1β levels have decreased. Humans with sepsis have elevated levels of HMGB1, and those whose levels were most elevated were at highest risk of dying.[46] In a mouse model of cecal ligation and puncture in which mortality rate was 75%, treatment with anti-HMGB1 monoclonal antibody 24 hours after injury decreased the mortality rate to 25%. It had no effect on recovery of bacterial counts from the spleens of these animals and thus did not appear to affect bacterial clearance.[47] A derivative of a Chinese herb, tanshinone IIA TSN IIA-SS, at concentrations (100 μmol/L) completely abrogated LPS-induced HMGB1 release.[48] This needs validation in other animal studies.

Chemokines are structurally and functionally related inflammatory cytokines with the ability to stimulate the chemotactic migration of distinct sets of cells, including neutrophils, monocytes, lymphocytes, dendritic cells, macrophages, fibroblasts, stem cells, and smooth muscle cells. The chemokine family is the largest family of cytokines, and although their main function is characterized as "chemotaxis," or directing migration through a concentration gradient, they also have a number of other functions, including cell activation, signaling, effects on angiogenesis and tumorigenesis, as well as immune cell polarization. To date there are 40+ identified chemokines.[49] They are small (~8 to 14 kDa), mostly basic molecules. They function through unique receptors that are G protein coupled and are seven membrane spanning

(i.e., have seven transmembrane domains).[50] The cytoplasmic domains of the receptors are critical for cell signaling and function. Chemokines may use more than one receptor for function. Chemokines are central to the process of extravasation of leukocytes that includes multiple steps involving interactions of adhesion molecules and the chemoattractant function of these proteins.[51] Chemokines are defined by structure, not function, and can be divided into two large and two small subgroups depending on the number and arrangement of conserved cysteines. The subgroups are CC, CXC, C, and CX3C. It should be appreciated that in the past 10 years, chemokines have been designated by their subgroup followed by ligand number; for example, IL-8 is CXCL8. Most chemokines are classified into two main groups according to function: (1) those concerned with hemostasis that are constitutively expressed and coordinate leukocyte trafficking during hematopoiesis and those with lymphocyte recirculation, and (2) those concerned with inflammation and tissue injury. Chemokines are produced by hematopoietic cells themselves as well as by endothelial cells, epithelial cells, and cells arising from the mesoderm, including fibroblasts, myocytes, hepatocytes, and lymphatic cells. Table 91-2 lists a select group of cytokines involved in infection and inflammation.

Granulocyte colony stimulating factor (G-CSF) and *granulocyte-macrophage stimulating factor* (GM-CSF) were initially identified by their ability to induce granulocytopoiesis and monocytopoiesis; however, they have marked effects on neutrophil and monocyte function. Although both G-CSF and GM-CSF are produced by bone marrow stromal cells, they are also produced by activated monocytes/macrophages and fibroblasts. G-CSF is also produced by epithelial cells of the gut and lung in response to inflammation. GM-CSF is produced by T lymphocytes and NK cells. G-CSF enhances the physiologic activation of mature neutrophils, whereas GM-CSF stimulates the functional activity of neutrophils, eosinophils, and monocytes/macrophages.[52,53] GM-CSF is critically involved in the normal surfactant turnover, and alveolar proteinosis is an autoimmune disease targeting GM-CSF.[54] Critical to the immune response is that production of G-CSF and GM-CSF results in increased neutrophil survival. Neutrophils usually have a half-life of less than 12 hours before removal from the circulation and undergo apoptosis. However, exposure to G-CSF or GM-CSF decreases apoptosis, leading to prolonged survival of circulating neutrophils and those that have moved to a site of infection. Removal of these cytokines, such as occurs in the resolution phase of inflammation, leads to induction of apoptosis and increased clearance of neutrophils. G-CSF and GM-CSF are approved for use in a variety of hematologic pathologies.[53] G-CSF and GM-CSF have been proposed for use in the nonneutropenic critically ill adult and neonatal population. However, studies to date do not support their routine use as either a treatment of established systemic infection or as prophylaxis to prevent systemic infection in high-risk individuals.[55-57]

Nitric oxide (NO) is a stable, free radical gas. Extensive work over the past 20 years has converged to establish NO as a major messenger molecule regulating immune function and blood vessel dilation as well as a neurotransmitter. NO is formed from arginine by the enzyme nitric oxide synthase (NOS). NOS-2 or inducible NOS (iNOS) is present in many tissues, whereas NOS-1 and NOS-3 are primarily present in neuronal and endothelial cells, respectively. NOS-1 and NOS-3 are present in low amounts and generate NO for neurotransmission and vasodilation. In contrast, NOS-2 is induced by microbial peptides and inflammatory cytokines and serves as a major bactericidal and tumoricidal agent. NO is critical in adaptive immunity to intracellular pathogens such as *Mycobacterium tuberculosis* and *Listeria monocytogenes*. NO enhances the activity of NK cells, γδ T cells, and macrophages. The condensation of NO and the reactive oxygen metabolite superoxide, O_2^-, results in the production of peroxynitrite ($OHNOO^-$), which decays to the highly reactive hydroxyl radical (OH) and nitrogen dioxide. These agents contribute in part to the killing of the microorganisms in tightly regulated structurally "isolated" areas of phagocytes, the phagolysosomes, discussed below.

Cellular Components of Immunity

The cellular components of immunity have traditionally been divided into innate and adaptive immunity, but such distinctions have become increasingly blurred and critical overlap occurs. For example, the dendritic cells and other antigen presenting cells, such as macrophages and monocytes, are part of the innate immune system; nonetheless, they directly drive adaptive immunity.

The cells of the immune system can be defined by the surface antigens they display. These surface antigens are denoted by the CD nomenclature and refer to cluster designation. These antigens denote the lineage and often the functional capacity of a cell. Surface antigens are revealed by using monoclonal antibodies, commonly with flow cytometry.

Lymphocyte types include the T cells, B cells, NK cells, and the NK T cell (NKT), which exhibits features of both NK and T cells. T cells got their name because the vast majority arise from the thymus. They mediate antigen-specific cellular immunity and play a critical role in facilitating antigen-specific B cell–dependent humoral immunity. B cells are the subset of lymphocytes that synthesize, express Ig on their surface, and differentiate to plasma cells that produce Ig. B cells arise from the bone marrow in humans and other mammals or bursa in birds.[58]

The major T-cell subsets are the $CD4^+$ helper/inducer and the $CD8^+$ suppressor/killer cells. Nearly all T cells bear a T-cell receptor composed of an α- and β-chain; they also express CD4 or CD8 coreceptors. Nearly all the αβ T cells recognize protein antigen in the form of peptide fragments bound to classic MHC molecules (MHC class I or MHC class II). The CD4 molecule augments binding to antigens presented in association with MHC II antigens, whereas CD 8 molecules are necessary for antigen binding to MHC I. The immunologic synapse is the highly ordered junction that forms between the APC, such as the dendritic cells or tissue macrophages, and the T cell during antigenic stimulation. The structure resembles a doughnut in which the T-cell receptor-peptide-MHC, CD3, CD4, or CD8 is in the center of the synapse. The costimulatory molecules CD2, CD28, CD54 (intercellular adhesion molecule-1 [ICAM-1]) on the T cell bind to their respective ligands LFA-3 (CD 58), CD80-CD86, LFA-1 (CD11a/CD18) on the APC on the perimeter of synapse (Figure 91-5).[59]

The $CD4^+$ naive cells, which are those never exposed to antigen, can differentiate into effector cells expressing specific patterns of cytokines. Originally designated as Th1 and Th2

Table 91–2 Chemokine/Chemokine Receptor Families (Partial List)

Name	Original Ligand Name*	Chemokine Receptor
CXCL1	GRO-α/MGSA-α	CXCR2>CXCR1
CXCL2	GRO-β/MGSA-β	CXCR2
CXCL3	GRO-γβ/MGSA-γ	CXCR2
CXCL5	ENA-78	CXCR2
CXCL7	NAP-2	CXCR2
CXCL8	IL-8	CXCR1, CXCR2
CXCL9	Mig	CXCR3
CXCL10	IP-10	CXCR3
CXCL12	SDF-1	CXCR4
C CHEMOKINE/RECEPTOR FAMILY		
XCL-1	Lymphotactin	XCR1
CX3C CHEMOKINE/RECEPTOR FAMILY		
CX3CL1	Fractalkine	CX3CR1
CC CHEMOKINE/RECEPTOR FAMILY		
CCL2	MCP-1	CCR2
CCL3	MIP-1α	CCR1,CCR5
CCL4	MIP-1β	CCR5
CCL5	RANTES	CCR1, CCR3, CCR5
CCL8	MCP-2	CCR3
CCL11	Eotaxin	CCR3
CCL19	MIP-3β	CCR7
CCL21	6Ckine	CCR7
CHEMOKINE RECEPTORS AND CELLULAR DISTRIBUTION		
XCR1	Lymphotactin	T,B, NK
CXCR1	IL-8, GRO-α	N,M, T, NK, En, Ms, Bs
CXCR2	IL-8, GRO-α,-β-γ, NAP-2, ENA-78	N,M,T,NK, Ms, As, Nn, En
CXCR3	IP-10, Mig	Activated T
CXCR4	SDF-1	Myeloid, T, B, Ep, En, DC
CX3CR1	Fractalkine	NK, M, T
CCR1	RANTES, MIP-1α, MCP-2, MCP-3	N, M, T, NK, B, Ms, As, Nn
CCR2	MCP-1	M, T, B, Bs
CCR3	RANTES, eotaxin	Eo, Bs, T
CCR5	RANTES, MIP-1α, MIP-1β, MCP-2	T, M, Mϕ
CCR7	MIP-3β, 6Ckine	T, B, DC

*All ligand names are human chemokines.
GRO, Growth regulating peptide; *MGSA,* melanocyte growth stimulating activity; *ENA,* epithelial-derived neutrophil attractant; *NAP,* neutrophil activating peptide; *IL-8,* interleukin-8; *IP-10,* γ-interferon-induced peptide 10; *SDF,* stroma derived factor; *MCP,* monocytes chemotactic peptide; *MIP,* macrophage inflammatory peptide; *RANTES,* regulated on activation, normal T cell expressed and secreted; *T,* T cell ; *B,* B cell; *NK,* natural killer cell; *M,* monocyte/macrophage; *N,* neutrophil; *Ms,* mast cell; *Bs,* basophil; *As,* astrocyte; *Nn,* neuron; *En,* endothelium, *Eo,* eosinophils; *DC,* dendritic cell; *Ep,* epithelial cell; *Mϕ* macrophage.
Modified from Murdoch C, Finn A: Chemokine receptors and their role in inflammation and infectious diseases, *Blood* 95:3032, 2000; and Zlotnik A, Yoshie O: Chemokines: a new classification system and their role in immunity, *Immunity* 12:121, 2000.

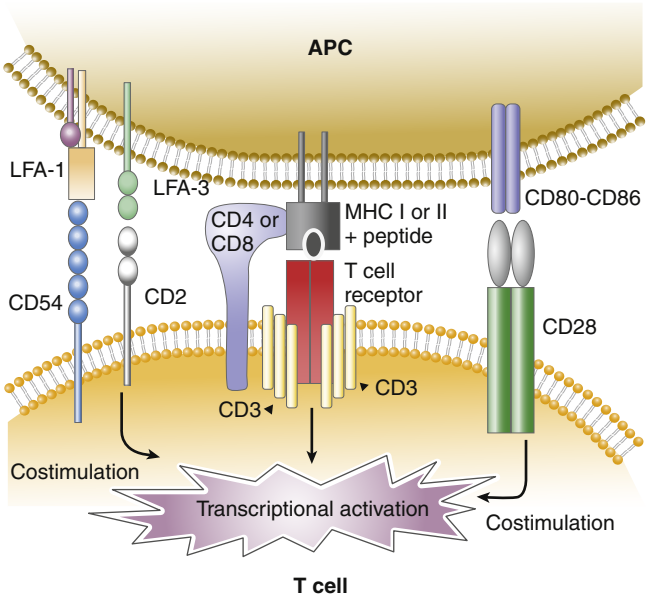

Figure 91–5. Immunologic synapse. Protein antigen bound to the major histocompatibility complex I or II (MCH I or II) is presented by the antigen presenting cell *(APC)* to the T-cell receptor. The T-cell receptor/CD3 complex is composed of the two chains of the T cell receptor (α and β) and the 6 subunits of the CD3(a γ and a δ subunit and two each of the ε and ζ subunits). CD8 or CD4 interacts with the MHC I or MHC II/antigen complex, respectively. Engagement of the T-cell receptor can then signal the T cell to activate a number of activities, including transcription. However, for activation to occur, there must be additional signals through costimulatory molecules on the T cell and APC. The T-cell receptor/CD3/CD4 (or CD8) complex is centered in the middle of the immunologic synapse, while the costimulatory molecules are in the periphery.

based on the cytokines they produce, there has been an explosion in the past 15 years delineating additional subtypes. Most of these cytokines produced by T cells are secreted, but some can be expressed on the cell surface. IL-12 and IFN-γ drive T cells into the Th1 pathway. IFN-γ is the signature cytokine produced by Th1 cells, but the Th1 cells also produce substantial amounts of IL-2, TNF-α, and TNF-β. The Th1 response is considered proinflammatory. IL-4 drives T cells into the Th2 pathway. Th2 cells also produce large amounts of IL-4 along with IL-5, IL-9, and IL-13. IL-4 and IL-13 (along with IL-10 produced by monocytes/macrophages) are considered anti-inflammatory or immunosuppressive. The Th2 response is critical for eosinophil function and is important in the development of IgE responses and the killing of parasites.

Th17 cells, which produce IL-17, result from activation of naive T cells by TGF-β plus an inflammatory cytokine (IL-21 alone, IL-6 + IL-23, or IL6 + IL-21).[36] IL-23 is produced by monocytes and dendritic cells. IL-21 is produced by Th17 cells and thus serves an amplification loop for Th17 differentiation. Important to highlight is that TGF-β is considered a prototypic antiinflammatory cytokine critical for the healing. It also serves as a warning of categorizing a particular molecule as either "pro" or "anti" inflammatory solely, which is often proven to be too simplistic as our understanding of immunity progresses. Th17 is critical for the control of extracellular cytokines, induces the destruction of matrix, and often synergizes with TNF and IL-1.[36]

TGF-β is produced by many cells. In the absence of IL-6, it will induce $CD4^+$ cells into a regulatory T cell, known as

a *T-reg*. T-reg cells are identified by a transcription factor, Foxp3+ (Forkhead box P3 transcription factor) and carry the IL-2 receptor CD25. Presence of Foxp3+ is implicated in the development of autoimmunity, allergy, and rejection in transplant medicine and suppression of immune responses to cancer.[60] There are several different types of T-regs. All require cell-to-cell contact for immune suppression.

Naive $CD8^+$ cells are not effective killer cells. However, after activation with antigen in the context of MHC class I by APCs in the presence of IL-2 and IL-12, they differentiate quickly into $CD8^+$ cytotoxic cells. These cells express perforin, granzymes, and Fas ligand and produce effector cytokines including TNF-α and IFN-γ. Perforins introduce pores into the target cell through which granzymes can enter, leading to the triggering of apoptosis and cell death. Alternatively, the cytotoxic T cell upregulates the Fas ligand (CD95L) that engages Fas (CD95) on the target cell, resulting in delivery of death signal culminating in apoptosis (Figure 91-6).

A small proportion of T cells in the circulation have γδ T-cell receptors that are not restricted to antigen recognition bound to either MHC I or MHC II. Thus γδ T cells do not have either CD4 or CD8 molecules on their surface. The γδ T cell recognizes either stress-induced or nonclassic MHC molecules directly or nonpeptide antigens, such as host or pathogen-derived lipids bound to these nonclassic MHC molecules. The γδ T cell is primarily located in epithelial tissues in certain species and performs effector functions that protect the host from infections and malignancy and maintains tissue integrity. These cells also play a critical role in regulating the immune response, leading to resolution of infection and inflammation.[61]

NK cells are large granular lymphocytes with innate immune function. They play a critical role in the early host defense against viral, bacterial, and other infections as well as cancer. NK cells recognize their targets through unique NK receptors and are able to recognize self-MHC class I or class I–like molecules that inhibit or enhance NK function. Their phenotype is characterized by the expression of the CD56 surface antigen and the lack of CD3. NK cells produce IFN-γ, TNF-α, IL-10, and GM-CSF. They exhibit spontaneous cytotoxic activity against virus-infected cells and mediate antibody-dependent cell cytotoxicity through FCRγIII (CD16). Cytotoxicity is the major effector function of NK cells. They bridge the innate and adaptive immune response (Figure 91-6).[62,63] The NKT cells express both CD56 and CD3 T-cell receptor and thus share receptor structures of both conventional NK and T cells. NKT cells are potentially capable of very rapid secretion of large amounts of Th1 or Th2 cytokines but also contain perforin. Both NK and NKT cells use the same mechanisms as the cytotoxic $CD8^+$ T cell for killing (i.e., perforin/granzyme cytotoxicity and Fas-ligand/fas cytotoxicity) (see Figure 91-6). The control and resolution of viral infections require the eliminate of the source of the virus, hence the destruction of the virus-infected cell before progeny virus is produced. This is mediated during the innate phase of the immune response by NK cells. In most cases, resolution of active viral infection ultimately requires the development of antigen-specific T lymphocytes, the majority of which are MHC class I–restricted $CD8^+$ T cells, although MHC class II $CD4^+$ cells and γδ T cells may also mediate cytotoxicity.

Phagocytic cells include neutrophils, eosinophils, monocytes/macrophages, and dendritic cells. They have in common

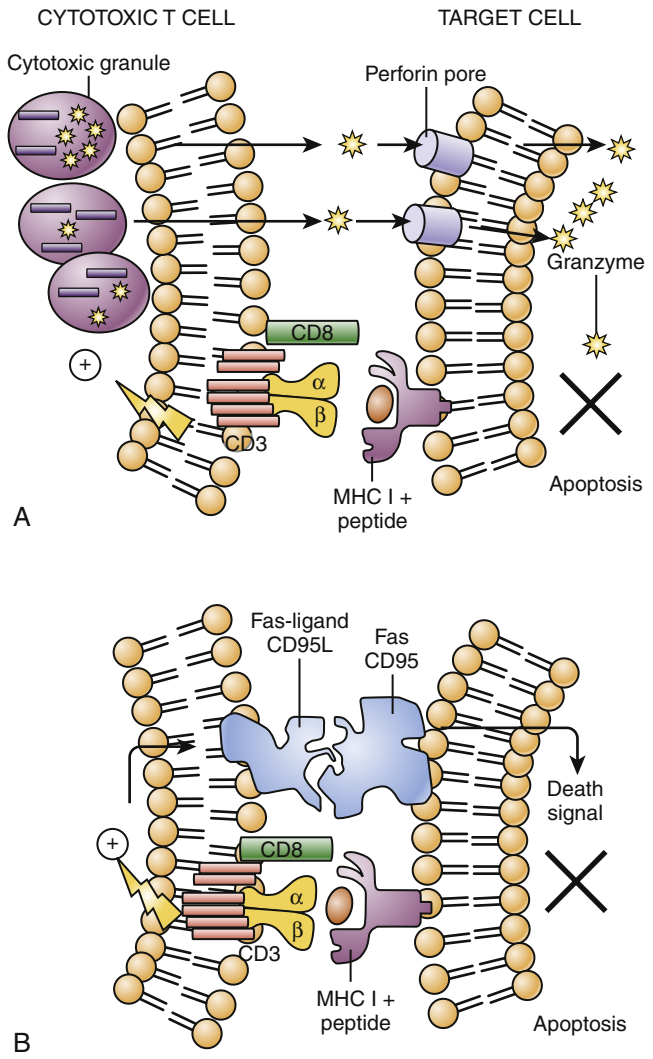

Figure 91–6. Mechanisms of antigen-specific MHC I–restricted T cell–mediated cytotoxicity. The engagement of the αβ T-cell receptor *(TCR)* in the CD3/CD8 complex of the T cell by antigenic peptide bound to MHC I on the target cell leads to T-cell activation and target cell death. **A,** Cytotoxicity occurs via the release of the contents of the cytotoxic granules from the T cell, including perforin and granzyme. A perforin pore is introduced into the target cell membrane by which granzymes can enter the target cell, leading to the triggering of apoptosis and cell death. **B,** Activation of the T cells leads to upregulation of the Fas-ligand *(CD95L),* which engages Fas *(CD95)* on the target cell, resulting in the delivery of a death signal culminating in apoptosis. Both of these mechanisms are also used by NK (natural killer) T cells and NK cells. *(Modified from Lewis DB, Wenwei T: The physiologic immunodeficiency of immaturity. Stiehm ER, Ochs HD, Winkelstein JA, editors:* Immunologic disorders of infants and children, *Philadelphia, 2004, Saunders Elsevier.)*

a number of different properties that are of prime importance to the host inflammatory response. Neutrophils, eosinophils, and monocytes/macrophages share the ability to phagocytose foreign material, release granule constituents, secrete inflammatory mediators and regulators, and synthesize reactive oxygen products through a unique reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme system present on the cell membrane. Neutrophils, eosinophils and basophils are all polymorphonuclear leukocytes (PMNLs). Neutrophils and eosinophils share similar mechanisms of cell migration, phagocytosis, and pathogen killing. All three cell types have segmented nuclei and contain granules, although

their granule content varies. Neutrophils are the host's main defense against bacterial and fungal infections. Eosinophils are important to the control of parasitic infections. Neutrophils may remain in the storage pool of the bone marrow for up to 5 days. Released from the bone marrow into the blood, about half the neutrophils circulate for about 10 hours; the other half remains in a marginated pool, so they are not accessible to phlebotomy. This marginated pool is thought to be in the spleen, along vessel walls, and in the lung microcirculation. Cells can be mobilized from this marginated pool by infection/inflammation and stress. Once circulating neutrophils migrate into the tissue they survive for 1 to 2 days, likely longer in the presence of G-CSF and GM-CSF.

Monocytes, macrophages, and dendritic cells are part of the mononuclear phagocyte system. Although these cells share characteristics with neutrophils and eosinophils, they also have unique properties, including antigen processing and interaction with lymphocytes in the generation of the immune response and extracellular killing of tumor cells. Monocytes are released from the bone marrow, circulate for 1 to 4 days, then migrate into the tissues. Three fourths of the circulating monocytes are localized to blood vessel walls in a marginated pool. Monocytes emigrate into tissue to replace resident macrophages and are either "free" or "fixed." Free macrophages are found in pleural, synovial, peritoneal, alveolar spaces and in inflammatory sites. Fixed macrophages are generally less motile and include those in the splenic sinusoids, Kupffer cells (liver), bone marrow reticulum, lamina propria of the gastrointestinal tract, lymph node reticulum, osteoclasts in the bone, and as microglia (in the central nervous system).[63] These macrophages are heterogenous in their phenotype and function. It has been hypothesized that macrophages have functional patterns such as seen with T cells (i.e., Th1- or Th2-driven phenotypes). However, work supports that monocytes and tissue macrophages develop their phenotypic function in response to changes in the microenvironment in which they are located rather than representing particular populations of monocytes that have been recruited there.[15]

The localization of phagocytes to a site of infection is reviewed in a subsequent section. However, after localization occurs, recognition of the pathogen by the phagocyte occurs through fragment receptors (FcRs; see previous section) and complement receptor or other pattern recognition receptors present on the phagocyte. On encountering a particle/pathogen, the appropriate receptors are activated and the phagocyte membrane ruffles. The phagocyte then assumes a bipolar configuration, with the formation of a "head," or pseudopod, and "tail," or uropod. The pseudopod surrounds a particle and fuses at its distal end to form a phagolysosome, thus internalizing the particle and a portion of the plasma membrane. The pseudopodia only advance over the portion of the particle or pathogen that is "opsonized" or where there are molecular patterns that fit the appropriate receptor on the phagocyte. Granules present in phagocytes then join this newly formed vacuole and discharge their contents within seconds. Neutrophils have at least three types of granules containing microbial enzymes, myeloperoxidase and lysozyme, proteases, cationic proteins, BPI, and defensins and acid hydrolases. They also contain molecules critical for adhesion and locomotion, such as Mac-1 (CD11b/CD18). Release of myeloperoxidase from primary granules is important in oxygen-dependent microbial killing. Release of other granule constituents, such as lysozyme, lactoferrin, defensins, and BPI, is of critical importance in decreasing the pH of the phagolysosome and in oxygen-independent microbial killing. Phagocytes are responsive to environmental cytokines such as TNF-α, IFN-γ, and chemokines that can prime the phagocyte for increased killing. Phagocytes also produce a large number of products in response to bacterial challenge. Monocytes/macrophages are a rich source of TNF-α and IL-1; even neutrophils produce TNF-α and IL-1, though in lesser amounts. Each cell produces chemokines that attract other leukocytes to the inflammatory focus. Phagocytes can also produce a number of lipid mediators that further stimulate the innate immune response.

The respiratory burst refers to the coordinated consumption of oxygen and production of metabolites that occur when phagocytes are exposed to appropriate stimuli. These events underlie all oxygen-dependent killing by phagocytes. Defects in the respiratory burst mechanisms result in the disorder chronic granulomatous disease. The NADPH oxidase system is a transmembrane electron transport system in which NADPH, the primary electron donor on the cytoplasmic side of the membrane, reduces oxygen in the extracellular fluid or within the phagolysosome to form O_2^- (superoxide). In turn two molecules of O_2^- spontaneously or enzymatically (through superoxide dismutase) generate hydrogen peroxide (H_2O_2). Although both O_2^- and H_2O_2 can directly injure bacteria, the oxidants that are formed from them are primarily responsible for microbicidal action. Myeloperoxidase released into the phagolysosome will enzymatically form hypohalous acids from halide anion. Hypohalous acids such as hypochlorous acid (HOCL) are extremely potent antimicrobials. These agents can then alternatively react with ambient amines (RNH_2) to form N-chloramines (RNHCL). RNHCL are lipophilic oxidizing and chlorinating agents that readily penetrate cellular membranes. The toxic effects of HOCL and RNHCL include sulfhydryl oxidation; hemoprotein inactivation; protein, amino acid, and DNA degradation; and inactivation of essential metabolic cofactors. Oxyradicals, in particular hydroxyl radical (HO), are some of the most powerful oxidizing substances known. In the presence of Fe^{3-}, O_2^-, and H_2O_2 combine to form HO. Presence of NOS-2 in phagocytes, in particular the macrophages, provides a source of NO that can react with O_2^-, producing peroxynitrite ($ONOO^-$), another toxic and powerful oxidant.[64]

Neutrophils from patients with chronic granulomatous disease retain some of the antimicrobial activity of normal neutrophils despite the inability to produce oxygen species. This is due to the many endogenous antimicrobials present in the granules that are critical to the killing of microbes. These antimicrobials, discussed earlier in the chapter, include defensins, bacterial permeability increasing protein, lactoferrin, and lysozyme. A number of other proteases, hydrolases, and nucleases in the granules of phagocytes, although not directly microbicidal, act synergistically with the antimicrobial agents to contribute to killing. These products can also result in host injury if released from the neutrophil. Neutrophil elastase, collagenase, and gelatinase (also known as matrix metalloproteinase-8, -9, respectively) can hydrolyze key components of the extracellular matrix. Neutrophil elastase not only can degrade almost all components of the extracellular matrix, but can also cleave a variety of key plasma proteins such as immunoglobulins, complement proteins, and clotting factors. The activity of the elastase outside the cells is regulated

primarily by α_1-proteinase inhibitor. Neutrophil elastase can mediate injury outside the neutrophil when α_1-proteinase inhibitor is inactivated by oxidants.[65]

Dendritic cells (DCs) are a distinct lineage of migratory leukocytes. They initiate the primary immune response yet are part of the innate immune system. DCs exist in most tissues of the reticuloendothelial system. They are prominent in tissues exposed to the external environment with frequent exposure to foreign antigen. DCs from different tissues have varying cell membrane markers and functions and include thymic DCs, interstitial DCs (heart, lung, kidney, intestine), interdigitating DCs (lymph nodes), and Langerhans cells (epidermis). The features these DCs have in common are that they originate from bone marrow $CD34^+$ stem cells and migrate through the bloodstream to tissues to become immature DCs. Immature DCs take up antigen or respond to environmental cues through pattern recognition receptors and other receptor and nonreceptor mechanisms. This then results in maturation of the DCs and production of unique sets of cytokines and receptors. Depending on the specific environmental signal, DCs will mature into different clones.[66,67]

Immature DCs migrate to and remain in the periphery, where they express low levels of MCH I and II. These immature DCs will then mature either after phagocytosis of foreign antigen or by activation of one of its receptors (e.g., TLR). The mature DC will then migrate to the local lymphoid organ; as they do, they increase cell surface expression of MHC as well as T costimulatory molecules (i.e., CD80-CD86) and begin to secrete specific cytokines. Mature DCs lose the ability to phagocytose. In the lymphoid organ, the DC will present antigen to the $CD4^+$ or $CD8^+$ T-cell receptor via MHC II or I, respectively. The DC costimulatory molecules CD80 or CD86 must engage their ligand, CD28, on the T cell for full activation (Figure 91-6). It should be noted that for the initial immune response, the DC (or APC) must be in geographic proximity of the $CD8^+$ and CD4+ cell. Alternatively, the DC or APC may be preconditioned by an activated $CD4^+$ cell that is then able to activate naive $CD8^+$ cells to become cytotoxic T cells.[66,67] Not all macrophages function well as antigen presenting cells; elicited peritoneal macrophages do, but alveolar macrophages and Kupffer cells do not.[15]

Platelets

As previously described, hemostasis and inflammation overlap. The endothelial surface that is usually *anticoagulant* becomes *procoagulant* in infection and inflammation. Platelets themselves have inflammatory, antimicrobial, and immune-modulating factors. In a platelet thrombus, neutrophils, and to a lesser extent monocytes, are recruited to the developing thrombus via adhesion receptors (discussed in the following section). In addition, leukocytes and platelets adherent to endothelial surface can attract the other cell type. Platelets secrete a number of stored chemokines that activate neutrophils and monocytes, T cells, and NK cells. These include the neutrophil-activating chemokines: NAP2 (CXCL7), PR4 (CXCL4), GRO-α, (CXCL1), ENA-78 (CXCL5), as well as the monocyte-activating chemokines: RANTES (CCL5), MIP-1α (CCL3), and MCP-3 (CCL7). Platelets also contain antimicrobial peptides such as thrombocytins as well as HMGB1. They can synthesize IL-1β. Platelet interactions with neutrophils alter the production of LTB_4 that may be important for T-cell homing. Platelets can also convert arachidonate metabolites supplied by neutrophils to leukotriene C_4 and lipoxins, providing additional modulatory signals in cell-to-cell interactions.[68] Platelets express TLR4, and complex interactions between platelets and neutrophils may lead to trapping of bacteria within the vasculature, which is discussed in following sections.[56]

Leukocyte Localization

In response to infection and in normal immune surveillance all leukocytes must travel from their sites of production to the point at which their function is required. There is a multiple-step process for localization to occur. Permutations in this process exist in specialized vascular beds such as the lung, liver, and kidney.[69,70]

In general, the multistep process begins by activation of the postcapillary venular endothelial surface by inflammatory cytokines such as IL-1, TNF, IL-4, and IFNγ. The surface transforms from a nonadhesive surface to one that is proadhesive through the expression of specific ligands. These ligands will recognize their cognate receptors on the circulating effector leukocytes (and platelets) (i.e., neutrophils, eosinophils, monocytes, NK cells, activated T cells). Endothelial ligands that are upregulated include members of the selectin family and IgSF (Table 91-3). Selectins are responsible for the initial capture of the leukocyte from the free-flowing stream as well as rolling on the endothelial surface of the IgSF that is critical for leukocyte slowing, arrest, and migration on the cell surface (Figure 91-7). The leukocyte ligand for E- and P-selectin is PSGL-1 (CD162, P-selectin glycoprotein ligand 1). The leukocyte receptors for the IgSF are the β2 integrins, in particular Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), and the β1 integrin VLA-4 (CD49d/CD29). The leukocyte integrins are heterodimers composed of an α and β subunit. The β subunit may be shared by multiple members of a subfamily, whereas the α subunit confers specificity. Mac-1 functions not only in leukocyte recruitment, but also as a receptor for complement fragment C3bi; hence its alternative name of complement receptor 3. LFA-1 also functions as coinducer of the immune response in the immunologic synapse as discussed above (Table 91-3). The endothelial surface also secretes a number of chemokines and other activating substances, such as PAF, that activate the leukocyte and mediate the transition from rolling to arrest. After the leukocyte has arrested, it polarizes, then "crawls" and emigrates through the endothelial lining of the vessel. This emigration, known as *diapedesis*, is in response to activating agents (chemokines, LTB_4) released by cells present in the subendothelial matrix, released bacterial products (N-formyl peptides), or through complement activation (C5a). This process is also dependent on leukocyte integrins that recognize IgSF on the endothelial cells necessary for transendothelial migration (see Figure 91-7). Locomotion through the subendothelial matrix requires additional leukocyte integrins (VLA-1, -2, -3, 5, -6) that recognize matrix proteins, including fibronectin, collagen, vitronectin, and vimentin. What effector cell is recruited and the tissue to which it is recruited depend on the adhesion molecules present on the endothelial surface and the effector cells as well as the "signals" released or presented at the endothelial surface and in the subendothelial region.[71-73]

Table 91–3 Adhesion Molecules in Inflammation and Hemostasis

Name	CD Classification	Primary Cell Expression	Ligand
INTEGRIN FAMILY			
β1 Integrins			
α1β1 (VLA-1)	CD49a/CD29	T and B-cell subsets, mono	COL I, COL IV, LN
α2β1 (VLA-2)	CD49b/CD29	T-cell subsets, mono, PLT, PMN	COL I, COL IV, LN
α3β1 (VLA-3)	CD49c/CD29	T-cell subsets, mono	FN, COL I, LN
α4β1 (VLA-4)	CD49d/CD29	T-cell, B-cell, Eos, mono, PMN, baso	FN, VCAM, Tsp, JAM2
α5β1 (VLA-5)	CD49e/CD29	T-cells, PMN, PLT	FN, Tsp
α6β1 (VLA-6)	CD49f/CD29	T-cells, PMN, PLT, EC	LN
α9β1		PMN, mono	VCAM-1, OSP, tenascin
β2 Integrins			
αLβ2 (LFA-1)	CD11a/CD18	PMNS, T- and B-cell, Eos, mono, NK, macro	ICAM-1, ICAM-2, ICAM-3, JAM-1
αMβ2 (Mac-1)	CD11b/CD18	PMNS, mono, Eos, NK, macro, lymph subset	ICAM-1, iC_3b, Fg, FN, Factor X,
αXβ2 (p150,95)	CD11c/CD18	PMN, mono, Eos, lymph subset	JAM-3, GPIb- IX-V
β3 Integrins			
αIIbβ3 (GPIIbIIIa)	CD41/CD61	PLTS	VWf, FN, Fg, VN, Tsp, COL
αVβ3 (vitronectin receptor)	CD51/CD61	Macro, mono, T-cell, PLT, EC, PMN	VWf, VN, FN, Fg, PECAM-1, Tsp, LN, OSP, tenascin, COL
β7 Integrins			
α4β7	CD49d/β7	Gut-associated lymphocyte	VCAM, MAdCAM-1, FN
αEβ7	CD103/β7	Gut-associated lymphocytes	E-CAD
IMMUNOGLOBULIN SUPERFAMILY (IGSF)			
ICAM-1	CD54	T+B-cell, mono, EC, pneumocyte, hepatocytes, epithelial cells, fibroblasts	LFA-1, Mac-1
ICAM-2	CD102	EC	LFA-1
ICAM-3	CD50	Lymph, PMN, mono	LFA-1, αDβ2
VCAM-1	CD106	EC	α4β1, α4β7
JAM-1		EC, epithelial cells, PMNs, mono, lymph, RBC	LFA-1, JAM-1
JAM-2		HEV, EC	JAM-2, JAM-3, α4β1
JAM-3		Lymph	Mac-1, JAM3
MAdCAM-1		Peyers patch HEV, mesenteric LN	α4β7, L-selectin
PECAM-1*			
SELECTINS			
L-selectin	CD62-L	Lymph, mono, Eos, baso, PMN	CD34, GlyCAM-1, MAdCAM-1, Unknown EC ligand, PSGL-1, PNAD, sLe^x-bearing ligands
P-selectin	CD62-P	EC, PLTS	PSGL-1, E-selectin, GPIb-IX-V
E-selectin	D62-E	EC	PSGL-1, sLe^X-bearing ligand(s), CLA
SELECTIN LIGANDS			
PSGL-1	CD162	PMN, Eos, mono, lymph	P-selectin, L-selection, E-selectin
GlyCAM-1		Lymph node + Lung EC	L-selectin
CD34	CD34	Peripheral LN HEV, leukocyte precursors	L-selectin
OTHER			
CD99	CD99	T cells, endothelial cells, monocytes	CD99, ?
PECAM-1*	CD31	EC, PMN, PLT, mono, lymphocyte subsets	PECAM-1, αVβ3

*PECAM-1 (platelet endothelial adhesion molecule-1) is now considered a member of the ITIM family, but by convention it is still listed in the IGSF and Other.
VLA, Very late antigen; *mono,* monocytes; *PLT,* platelet; *Eos,* eosinophils; *PMN,* polymorphonuclear leukocyte; *baso,* basophil; *EC,* endothelial cell; *COL I,* collagen type I; *COL IV,* collagen type IV; *LN,* laminin; *FN,* fibronectin; *VCAM,* vascular cell adhesion molecule; *Tsp,* thrombospondin; *NK,* natural killer cell; *macro,* macrophages; *ICAM,* intercellular adhesion molecule; *JAM,* junctional adhesion molecule; *lymph,* lymphocytes; *iC3b,* inactivated form of complement component C3b; *Fg,* fibrinogen; *OSP,* osteopontin; *MAdCAM-1,* mucosal addressin cell adhesion molecule-1; *E-CAD,* E-cadherin; *GlyCAM-1,* glycosylation-dependent cell adhesion molecule-1; *PSGL-1,* P-selectin glycoprotein ligand-1; *sLe^x,* sialylated Lewis X antigen; *CLA,* cutaneous lymphocyte-associated antigen; *vWf,* von Willebrand factor, *Vn,* vitronectin; *PNAD,* peripheral node addressin; *GP1b-IX-V,* glycoprotein complex present on the surface of platelets.

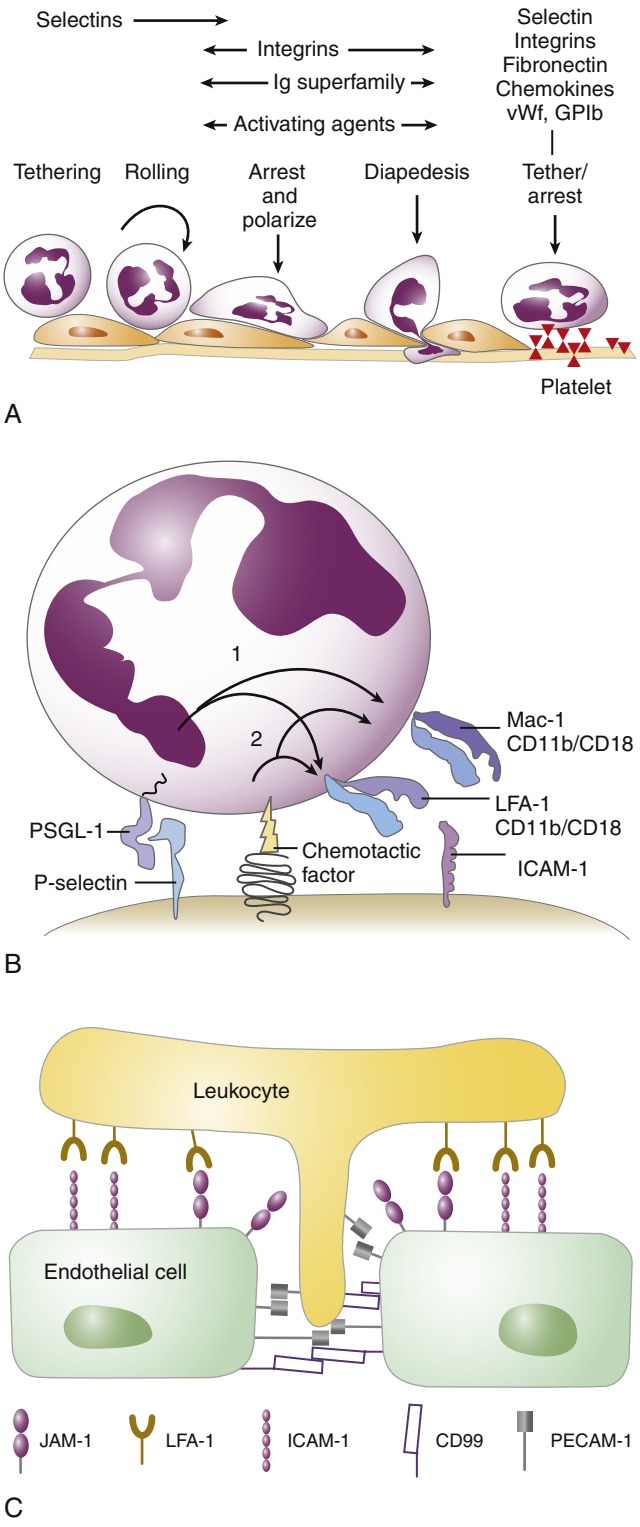

Figure 91–7. Leukocyte localization. **A,** Leukocytes are captured from the free-flowing stream (tether) and roll on the endothelial lining of the blood vessel. This interaction is mediated by all three members of the selectin family. The leukocyte slows, arrests, and changes shape (polarizes). Integrins and their ligands, the immunoglobulin superfamily (IgSF), mediate these steps. The cells then crawl, or diapedese, over the surface of the endothelium until they migrate through the endothelium. The integrins, members of the IgSF, and CD99 all have a role in this response. A leukocyte also may be tethered by adherent platelets or adherent leukocytes. Platelets through β3 integrins and GPIb-IX-V can bind directly to collagen or fibronectin on exposed basement membrane, or alternatively to von Willebrand factor bound to the endothelium or basement membrane. Platelets can release cytokines that activate leukocytes directly once tethered. Leukocytes can bind to platelets directly through integrins or to fibrinogen that is bound to platelets. **B,** Model of leukocyte activation leading to arrest. Leukocytes tether to the endothelium expressing P-selectin via P-selectin-glycoprotein-ligand 1 *(PSGL1).* In the presence of shear, PSGL-1 can activate the leukocyte integrins LFA-1 and Mac-1 (*arrow 1*). Chemotactic factors expressed on the endothelial surface can also directly activate LFA-1 and Mac-1. LFA-1 and Mac-1 both can bind to endothelial ICAM-1 at domains 1 and 3, respectively. **C,** Proposed mechanisms for transendothelial migration. With stimulation of the endothelial cell, ICAM-1 is upregulated. JAM-1, which is localized at the interendothelial cleft, is mobilized away from the cleft. With activation of the leukocytes, migration across the vascular endothelial can then occur via LFA-1, PECAM-1, JAM-1, and CD99. Leukocyte LFA-1 can bind to JAM-1 and ICAM-1 on the endothelial surface. Leukocytes can then traverse the interendothelial cleft through sequential transhomophilic interactions of PECAM-1 and CD99. *Ig,* Immunoglobulin; *vWF,* von Willebrand factor; *JAM,* junctional adhesion molecule; *PECAM,* platelet endothelial adhesion molecule. *(From Mariscalco M: Integrins and cell adhesion molecules. Polin RA, Fox WW, Abman SH, editors:* Fetal and neonatal physiology, *Philadelphia, 2004, Saunders Elsevier.)*

This multistep paradigm is also critical for the homing of lymphocytes to the high endothelial venules, a specialized endothelium of the secondary lymphoid organs. Here naive lymphocytes (rather than activated cells) tether, roll, arrest, and emigrate through the endothelial surface. The naive lymphocytes migrate toward DC or APC that secrete cytokines and chemokines necessary for activation of the T cell through the T-cell receptor.[74] One critical chemokine is SDF-1 (CXCL12). Its receptor, CXCR4, is present on almost all lymphocytes and many monocytes. The multistep paradigm is not operative in all vascular beds. In lungs the inflammatory cells do not "roll," but instead are physically trapped in the pulmonary capillary bed and emigrate from this area rather than in the postcapillary venules.[75] In the liver, leukocytes are physically trapped in the sinusoids. Because the sinusoidal endothelia has large pores, the leukocytes can easily interact with the underlying hepatocytes[76] The platelet can also function as a surface to which a leukocyte can bind by the activated release from the Weibel-Palade body of P-selectin at sites of injury or inflammation to the endothelium (see Figure 91-7).

An increasing number of genetic defects in leukocyte localization have been identified. Those that involved adhesion receptors critical for neutrophil recruitment result in neutrophilia and severe, recurrent skin abscesses. In patients with leukocyte adhesion deficiency type-1 (LAD-1), there is a selective defect in the expression and/or functional activation of β2 (CD18) integrins. In patients with the rarer defect, LAD-2, there is defective rolling of leukocytes on inflamed endothelium due to lack of fucosylated glycoconjugates on the selectins. Finally, patients with LAD-3 have a functional defect in the activation of β1 and β2-integrin avidity, leading to defective leukocyte arrest on vascular endothelium.[71,77,78]

Host Response to Infection: A Summary

There is a coordinated and highly regulated response by the body to microbial infection. As outlined in Figure 91-8, the first defense is local immunity. The epithelial surface functions

as a physical barrier. Through the release of antimicrobial peptides from the epithelium and secretory IgA from submucosal plasma cells, microbial burden is decreased. The epithelial cells at the site of infection will produce cytokines and chemokines that regulate the invasion of the area by leukocytes. However, these cytokines will also modulate the submucosal macrophages and plasma cells that are constitutively present. The presence of soluble agents critical for opsonization (including Ig and complement components) permit the efficient phagocytosis of organisms by recruited neutrophils and monocytes as well as resident macrophages. The presence of T cells and plasma cells early in the infection depends on a previous encounter with the organism. If the host has immunologic memory for the microbe, then there will be fairly rapid (i.e., within 1 day) expansion of the memory T cells to effector cells (i.e., cytotoxic T cells) and expansion of memory B cells and differentiation to plasma cells to produce IgG. It should be noted that at each step of the process, the number of bacteria decrease.[76,79]

If the host must mount a primary immune response to control and eliminate the infection, it may take 3 to 5 days for microbial or viral elimination to occur if local mechanisms or innate immune systems response are inadequate. As outlined in Figure 91-9, the initiation of adaptive immunity for a typical viral infection occurs within 2 days. Between 3 and 4 days, there is the establishment of the adaptive immune response with

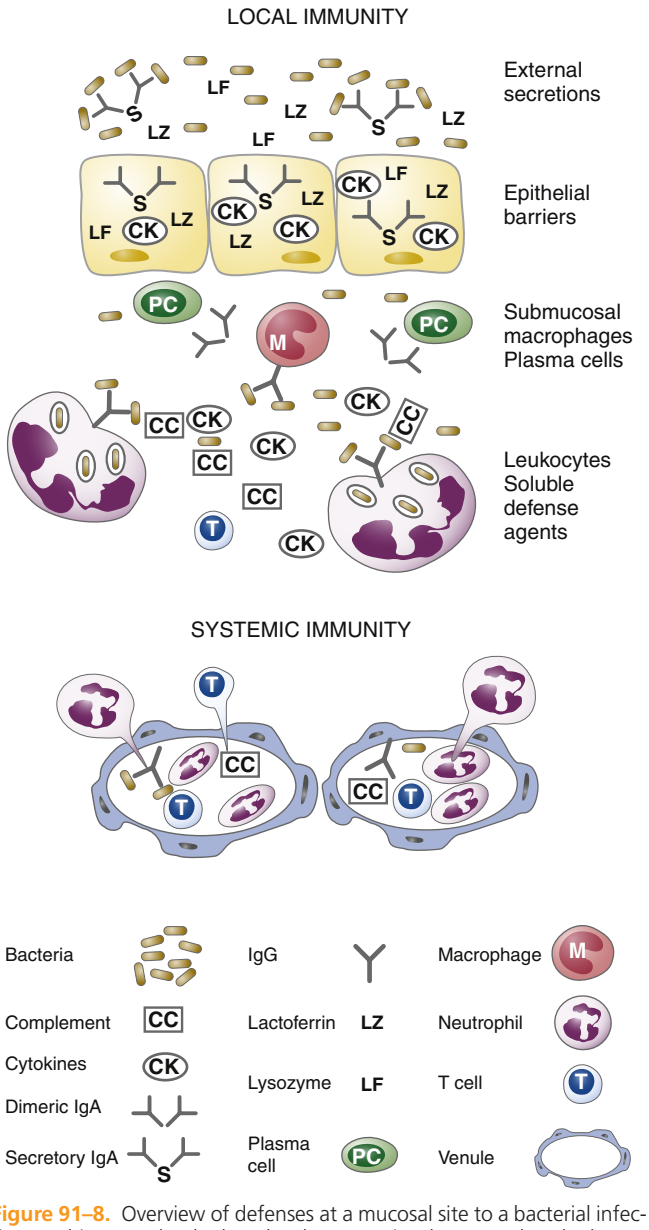

Figure 91–8. Overview of defenses at a mucosal site to a bacterial infection. In this example, the host has been previously exposed to the bacterial pathogen. Thus there is a rapid innate immune response, specific antibody, and T-cell response. The number of bacteria decreases as each level of defense is encountered. *(Modified from Goldman AS: Back to basics: host responses to infection,* Pediatr Rev *21:342, 2000.)*

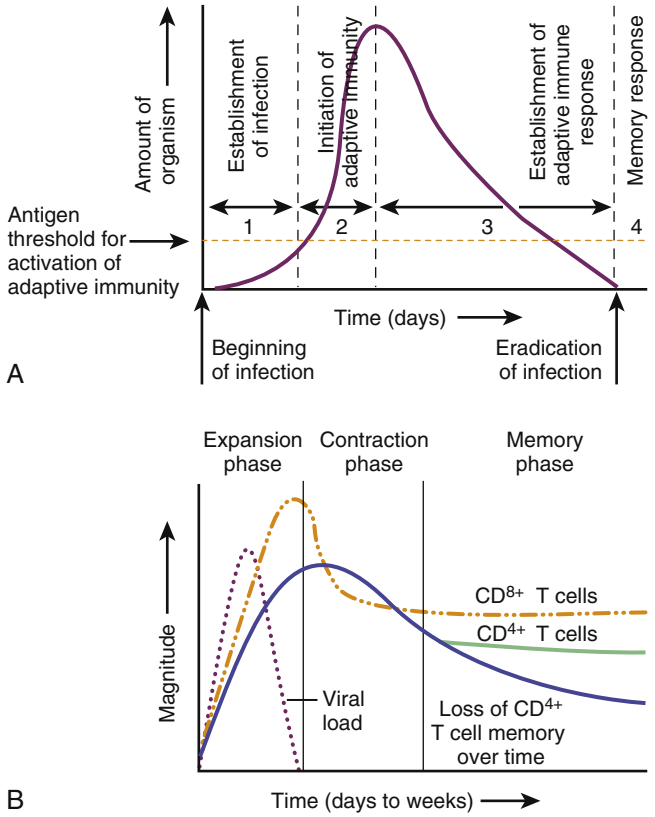

Figure 91–9. Time course of a typical acute infection. **A,** During period 1, the infectious agent (bacterial or viral) replicates. In period 2, an immune response is initiated when the numbers of pathogen exceed the threshold dose of antigen required for an adaptive immune response. Simultaneously, the pathogen continues to replicate, retarded only by the innate and nonadaptive responses. Immunologic memory is believed to be initiated during this stage. During period 3, after 4 to 5 days, effector arms of the immune response begin to clear the infection. In period 4, the clearance of the infectious agent and the decrease in the antigen dose below the response threshold results in the cessation of the response. The presence of antibody, residual effector cells, and immunologic memory provide lasting protection against reinfection. **B,** During a viral infection, antigen-specific T cells clonally expand during the first phase in the presence of antigen. Soon after the virus is cleared, the contraction phase follows and the number of antigen-specific T cells decreases due to apoptosis. After the contraction phase, the number of virus-specific T cells stabilizes and can be maintained for great lengths of time (memory phase). Magnitude of the CD4+ T-cell response is less than that of the CD8+ cells, and the contraction phase can be less pronounced. The number of memory CD4+ T cells may decline slowly over time. *(Modified from Huang AYC, Rigby MR: The immune response: generation, regulation and maintenance. Stiehm ER, Ochs HD, Winkelstein JA, editors:* Immunologic disorders of infants and children, *Philadelphia, 2004, Saunders Elsevier.)*

clonal expansion of $CD8^+$ and $CD4^+$ effector cells, and eradication of the infection occurs. After eradication of the infection there is contraction of the clonal response, but the continued presence of antibody, residual effector cells, and immunologic memory provide lasting protection against reinfection.

Apoptosis is the process of programmed cell death necessary for the resolution of the inflammatory response (see Chapter 100). As cells begin to die, they express ligands on their surfaces that signal resident tissue macrophages for removal via phagocytosis. During apoptosis the cell's nucleus and cytoplasm condense, nuclear DNA is degraded into small dense pieces, and marked cytoplasmic vesiculation and blebbing of the plasma membrane occur. In the final stages the cell collapses into multiple fragments (apoptotic bodies). Apoptosis can be triggered by external forces such as interaction of CD95 ligand (Fas ligand) on cytotoxic T lymphocytes or NK cells with CFD95 on a target cell such as a virally infected cell (see Figure 91-6). Apoptosis can also be initiated by signals arising from DNA or mitochondrial damage.[80,81] The signals converge on activation of a family of proteases called *caspases* that cleave multiple substrates to induce destruction of the cell from within. This process is central to peripheral deletion of excess T and B lymphocytes as the immune response wanes, to clearances of infected cells, and to resolution of inflammation with the removal of emigrated leukocytes.[82] The final step of apoptosis is the removal via the tissue macrophage.[83] In the process of eliminating apoptotic cells, the macrophage produces "immunosuppressive" cytokines such as TGF-β and other cytokines that downregulate the inflammatory response (e.g., IL-10).

It is clear that phagocytic members of the reticuloendothelium system, in particular the Kupffer cells and the NKT cells of the liver, work to trap and kill bacteria in the bloodstream. However, it is also clear that neutrophils are also critical to this process; patients with neutropenia have bacteremia despite having adequate macrophage function. Only recently has there been some understanding as to the mechanism. Neutrophils under select conditions can be activated to cause the release of "neutrophil extracellular traps" (NETS), which are weblike structures of DNA. These NETS contain proteolytic activity that can trap and kill bacteria.[70] Using intravital microscopy, Clark et al.[84] demonstrated that platelet TLR4 detects TLR4 ligands in the blood and induces platelet binding to adherent neutrophils. The NETS were present and functional under flow conditions and ensnared bacteria within the vasculature. The formation of the NETS occurred primarily in the liver sinusoids and pulmonary capillaries.[84]

References are available online at http://www.expertconsult.com.

VI

Chapter 92

Congenital Immunodeficiencies

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PEARLS

- A congenital immunodeficiency should be considered in patients with a family history of immunodeficiency, recurrent or persistent infections, infections with unusual organisms, or severe infections with pathogens of low virulence.
- The absolute lymphocyte count is highest during the first year of life. Persistent lymphopenia (<2000 cells/μL) in a child younger than1 year warrants evaluation for combined immunodeficiency.
- Immunoglobulin (Ig) levels of IgG, IgA, and IgM in peripheral blood are influenced by age. Transplacentally acquired IgG antibodies reach a nadir at approximately 3 to 4 months of age.
- Collection and banking of 1 to 3 mL of serum prior to any gamma-globulin delivery is a useful and practical recommendation; subsequent serology studies will be influenced by the IgG content in any gamma-globulin preparation given to the patient and not a reflection of the patient's own gamma-globulin G.
- IgG serology testing for infectious diseases in the presence of agammaglobulinemia is not helpful and gives a false sense of security.

The discovery of antimicrobials in the middle of the last century allowed for the description of patients with defects of immune function. These classic descriptions recognized the primary immunodeficiency diseases (PIDs) in association with recurrent or persistent infection, infections with unusual organisms (opportunistic pathogens), or unusually severe presentations of infectious diseases with pathogens of low virulence. These patients became the experiments of nature that established the immune system as essential for host defense.[1] The subsequent observation that many of these patients succumb to malignancy or autoimmune diseases further underscores the role that the immune system plays in the pathogenesis of these disease states.

Taken together, PIDs are a group of more than 150 different heterogeneous disorders of immune function in which more than 100 different defective genes have been recognized (Figure 92-1).[2] The estimated overall prevalence varies, but is generally accepted to be close to 1:10,000. This suggests that there may be approximately 400 new cases of primary immunodeficiency in infants born in the United States each year (4.0 million live births).[3] Early and prompt diagnosis is essential because curable and life-saving therapies are available. If a molecular diagnosis is established, prenatal diagnosis can be offered to parents and family members.

Classically, PIDs are congenital and hereditary; most newly diagnosed patients are infants and children, and a family history is occasionally recognized. However, because we live in an antibiotic era, some of these children may survive into young adolescence and adulthood before a diagnosis is made. The specialist in critical care may be the first physician to think about the diagnosis in a child who presents with a life-threatening infection to the intensive care unit (ICU).

Although there may not be a particular physical phenotype to encompass all these disorders because most children with PID appear normal, some physical findings that should make the clinician think about a congenital immunodeficiency include failure to gain weight, absent tonsils, persistent thrush, difficulties with healing, rashes and eczema that do not resolve with conventional therapies, severe warts, gum disease, cutaneous granulomas, unexplained hepatosplenomegaly, telangiectasias in eyes and ears, ataxia, dwarfism, cartilage abnormalities, and oculocutaneous albinism (Box 92-1).

There are particular syndromes associated with defects in immune function. These include, among others, DiGeorge syndrome, defects of DNA repair (ataxia/telangiectasia, Nijmegen breakage syndrome, Bloom syndrome), immuno-osseous dysplasias (cartilage/hair hypoplasia and Schimke syndrome), Hoyeraal-Hreidarsson syndrome, immunodeficiencies with associated defects in pigmentation (Chediak-Higashi syndrome, Griscelli syndrome, Hermansky-Pudlak syndrome), and those with associated phagocytic defects (Kostmann syndrome, Papillon-Lefevre syndrome, and Shwachman-Diamond syndrome).[3]

Despite 6 decades of advances in the field of immunology, the clinical and immunologic phenotypes that define patients with classic PIDs remain the same. This chapter provides a practical, general overview of those PIDs that may be encountered by the critical care specialist, discusses recommendations for laboratory evaluations and the value of screening tests, and provides recommendations for consultation with immunology specialists and initial therapies.

The Immune System and the Classification of the Primary Immunodeficiency Diseases

The human immune system has evolved to protect the individual from infectious microbes. It does this by using a complex interactive network of cells, proteins, and organs. This response is both innate and adaptive based on unique characteristics.

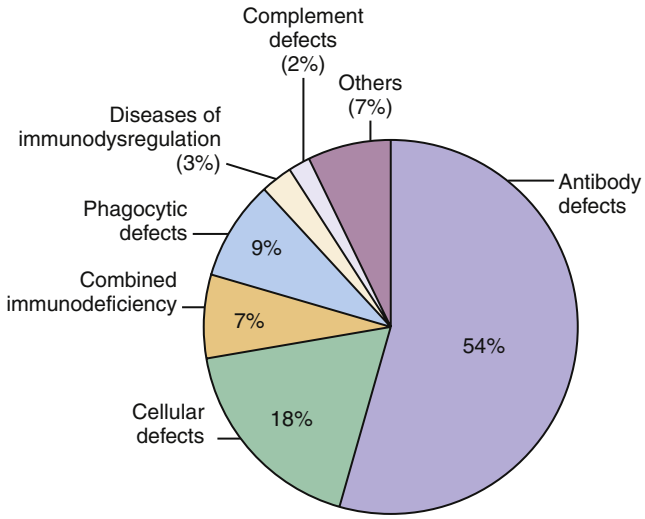

Figure 92–1. Distribution of the major primary immunodeficiency disorders. *(Data from The Jeffrey Modell Foundation Survey, 2009.)*

Box 92–1 Physical Exam Findings that may Suggest a PID

- Dysmorphic facial features
- Heart murmur
- Persistent oral thrush
- Failure to thrive and gain weight
- Atypical dermatitis and erythroderma that does not resolve with standard therapies
- Absent or small tonsils for age
- Gingival disease
- Persistent lymphadenopathy and/or hepatosplenomegaly
- Telangiectasias

The innate response to a pathogen occurs immediately (within hours), lacks clonal specificity for a particular pathogen, and does not confer long-lasting protection—that is, immunologic memory. Both cellular and humoral factors constitute its major components. These include (1) antimicrobial products and physical barriers such as the skin and mucosal surfaces; (2) receptors for pathogen molecules, including the family of Toll-like receptors (TLRs); (3) the phagocytic cells (neutrophils and macrophages); (4) dendritic cells; (5) the complement system; and (6) natural killer (NK) cells.[4]

The adaptive immune response, while triggered by components of innate immunity, takes days to evolve, requires processing and presentation of antigens derived from the pathogen, is specific to the particular pathogen and, more importantly, confers immunologic memory; that is, the individual "remembers" the signature of a pathogen on subsequent encounters. Specificity is determined by the vast range of molecular diversity of the antigen receptor (the T-cell receptor [TCR] complex and the immunoglobulin molecule). Immunologic memory is the ability to respond rapidly and effectively to pathogens previously encountered. This mechanism implies the preexistence of antigen-specific lymphocytes.

The effector cells of the adaptive immune response are T and B lymphocytes. These cells derive from a hematopoietic stem cell (HSC) precursor. It is generally accepted that HSCs differentiate into a common lymphoid progenitor (CLP) that gives rise to T, B, and NK cells. Lymphopoiesis is tightly regulated and leads to the expression of a functional antigen receptor on the surface of the lymphocyte. For the B cell, it is the immunoglobulin molecule; for the T cell, it is the TCR complex. Cellular microenvironment, growth factors, cytokines, and chemokines, along with silencing or activating certain genes at different stages of lineage commitment, are some of the multiple factors contributing to a successful and mature lymphocyte. Although mouse lymphoid development has been well elucidated, human lymphoid development has been fragmented; our knowledge is patched together from in vitro analysis of bone marrow–derived cells, patients, and comparisons to the mouse models.[4]

Patients with PID have taught us that despite the apparent redundancy of the system, quantitative and qualitative defects in individual components and/or pathways result in abnormal function and susceptibility to particular infections.[1]

Historically, defects of cellular, humoral, phagocytic function, and complement defects constituted the classic classification of PID (see Figure 92-1). As understanding of the immune system has evolved, PIDs can also be considered as defects that involve either innate or adaptive immune responses. In the 1970s, the World Health Organization sponsored a committee of experts in the field of PID to classify and define these disorders. Since then, the International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies has met regularly to update the classification of PID. The most recent publication was published in the *Journal of Allergy and Clinical Immunology* in December 2009.[2] In this review, PIDs are classified as being (1) combined T- and B-cell immunodeficiency, (2) predominately antibody deficiencies, (3) well-defined immunodeficiency syndromes, (4) diseases of immune dysregulation, (5) predominately phagocytic defects, (6) defects of innate immunity, (7) autoinflammatory disorders, and (8) complement deficiencies. As new clinical phenotypes are identified and the genetics of these disorders are unraveled, future classifications will reflect advances in the understanding of disease pathogenesis.[5]

Laboratory Diagnosis of Congenital Immunodeficiencies

Most patients admitted to the ICU have many laboratory tests performed. It is important to recognize laboratory results that should not be arbitrarily dismissed as attributable to the severity of the patient's illness. Initial tests and radiologic studies performed on presentation can provide clues that, together with the clinical course and identification of pathogens (Table 92-1), suggest further evaluation or consultation with an immunologist.

The most common of the complement defects are defects of the classic complement cascade. The standard approach that screens for the integrity of this pathway measures the hemolytic capacity of a patient's serum to lyse 50% of antibody-coated sheep erythrocytes. This test is called the total hemolytic complement 50 (TCH50).

Initial screening laboratory studies for PIDs are outlined in Table 92-2. These include (1) complete blood cell count (CBC), (2) quantitative immunoglobulins, (3) specific responses to vaccinations in immunized individuals, (4) lymphocyte subpopulations, and (5) total hemolytic complement.

CBCs can be very informative. Presence or absence of leukocytosis may suggest a normal or abnormal response of the

Table 92–1 Pathogens Suggestive of Immunodeficiency

Organism	Disease
Pneumocystis jiroveci	HIV, SCID, hyper IgM, XLA
Serratia marcescens	Chronic granulomatous disease
Aspergillus spp., *Nocardia* spp.	Chronic granulomatous disease
Pseudomonas sepsis	XLA and ARA
Mycobacterium/*Salmonella* spp.	IFN-γ/IL-12 pathway

HIV, Human immunodeficiency virus; *SCID,* severe combined immunodeficiency; *XLA,* X-linked agammaglobulinemia; *ARA,* autosomal recessive agammaglobulinemia; *IFN,* interferon; *IL,* interleukin.

Table 92–2 Screening Tests for Evaluation of Immune Function

WBC and differential	Absolute neutrophil count Absolute lymphocyte count Platelet count and morphology
Serum immunoglobulins	IgG, IgA, IgM, IgE
Functional antibody responses to immunizations	Anti-tetanus Anti-diphtheria Anti-HIB Anti-pneumococcal
Lymphocyte subpopulations	T cells: CD3 B cells: CD19 NK cells: CD16/56
Complement studies	Total hemolytic complement

marrow to infection. Cytopenia such as neutropenia (as indicated by the absolute neutrophil count) is a common feature of a series of PIDs and may allow their recognition in context of other findings.[6] Total lymphocyte count should be calculated and matched to appropriate aged-matched controls.[3] It is important to recognize that the absolute lymphocyte count (ALC) is highest during the first year of life.[7] An ALC of less than 2000 cells/μL is not a common consistent finding in consecutive CBCs in infants younger than 1 year. This finding warrants further investigation because it may be the first objective data to suggest a diagnosis of combined immunodeficiency.[8] Anemia may indicate autoimmunity and in this context is characteristic of several defects of immune function.[2] Thrombocytopenia in a child with severe eczema should prompt the clinician to review the peripheral smear carefully with a pathologist to determine the platelet size; this would allow the diagnosis of Wiskott-Aldrich syndrome. The careful examination of the peripheral smear can identify presence of Howell-Jolly bodies, which are seen in asplenia. Unique morphologic abnormalities of neutrophils are pathognomonic of diseases such as Chediak-Higashi syndrome (Figure 92-2).

Quantification of immunoglobulin (Ig) G, IgA, IgM, and IgE should be performed. As is the case with ALCs, the levels of immunoglobulins in circulation is influenced by the age of the child.[3] At birth, term infants have serum IgG levels that are equal to the maternal level or exceed it by 5% to 10%.[9] Transplacentally acquired antibodies disappear rapidly after birth, reaching a nadir at 3 months. Average concentrations at this time are 60 mg/dL for infants born at 25 to 28 weeks of gestation, 104 mg/dL for infants born at 29 to 32 weeks, and 430 mg/dL for infants born at term.[3,10,11] However, these low levels of maternal IgG antibody appear to be associated with less risk of infection than might be expected. A longitudinal study of the ability of preterm infants to form specific antibodies provides a partial explanation for this low risk.[12] By about 9 months of age, infants have formed specific IgG antibodies in response to immunization with diphtheria, tetanus toxoids, and pertussis vaccine. Also by about this age, their antibodies have functional opsonic activity against *Escherichia coli* and coagulase-negative staphylococci. The ability of newborn infants to produce an active antibody response to antigenic stimulation develops in an orderly fashion. An adult pattern of antibody responses is not acquired until 4 to 5 years of age. Analysis of the factors responsible for this developmental pattern is complex because production of antibody depends not only on B lymphocyte maturity, but also on interactions with other cells that may mature at different rates.

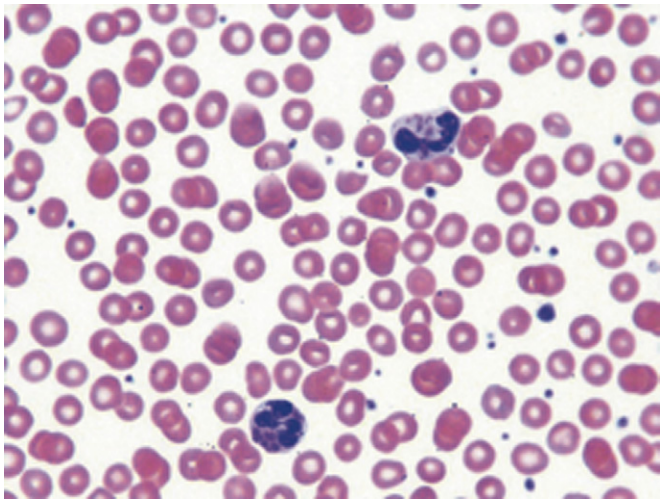

Figure 92–2. Peripheral smear showing mature and band neutrophils (*top*) with basophilic cytoplasmic inclusion consistent with Chediak-Higashi syndrome.

Fetuses can produce serum antibodies and IgM, predominantly in response to intrauterine infection.[13] Preterm infants respond nearly as well as term infants to immunization beginning at 2 months with DTP, poliovirus, and hepatitis B vaccines.[14-16] Term infants immunized or infected during the first few days of life usually produce protective antibody responses, although at somewhat lower levels than do adults.[17-19] The presence of fetal bone marrow B lymphocyte pools similar in size to those of adults and with comparable isotype diversity suggests that their functional deficits may reflect a developing memory repertoire with increased specificity to antigen or the need to generate T lymphocytes capable of producing strong B lymphocyte signals, rather than inherent B lymphocyte immaturity as a sole factor.

Responses to childhood immunizations are very helpful for evaluation of the functional antibody responses. Appropriate responses speak to cognate T- and B-cell interaction necessary for T-dependent antigen responses, and polysaccharide responses speak to antigen responses that do not require T cell help, such as those of the blood group antigens. The collection of 1 to 3 mL of serum that is saved before any gamma-globulin administration is a useful practical recommendation because subsequent serology studies will be

influenced by the specific gamma-globulin content of the unit delivered to the patient.

Analysis of lymphocyte subpopulations by flow cytometry is essential when defects of adaptive immunity are entertained. Circulating lymphocytes are distinguished by unique surface molecules that permit their identification. Cluster of differentiation (CD) is a surface marker that identifies a particular differentiation lineage recognized by a group of monoclonal antibodies. Classification of lymphocytes by CD antigen expression is widely used in clinical medicine. Thus T cells are identified as carrying CD3 helper T cells; CD3 and CD4 cytotoxic T cells; CD3 and CD8 NK cells by CD16/56. CD19 identifies circulating B cells. As with ALC, the percent and absolute numbers of different circulating lymphocytes is age dependent.[7] In general terms, two thirds of circulating lymphocytes are T cells and one third are B cells; two thirds of T cells are $CD4^+$ and one third are $CD8^+$.

These initial screening laboratory tests will rule out the following PIDs (see Table 92-2): (1) antibody defects such as X-linked agammaglobulinemia (XLA), IgA deficiency, common variable immunodeficiency (CVID), or transient hypogammaglobulinemia of infancy (THI); (2) cellular defects such as severe combined immunodeficiency (SCID), DiGeorge syndrome, and Wiskott-Aldrich syndrome; (3) phagocytic defects defined by neutropenia; and (4) defects in the classic complement pathway.

The screening tests of immune function described are not be able to identify other immunodeficiencies that require more advance testing and consultation with an immunologist. Examples include chronic granulomatous disease, defects of Toll signaling, diseases of immune dysregulation, and defects of the alternative complement pathway.

1. Defects of innate immunity:
   - Phagocyte defects: chronic granulomatous disease, leukocyte adhesions defects, and defects in the interferon (IFN)-γ and interleukin (IL)-12 axes
   - Defects of Toll signaling pathways: IL-1-associated kinase-4 (IRAK-4), the adaptor protein myeloid differentiation primary response gene (MyD88), and defects in NEMO
2. Unique syndromes associated with immunodeficiency: hyper IgE syndrome
3. Diseases of immune dysregulation:
   - Familial hemophagocytic lymphohistiocytosis (HLH)
   - Autoimmune and nonautoimmune lymphoproliferative syndromes
   - Autoinflammatory disorders associated with periodic fevers
4. Complement deficiencies: alterations of the lectin or the alternative complement pathways

Advanced testing generally require functional assays that are not commonly accessible to small laboratories and many times require referral to outside centers with unique expertise. Included among these studies are proliferative assays to mitogens and antigens, enzyme analysis, assays that result in expression of molecules of cellular activation (e.g., CD40 ligand on activated T cells for the diagnosis of hyper IgM), neutrophil oxidative activity (dihydrorhodamine analysis by flow cytometry or nitroblue tetrazolium testing), or analysis of the alternative complement pathway, among others. In general, these studies would require the discussion with a specialist in clinical immunology to guide the evaluation and help with the interpretation of the results.

Clinical Presentations of Congenital Immunodeficiency Syndromes

This review is not intended to discuss all known immunodeficiency syndromes characterized thus far. Instead, it focuses on those PIDs that can be encountered by the intensive care specialists and, if left unrecognized, contribute to delayed diagnosis and are life threatening.

Combined T- and B-Lymphocyte Defects

Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) was first recognized in the late 1950s and was subsequently divided into Swiss-type agammaglobulinemia (i.e., autosomal recessive) and sex-linked lymphopenic immunologic deficiency.[20] X-linked SCID (XLSCID), today known as *common gamma-chain deficient SCID* or *γc-SCID,* is the most common of all forms of SCID. This combined immunodeficiency is due to mutations in the common γ-chain, an essential signaling molecule. XLSCID comprises 40% to 50% of all SCID phenotypes. Five different cytokine receptors (for IL-2, -7, -9, -15, and -21) require signaling through this molecule. Fourteen different autosomal recessive forms of SCID have been identified.[2] The common characteristic of all forms of SCID is the occurrence of a block in the differentiation of T cells, whereas B cells may or may not be present, but are unable to function, and normal or abnormal development of NK cells occurs. Cytokine-dependent signaling, premature lymphocyte cell death, defective recombination or assembly of the antigen receptor, and inability of the T cells to egress effectively from the thymus explain some of the molecular mechanisms that result in the different SCID phenotypes (Table 92-3).[2] The incidence ranges from 0.89 to 1.40 per 100,000 live births/year[21-23]; these disorders are fatal if not promptly recognized and treated.

Clinical Presentations and Laboratory Findings in SCID. Common clinical presentations among most forms of SCID that should alert the clinician to consider this condition in the differential diagnosis[8,24] include (1) normal birth and delivery; (2) age of presentation to medical attention and/or admission to an ICU usually before 1 year of life (frequently after 3 months of life because of the protection

Table 92–3 Lymphocyte Phenotype Pattern and Genotype in SCID

Lymphocyte Phenotype	*Main Mechanism*	Molecular Defect
$T^-B^+NK^-$	Signaling pathway	γC, JAK3
$T^-B^-NK^-$	Cell death	ADA, PNP
$T^-B^-NK^+$	Ag receptor assembly	RAG1/2, artemis, DNA ligase IV, DNAPKcs, cernunos
$T^-B^+NK^+$	Other signaling molecules	CD45,IL7R, CD3ζ,ε,δ, coronin-1 A

γC, Common gamma chain; *JAK3,* Jannus-associated kinase 3; *ADA,* adenosine deaminase; *PNP,* purine nucleoside phosphorylase; *RAG,* recombinase activating gene; *DNAPKcs,* DNA-activated protein kinase catalytic subunit; *IL,* interleukin.

provided by transplacental transfer of maternal IgG antibodies); (3) overwhelming infections with common pathogens such as rotavirus, respiratory syncytial virus (RSV), cytomegalovirus (CMV), parainfluenza virus and adenovirus; (4) opportunistic infections such as *Pneumocystis jiroveci;* (5) persistent oral candidiasis and failure to thrive; (6) chronic hepatitis or sclerosing cholangitis; (7) persistent diarrhea; (8) skin rash that does not resolve with standard therapies; (9) enteroviral encephalitis; and (10) disseminated varicella zoster postvaccination. It is important to recognize that children with SCID, if transfused with nonirradiated packed red blood cells, may develop overwhelming and life-threatening graft-versus-host disease within 1 to 2 weeks because of clonal expansion of donor-derived leukocytes present in the blood product.

Absent thymic shadow on the initial admission chest radiograph and persistent lymphopenia (<2000 cells/μL^3) since admission can be easily overlooked. Many cases of SCID could be predicted by reviewing the absolute lymphocyte count at birth.[25]

When SCID is suspected, urgency in the confirmation of the diagnosis is necessary because these children can survive if prompt therapies are instituted. Rapid laboratory evaluation and consultation with an immunologist are recommended. HIV must be quickly ruled out and the following studies performed:

1. Lymphocyte subpopulations by flow analysis to identify both the percentage and absolute numbers of circulating T cells (CD3, CD4, CD8), B cells (CD19), and NK cells (CD16/56); this allows for the phenotypic characterization of the type of SCID.
2. Quantitative immunoglobulins (IgG, IgA, and IgM). It is important to recognize that if the child is younger than 3 months, maternal IgG antibodies may still be present. In young infants with hyper IgM, the level of IgM may not be elevated.
3. Lymphocyte proliferative responses to mitogens (phytohemagglutinin A, concanavalin-A, pokeweed mitogen) and antigens (*Candida* and tetanus toxoid, if the child has been previously immunized). These latter tests evaluate the integrity of signal transduction essential for cell proliferation when encountering an antigen.

Therapy for Patients with Clinical Suspicion or Diagnosis of SCID. While managing a child with suspected SCID, medical therapies should be targeted at both identifying pathogens (often more than one pathogen may be identified in the same individual) and instituting both targeted and prophylactic antimicrobials. Fungal and prophylaxis against *Pneumocystis jiroveci* should be started. Trimethoprim-sulfamethoxazole (TMP/SMX) may be initiated as early as 1 to 4 weeks of age with close monitoring of liver function and transaminases.[26] Storage of 1 to 3 mL of serum before gamma-globulin infusions is helpful, as previously mentioned. Gamma-globulin should be give at doses of 400 to 500 mg/kg every 3 to 4 weeks intravenously (IV). If IV access is difficult, subcutaneous administration of IgG is possible. Blood products should be irradiated and CMV negative. No live vaccines such as rotavirus or varicella should be given to the patient or family members in contact with the child. Rotavirus vaccine strains have been reported as causing diarrhea and being the first manifestation in several children with SCID.[27]

After the diagnosis is made, the patient should be transferred to a center with experience in the management and treatment of these disorders. Human leukocyte antigen (HLA) typing of patient and family and consultation with the stem cell transplant team should be pursued. Without a hematopoietic stem cell transplantation (HSCT), children with SCID die.[24] Now considered standard of care, this procedure has achieved the most successful survival record, ranging from 63% to 100% when an HLA-matched sibling donor has been available and 50% to 77% when haploidentical or HLA-mismatched donor is used.[28-35] The lack of donor availability, variable evidence of long-term immunologic reconstitution, and other limitations have led to the extensive use of unrelated but matched donors as a source of stem cells for SCID. The outcomes have improved over the recent years, with survivals ranging from 63% to 80%.[31-33,36]

Other Combined Immunodeficiency Disorders

Many other forms of combined immunodeficiency have been described. In general, these are rare conditions, and similar general concepts of diagnosis and management strategies as for SCID should apply. Family histories are helpful because consanguinity is not uncommon. Microcephaly, deafness, ectodermal dysplasia features, cartilage abnormalities, and hematologic abnormalities such as eosinophilia and cytopenia may be clues that can further guide the molecular analysis.[2]

Hyper Immunoglobulin M Syndrome

Hyper IgM comprises a group of disorders of Ig isotype class switch recombination.[37] First described by Rosen et al.,[38] it was initially classified as a defect in antibody production. Patients had very low levels of circulating IgG and IgA antibodies and elevated levels of IgM. By 1985, Mayer,[39] in critical co-culture experiments, demonstrated that B cells, isolated from hyper IgM patients, could produce IgG and IgA in vitro when incubated with T cells derived from a Sezary T-cell lymphoma and suggested a role for T lymphocytes in Ig isotype switching.[39] It was not until 1993 that three independent groups identified CD40 ligand (also known as CD154) as the molecule responsible for the X-linked, and most common form, of hyper IgM (XHIGM).[40-42] As molecular mechanisms of class switch recombination have been elucidated, so have the identification of autosomal recessive forms of hyper IgM.[43]

IgM molecules are not opsonins because there are no receptors on phagocytes for the Fc portion of this immunoglobulin molecule. Phagocytosis is promoted by complement activation, C3 deposition on the bacterial surface, and subsequent phagocytosis. XLHM patients are deficient in antibody responses that require T-cell help. Examples include protein antigens such as bacterial toxins or bacterial capsules wall proteins as seen in *Staphylococcus pyogenes*. The "combined" nature of this immunodeficiency is due to the role that CD40 ligand plays in the effector function of both macrophages and T cells. For example, activation of macrophages against opportunistic infections such as *Pneumocystis jiroveci* requires binding of CD40 found on the macrophage surface to its ligand, which is expressed on an activated T cell. This T cell/macrophage interaction allows for activation of the macrophage and subsequent microbial killing by intracellular production of oxygen radicals, nitric

oxide, and lysosomal enzymes. Therefore these patients are susceptible to infections similar to those seen in other hypogammaglobulinemic states and pathogens that require intact T-cell function such as viruses, fungi, and parasites.[44-46]

Clinical and Laboratory Presentation of X-Linked Hyper Immunoglobulin M. This is a rare immunodeficiency that becomes manifest in most cases before the age of 4 years. In a cohort of 79 patients studied, *Pneumocystis pneumonia* was the initial presentation in more than 50% of patients.[46] Neutropenias (seen in >50% of cases), other cytopenias, sclerosing cholangitis–associated cryptosporidium infection, hepatitis, progressive neurodegeneration,[47] and gastrointestinal malignancies[48] contribute to morbidity and mortality.[45,46] When a patient presents to the ICU in respiratory failure and *P. jiroveci* is isolated from bronchoalveolar lavage, after HIV is ruled out three PIDs should come to mind: SCID, hyper IgM, and X-linked agammaglobulinemia (XLA).

Laboratory studies in patients with XHIGM demonstrate an inability to muster a leukocytosis in the face of severe infections. This is due to a lack of GM-CSF production by macrophages. Circulating numbers of T and B cells are normal with the exception of decreased memory T cells (CD45RO). Poor antibody responses to protein antigens and lack of CD154 (CD40 ligand) expression on the T cells when these are stimulated in vitro are features of hyper IgM. Similar to XLA patients, germinal centers within the lymph nodes are not developed in XHIGM.

In contrast, patients with a rare autosomal recessive form of hyper IgM due to mutations in activation-induced cytidine deaminase (AID), an enzyme involved in isotype switching, come to medical attention in early childhood with recurrent bacterial sinopulmonary and gastrointestinal infections. Opportunistic infections and neutropenia are uncommon. Cellular immunity is normal, and yet massive lymphadenopathy and lymphoid hyperplasia are characteristic.[49]

Treatment of hyper IgM is directed at replacing antibodies and preventing opportunistic infection. Gamma-globulin infusions at dose of 400 to 500 mg/kg every 3 to 4 weeks, TMP/SMX prophylaxis, and G-CSF as needed for neutropenias are standard therapies. HSCT has also been successfully performed in XHIGM.[50]

Antibody Deficiency Syndromes

Antibody deficiency syndromes represent the most common type of PID (see Figure 92-1). Colonel Ogden Bruton was first to publish and describe a patient with absent gamma-globulins who had been admitted multiple times (19 admissions) for infections with *Streptococcus pneumoniae*.[51] The understanding of the function of gamma-globulins at that time provided the human experiment that linked infections with encapsulated organisms and the absence of gamma-globulin proteins. As happens many times in science, luck participated in this discovery; a novel Tiselius electrophoresis apparatus had recently been incorporated for clinical use at the Walter Reed Hospital, and this child's serum happened to find its way into the machine.[52] Years later, interestingly, the first child described appeared to best resemble a patient with common variable immunodeficiency (CVID) rather than XLA or Bruton agammaglobulinemia. The description of this patient, coupled with the successful isolation of gamma-globulin from human sera, allowed or life-saving therapy with gamma-globulin infusions. Today, gamma-globulin use is not limited to patients with XLA.[53] This initial case report along with others at the time provided the stage for successful decades of discoveries of PID and their therapies. The careful analysis of children with PID by pioneers such as Robert Good, Fred Rosen, Charlie Janeway, and Jerry Winkelstein initiated the field of clinical immunology as it is understood today.

It took almost 4 decades for the discovery of the molecular defect responsible for XLA.[54,55] Called *Bruton's tyrosine kinase* (BTK), this molecule is essential for B-cell development. Children with XLA have absent or extremely low circulating B cells and therefore absent circulating antibody levels. Autosomal recessive agammaglobulinemia from other defects of B-cell development has similar clinical and laboratory findings as XLA. Mutations in the μ heavy chain locus, surrogate light chain (λ5), signaling, and adaptor components of the B-cell receptor (Igα, Igβ, and *BLNK* gene) are among more than 15 intrinsic B-cell immunodeficiencies.[56-58]

Other clinical defects of antibody production include (1) CVID, (2) IgA deficiency, (3) transient hypogammaglobulinemia of infancy, (4) specific antibody deficiency with normal Ig concentrations, and (5) isotype or light chain deficiencies with normal numbers of B cells.[2] The pattern of circulating immunoglobulins, presence or absence of B cells, response to childhood vaccination, and need for lifelong IgG replacement are key laboratory and therapeutic characteristics that help the clinician distinguish the clinical phenotypes of antibody deficiency production. Good syndrome, thymoma associated with agammaglobinemia or hypogammaglobinemia, is a rare entity of unknown etiology that usually presents in adults.[59]

Clinical Presentations and Laboratory Findings in Antibody Defects. Antibodies are essential for host defense. These molecules participate in neutralization of bacterial toxins and viruses, opsonization of bacteria for successful phagocytosis, and complement activation of encapsulated bacteria. Recurrent and persistent otitis media, sinusitis, pneumonias, and gastrointestinal infections are the classic manifestations of antibody deficiency syndromes.[56,60,61] In general, most children with XLA/ARA will present to medical attention within the first 2 years of life[56] as maternal transplacentally acquired antibodies disappear. Yet when treated promptly, antibiotic therapies can be very effective; therefore it is not uncommon for these children to be diagnosed later in life.

By consensus, CVID is defined as occurring in a patient older than than 2 years with (1) low IgG and low IgA and/or IgM below two standard deviations of the mean; (2) B cells present; (3) failure to make specific antibodies in response to infection or routine vaccinations; and (4) variable T-cell abnormalities.[62] Several molecular defects have been described that speak to the heterogenous nature of the condition.[63-66] Bronchiectasis, granulomas, diffuse lymphadenopathy, autoimmunity, and malignancy are common clinical associations.[67] In a recent retrospective analysis of 32 pediatric patients who met the criteria for CVID, meningitis was found in 25% and sepsis in 16% of those older than 4 years.[68]

IgA deficiency, the most common of the antibody deficiency syndromes (1:400 to 1:700 live births), rarely will appear in a patient presenting to the ICU in septic shock, but recurrent sinopulmonary infections and gastrointestinal infections with *Giardia* are not uncommon.

Transient hypogammaglobulinemia of infancy represents a state in which the physiologic nadir of circulating IgG levels is prolonged. Most of these children do well, but case reports of severe overwhelming infections have been described.

Streptococcus pneumoniae and *Haemophilus influenzae* are infectious agents frequently isolated from patients with antibody defects.[64,67,69-71] It is important to recognize that asplenia should also be considered in the differential diagnosis of the immunized patient with overwhelming sepsis due to *S. pneumonia* and *H. influenzae.* Careful review of the peripheral smear will identify the presence of Howell-Jolly bodies.

Staphylococcus aureus and *Pseudomonas aeruginosa* can cause sepsis in XLA or ARA patients.[60,69,71,72] This suggests that antibodies probably play an important role in the clearance of these pathogens. However, the role of neutrophils cannot be underestimated because many patients with XLA/ARA have associated neutropenias at time of presentation. Encephalomyelitis from enteroviruses and hepatitis viruses can cause significant morbidity in children with XLA/ARA and CVID despite receiving IgG replacement.[60,73] Enteroviruses, mycoplasma, and *Ureaplasma urealyticum* have been isolated from joints of patients with XLA.[61,74,75] Although rare, patients with XLA have been described as presenting with *Pneumocystis jirovecii*.[72] *Giardia lamblia* is a common pathogen isolated in patients with both cellular and antibody deficiency.[60,67]

Treatment of antibody deficiency syndromes requires gamma-globulin infusions for life. These are given at doses of 400 to 500 mg/kg every 3 to 4 weeks, and levels are maintained at greater than 600 to 800 mg/dL.

Congenital Defects of Phagocytes

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) was initially described by two groups. In 1954, Janeway and colleagues[76] reported a group of males with hypergammaglobulinemia and recurrent infections and proposed that the former was the cause for the latter. Five years later, Robert A. Good's group at the University of Minnesota corrected the misinterpretation and demonstrated that the hypergammaglobulinemia was the consequence of infections and that the cause was ineffective microbial killing by neutrophils.[77] Both X-linked and autosomal recessive forms are described. The fundamental defect in CGD is the inability of phagocytes to generate superoxide anion (O^-) caused by the absence or dysfunction of one of the components of the NADPH oxidase system.[78] Many pathogens normally produce hydrogen peroxide (H_2O_2) when ingested by phagocytes. Aerobic pathogens produce catalase, which breaks down the H_2O_2 produced by microbes. CGD neutrophils cannot produce their own reactive oxygen species. They are uniquely susceptible to infection with catalase-positive organisms such as *S. aureus, Burkholderia cepacia, Serratia marcenses, Aspergillus,* and *Nocardia* spp. Pulmonary disease, deep-seated abscesses, and suppurative lymphadenitis are common sites of infectious presentations.[79] Interestingly, these patients are rarely bacteremic. Perianal abscesses, colitis, and gastric outlet obstruction may be the initial presenting signs for patients with common gastrointestinal manifestations.[80] Laboratory findings include mild to moderate leukocytosis and hypergammaglobulinemia. Different laboratory methods have been used to assay superoxide production. The nitroblue tetrazolium test, one of the first tests developed, relies on the reduction of nitroblue tetrazolium by reactive oxygen intermediates from a yellow color to an insoluble blue. In CGD phagocytes, dye is not reduced to blue, so no color appears within the neutrophils. This assay is currently rarely used and is mainly of historic value. Currently the most commonly used method of analysis is the dihydrorhodamine test (DHR) by flow cytometry. Nonfluorescent DHR is taken up by normal phagocytes. DHR is then oxidized to rhodamine, which produces a green fluorescence providing quantitative fluorescence that can help differentiate between X-linked forms (*no* increase in fluorescence with stimulation) and the autosomal recessive form (*small* amount of increased fluorescence). Carriers of X-linked mutations will show a *mosaic* pattern of fluorescence (some with normal fluorescence and some without). Therapy for CGD includes antimicrobial prophylaxis (e.g., TMP/SMX and itraconazole)[81] and immunomodulators such as IFN-γ.[82] Aggressive management of infections and need for invasive diagnostic tests to obtain culture-driven targeted therapies are often necessary.

Long-term follow-up data suggest significant morbidity caused by infections and only 50% to 55% survival through the third and forth decades of life.[83,84] Hematopoietic SCT has been a therapeutic option for the past 2 decades.[85,86] In 2002, the European Group for Blood and Marrow Transplantation (EBMT) reported results of 27 transplants from 1985 to 2000. Almost all (22 of 23) patients survived. These patients had received a myeloablative busulfan-containing conditioning regimen from HLA-identical donors, achieving full and stable donor chimerism.[87] More recently, excellent survival (90%) after HSCT has been reported by the Newcastle group, with a median 61 months of follow-up.[88]

Complement Deficiencies

Recognized as "complementing" the antimicrobial activity of antibodies, the complement system encompasses a series of serum proteins that bind the surface of pathogens or circulating complexes of antibody bound to antigen. On activation, a cascade of sequential biochemical events results in opsonization and killing of bacteria, recruitment of inflammatory cells, clearance of immune complexes, and disposal of apoptotic cells. The first report of absence of a complement protein was identified by chance.[89] Since then, defects in individual complement proteins or those regulatory proteins that prevent the progressive activation of the inflammatory cascade have been described.[90] Most defects in complement proteins are autosomal recessive. However, deficiency of the inhibitor of C1 (C1INH) is autosomal dominant, whereas the deficiency of properdin is X-linked recessive.

The clinical presentation of patients with complement deficiencies can be varied. Blood-borne or systemic pyogenic infections with encapsulated organisms, especially *Neisseria meningitidis* but also *Streptococcus pneumoniae* and *H. influenzae,* are common. Bacteremia, sepsis, and meningitis represent frequent initial clinical presentations that often require ICU admission.[91] The association of complement defects and rheumatologic disorders is well established. In general, defects in early complement components such as C2 or C4 are frequently linked with systemic lupus erythematosus, discoid lupus, dermatomyositis, and scleroderma. Hemolytic uremic syndrome and glomerulonephritis are common manifestations of factor H deficiency.[92]

Hereditary angioedema (HAE) is caused by deficiency in the inhibitor of C1 (C1INH). As a consequence of this lack of inhibition, factor XII becomes activated and leads to the activation of kallikrein and plasmin; kallikrein then catalyzes the formation of bradykinin and plasmin activates C1, which cleaves C2 and generates C2a, which is further cleaved by plasmin to generate C2 kinin. Both bradykinin and C2 increase vascular permeability leading to the edema. Clinical manifestations include localized swelling of the skin, respiratory tract, and gastrointestinal tract. The ICU specialist may be the first to recognize this disorder because attacks involving the upper airway may be life threatening. Epinephrine, corticosteroids, and antihistamines are not effective, and fresh frozen plasma in an acute attack may contribute to worsening edema due to availability of substrate. In 1972, two reports demonstrated the benefit of antifibrinolytic therapy for patients with HAE.[93,94] Four years later, androgens were demonstrated to be effective in preventing HAE.[95] Unfortunately, androgens do not have effect until 24 to 48 hours, so careful monitoring is necessary to ensure that the edema does not progress. By 1980, C1INH concentrate had been isolated and demonstrated as an effective therapy in randomized controlled trials.[96,96a] Attacks usually begin to subside 30 to 60 minutes after 200 to 500 units of the C1 inhibitor. Recent clinical trials using bradykinin-directed therapies (plasma kallikrein inhibitor or a β_2 bradykinin receptor antagonist) also suggest possible benefit in treating patients with HAE.[97]

Other Well-Defined Immunodeficiency Syndromes

Wiskott-Aldrich Syndrome

Described first by Wiskott[98] and then by Aldrich et al,[99] this X-linked disorder is classically defined by the clinical triad of severe eczema, microthrombocytopenia, and immunodeficiency and affects 1 in 10^5 to 1 in 10^6 live male births/year.[100,101] The gene responsible for Wiskott-Aldrich syndrome (WAS) was identified by positional cloning by Derry et al.[102] in 1994. The gene encodes a protein (WASp) that is constitutively expressed in all hematopoietic stem cell–derived lineages. The structure of WASp is complex, and its role in actin cytoskeletal rearrangements explains many of the clinical consequences of impaired immune function. Lack of inflammatory cell recruitment and defects in signaling pathways, immunologic synapse formation, and phagocytosis are some explanations of how lack of WASp expression affects immune function.[103] Furthermore, failure of adequate immune surveillance can lead to the development of autoimmunity and malignancy seen in these patients.[104,105] Mutations in WASp can also be identified in patients with X-linked thrombocytopenia.[106,107] In contrast to WAS, these patient with X-linked thrombocytopenia do not have associated immunodeficiency or malignancy and overall prognosis is better, although the incidence of infection is increased in splenectomized patients.[108] When WASp mutations result in constitutive activation of WASp, a different clinical phenotype characterized by congenital neutropenia and severe bacterial infections has been described.[109,110] Together, these highlight the important role that WASp has in hematopoietic development and function.

Clinical and Laboratory Presentation of Wiskott-Aldrich Syndrome. Petechiae in the newborn period, bloody diarrhea, and bleeding with circumcision are key historic clues. Eczema is a major clinical feature. Although usual therapies for severe atopic dermatitis are used, many times the disease is difficult to control and bacterial and viral superinfections occur. The most consistent laboratory finding is thrombocytopenia (usually between 3000 and 70,000/μL) with low platelet volume (usually <5 fL).

Immunodeficiency is a consistent feature in WAS. Clinical manifestations commonly take the form of skin abscesses, recurrent sinopulmonary infections, and life-threatening meningitis and sepsis. *Staphylococcus* spp., *S. pneumoniae, Pseudomonas* spp., *Pneumocystis* spp., and systemic fungal infections are common pathogens. Viral infections with CMV, herpes simplex, and disseminated varicella have also been described.[105,111]

Immunologic studies may demonstrate variable function that can change with time and the age of the child. Typical manifestations include generalized progressive lymphopenia; variable immunoglobulins levels, but a general pattern of elevated IgA, low IgM, normal IgG, and elevated IgE[112]; poor specific antibody responses to both protein and more particularly to polysaccharide antigens, including reduced isohemagglutinin levels[113]; and abnormal T-cell proliferation to both mitogens and antigens are commonly seen.

Intensive care specialists must recognize that up to 30% of these patients may present with a life-threatening intracranial, gastrointestinal, or pulmonary bleeding episode.[105] Random donor platelet concentrates are effective for prophylaxis and after hemorrhagic complications. All blood products must be CMV negative and irradiated. It is important to not administer drugs that interfere with platelet function. Treatment with monthly gamma-globulin infusions and prophylactic antibiotics has changed long-term outcomes for these patients.[114] Nonetheless, the only definitive therapy for WAS is HSCT. A collaborative study of the International Bone Marrow Transplant registry analyzed 170 transplantations performed for WAS between 1968 and 1996. The overall 5-year probability of survival was 70% (95% confidence interval [CI], 63% to 77%). Best outcomes were noted for patients receiving donation from an HLA-identical sibling: 87% (74% to 93%) compared with 52% (37% to 65%) for those receiving an other related donor's cells. Matched unrelated donor transplantation demonstrated a 5-year probability of survival of 71% (58% to 80%). Of interest, if children receiving matched unrelated donor cells were transplanted before the age of 5 years, the outcome was similar to HLA-matched sibling transplants.[115]

A more recent long-term outcome analysis for patients transplanted for WAS was performed by the European Society for Immunodeficiencies (ESID) and EBMT.[116] Included in the study were patients who had survived at least 2 years after HSCT. Survival was similar: 7-year event-free survival of 75%. Yet a 20% incidence of autoimmunity was associated with mixed chimerism independent of chronic graft-versus-host disease. Furthermore, infection related to splenectomy was identified as an iatrogenic complication.[116]

DiGeorge Syndrome

The original descriptions of congenital absence of the thymus gland are attributable to Henry Harington in 1928[117] and subsequently by David Lobdell in 1959.[118] In 1965, an abstract was presented by Max Cooper to the Society of Pediatric Research, "A New Concept of the Cellular Basis Of

Immunity."[119] In it, Angelo DiGeorge introduced for the first time autopsy findings of children with congenital hypoparathyroidism who died of overwhelming infections. The finding of thymic aplasia strongly argued for the role of the thymus in the control of infections in humans and supported the theory that Cooper and Good were proposing from experimental studies. A dual immune system was hypothesized: cellular or thymic origin and humoral (i.e., antibody driven). Today DiGeorge syndrome (DGS) is recognized as a heterogenous disorder characterized by a triad of clinical features: congenital heart disease, immunodeficiency, and hypocalcemia. Cytogenetic and molecular studies have demonstrated that in greater than 90% of patients with DGS, a deletion of chromosomal region 22q11 occurs. Other genetic disorders such as velocardial facial syndrome and the conotruncal anomaly facial syndrome represent genetic syndromes with overlapping characteristics with DGS. Facial characteristics; midline defects, including palatal abnormalities, cleft lip and palate; swallowing difficulties; umbilical hernia; skeletal, renal, urogenital anomalies; learning disabilities; and neuropsychiatric disorders are common features of children with the 22q11 syndrome.[120,121]

Clinical and Laboratory Presentation of DiGeorge Syndrome. The spectrum of immunodeficiency is broad. Complete and partial DGS defined the clinical spectrum of immunodeficiency, in which those with complete DGS have absent or very low T-cell numbers, have severely impaired immunologic function, and will present within the first year of life with the same types of infections as children with SCID. Viral and opportunistic infections may be life threatening. Complete diGeorge syndrome is fatal within the first 2 years of life. In contrast, children with partial DGS may demonstrate improvement of T-cell defects over time. Autoimmune cytopenias, malignancies (particularly B-cell lymphomas), and juvenile idiopathic arthritis are other clinical features seen in patients with DGS.

Intensivists caring for children with congenital heart disease must have an understanding of the degree of T-cell defects in these patients because it will guide management and institution of prophylactic therapies if indicated. Attention should be directed toward simple studies available before any surgical procedures; chest radiograph looking for the presence of a thymic shadow and a CBC are generally readily available and provide invaluable information. Profound lymphopenia should alert the clinician to the potential diagnosis of complete DGS and therefore SCID phenotype. Lymphocyte subpopulations and consultation with a clinical immunologist are indicated. Irradiated blood products and live vaccines should not be administrated until immunologic function is understood. Depending on the degree of immunologic function, prophylaxis against *Pneumocystis* and/or fungal infections may be indicated.

DNA Repair Defects with Immunodeficiency

DNA repair defects comprise a group of disorders that include ataxia telangiectasia (AT), Nijmegen breakage syndrome, and Bloom syndrome. All are characterized by defects in DNA repair and genome instability. The immunodeficiency is variable but can progress over time. AT is a rare autosomal recessive disorder characterized by cerebellar cortical degeneration, ocular and cutaneous telangiectasias, immunodeficiency, and predisposition for development of malignancies. Sinopulmonary infections can lead to pulmonary fibrosis and death.[122] AT cells are sensitive to ionizing radiation and radiomimetic chemicals because the cells fail to activate cell cycle checkpoints after treatment with these agents. When an infant is diagnosed with lymphoma or leukemia, attention to a potential diagnosis of AT is important because radiation therapy should be avoided or changed from conventional dosing.[123] The AT gene encodes a protein involved in cell cycle control and DNA repair pathways. Progressive decrease in circulating T cells and a decrease in IgA with elevated IgM are common laboratory findings.

Hyper Immunoglobulin E Syndrome

Hyper IgE syndrome, previously called *Job syndrome,* has been recently understood in molecular terms. An autosomal dominant or sporadic form is caused by mutations in signal transducer and activator of the transcription 3 gene (*STAT3*). A rare condition, this form of hyper IgE is characterized by elevated levels of IgE, recurrent skin boils (mainly due to *S. aureus)*, pneumonia with pneumatocele formation, eczema, coarse facial features, delayed shedding of primary teeth, and hyperextensible joints.[124,125] A recent report on the cause of death in patients with hyper IgE underscored the role that *Pseudomonas* and *Aspergillus* species play in these patients and suggested intensified antifungal and gram-negative bacterial prophylaxis as possible strategies to prevent these infectious complications in those patients who have cystic lung disease.[126]

A second form of hyper IgE is due to mutations in tyrosine kinase 2 (TYK2), which is an inherited autosomal recessive disorder. These patients have unique susceptibility to intracellular bacteria (*Mycobacterium* and *Salmonella* species), fungi, and viruses. Skeletal and connective tissue abnormalities are not seen. Central nervous system hemorrhage associated with infections has been described.[2,127]

Diseases of Immune Dysregulation

Diseases of immune dysregulation comprise a group of diseases that include familial hemophagocytic lymphohistiocytosis (FHLH), immunodeficiency with hypopigmentation (Chediak-Higashi and Griscelli syndromes), lymphoproliferative syndromes, and syndromes with associated autoimmunity.[2]

Familial Hemophagocytic Lymphohistiocytosis. Degranulation of cytotoxic T lymphocytes (CD8 cells) and NK cells are an essential component of both viral and intracellular bacterial clearance. Molecular defects that interrupt this granule-dependent cytotoxic activity of lymphocytes are responsible for the familial forms of HLH. Defects in perforin, hMunc 13-4, and syntaxin-11 describe FHLH types 2, 3, and 4.[128] Patients with Chediak-Higashi syndrome (see Figure 92-2), a rare autosomal recessive disorder characterized by partial albinism and giant intracytoplasmic granules within all granulated cells, have mutations in the *CHS/LYST* gene that presumably is responsible for the lack of secretion of lytic granules,[129] thereby impairing NK and cytotoxic T-cell function. In patients with Griscelli syndrome type 2, the immune dysregulation is the result of mutations in RAB27A, a member of the GTPase family of proteins, which also results in NK and cytotoxic T-cell dysfunction due to an inability of these cells to release their

cytolytic granules.[130] Patients with X-linked lymphoproliferative syndrome (XLP) succumb to infections with Epstein-Barr virus (EBV) infections. The defect lies in an SH2-associated protein (SAP) that associates with the SLAM (surface receptors of the signaling lymphocytic activating molecules) family of receptors. In the absence of SAP, NK-mediated cytotoxicity is impaired and is thought to be responsible for compromising the clearance of EBV-infected B cells.[131]

As a consequence of ineffective cytotoxicity, uncontrolled activation and proliferation of T lymphocytes occurs, macrophages are activated, and cytokines are released, resulting in a life-threatening clinical syndrome. The clinical presentation of persistent fevers, hepatosplenomegaly, and cytopenia associated with a systemic uncontrolled inflammatory response should alert the clinician to these disorders.

Classification and terminology of HLH can be confusing, but it is generally accepted that both genetic and acquired forms exist (Box 92-2). The estimated incidence of FHLH is 1 in 50,000 births.[132] Secondary HLH is considered an acquired form and is associated with infection, autoimmunity, and malignancy. It is important to recognize that the identification of a pathogen associated with this clinical syndrome does not distinguish between familial or secondary forms; many times a prodromal infectious process is described in patients in whom a diagnosis of FHLH is made.[133] The histologic findings include the infiltration of lymphocytes and histiocytes with hemophagocytic activity.

Laboratory findings include hypofibrinogenemia, hypertriglyceridemia, liver dysfunction, and progressive pancytopenia. A recent retrospective chart review by Allen et al.[134] suggest that ferritin levels higher than 10,000 μg/L may be specific and sensitive for the diagnosis of HLH.[134]

Because of the mortality associated with HLH, in 1991 the HLH Study Group of the Histiocytic Society published the first diagnostic guidelines for HLH (since revised by Henter et al.[135] in 2007). A diagnosis of HLH can be established by molecular testing or by demonstrating five of the eight following criteria: (1) fever; (2) splenomegaly; (3) cytopenias involving two or more cell lines (hemoglobin <9.0 g/dL or, for children <4 weeks of age, <12.0 g/dL; platelets <100,000/μL; neutrophils <1000/μL); (4) hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥3 mmol/L, fibrinogen <1.5 g/L); (5) ferritin greater than 500 μg/L; (6) soluble CD25 (interleukin-2 receptor) 2400 U/mL or higher; (7) decreased or absent NK cell activity; and (8) hemophagocytosis in bone marrow, cerebrospinal fluid, or lymph nodes.[135]

Despite the usefulness of guidelines, these diagnostic criteria lack specificity. Thus a diagnostic clinical algorithm has been proposed based on perforin expression.[136] In 19 patients diagnosed according to the 1991 criteria,[137] mutations in perforin were identified in all subjects who demonstrated absent perforin expression by flow cytometry.[136]

Box 92–2 Classification of Hemophagocytic Lymphohistiocytosis

Primary (Genetic Forms)

Familial forms (usually <1 year of age in 70%–80%)
- FHLH 1: Gene unknown, AR, infancy
- FHLH2: Perforin (20%–40%)
- FHLH 3: hMunc 13-4
- FHLH 4: Syntaxin 11 (STX)

Immunodeficiency syndromes
- Chediak-Higashi syndrome: Lyst
- Griscelli syndrome: RAB27A
- XLP: SAP
- WASp
- SCID: AR and X-linked

Secondary (Acquired)

Infection-associated HLH
Autoimmunity
Malignancy

FHLH, Familial hemophagocytic lymphohistiocytosis; *HLH,* hemophagocytic lymphohistiocytosis.

Effective treatment of HLH consists of combinations of proapoptotic chemotherapy, immunosuppression, and HSCT for patients with FHLH and those with persistent disease despite immunosuppression.[138] Results with HLH-94 treatment protocol showed a 55% disease-free survival at 3 years.[139] However, nearly a quarter of these patients demonstrated persistence or recurrence of disease.

The similarities in the clinical presentations of HLH, systemic inflammatory response syndrome, multiorgan dysfunction, and macrophage activation syndrome warrant further prospective studies that test the specificity and sensitivity of current HLH diagnostic guidelines (see Chapter 98).

Summary

PIDs represent a heterogenous group of disorders, many of which are life threatening. For many PIDs, prompt diagnosis can be easily established with simple laboratory studies available to the practicing clinician. Recognizing clinical phenotypes of antibody, cellular, phagocytic, and complement defects is essential because life-saving therapies are available. With the institution of newborn screening for SCID, the next decades will provide insight into the true incidence of this fatal disease and allow for the healthy survival of many such infants.

References are available online at http://www.expertconsult.com.

VI Chapter 93

Acquired Immune Dysfunction

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PEARLS

- Most patients admitted to the pediatric intensive care unit are immunosuppressed to varying degrees.
- Critical illness induces immunoparalysis, a phenomenon marked by downregulation of major histocompatibility complex class II molecule expression on the surface of monocytes, but not B cells. Suppressed monocyte/macrophage function reduces clearance of immune complexes, impairs antigen-presenting capabilities, and decreases natural killer cell function.
- The long-term effects of transfusions on the immune system and subsequent disease susceptibility are unknown, but even 19 years after a blood transfusion, recipients have fewer peripheral T cells, particularly helper T cells, than nonrecipients.
- Pneumocystosis is still the most common AIDS-defining illness in children and can present with variable pulmonary infiltrates; but hypoxemia is often out of proportion to clinical and radiographic examination.
- Malignancies account for 2% of AIDS-defining illnesses in pediatric patients. The increase compared to non-HIV-infected children is attributed to lymphoma. Lymphomas in immunodeficiencies are generally of B-cell type and often arise in the central nervous system.
- Postexposure prophylaxis for occupational HIV exposure should begin as soon as possible and continue for 4 weeks.

Acquired immune dysfunction is by definition a secondary phenomenon following another disease process, such as infection or trauma, or an intended or unintended effect of therapy. Protein calorie malnutrition probably accounts for the greatest number of immunodeficient patients in intensive care units (ICUs) worldwide, whereas human immunodeficiency virus (HIV) infection is the most widely recognized cause of acquired immune deficiency. Impairments in humoral and cellular immunity occur as a consequence of immaturity, malignancy, transfusion, sepsis, shock, viral infections, tuberculosis (TB), and malaria.[1] Iatrogenic immunosuppression occurs most frequently with medications given to either inactivate or kill lymphocyte populations, particularly those used in cancer chemotherapy and autoimmune disease, and to control transplant rejection.[1] When all these precipitants of immunodeficiency are taken into account, it becomes apparent that most patients admitted to the pediatric ICU are immunosuppressed although to varying degrees. Patients with acquired immunodeficiency are at risk for opportunistic infections and unusual presentations of common infections. If immunosuppression is known or suspected, the physical exam should focus on the mucosal surfaces, catheter entry sites, the skin (including wounds), and the central nervous system. Understanding patterns of disease that are specific to each type of immune dysfunction can lead to both earlier appropriate empiric therapy and diagnostic tests (Table 93-1).[1,2] Unlike congenital immunodeficiency, many cases of acquired immunodeficiency are reversible.

Immune Function and Critical Illness

Critical illness often involves the activation of the inflammatory cascade that must be turned off for the patient to survive.[3] In response to stress, proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α); interferon; and interleukin-1 (IL-1), IL-6, and IL-12 are produced along with antiinflammatory agents such as IL-10 and TNF receptor.[3-6] The production of IL-10 is associated with downregulation of major histocompatibility complex class II (human leukocyte antigen [HLA]-DR) molecule expression on the surface of monocytes, but not B cells. If the resulting downregulation of the immune system is prolonged a condition occurs known as immunoparalysis. Suppressed monocyte/macrophage function reduces clearance of immune complexes, impairs antigen-presenting capabilities, and decreases natural killer cell function. Activated T cells are important sources of interferons, which in turn control infection by stimulating nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and nitric oxide production and by increasing adhesion molecule expression. Immunoparalysis is confirmed in the laboratory by reduced expression of HLA-DR antigens on peripheral blood monocytes and decreased TNF-α production in response to lipopolysaccharide (LPS) exposure.[5] Immunoparalysis and has been shown in patients after trauma, neurosurgical procedures, and cardiopulmonary bypass operations.[7-11] This phenomenon may in part explain the increased incidence of life-threatening nosocomial infections including those considered opportunistic in these patients.[12, 13]

Absolute lymphocytopenia has often been reported in previously healthy patients in response to critical illness, including burns, neurotrauma, cardiopulmonary bypass, and viral inefections.[14-17] Total lymphocyte counts measured in 22 children fell to a nadir at 6 hours after anesthesia for major surgery with minimal recovery out to 48 hours.[14] Helper

Table 93–1 Infections Seen with Various Types of Immune Deficiency

	Common	Less Common
GRANULOCYTOPENIA		
Bacteria	*Staphylococcus aureus, Staphylococcus pneumonia, Klebsiella, Pseudomonas*	*Enterobacter, Acinetobacter, Stenotrophomonas*
Fungi/molds	*Candida, Aspergillosis, Zygomycosis*	
Parasites		
Viruses		HSV1 or 2, VZV
CELLULAR DEFECTS		
Bacteria	*Legionella, Nocardia*	*Mycobacterium tuberculosis*
Fungi/molds	*Pneumocystis, Cryptococcus, Mucormycosis*	
Parasites	*Toxoplasma*	
Viruses	CMV, EBV, adenovirus, VZV	
HUMORAL DEFECTS		
Bacteria	*S. pneumonia, Haemophilus influenzae*	
Fungi/molds		Pneumocystis
Parasites		*Giardia lamblia*
Viruses		VZV
COMBINED DEFECTS		
Bacteria	*S. aureus, S. pneumonia, Klebsiella, Pseudomonas*	*M. tuberculosis, Listeria monocytogenes, Legionella*
Fungi/molds	Pneumocystis, aspergillosis, *Cryptococcus*	Zygomycosis, murcomycosis
Parasites	*Toxoplasma*	
Viruses	CMV, VZV, influenza, parainfluenza, RSV, adenovirus	HSV 1 or 2

CMV, Cytomegalovirus, *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *VZV,* varicella-zoster virus.
Modified from Safdar A, Armstrong D: Infectious morbidity in critically ill patients with cancer, *Crit Care Clin* 17:531, 2001.

cells were most affected. Cardiopulmonary bypass further induced lymphocyte apoptosis compared to surgery alone.[15] Exogenous corticosteroids have long been known to induce lymphocute apoptosis. Because critical illness also evokes a hormonal stress response, elevated endogenous corticosteroids are hypothesized to induce lymphopenia; however, there is no direct correlation between cortisol levels and lymphocyte counts.[16,17] In contrast, prolactin levels have been shown to correlate with lymphopenia in several studies and prolonged suppression of prolactin was associated with lymphocyte depletion, nosocomial infection and death.[17,18] Prolactin is required for lymphocyte proliferation and protects lymphocytes from steroid induced apoptosis. Other drugs used in critically ill patients may contribute to lymphopenia. Dopamine inhibits prolactin release even at very low doses, whereas metoclopramide increases prolactin release.[18,19] Dopamine and dobutamine also affect lymphocyte function directly.[20] Growth hormone deficiency is associated with decreased natural killer cell activity.[21]

Critically ill patients frequently receive blood transfusions that are known to modify the immune response see also Chapter 82, Transfusion Medicine. Patients with cancer who receive transfusion at the time of resection have greater risk of dying than those who do not.[22] In contrast, certain patients who receive blood transfusion before transplant have a lower incidence of rejection[22]; however, transplant recipients who receive an HLA-DR mismatched transfusion have accelerated graft rejection.[23] The long-term effects of transfusions on the immune system and disease susceptibility are unknown, but even 19 years after transfusion, blood recipients have fewer peripheral T cells, particularly helper T cells, than patients who did not undergo transfusion.[24] Blood transfusions after trauma or cardiopulmonary bypass are associated with increased infection; however, in major surgery or trauma it is difficult to sort out the effect of transfusion compared with the effect of critical illness.[25,26] The use of autologous transfusion in elective surgery may reduce the risk of immunosuppression.[27]

In addition to HIV, viruses such as measles, influenza, and human T-cell lymphotrophic virus-1 can suppress the immune response.[28-31] The neutrophils of patients infected with measles are not activated and therefore are unable to phagocytize and kill bacteria.[28] Lymphopenia has been associated with measles and respiratory syncyctial virus (RSV) and two paramyxoma viruses that can infect monocytes.[29-32] In both infections, mortality is often related to secondary infections. Okada et al. documented that the measles virus infected only small number of lymphocytes but apoptosis occurred in noninfected lymphocytes.[29] The duration of lymphopenia was age dependent and was most prolonged in infants. The same response was not observed in response to a live measles vaccine.[30] Absolute lymphocyte counts were lower in hospitalized RSV-infected patients than controls and were lowest in patients admitted to the intensive care unit.[31] No mortality was observed and lymphocyte counts recovered. In children with a known immunodeficiency such as following cancer therapy and RSV, the development of lower respiratory tract infection was associated with profound lymphopenia (<100 cells/μL) and mortality was 31%.[32]

Although for many previously healthy children immune dysfunction recovers with time, treatment of the underlying condition and/or withdrawal of immuosuppression, for others it does not. This phenomenon is associated with multiple organ failure and death.[12,13,18] For example, an absolute lymphocyte count less than 1000 cells/μL lasting longer than 7 days was associated with a more than sixfold increase risk of death in one pediatric study.[18] For this reason, several investigators have attempted to proactively reverse this process.[33-41] In neutropenic patients with sepsis, granulocyte stimulating factor (G-CSF) reduces the likelihood of death; however, in non-neutropenic patients only one clinical trial has yet shown benefit.[36] Adults with severe community-acquired pneumonia treated with G-CSF plus antibiotics had less sepsis-related organ failure than those treated with antibiotics alone.[37] During immunoparalysis, interferons, which are major activators of monocytes, are reduced. Exogenous interferon gamma-1b therapy administered to 10 consecutively admitted patients

with less than 30% HLA-DR expression restored both HLA-DR expression and production of IL-6 and TNF-α.[39] Aerosolized interferon-γ administered to trauma patients with immunoparalysis (defined as suppressed HLA-DR expression on alveolar macrophages) was associated with a lower incidence of ventilator-associated pneumonia.[40] Monocytes can also be stimulated by granulocyte macrophage colony stimulating factor (GM-CSF). In nine consecutive patients with immunoparalysis documented by reduced mean HLA-DR expression in peripheral blood monocytes, 5 μg/kg of GM-CSF produced a fourfold increase in mean HLA-DR expression and a ninefold increase in TNF-α response to LPS in as little as 24 hours.[41] When given to septic patients with acute respiratory distress syndrome (ARDS), GM-CSF was associated with improved gas exchange and increased neutrophil respiratory burst.[38] Clinical investigations aimed at reversing the downregulated immune system are ongoing and not without risk.

Malnutrition and Immune Deficiency

A significant proportion of children admitted to ICUs (even in affluent countries) have been noted to be malnourished, whereas many others will receive inadequate nutritional intake during their stay in intensive care, implying that many critically ill children will have abnormal immune function secondary to nutritional problems.[42-45] Immune system dysfunction occurs so early in the course of malnutrition that measures of immune competence such as anergy and total T-cell numbers are sensitive indicators of a patient's nutritional status.[46] Nutrition influences the course of HIV and tuberculosis, susceptibility to infection in older patients, the body's ability to respond to vaccines, and many other aspects of immune function.[45-48]

Protein or protein-calorie malnutrition is generally only studied in humans in its most severe form. Because of interspecies variability in immunoglobulin synthesis and cytokine regulation, extrapolation of animal data to humans may be inappropriate.[48] Protein malnutrition alters production of epithelial cell membrane glycoprotein receptors, immunoglobulin A, and mucus, increasing the risk of bacterial colonization.[48] Mobilization of neutrophils is delayed, natural killer cell lytic activity is reduced, and imbalances in critical T-cell subsets occur. All contribute to increased susceptibility to infection. Severe malnutrition attenuates the acute phase response and interferon production, but other proinflammatory compounds and T-cell subsets are upregulated. The common tautology that protein deficiency reduces all protein synthesis is not supported by available data.[48] In the human condition, selective protein deficiency without concomitant essential fatty acid and micronutrient deficiency is unlikely.

By definition, essential fatty, linoleic, and alpha-linoleic acids, cannot be synthesized by mammalian cells and must be obtained through the diet.[49] Linoleic acid is found in plant oils and animal fats, alpha-linolenic acid in plant oils.[49,50] For children in many parts of the world access to fat other than cow's milk is severely limited. The n-3 polyunsaturated fatty acids (PUFAs), eicosopentaenoic acid and docosahexaenoic acid (DHA), synthesized from alpha-linolenic acid or obtained from a diet of fish, suppress lymphocyte responses to mitogen stimulation.[48] Accumulating evidence suggests that dietary supplementation with n-3 PUFAs is a "natural" immunosuppressant that may be useful in autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, and diabetes mellitus.[49] Moderate n-3 PUFA intake can enhance the immune response. For example, supplementation of infant formula with a small amount of DHA accelerates development of T-cell responsiveness in preterm infants (see also Chapter 75).[50]

There are many specific nutrients now identified as vital to immune function. Vitamin A has essential functions in immune cells and indirectly contributes to protection from infection through maintenance of vital epithelial cell differentiation and barrier function of the lung and intestine.[51] Vitamin A deficiency occurs in an estimated 100 million children worldwide[52] and is a risk factor for increased death from pneumonia and diarrhea.[45] A survey of hospitalized children in Malawi showed that one third had severe vitamin A deficiency and one third had moderate deficiency.[52] Paradoxically, these children exhibited monocytes with preferential synthesis of TNF-α as compared with IL-10. This shift was perhaps triggered by the underlying disease that prompted hospitalization. Results of several randomized, double-blinded, placebo-controlled trials conducted in malnourished children have shown improved antibody response to vaccines and fewer diseases of the gastrointestinal and respiratory systems after vitamin A supplementation.[45,51,52] Vitamin A supplementation in individuals who are not deficient has no benefit, whereas high retinal levels are associated with an increased diarrhea and pneumonia.[53] Vitamin C (ascorbic acid) is highly concentrated in leukocytes, and low leukocyte vitamin C concentrations are associated with reduced immune function.[50] Epidemiological data suggest that higher vitamin C consumption lowers the risk of cancer and cardiovascular disease, but despite numerous clinical trials with participants of both sexes and varying ages, no definitive evidence that vitamin C supplementation reduces the frequency or symptoms of upper respiratory infections exists. High-dose vitamin C does improve several measures of immune function and does not appear to have any side effects.[45] Vitamin D receptors are found on numerous immune cell types.[54] Vitamin D deficiency is associated with depressed macrophage function and impaired delayed hypersensitivity.[53] Vitamin E (-tocopherol) is a potent lipid-soluble antioxidant. Study results of vitamin E supplementation ranging from 200 to 800 mg/day in healthy adults showed increasing CD4/CD8 ratios, mitogen responsiveness, antibody production, and decreasing free radical production; however, a dosage of 300 mg/day for 3 weeks resulted in suppressed bactericidal activity in humans.[46] Optimal daily requirements of these nutrients in health and disease remain to be determined.

Of the trace elements that may affect the immune system, selenium, zinc, and iron have been the most widely studied. Selenium balances redox states and suppresses inflammation through its vital role in several antioxidant enzymes and intranuclear factors, including the glucocorticoid receptor, activator protein-1, and nuclear factor-κB.[47] In HIV infection, selenium supplementation modifies cytokine release, decreasing TNF and IL-8 while increasing IL-2. Selenium improves T-cell proliferation and differentiation. Selenium deficiency in the host enhances the mutation rate

of Coxsackie and influenza viruses, but excessive selenium intake is toxic to the immune system and other organs.[47] Zinc, as with selenium, is required for the activity of more than 100 enzymes.[52] Zinc supplementation increases the number of CD4+ T cells; thus, the CD4/CD8 T-cell ratio is improved. Zinc deficiency has been documented in alcoholics and in patients with burns and gastrointestinal disorders.[53] Zinc supplementation reduces bacteremia, hospitalization rates, and vaso-occlusive crises in patients with sickle cell anemia.[47] In young children, zinc supplementation reduced the duration of diarrhea and frequency of respiratory infections.[47] Worldwide, 20% to 25% of the population has iron deficiency, that results in impaired cell mediated immunity, particularly in neutrophil and natural killer cell function.[56] Although an association between iron availability and susceptibility to certain bacterial infections exists, there is little evidence that iron supplementation in deficient individuals inhibits immune responses or increases susceptibility to infections.[47]

Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome

Acquired immune deficiency syndrome (AIDS) is a clinical syndrome resulting from infection by HIV-1 (and very rarely HIV-2), an RNA retrovirus dependent on a reverse transcriptase for replication.[57] Surrounding the RNA and its reverse transcriptase are core proteins p24 and p18. A viral envelope is composed of the host cell membrane studded with glycoproteins gp120 and gp40. Entry of HIV into cells is mediated by the binding of gp120 to the CD4 membrane protein of the host's T-helper cells in the presence of a host coreceptor of the chemokine family, either CCR5 on macrophages or CXCR4 on other cell lines. After HIV replication, the host's T-helper cells undergo apoptosis resulting in severe deficiency of both cell-mediated and humoral immunity. Because pediatric HIV infection is most commonly transmitted from mother to infant, the acquired immunodeficiency is occurring in a host whose immune system, unlike the adult's immune system, is relatively naive and has developed little natural immunity.[57,58] This may in part explain the shorter time required for progression of HIV infection to AIDS in perinatally infected children when compared with children infected after the age of 2 years.[59] Antiretroviral therapy can effectively reverse this immune dysfunction.[60]

The diagnosis of HIV-1 infection in adults and children older than 18 months is accomplished by identification of antibodies specific to viral proteins: first through a rapid enzyme-linked immunosorbent assay and then confirmed by the more time-consuming Western blot analysis.[60] Because infants carry transplacentally acquired maternal antibodies, HIV infection in infants younger than 18 months must be documented by HIV DNA polymerase chain reaction (PCR) or HIV RNA assay.[60] Generally DNA PCR is repeated three times (between 14 and 21 days, at 1 to 2 months, and at 4 to 6 months of age) with sensitivity increasing over time. [57] Some centers also perform testing at birth. Subtypes of HIV have been identified with subtype B predominating in the United States.[57] The DNA PCR assays are less sensitive for non-B subtypes than are RNA assays. If either test is positive, the child's HIV enzyme-linked immunosorbent assay can be repeated at 1 year to document seroconversion.[57]

The diagnosis of AIDS requires confirmation of both HIV infection and an AIDS-defining illness.[61] AIDS-defining illnesses include nonspecific findings such as fever; weight loss; lymphadenopathy or diarrhea for more than 2 months; and specific findings such as encephalopathy, lymphoid interstitial pneumonitis (LIP), opportunistic infections, recurrent infections, and associated malignancies. In 1994 the United States Centers for Disease Control and Prevention modified an earlier classification system for HIV infection ranging from indeterminate to asymptomatic to severely symptomatic (i.e., AIDS) in an effort to stratify the severity or progression of the disease, by adding age specific CD4+ T cell counts and percentages.[61] These categories aside, there appear to be at least two patterns of response to HIV infection in untreated children.[59,62] Children younger than 4 years, especially those aged 1 year or younger, are more likely to have *Pneumocystis carinii* pneumonia (PCP); have severe progressive encephalopathy, wasting, or both; and die earlier. Older children tend to have a less serious course, characterized by recurrent bacterial infections, LIP, nephropathy, and thrombocytopenia. The time course for vertically transmitted HIV infection to progress to AIDS in children is variable and may be more than 10 years; however, in children, AIDS is most commonly seen between 5 and 8 months.[63] The density of CCR5 receptor on nonactivated T cells correlates with the decline of CD4+ T cells and prognosis.[64]

Epidemiology

In North America at the end of 2007, the adult prevalence of HIV was 0.6% compared with 5% in sub-Saharan Africa.[65] Ninety-six percent of individuals living with HIV reside in low and middle income countries. Sub-Saharan Africa had the highest incidence of HIV infection accounting for 67% of the world's cases with young women three times more likely than men to be infected. East Africa and Central Africa have reduced the prevalence of HIV infection through educational programs. In Western Europe many new cases of HIV/AIDS are reported from persons who emigrated from or traveled to countries with a high HIV prevalence.

As of December 2007, 2 million children lived with HIV/AIDS worldwide, of which 370,000 were newly infected and 270,000 died annually.[65] Vertical transmission of HIV infection from untreated mother to fetus occurs at a rate of 20% to 35% but is reduced by 66% when antiretroviral therapy monotherapy (zidovudine [ZDV]) is taken during pregnancy, delivery, and the neonatal period.[65,66] Even though simple inexpensive monotherapy can reduce vertical transmission by 40% to 50%, only 33% of infected pregnant women receive treatment.[65,66] When used in combination with elective cesarean delivery and formula feeding, perinatal antiretroviral therapy has reduced the vertical transmission of HIV to less than 2% in the United States. Currently trials suggest that highly active antiretroviral therapy (HAART) in pregnancy may be more effective in preventing transmission than monotherapy.[67,68] It may also be important to extend antiretroviral therapy for the mother during the period of breastfeeding.[67,69,70] Although there has been extensive development of appropriate therapies, a major challenge has been actual delivery of programmes to prevent mother to child transmission.[71-73]

Antiretroviral Therapy

In the United States, antiretroviral therapy for HIV-infected children was initiated in 1985 with zidofovir, a reverse transcriptase inhibitor, as monotherapy.[74] As of February 2009, 22 antiretroviral agents were approved and available for use in the United States, 17 have a pediatric indication.[60] Because resistance develops with monotherapy, multiple drug regimens known as HAART are used in children and adults.[75] There are five classes of agents available and three drugs are typically selected from at least two classes. Measurement of both HIV-1 viral load (by RNA PCR) and the number of CD4+ T cells is performed to monitor the effectiveness of HAART.[60] Baseline viral loads are higher in children than in adults and have a slower decay rate after the introduction of HAART.[66] Pediatric studies in which dosage adjustments were directed by pharmacokinetics resulted in superior decreases in viral loads compared with fixed dosages based on weight.[60] Each antiretroviral therapy has its own toxicity and potential for drug interactions (Table 93-2). Antiretroviral therapy is rapidly evolving and should be directed by a specialized practitioner.[60]

Initiation of antiretroviral therapy can result in rapid immune recovery. A subset of patients experience an inflammatory response as the immune system is reconstituted.[76] Most cases have another occult infection in addition to HIV. In one study, nearly 50% were associated with mycobacterial infections such as *Mycobacterium avium intracellulare* and herpes viruses such as *Varicella zoster*. Clinical presentation is related to the focus of infection. Enhanced screening and subsequent treatment of opportunistic infections such as tuberculosis program before beginning HAART may prevent the reconstitution inflammatory syndrome. The World Health Organization has recommended prednisone for patients with tuberculosis who experience severe paradoxical reactions. However, there are no randomized controlled trials to support this practice.[76]

The number of people receiving HAART surpassed 2 million in 2007, but two thirds of those who need it still have no access to drug.[65] Ninety percent of HIV-infected children live in sub-Saharan Africa and underdeveloped countries of Asia.[65] Because of cultural, economic, and political factors, HIV prevention and treatment have been only slowly introduced in these regions. In Malawi, without antiretroviral therapy, the mortality rate at 3 years of age for HIV-infected children reached 89%.[78] This high mortality rate may be related to the burdens of infectious diseases and malnutrition, and is seen in other parts of the world. The care of these children is complicated by overcrowding, limited access to clean water, and malnutrition, that contributes to the high frequency of TB, cytomegalovirus (CMV), hepatitis, and gastroenteritis seen in this population. Still there is growing evidence that antiretroviral can be provided successfully to children in resource limited settings.[79,80] Even in this environment, the efficacy of early initiation of anti-retroviral therapy in children has been confirmed.[81] In the United States 75% of HIV-infected children in the United States are alive at age 5 years.[80] Most data regarding outcome and survival of HIV-infected children presented in this chapter are drawn from patients who did not receive antiretroviral therapy from the time of birth and may have never received it. Such data are likely still applicable to underdeveloped countries.

Table 93–2 Adverse Effects of Antiretroviral Agents

Agent	Effect
NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS	Almost all produce headache, gastrointestinal distress, fever; less frequently peripheral neuropathy, pancreatitis, and lactic acidosis with hepatomegaly
Abacavir	5% have severe hypersensitivity reaction (HLA-B 85701 allele)
Didanosine (ddI)	
Emtricitabine	Hyperpigmenation
Lamivudine	
Stavudine	
Tenofovir	
Zalcitabine	
Zidovudine	Bone marrow suppression, myopathy, mitochondrial dysfunction, liver toxicity
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	Almost all produce headache, fatigue, gastrointestinal distress, and rash, sometimes progressing to Stevens-Johnson syndrome
Efavirenz	Central nervous system alterations: somnolence, delirium
Nevirapine	Hepatitis, hypersensitivity reaction
PROTEINASE INHIBITORS	Almost all produce headache, gastrointestinal distress, paresthesias, rash; less frequently pancreatitis, hyperglycemia
Atazanavir	Jaundice
Darunavir	
Fosonprenavir	
Indinavir	Asymptomatic hyperbilirubinemia, nephrolithiasis, elevated lipid levels
Lopinavir/ritonavir	
Nelfinavir	
Ritonavir	Increased liver transaminases
Saquinavir	Exacerbation of chronic liver disease
Tipranavir	
INTEGRASE INHIBITORS	
Raltegravir	Headache, gastrointestinal distress, fatigue, pruritus, myopathy
ENTRY INHIBITORS	
Maraviroc	Rash
FUSION INHIBITORS	
Enfuvirtide	Inflammation at infection site

Modified from Van Rossum AM, Fraaij PL, de Groot R: Efficacy of highly active anti-retroviral therapy in HIV-1 infected children, Lancet Infect Dis 2:93, 2002.

Pulmonary Complications and Respiratory Failure

Pulmonary complications remain the most frequent indication for admission of children with AIDS to an ICU.[82,83] Bacterial pneumonia is common in this population.[84,85] Along

with the usual pathogens frequently seen in childhood, such as *Streptococcus pneumoniae* and mycoplasma, immunodeficient children are also susceptible to pseudomonal and staphylococcal infections.[66,67] The incidence of *Haemophilus influenzae* infection is declining where vaccination is available, whereas immunization against pneumococcal infections has been associated with a significant drop in pneumococcal disease in HIV infected children.[86] Empiric therapy for pneumonia in such children should cover the most common pathogens and be based on hospital-specific susceptibility profiles, but it is important to note that children with HIV infections may not respond to standard antibiotic therapies for lower respiratory tract infections.[87]

Pneumocystis Jirovecii Pneumonia

Although increased emphasis on early prophylaxis has reduced its incidence, PCP is still the most common AIDS-defining illness in pediatrics.[88,89] Children not previously recognized to be infected with HIV may present as early as 3 to 4 weeks of age, whereas the median age or presentation to intensive care units is between 3 and 6 months of age, and coincides with the timing of a natural decline in maternal antibodies.[83] In children known to be at risk of HIV infection, PCP prophylaxis is indicated starting at 4 to 6 weeks of age as CD4+ T cell counts obtained before the development of infection are not predictive of infection and can drop precipitously.[90] *Pneumocystis jiroveci* is unique to humans and has a predilection for the lung.[91] PCP generally presents with cough, fever, tachypnea, and dyspnea of several days' duration.[91] Physical examination typically reveals retractions and grunting. Auscultation of the chest may reveal normal examination findings or rales, rhonchi, and wheezing. The chest radiograph generally shows diffuse interstitial infiltrates, but pulmonary infiltrates can be variable in children, in part because infants have a greater propensity for atelectasis.[91,92] Hypoxemia is often out of proportion to clinical and radiographic examinations. A selectively elevated serum lactate dehydrogenase level is suggestive, although not diagnostic of PCP.[91] For a confirmation of a PCP diagnosis, bronchoalveolar lavage should be performed. Flexible fiberoptic bronchoscopy has a diagnostic yield of 90% to 97% and allows one to look for other pathogens as well.[91,93] Nonbronchoscopic bronchoalveolar lavage and sputum induction can also be used.[93] Patients in whom no diagnosis is obtained from bronchoalveolar lavage should undergo an open lung biopsy. This procedure has a diagnostic yield for PCP of 97% in the study of patients with underlying malignancy or immune suppression.[91]

The preferred antiprotozoal therapy for PCP is the combination of trimethoprim and sulfamethoxazole (TMP-SMX) (20 mg/kg/day trimethoprim).[91] Patients in whom this combination agent fails have not been shown to respond to a change in antiprotozoal therapy. In fact, higher doses of both components may be required to achieve therapeutic levels in critically ill patients.[91] Sulfa allergy as manifested by severe drug eruptions including Stevens-Johnson syndrome is less frequent in children than in adults; however, this complication may prompt a change to therapy with pentamidine isethionate (4 mg/kg/day). When adverse events such as pancreatitis and renal failure occur as a result of pentamidine, atovaquone (40 mg/kg/day) is an alternative treatment.[91] Twenty-one days of therapy are followed by prophylactic therapy, for which TMP-SMX is also the agent of choice. For patients allergic to sulfa, PCP prophylaxis can be achieved with pentamidine, dapsone, or atovaquone, although these agents have not been rigorously studied in children.

Several adult randomized controlled trials showed efficacy of high-dose steroids in HIV positive adults with moderate PCP.[91] Although no controlled studies have been performed in children, improved outcomes in children who received corticosteroids have been described in several case series.[94-97] Even in the face of respiratory failure, the survival rates reported with adjunctive corticosteroids therapy are 91% to 100% in a limited number of children.[96,97] Because PCP mimics other diseases such as miliary TB and CMV pneumonitis, PCP should be confirmed and other coinfections excluded before corticosteroid administration. Adults who have respiratory failure despite adjunctive corticosteroids have a high risk of death. Failure to improve after 5 days of mechanical ventilation and the development of pneumothorax were strongly predictive of death in adults.[98]

Pneumocystis pneumonia has also been reported in patients receiving high dose steroids, transplant related immunosuppression and the new monoclonal antibodies that modulate the immune system.[91] Pneumocystis pneumonia behaves differently in non-HIV-infected patients. The onset of the disease may be more abrupt. The mortality is greater in cancer patients than AIDS patients and corticosteroids are not as clearly beneficial.

Because the alveoli of patients infected with pneumocystis are filled with protozoal and inflammatory cells, PCP is associated with a reduced functional residual capacity. Many of these patients are small infants in whom the second inflection point of the lung's pressure-volume curve is reached at relatively low peak and mean airway pressures; thus, early institution of high frequency oscillatory ventilation may be warranted.

Cytomegalovirus Pneumonitis

Children at risk for vertical transmission of HIV are also at risk for CMV infection. Pneumonitis from CMV is also a common complication of solid organ and hematopoietic stem cell recipients. The presentation of CMV pneumonitis can closely mimic that of PCP with diffuse interstitial infiltrates and hypoxemia, but there is generally a more insidious onset; however, some reports of a more fulminant course exist.[99] Failure of PCP to respond to conventional therapy may be evidence of concomitant CMV infection. Signs of retinitis, hepatitis, or colitis should be evaluated in patients with pneumonia because they may indicate widespread CMV disease.

The definitive diagnosis of CMV pneumonitis must be made by identification of characteristic intracellular viral inclusion bodies in pulmonary macrophages or biopsy specimen because recovery of CMV from bronchoalveolar lavage by culture may represent viral shedding rather than invasive disease.[99] Detection of viral antigen by immunofluorescence is a second confirmatory test.[99] Serological markers of CMV are not useful in HIV-infected adults.[99] The treatment for CMV disease, in addition to HAART, is ganciclovir 5 mg/kg given twice daily followed by long-term suppressive therapy.[99,100] Foscarnet and cidofovir have been used in other immunosuppressed patients, but these drugs have significant nephrotoxicity.[99,100] Although solid organ transplant recipients receive prophylaxis against CMV disease with ganciclovir, this

approach has not been applied to patients with AIDS. The use of leukoreduced blood products may reduce the risk of primary infection.

Other Viral Pathogens

Children with AIDS are more likely to experience lower tract disease and pneumonia when contracting RSV and influenza.[101,102] For RSV, the estimated incidence of lower tract disease was twofold greater in HIV-infected children. It is not clear that HIV infection increases the likelihood of death.[102,103] The incidence of lower respiratory tract disease requiring hospitalization in influenza was eightfold higher in children with HIV infection.[102] HIV-infected children with influenza pneumonia were older and more likely to have another underlying disease or concurrent infection. Despite these comorbidities there was no difference in clinical outcome. Other pathogenic viruses recovered from pediatric patients with AIDS include adenovirus, parainfluenza, herpes simplex, and measles. In vitro data suggest ribavirin and cidofovir may be effective against some of these viral pathogens; however, evidence of in vivo efficacy is limited to anecdotal reports in immunosuppressed patients.[103,104] Immunosuppressed children have been noted to shed viral pathogens such as RSV and influenza for a prolonged period time, and therefore nosocomial viral infections may be a significant problem if infection control practices are not maintained.[105,106]

Mycobacterial Pathogens

Worldwide, approximately one third of the human population is infected with the Mycobacterium bacillus.[107] Most of these individuals live in developing countries where the prevalence of HIV infection is high. The incidence of *M. tuberculosis* appeared to level off in the United States by 1985 but began rising steadily in 1988—an increase attributed to the AIDS epidemic.[109] The increased incidence of pediatric TB is likely due to increased exposure to adults with active infection. HIV-infected children with TB have higher CD4+ T-cell counts than those observed with other classic opportunistic infections.[63] Although adults generally acquire HIV infection after acquiring TB, the opposite is true in children. Thus the HIV-infected child never has a chance to mount an immunological response to *M. tuberculosis*. In contrast to adults who have apical, cavitary lesions, children have more peripheral disease.[107] Most pediatric patients with AIDS have diffuse infiltrates consistent with LIP or PCP.[109] These children also have a high incidence of extrapulmonary manifestations such as hepatosplenomegaly and meningitis.

Aggressive efforts to confirm mycobacterium infection by culture are required because anergy obscures Mantoux testing, as well as the development of pleural effusions and localized lymphadenopathy. Use of PCR to identify *M. tuberculosis* nucleic acids in bronchoalveolar lavage and cerebrospinal fluid (CSF) specimens can accelerate the ability to diagnose this infection.[112] Recovery of mycobacterium by sputum induction has been reported in infants and very young children.[88] In some regions, organism recovery is necessary for antimicrobial susceptibility determination; 25% of isolates are resistant.[107,111,112] In countries where the diagnostic approaches are not readily available, it is useful to obtain radiographs of family members.[112]

Pending sensitivity reports, treatment of TB is initiated with a five-drug regimen.[113] The presence of multidrug resistance increases the likelihood of death. These patients should simultaneously be treated with antiretroviral therapy; however, rifampin is contraindicated with protease inhibitors and nonnucleoside reverse transcriptase inhibitors.[113] During HAART, reconstitution of the immune system may increase the inflammatory response to pulmonary TB. Children with TB and HIV infection who are not treated with HAART have a higher mortality rate than children not infected with HIV.[113] They must be treated for a longer time, perhaps because of poor drug absorption and a weakened immune system.[113] Before the introduction of HAART, isoniazid prophylaxis prevented both tuberculosis and death in HIV-infected children[114]; however, this has not been shown in the era of antiretroviral therapy.[11]

Mycobacterium avium-intracellulare complex (MAC) can also be recovered from the lungs of children with pneumonia.[82] Colonization is difficult to differentiate from invasive disease. Treatment options include coverage with clarithromycin in combination with ethambutol, rifabutin, or amikacin. Primary prophylaxis once a week with azithromycin is recommended in children older than 2 years and younger than 1 year with CD4 counts persistently below 75. Children between 1 and 2 years of age should receive prophylaxis for CD4 counts less than 50.[90]

Fungal Infections

Candida is frequently recovered from sputum and bronchoalveolar lavage samples in children with AIDS, but whether it is a true pathogen is questionable. In adults in whom a biopsy specimen can be obtained by bronchoscopy, *Candida* is thought to be a rare cause of pulmonary disease but a more frequent cause of bronchitis.[116] Aspergillosis has also been reported in older children with multiple opportunistic infections, prolonged hospitalization, neutropenia, and corticosteroid use.[117] Unlike *Candida*, recovery of aspergillosis from the respiratory tract is indicative of invasive disease. Cryptococcosis occurs in 5% to 15% of adults but in only 0.6% to 1% of children.[117] This ubiquitous organism enters the body through the respiratory tract. Therefore initial symptoms are generally both pulmonary and nonspecific. Bronchoalveolar lavage fluid should be examined by India ink stain and culture. Blood culture and latex agglutination are also necessary. Recommended therapy is amphotericin B in combination with 5-flucytosine (100 mg/kg/day) for 2 weeks followed by fluconazole (12 mg/kg/day divided in two doses) for 8 additional weeks.[118] Cryptococcal antigen titers are useful in the evaluation of possible relapse. Prophylaxis for the prevention of cryptococcal disease is not recommended in children. Fusariosis has been reported in neutropenic patients with AIDS. Other fungal infections such as histoplasmosis, cryptococcosis, coccidiomycosis, and disseminated *Penicillium marneffei* are reported in patients with AIDS who are living in or traveling through endemic areas. [82,119]

Lymphoid Interstitial Pneumonitis

LIP is a lymphoproliferative disorder associated with viral infections. In children LIP is almost exclusively seen with Epstein-Barr virus (EBV) and HIV.[120] LIP occurs in

30% to 50% of pediatric patients with AIDS, presenting in the second year of life in that patient population with high antibody titers and recurrent bacterial infections. Generally the children also have diffuse lymphadenopathy and hepatosplenomegaly. Children with LIP may have mild pulmonary symptoms such as dry cough but generally are admitted to the pediatric ICU only when an acute infection is superimposed on their chronic condition. When such is the case, maximal therapy of the acute exacerbation is indicated, including mechanical ventilation. On chest radiograph hilar adenopathy and reticulonodular infiltrates are seen. Pulmonary function tests reveal reduced lung volumes and diffusing capacity. Histologically, peribronchial lymphoid nodules containing plasma cells and lymphocytes are observed. Most specimens show predominantly CD8-positive T cells.

Spontaneous radiographic resolution was reported in 65% of children with LIP.[121] Patients with hypoxemia are treated with steroids, and resolution is seen in most patients in 2 to 4 weeks. If the patient is persistently febrile, MAC infection should be ruled out before steroid administration.[82]

Upper Airway Obstruction

Young children and infants exhibit upper airway obstruction with greater frequency than adults. Whereas classic viral laryngotracheitis is the most common cause in the immunocompetent patient, immunocompromised patients are susceptible to a greater variety of infectious entities, including bacterial tracheitis, CMV-related ulceration of the trachea, and *Candida* infections of the airway oropharynx.[122,123] The clinical course in HIV-infected children is different with many requiring tracheostomy.[123] Although in the general population *Staphylococcus aureus* is the most commonly reported cause of bacterial tracheitis, *Pseudomonas* species are a frequent cause of tracheitis in patients with AIDS. Given the complexity of the differential diagnosis of stridor in this population, early laryngoscopy and bronchoscopy are indicated.[97] Recurrent tracheitis may be an indication for tracheostomy. Length of stay and outcome are not affected by the presence of HIV infection.[97]

Cardiovascular Complications

Septic Shock

After the introduction of PCP prophylaxis, severe sepsis became the most common reason for ICU admission in patients with AIDS.[124] Of bacteremia episodes with an identified organism identified in the Pediatric AIDS Clinical Trials Group, 69% were pneumococcal.[63] In this study there was a low incidence of *H. influenzae* probably because of vaccination. HIV-infected patients do appear to be more susceptible to *S. aureus* and pseudomonas infections. In one series of pediatric patients with AIDS, 10% of patients had gram-negative bacillary bacteremia with a risk of death that was greater than 40%.[125] *Pseudomonas* sepsis accounted for 26% of these episodes.[126] *Pseudomonas* infection is frequently associated with neutropenia, that may be a cause or effect phenomenon.[125,126]

Vasculitis

Vasculitis has been reported in patients with HIV infection, but it is not clear if HIV causes the condition or is merely an association although there are a variety of suggested mechanisms.[127-131] Many infections reported in HIV-infected patients, including herpes viruses and mycobacterium, can cause inflammation by direct infection or an immune-mediated response. The most frequently involved organs are skin, peripheral nerve or muscle, and the central nervous system (CNS).[129] Several cases of polyarteritis nodosa have been reported.[129] When vasculitis is noted, an infectious agent should be sought. The authors have observed an increased incidence of arterial catheter complications among HIV-infected children and it is probably wise to exercise caution in the use of central venous and arterial catheters in HIV-infected children.

Myocardial Dysfunction

Cardiac dysfunction develops in 19% to 25% of HIV-infected children and is the presenting sign in a minority of children.[132,133] About 10% of a survey population had chronic congestive heart failure, whereas another 10% had transiently decreased ventricular function.[106] Cardiac complications appear to occur more frequently in rapidly progressing patients with encephalitis and other AIDS-defining illnesses. Because tachycardia and hepatomegaly are so common in pediatric AIDS patients with fever, pulmonary infection, and anemia, a clinical diagnosis of cardiac involvement is difficult to make. Enlargement of the cardiac silhouette may not be appreciable even in patients with significant muscle hypertrophy or pericardial effusion. Given these inherent difficulties in the detection of cardiac disease, assessment of a critically ill child with AIDS should include echocardiography. When assessment is prospectively followed by echocardiography, the earliest sign of cardiac involvement is diastolic dysfunction.[133] At autopsy, aside from biventricular dilation, macroscopic evidence of cardiac dysfunction has been difficult to find in adults or children. Microscopically, in a limited number of cases, lymphocytic infiltrates are observed, but actual myocyte necrosis is rare.[134] Mild foci of lacy interstitial fibrosis may also occur.[134,135] True myocyte inflammation or myocarditis is rare in children.

HIV cardiomyopathy likely has several causes. Direct evidence of myocardial infection by HIV-1 has been documented by culture, Southern blot test, and in situ hybridization,[134,135] but it is unclear if the myocytes, that express no CD4 receptors, actually harbor HIV. Coxsackie B3 virus, CMV, adenovirus, EBV, and *Toxoplasmosis gondii* have also been identified as pathogens.[136,140] Of 32 HIV-infected children who died, 7 had evidence of CMV infection and 10 had evidence of adenovirus infection by PCR performed on myocardial tissue.[136] Selenium deficiency has been documented in severely malnourished children with AIDS whose cardiac function improved after selenium supplementation.[139] In additional case reports, ZDV is indicated as a cause of cardiac failure.[137]

In the ICU, patients with severe cardiac dysfunction respond to management of preload, increasing contractility, and afterload reduction. Endocarditis, myocardial ischemia, and other potentially treatable causes of cardiac dysfunction should be ruled out with electrocardiography and echocardiography. Pharmacological afterload reduction should be considered as first-line therapy, with digitalization and diuretic therapy as appropriate. Other than selenium supplementation there is no direct therapy available for HIV-related cardiomyopathy.[139] Agents that are associated with myocardial dysfunction, such as pentamidine, foscarnet, and dideoxyinosine (ddI), should

be avoided.[137,140] A small population of patients has been noted to have transient cardiac dysfunction manifested by tachycardia and poor peripheral perfusion despite adequate filling pressures. This has been noted during PCP infection and may be related to cytokine release. Survival data following clinically evident congestive heart failure in children undergoing HAART have not been reported.

Dysrhythmias

In a survey of 81 HIV-infected children, dysrhythmias occurred in 35%, including atrial and ventricular ectopy, ventricular tachycardia, and ventricular fibrillation.[132] A syndrome of autonomic dysfunction has been reported in adult patients with AIDS, and similar lability in blood pressure and heart rate has been noted in a number of HIV-infected children. Catecholamine surges have been described in adults. Additionally peripheral neuropathy may contribute to altered vascular regulation and a propensity for cardiac arrhythmias.

Pericardial Disease

Pericardial disease is reported in approximately 30% of HIV-infected children undergoing echocardiography or autopsy.[132,135] In five pediatric patients in whom fluid was cultured, no pathogens were identified. In 14 adult patients in whom fluid was obtained, atypical mesothelial cells were identified. One patient had lymphoma, one had histoplasmosis, and a third had CMV identified by a pericardial biopsy specimen. A pericardial effusion greater than 5 mm in diameter was detected in 5.4% of prospectively evaluated HIV-infected children, but no episodes of tamponade were reported.[134,141] Cardiac arrest due to tamponade has been reported in five adult patients with AIDS.[142]

Renal Failure

HIV nephropathy was first reported in 1983 and may often be the first manifestation of AIDS.[143-146] This complication generally arises between ages 2.5 and 4.9 years. It appears to be more prevalent in children of African or Afro-Caribbean descent. The usual presentation of renal dysfunction is severe proteinuria (>3.5 g/day) with hypoalbuminemia and anasarca. This may be associated with renal tubular acidosis. Creatinine clearance is usually normal. Proteinuria may be accompanied by hematuria. Immunoglobulins are usually elevated while complement is normal. On ultrasound, the kidneys are enlarged. Biopsy specimens show focal and segmental glomerulosclerosis.[144] The course of the disease before HAART was usually fulminant, with end-stage renal disease developing in 8 to 9 months. Effective antiretroviral therapy slows or reverses the course of HIV nephropathy.[145,146] Atypical hemolytic uremic syndrome or thrombotic microangiopathy is also described in pediatric patients with AIDS.[146,147]

Potentially nephrotoxic drugs to which the HIV-infected patient may be exposed are legion. Indinavir and tenofovir are associated with increased risk of chronic renal failure.[118,121] Pentamidine-induced renal toxicity usually occurs in the second week of therapy. Proteinuria and particularly hematuria, that may be falsely attributed to HIV nephropathy or catheter-induced trauma, are hallmarks of pentamidine toxicity. Early recognition of this complication and cessation of pentamidine are key to recovery; rechallenge with the drug will prompt early return of proteinuria and hematuria. Toxicity from sulfadiazine during the treatment of toxoplasmosis is also reported and can be reduced by hydration.[147] Amphotericin-induced nephrotoxicity is particularly problematic when the drug is used in combination with aminoglycosides. Liposomal-encapsulated amphotericin B allows for higher doses with less toxicity.

In critically ill patients with AIDS, acute tubular necrosis may be precipitated by sepsis, hypovolemia, or hypoperfusion, and as in non–HIV-infected patients, it is reversible.[146] Thus the same principles for management and support of a patient with reversible acute renal failure apply to the HIV-infected population. For patients who are seen in the ICU with end-stage renal disease due to HIV nephropathy, the indications for dialysis are the same as in other patient populations, but the decision to undertake dialysis must be made on an individual basis (see also Chapter 72). Peritonitis during ambulatory peritoneal dialysis in pediatric patients with AIDS does not occur with any apparent greater frequency than in immunocompetent patients.[149] Kidney transplant has been successful in carefully selected HIV infected patients.[146]

Abdominal Complications

Patients with AIDS have multiple gastrointestinal complaints including dysphagia, abdominal pain, and chronic diarrhea, but these are generally not important in the ICU except that they affect nutritional status.[150] Other more life-threatening complications include severe dehydration, intra-abdominal sepsis, pancreatitis, and hepatic failure (Box 93-3).

Diarrhea occurs in 40% to 60% of children with AIDS and may produce severe dehydration.[151] Worldwide, acute diarrhea is the most common cause of death in children with AIDS.[151] In underdeveloped countries where poor sanitation increases the risk of diarrheal diseases, HIV-related hypovolemic shock is a common indication for pediatric ICU admission. Copious diarrhea is suggestive of small intestine involvement, whereas tenesmus suggests infection involving the distal colon and rectum. Diffuse enterocolitis produces a secretory diarrhea with profound volume losses. Patients with AIDS may have typical infectious enteritis and enterocolitis caused by *Salmonella, Shigella, Giardia*, *Campylobacter,* and rotavirus, but may also have an atypical, more prolonged course.[150,151] The frequent use of systemic antibiotics in HIV-infected children results in *Clostridium difficile* colitis. *Mycobacterium avium intracellulare*, cryptosporidium, *Giardia*, *Isospora belli*, CMV, and adenovirus may all induce opportunistic small bowel enteropathy.[150-152] Patients with MAC, CMV, and *Candida* infection typically also have extragastrointestinal infection.[153] A nonspecific enteropathy may arise as a result of the overgrowth of normal gut flora due to the effects of local immunodeficiency and antibiotic use. It is not uncommon to find heavy growth of *C. albicans* or *Pseudomonas aeruginosa* in stool cultures.

If findings from stool culture and analysis are negative, a flexible sigmoidoscopy with a rectal biopsy should be considered in the child with rectal bleeding, tenesmus, or both. Aspiration of duodenal secretions is particularly helpful in evaluation of patients from underdeveloped countries in that the aspirate may reveal infection with *I. belli*, *Cryptosporidium parvum*, or helminthic species. Additional evaluation may be desirable, including small bowel radiography or abdominal computed tomography (CT) scanning. If results of all diagnostic studies are negative,

Box 93–1 Gastrointestinal Complications in Immunodeficient Patients

Diarrhea

Bacteria
- *Salmonella*
- *Shigella*
- *Clostridium difficile*

Fungi
- *Candida*
- *Pneumocystis*

Viruses
- Cytomegalovirus
- Herpesvirus
- Varicella-zoster
- Adenovirus
- Rotavirus

Parasites
- Cryptosporidium
- Microsporidium
- *Entamoeba histolytica*
- *Giardia intestinalis*
- *Blastocystis hominis*

Medications
- Atovaquone
- Antiretrovirals

Pancreatitis

Infections
- Cytomegalovirus
- Adenovirus

Medications
- Protease inhibitors
- Pentamidine
- Foscarnet

diarrhea may be due to HIV therapy because most antiretroviral agents are associated with diarrhea (see Box 93-1).[154]

Recovery of MAC from the blood generally indicates invasive disease, but percutaneous needle aspiration with CT guidance of enlarged intraabdominal nodes may be confirmatory.[152] Antimicrobial therapy of disseminated MAC infection before HAART was unrewarding, and disseminated MAC was rapidly fatal. Current antimicrobial therapy is a double drug regimen of clarithromycin and ethambutol with the possible addition of a third agent, including rifabutin, ciprofloxacin, or azithromycin. Prophylaxis against MAC with azithromycin is indicated in children with CD4 counts less than 75 cells/uL and in infants with counts less than 100 cells/uL.[90] In patients treated with HAART diarrhea often persists despite improvements in immunologic function. [154]

The Acute Abdomen

The evaluation and management of acute abdominal pain in HIV-infected children is complicated by their immunosuppressed state. Localized signs of infection can be masked by immunosuppression, debilitation, and previous or current use of antibiotics. In fact, a significant intra-abdominal abscess may result in minor symptoms, with unremarkable elevations in white blood cell count or temperature. Thus diagnostic imaging with abdominal CT scan is invaluable for evaluation in this population. Although morbidity after surgical intervention is somewhat higher in patients with AIDS, there is still a significant survival when such intervention is undertaken promptly.[155-158] Gastric and proximal small bowel symptoms such as pain or bleeding may arise from stress gastritis and infiltrative processes caused by viruses, particularly CMV and adenovirus, *Giardia lamblia*, tuberculosis, and lymphoma. Supportive management of these conditions is the same as that for immunocompetent patients, although the appropriate antimicrobial therapy may be different.

Pancreatitis

Pancreatitis in the AIDS population results from both the disease and its treatment.[60,159,160] Pancreatitis presents as acute or persistent midepigastric pain and/or back pain and elevation of serum amylase, lipase, and triglyceride levels. Infectious causative entities include CMV, adenovirus, mycobacterium, fungal infections, cryptococcus, herpes simplex virus (HSV), and protozoal infections such as toxoplasmosis, *Pneumocystis*, and cryptosporidium. The list of drugs known to cause pancreatitis is extensive and includes the antiretroviral agent zalcitabine and the antiprotozoal agent pentamidine. The mechanism by which drugs induce pancreatitis is unknown.

Pancreatitis often goes undiagnosed. Autopsy findings reveal significant pancreatic lesions in approximately 10% of patients with AIDS, yet pancreatic lesions are rarely recognized during life.[159] Nine (17%) of 53 children seen at one institution demonstrated pancreatitis.[160] Four of five of these carried CMV. In one of these patients CMV was cultured from pancreatic duct fluid. Six of nine had serological evidence of EBV. Five children were receiving pentamidine at the time of presentation. Maintaining a high index of suspicion for pancreatitis is important because vomiting, abdominal distension, and malabsorption are common complaints in the HIV-infected child. Evaluation of these patients should include both serum lipase and amylase determinations because parotid inflammation seen in HIV infection can cause isolated elevations of serum amylase concentrations. Abdominal ultrasound is only useful in the detection of a large edematous pancreas and in follow-up assessment for pancreatic pseudocyst.

Treatment includes bowel rest and hyperalimentation along with removal of the offending agent as in the case of drug-induced pancreatitis. In infectious pancreatitis, treatment of the underlying cause, while indicated, may not change the course of the disease.[160] Despite intervention, seven of eight reported children with pancreatitis had active or recurrent disease at the time of death. The mean survival time from onset to death was 8 months (range, 0.5 to 13 months).[160] In this patient population anatomical abnormality is rarely the cause of pancreatitis, and there is little role for surgical intervention.

Hepatobiliary Failure

The cause of hepatic failure in HIV-infected patients differs from that of other adults and is affected by the patient's degree of immunosuppression.[161] In early stages, hepatic disease is usually a result of drug toxicity or hepatotropic virus infection. Drug-induced hepatotoxicity has been reported with sulfa drugs, isoniazid, rifampin, and rifabutin.[161,162] Several

antiretroval agents can cause heptatis.[60] If HIV progresses to AIDS the liver manifests systemic involvement of opportunistic infections.[161,163] Reviews of hepatic tissue disease in HIV-infected children document that CMV and mycobacterial disease are common in children, whereas classic viral hepatitis is relatively rare.[161,164,165] As the immune system is reconstituted in response to HAART, hepatitis B can flare up.[154] Chronic hepatitis becomes clinically significant as survival increases in patients receiving HAART.[154] Cholangitis and cholecystitis are well described in adult patients with AIDS. Biliary tract infections have been attributed to CMV, adenovirus, cryptosporidium, and microsporidia.[164-166]

Liver biopsy is only indicated when mycobacterial disease is expected or jaundice is present, as most diseases can be diagnosed by serological testing or PCR.[161] Drug toxicity has no specific biopsy finding. The HIV virus itself can cause a giant cell hepatitis. Dense lymphoid infiltrates, similar to those in the lung in LIP, are also described. Adenovirus, CMV, and HSV and other oppurtunistic infections can cause acute jaundice and hepatitis with fever.[163,165-169] Hepatitis B and C can occur in patients with AIDS.[154,170] In certain established diagnoses, biopsy may be indicated to assess disease progression and response to therapy.[161]

Because drug-induced hepatotoxicity may be reversible upon drug withdrawal, aggressive support for this cause of hepatic failure is indicated. Hepatitis B can be treated with the antiretroviral agents lamivudine in combination with the antiretrovirals tenofovir or entecovir.[154] Hepatitis C can be treated with ribavirin and interferon.[154] In most cases HAART is suspended during hepatitis C therapy.[154,170] Liver transplantation can be successful with proper patient selection.[171]

Hematologic Complications

Hematologic abnormalities are common in patients with HIV/AIDS. Isolated thrombocytopenia is likely mediated by antiplatelet antibodies and should prompt HIV testing.[172-174] As with other forms of antibody-mediated thrombocytopenia, this may respond to immunoglobulin, steroids or subtotal splenectomy.[173,175] Neutropenia may be antibody mediated, drug related, or secondary to sepsis. Granulocyte colony growth factors have reduced the incidence of sepsis in this setting.[176]

Anemia occurs in 20% to 73% of HIV-infected children and is an independent predictor of death from AIDS.[177,178] Most HIV-infected patients have normal erythrocyte size and shape but inadequate reticulocytosis. Iron deficiency, possibly related to malabsorption, accounts for 10% to 45% of anemia in HIV-infected children. Nutritional deficiencies of folate and vitamin B_{12} may also contribute to anemia. Many medications that are given to patients with AIDS cause anemia, including ZDV, acyclovir, TMP-SMX, and pentamidine. Anemia of chronic disease, mediated by inflammatory cytokines, likely accounts for additional cases. Rarely, antierythrocyte and antierythropoietin antibodies have been reported in patients with AIDS.[179] Pediatric patients with AIDS who have renal failure may lack erythropoietin.

Malignancies

Malignancies account for 2% of AIDS-defining illnesses in pediatric patients.[180] Of 162 pediatric AIDS patients with malignancy reported to the Centers for Disease Control and Prevention, 134 had non-Hodgkin lymphoma and 28 had Kaposi sarcoma.[180] Lymphomas are generally of the B-cell type and often arise in the CNS. Other reported conditions include B-cell leukemia, hepatoblastoma, leiomyomas or leiomyosarcomas, and cervical carcinoma.[180] In a cohort study of perinatally HIV-infected children, the cancer rate was nearly four times higher in children treated with HAART for less than 2 years when compared to those treated for more than 2 years.[181] The rates of childhood malignancy were compared between this cohort and the Surveillance, Epidemiology and End Result (SEER) Cancer Statistics Review. The higher rate in perinatally HIV-infected children was related to lymphomas. The development of cancer was 3 times more likely in those with low CD4+ T cell counts.

Several of these malignancies are associated with chronic viral infection. EBV DNA has been identified in most CNS tumors and in soft tissue tumors such as leiomyosarcomas or rhabdomyosarcomas reported in patients with AIDS. Infection with EBV is also associated with a polyclonal, polymorphic B-cell lymphoproliferative disorder similar to that seen in transplant patients receiving immunosuppression. In addition, in body cavity–based lymphoma, infection with human herpes virus type 8 (HHV-8) has been implicated. Human papilloma virus is associated with invasive cervical cancer. Hepatitis B infection is associated with the development of hepatocellular carcinoma.[154] Kaposi sarcoma is a malignancy associated with chronic infection with HHV-8 and unique to acquired immunodeficiencies seen in transplant and AIDS patients.[181] Its true incidence in the pediatric AIDS population is unknown because many tumors are intraabdominal and intrathoracic; thus, they are only noted on autopsy. Cutaneous manifestations are uncommon in the pediatric age group.

Neurologic Complications

CNS involvement occurs in 20% to 60% of HIV-infected children.[182] The clinical manifestations of CNS involvement are many, but generally it is the comatose patient with AIDS in the ICU who is a diagnostic dilemma. In this situation, treatable conditions must be ruled out before the diagnosis of AIDS encephalopathy can be made. Acute neurological manifestations include seizure disorders, cerebral vascular accidents, CNS lymphoma, and aseptic meningitis. Evaluation of these patients generally requires a series of biochemical and radiological tests. Biochemical tests can reveal hyponatremia, hypoglycemia, and hyperammonemia, which can arise from severe malnutrition, hepatic dysfunction, and pancreatitis. A toxicology screen can rule out ingestion. Imaging studies such as CT and magnetic resonance imaging (MRI) can reveal mass-occupying lesions such as intracranial hemorrhage, malignancies, or calcifications consistent with infection.[183] Lumbar puncture is necessary to rule out infection and cerebral spinal fluid should be routinely cultured and investigated for specific pathogens.

Human Immunodeficiency Virus Encephalopathy

Primary HIV infection of the CNS probably occurs in 4% of HIV-infected children by the age of 12 months.[183] This entity is termed HIV encephalopathy and can generally

be divided into two types: static with developmental delay or progressive similar to AIDS dementia in adults with progressive decline in neurologic functioning.[185] Direct HIV infection of the macrophages and microglia of the CNS is thought to cause release of inflammatory neurotoxins such as TNF or platelet-activating factor. Pathologically gliosis, microglial nodules, demyelination, and multinucleate giant cells are seen. Spinal cord examination similarly shows degeneration of corticospinal tracts, which clinically present as spastic diplegia. Vacuolar myelopathy involving the lateral and posterior columns, that presents as progressive muscle wasting and sensory loss, has also been observed in children.[182,184]

Diffuse atrophy is noted on CT.[186] Bifrontal white matter abnormalities are commonly seen on MRI.[183-186] In more severe cases periventricular and centrum semiovale hypodense areas may occur. One third of infected children may show calcifications of the basal ganglia. Calcifications observed before age 10 months are more likely due to an infection other than HIV, such as toxoplasmosis or CMV.[186]

AIDS encephalopathy is a diagnosis of exclusion. Other pathogens must be ruled out. Therefore evaluation includes imaging of the brain by CT or MRI and blood and CSF studies in search of specific pathogens such as cryptococcus, mycobacterium, CMV, HSV, varicella-zoster virus, and *Treponema pallidum*. If no alternative pathogen is identified, then therapy is directed at reducing the HIV RNA viral load.[187]

Cerebrovascular Disease

Vascular complications involving the CNS in HIV-infected patients are many.[188] A cerebral vasculopathy was reported to occur in 25% of patients who underwent an autopsy. Although infarctions were first thought to be a consequence of direct HIV injury to the vascular endothelium, others now argue that the vascular injury results from other infections.[189,190] Cerebral vasculitis has been reported in CMV, HSV, neurosyphilis, and other infections of the CNS, even when they occur in non–HIV-infected patients. A hypercoagulable state associated with elevated levels of anticardiolipin antibody and antiphospholipid antibody, decreased levels of protein S, and a clinical condition similar to thrombotic thrombocytopenic purpura has also been described in association with HIV infection.[191] Although stroke is common in patients with AIDS, intracranial hemorrhage is relatively rare. Autoimmune-mediated thrombocytopenia, diffuse intravascular coagulation, and CMV infection have been reported to lead to intracranial hemorrhage in patients with AIDS.[182,188,192,193]

Central Nervous System Malignancy

High-grade B-cell lymphoma is found in 4% of HIV-infected children and is the most common mass lesion found in the CNS of children with AIDS.[181,182] It generally presents between ages 5 and 10 years. Lymphoma can be distinguished from toxoplasmosis by increased uptake of tracer on single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging. It most frequently arises in periventricular white matter and is associated with EBV infection. Metastatic lymphoma can also occur.

Infections of the Central Nervous System

CNS infection by usual and opportunistic organisms in childhood AIDS accounts for only 13% of neurologic complications.[194-196] Primary CNS infections in HIV-infected children are caused by the usual etiologic bacterial organisms and *M. tuberculosis*. The usual presenting signs and symptoms are seen. Opportunistic infections such as CMV and aspergillosis are frequently observed at autopsy and generally result from disseminated disease.[194] Reactivated infections such as toxoplasmosis, herpes zoster, and progressive multifocal leukoencephalopathy caused by Jacob-Creutzfeldt virus infection also occur but are rare when compared with those in the adult population.[182,196]

The protozoal infection toxoplasmic encephalitis occurs in 30% of adult patients with AIDS but is generally seen in only older children. The incidence of maternal-fetal transmission does not appear to be affected by maternal HIV infection. Combination therapy with sulfadiazine and pyrimethamine is generally effective if initiated early. Clindamycin is an appropriate alternative in patients with sulfa allergy.[197] Corticosteroids are sometimes used in addition to first-line therapy to reduce edema. Relapse is common after treatment is stopped and maintenance therapy is necessary. Primary prophylaxis is offered to adults with serological findings that are positive for toxoplasma and a CD4 count of less than 200.

Progressive multifocal leukoencephalopathy presents with ataxia, aphasia, weakness, and lethargy.[194,198] CT may be relatively unremarkable with one or two nonenhancing hypodense areas of demyelination generally in subcortical white matter. MRI is more sensitive than CT for detection of these lesions. Presumptive diagnosis can be confirmed by stereotactic biopsy and identification of virus by DNA probes. There is no treatment for this condition, and death usually results from apnea.

Although not considered a reactivated infection, cryptococcal meningitis is typically seen in older children.[182,196] Cryptococcus spreads via the bloodstream to the CNS. Classic presentation includes fever, headache, and preceding alterations in mental status. Focal signs and meningeal signs are minimal. CSF counts may be normal, although intracranial pressure (ICP) is typically elevated. CT findings are nonspecific.

Treatment of coma in the HIV-positive patient is directed at the underlying cause. Supportive care follows the principles of therapy for all comatose patients, including airway protection, control of ICP where appropriate, and nutritional support. Specific therapy for the underlying condition must be applied. In situations in which no explanation for an acute neurologic deterioration is readily available, we have initiated antiviral therapy with ganciclovir, acyclovir, or both and awaited clinical improvement. This decision was based on evidence that CMV coinfection may be responsible for neurologic deterioration.[190,196] Some improvement has been reported in patients with HIV encephalopathy who were treated with ZDV or ganciclovir therapy, but the waxing and waning nature of the condition even without therapy makes any intervention difficult to evaluate.

Ethical Issues

The ethical issues surrounding the care of children with HIV infection are complex. The history of respiratory failure due to PCP pneumonia in HIV-infected patients provides a vignette that shows many of the dilemmas surrounding the care of

patients with AIDS. When the death rate was first reported as greater than 90% for these patients, many physicians refused to institute mechanical ventilation for this condition. Meanwhile, other physicians who would not concede that mechanical ventilation was hopeless eventually reported that the death rate for PCP-related respiratory failure was possibly only 50%, thereby stressing that such therapy was not futile. Physicians who were willing to try new therapies for PCP subsequently reported that the death rate could be reduced to 10% if corticosteroids were given. This story confirms that it is impossible to determine a therapy's efficacy at the outset of an individual patient's illness and a refusal to intervene only perpetuates the myth of futility. Only by continuing to care for these patients did physicians increase their clinical skills and obtain an opportunity to ultimately improve the survival of these patients.

In wealthy countries there is little doubt that children with HIV infections can be offered intensive care unless the admission diagnosis carries a grim prognosis. In developing countries the situation is much more complex. Many countries with high incidence of pediatric HIV infection simply don't have intensive care facilities for children or even adults.[199,200] Those countries with intensive for care for children may deny PICU care on the basis of ethical resource allocation.[201] The provision of invasive ventilation to HIV-infected children with severe pneumonia may not be successful without access to antiretroviral therapy.[202] Even if short-term patient outcomes improve, HIV infected children may be denied care based on long-term prognosis or resource utilization.[83]

Occupational Human Immunodeficiency Virus Exposure

Serious exposure to HIV in the health care setting is most likely to occur in the emergency department or ICU. The risk of exposure is 0.3% after a percutaneous exposure, and 0.09% after blood or body fluid contact with non-intact skin or mucous membrane. Risk assessment is based on the viral load, the volume of exposure, the type of exposure and the possibility of drug resistance.[171] Treatment recommendations of two versus three medications are based on the degree of risk. Most facilities have a contact person and procedure to begin prophylaxis within 2 hours.

Summary

A critically ill child with a life-threatening infection or trauma should be presumed to be immunodeficient. The approach to such patients requires selective surveillance and a low threshold for empiric therapy. Through experience, patterns of infections characteristic of specific immunodeficient states can be recognized, but the unusual presentation is always possible. In the future, immune stimulants may also be part of the physician's armamentarium, in addition to antimicrobial therapy.

References are available online at http://www.expertconsult.com.

Bacterial Infection, Antimicrobial Use, and Antibiotic-Resistant Organisms in the Pediatric Intensive Care Unit

John S. Bradley, Christopher R. Cannavino, Deborah E. Franzon, and Susan Duthie

PEARLS

- Delays in initiation of treatment are associated with worse outcomes. Early aggressive empiric therapy with broad-spectrum antibiotics will obtain the best clinical and microbiologic outcomes.
- The basic mechanisms of resistance include (1) alteration of the antibiotic structure by bacterial enzymes, (2) alteration of the antibiotic's target site within the pathogen, (3) extrusion of the antibiotic from the organism by efflux pumps, and (4) changes in the cell wall that prevent movement of the antibiotic into the organism.
- The prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* has increased over the past decade.
- Antimicrobial stewardship programs that include implementing strategies that reduce unnecessary antimicrobial use, optimizing dose and duration, and minimizing adverse affects of antimicrobials can be cost-effective programs that address resistance in the intensive care unit setting.

Because of the severity of illness of children in the pediatric intensive care unit (PICU), there is little room for error in selecting the appropriate agent or combination of agents to treat bacterial infections. Antibiotic resistance has been increasing for both community-acquired pathogens and nosocomial pathogens, which has madethe task of antibiotic selection increasingly difficult. Each PICU has access to the susceptibility patterns of both community-acquired and nosocomial pathogens from the institution's microbiology laboratory, which tracks antibiotic resistance of isolated pathogens and distributes these data within the hospital as the antibiogram. These data can provide the clinician with the percentage of each pathogen that is susceptible to each antibiotic.

It is important to treat infections aggressively to obtain the best clinical and microbiologic outcomes. Judicious use of antibiotics is also important to reduce antibiotic pressure on pathogens and reduce the creation of antibiotic resistance. This chapter reviews the most clinically important classes of antibiotics, including those currently under investigation and not approved by the U.S. Food and Drug Administration (FDA) for use in children. Many textbooks about infectious diseases have excellent in-depth reviews of antibiotic characteristics,[1-3] and an annually updated review of all available, the FDA-approved document published by the American Society of Health-System Pharmacists.[4] Mechanisms of antibiotic resistance are reviewed, as is antibiotic therapy designed to meet the challenge of currently isolated antibiotic-resistant organisms. Tissue penetration characteristics and dosing of the antibiotic are critical; pharmacodynamic characteristics of different classes of antibiotics against different types of pathogens often help determine the dosing regimen required for microbiologic and clinical cure.[5,6] Inadequate dosing of antibiotics may actually facilitate the development of antibiotic resistance.[7] Timing of the first dose of antibiotics is also critical, and delay may increase morbidity and mortality.[8-10]

Antibiotic Classes

β-Lactam Antibiotics

β-Lactam antibiotics are a diverse group of antibiotics. The β-lactam ring that characterizes these compounds is usually attached to a ring structure that defines the class of antibiotic agents as penicillins, cephalosporins, carbapenems, or monobactams (Figure 94-1). The β-lactam structure is thought to interfere with bacterial cell wall synthesis and repair by preventing transpeptidation and transglycosylation of the pentapeptide precursors in the formation of peptidoglycan in the creation of the cell wall.[11] The target transpeptidase enzymes, also known as *penicillin-binding proteins* (PBPs), are vital for creating cell wall integrity to maintain the osmotic gradient between the organism and the external environment. The PBPs carried by different bacterial species have different

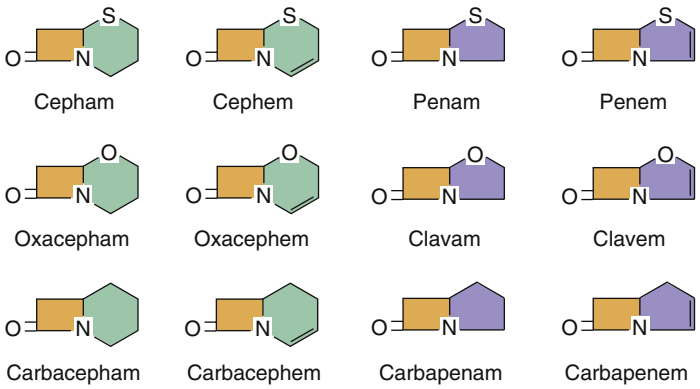

Figure 94–1. Structures of β-lactam antibiotics.

structures, leading to differences in the binding affinity for various β-lactam agents. Each organism may actually produce several PBPs. As a class of antibiotics, β-lactam are bactericidal at concentrations up to 2 to 4 times the minimum inhibitory concentration (MIC) of the agent.

Penicillins

Penicillins were the first agents of the β-lactam class to be developed and can be divided into groups that are based largely on spectrum of activity and chemistry: the natural penicillins (penicillin G, penicillin V), the aminopenicillins (ampicillin and amoxicillin), the penicillinase-resistant penicillins (methicillin, oxacillin, nafcillin), and the extended-spectrum penicillins (carbenicillin, mezlocillin, ticarcillin, piperacillin). Penicillin G was discovered by Alexander Fleming more than a half century ago and is primarily active against gram-positive organisms, both aerobic and anaerobic. The aminopenicillins are more active against gram-negative organisms such as *Escherichia coli* and *Haemophilus influenzae*. Penicillinase-resistant penicillins were developed to meet the challenge of the rapid development of penicillinase-mediated resistance in *Staphylococcus aureus*. These penicillinase-resistant penicillins are all active against *S. aureus*, except methicillin-resistant *S. aureus* (MRSA). They are also active against streptococci (except *Enterococcus* spp.). Nafcillin differs pharmacologically from the others in being excreted primarily by the liver rather than by the kidneys. Nafcillin displays a relative lack of nephrotoxicity compared with methicillin. Oxacillin also has a better renal safety profile than methicillin. Long-term, high-dose use of all β-lactam agents may be associated with reversible neutropenia.

The extended-spectrum penicillins all display enhanced gram-negative activity compared with the aminopenicillins. There are some variations in the activity demonstrated against *Klebsiella, Enterobacter, Serratia, Citrobacter,* and *Pseudomonas*. All the agents in this class are susceptible to the type I, chromosomal β-lactamases that are inducible or constitutively produced in strains of *Enterobacter, Serratia, Citrobacter,* and *Pseudomonas.* Exposure to the extended-spectrum β-lactams will select out strains that constitutively produce these β-lactamases. These strains are considered antibiotic resistant. Some experts think that the addition of an aminoglycoside to the β-lactam agent will prevent or retard the emergence of β-lactam resistance. In addition, the extended-spectrum penicillins are susceptible to the newly evolving plasmid-mediated extended-spectrum β-lactamases (ESBLs), which are constitutively produced by organisms that harbor them. Piperacillin and ticarcillin are currently the only available extended-spectrum penicillins in the United States and only in fixed combinations with β-lactamase inhibitors.

β-Lactam Antimicrobial plus β-Lactamase Inhibitor Combination

Timentin, (ticarcillin/clavulanate), Zosyn (piperacillin/tazobactam), and Unasyn (ampicillin/sulbactam) are all combinations of two β-lactam drugs. The first β-lactam drug, the true antibiotic, effectively binds to the target site in the bacteria and results in the death of the organism, assuming that the second β-lactam drug neutralizes the organism's β-lactamase. The second β-lactam drug has poor intrinsic activity as an antibiotic but still displays high affinity to and may bind irreversibly to and neutralize the β-lactamase enzyme the organism has produced. This agent is also known as a β-*lactamase inhibitor*. The combination adds to the spectrum of the original antibiotic when the mechanism of resistance is a β-lactamase enzyme. Not all β-lactamase inhibitors have an equal ability to inhibit all β-lactamases. Timentin and Zosyn have no significant activity against *Pseudomonas* beyond that of ticarcillin or piperacillin because their β-lactamase inhibitors do not effectively inhibit the β-lactamases of *Pseudomonas*. In general, the β-lactamase inhibitors present in the antibiotics Timentin, Zosyn, and Unasyn do not inhibit the adenosine monophosphate 3′5′ (AmpC), type 1 chromosomal β-lactamases present in *Enterobacter, Serratia*, and *Citrobacter*. They do, however, inhibit enzymes present in a number of other pathogens, including the β-lactamases often present in strains of *H. influenzae*, *Bacteroides fragilis*, and *S. aureus*.

Cephalosporins

Cephalosporins can be distinguished on the basis of activity against gram-negative pathogens and stability of the antibiotic to a number of the gram-negative β-lactamases. The cephalosporins fall roughly into five categories ("generations") on the basis of these characteristics. First-generation cephalosporins (cephalothin, cefazolin) are active against most strains of *E. coli* but are not entirely stable to the β-lactamases produced by some strains of *E. coli* and *H. influenzae*. The activity of these antibiotics against gram-positive pathogens such as *S. aureus* is close to that of oxacillin and nafcillin; however, none of the current cephalosporin antibiotics of any generation displays reasonable activity against the enterococci. Clinically relevant activity against *B. fragilis* does not exist for the first-generation

cephalosporins. The second-generation cephalosporins (cefamandole, cefuroxime) have chemically increased intrinsic activity against gram-negative organisms, including *E. coli* and *Klebsiella*. They are also more stable against the principal β-lactamases of *E. coli* and *H. influenzae*. Activity against *S. aureus* is significantly decreased compared with the first-generation cephalosporins but is sufficient to achieve clinical success in many situations and to warrant FDA approval for treatment of these organisms. A slightly different group of antibiotics, the cephamycins (cefoxitin, cefotetan), have activity against the gram-negative enteric bacilli similar to the second-generation cephalosporins but display enhanced anaerobic activity against *B. fragilis* and may play a role in the treatment of intra-abdominal infections. Their activity against *B. fragilis*, however, is inferior to metronidazole, clindamycin, or the carbapenems.The third-generation cephalosporins, cefotaxime and ceftriaxone, have enhanced stability against the most prevalent β-lactamases of *H. influenzae*, *E. coli*, and *Klebsiella* and enhanced activity against many of the enterobacteriaceae but are, unfortunately, not stable to the inducible chromosomal β-lactamases (AmpC, type I) of *Enterobacter*, *Serratia*, or *Citrobacter*. Ceftazidime, another third-generation cephalosporin, has far greater intrinsic activity against *Pseudomonas aeruginosa* than previous cephalosporins, but it too is degraded by the inducible chromosomal β-lactamases of *Enterobacter, Serratia,* and *Citrobacter*, as well as the chromosomal β-lactamases of *Pseudomonas*. None of the third-generation cephalosporins are as active against *S. aureus*. Cefepime, a fourth-generation cephalosporin, has the best overall activity against both gram-negative and gram-positive pathogens, with activity against *P. aeruginosa* equivalent to ceftazidime and activity against *S. aureus* equivalent to second-generation cephalosporins. It is also the most stable to β-lactamase degradation by all but some of the ESBL class of β-lactamases. The novel fifth-generation cephalosporins, ceftobiprole and ceftaroline, are the first β-lactam antibiotics with activity against MRSA. Ceftobiprole was recently approved by the FDA for the treatment of complicated skin and skin structure infections in adults. Ceftaroline is currently in phase III clinical development. In addition to activity against MRSA, the fifth-generation cephalosporins have a spectrum of activity similar to that of third- and fourth-generation cephalosporins. Ceftobiprole also exhibits in vitro activity against enterococci and *Pseudomonas*. Ceftaroline is not reliably active against ESBLs, whereas ceftobiprole has activity against *P. aeruginosa* similar to that of cefipime. Although still in phase III trials, ceftobiprole has potential for use as empiric monotherapy for serious infections in the ICU because it has activity against both MRSA and *P. aeurignosa*.[12]

Carbapenems

Three carbapenems, imipenem (combined with cilastin, an inhibitor of a renal tubular dehydropeptidase enzyme, to avoid nephrotoxicity), meropenem, and ertapenem are currently FDA approved in pediatric patients older than 3 for treatment of complicated skin and skin structure infections (SSI), complicated intra-abdominal infections, and meningitis. Pediatric clinical investigation of doripenem, a fourth-generation carbapenem recently FDA approved for adults, is ongoing. The carbapenems have a β-lactam ring structure that differs slightly from the penicillins and cephalosporins (see Figure 94-1), with chemical modifications to enhance activity and stability similar to those of cephalosporins. The broad antimicrobial spectrum of activity of the carbapenems is similar and includes gram-negative, gram-positive, and anaerobic organisms. Relevant gram-negative pathogens include enteric bacilli such as *E. coli*, *Klebsiella*, *Enterobacter*, and *Citrobacter* in addition to *P. aeruginosa*. They are active against gram-positive organisms including *S. aureus* and streptococci, although activity against the enterococci is substantially less than penicillin G or ampicillin. Meropenem is slightly more active against gram-negative pathogens and imipenem is slightly more active against gram-positive pathogens, although there is probably no clinical significance in these differences for most infections being treated. Although not FDA approved for the treatment of nosocomial pneumonia, meropenem has been shown to be effective in numerous clinical trials. Both agents are active against anaerobes, including β-lactamase–positive strains of *B. fragilis*. Ertapenem has a similar spectrum of activity to the other carbapenems, although intrinsic activity against *P. aeruginosa* is less than that of the other carbapenems. Nevertheless, it has a prolonged serum elimination half-life compared with the other agents, allowing for once- or twice-daily therapy compared with three or four times daily. Doripenem was recently approved for the treatment of complicated intra-abdominal and complicated urinary tract infections in adults. Its spectrum of activity is similar to the other carbapenems; however, it appears to have more potent in vitro activity against *P. aeruginosa*.

With respect to toxicity, the carbapenems are well tolerated, although imipenem displays interference with central nervous system (CNS) γ-aminobutyric acid inhibition of neuron activity and was shown to be associated with an increase in seizure activity in children treated for bacterial meningitis compared with historic controls.[14] On the basis of these observations, meropenem is the preferred carbapenem for children at risk for seizures or with CNS infections and inflammation. Meropenem is well tolerated in children. In pediatric trials, diarrhea and rash occur in less then 5%, and drug-related seizures were not observed in children with meningitis treated with meropenem.

Monobactams

Aztreonam, the only monobactam currently available, has a unique chemical structure in which the β-lactam ring is not attached to an adjacent 5- or 6-membered ring but does have chemical additions to the β-lactam ring that enhance activity and stability to β-lactamases. It displays aerobic, gram-negative activity, including activity against many strains of *P. aeruginosa*.

Aminoglycosides

Aminoglycoside antibiotics are bactericidal in a concentration-dependent fashion against a wide range of aerobic pathogens. The first antibiotic in this class, streptomycin, was isolated from *Streptomyces griseus* and was first available in 1944. Subsequently, other aminoglycosides have been isolated from fungi, and chemical modifications to enhance activity and decrease toxicity have been made to older agents. These agents inhibit protein synthesis by irreversible binding to the 30S ribosomal subunit. The gram-negative spectrum of activity is extensive, including enteric bacilli (*E. coli*, *Klebsiella, Enterobacter, Serratia*), *P. aeruginosa*, and many free-living gram-negative bacilli that may only be pathogenic for

immunocompromised children or those with trauma in which environmental contamination of deep tissues has occurred. These antibiotics have no clinically relevant anaerobic activity.

Although the first aminoglycosides exhibited substantial renal toxicity and ototoxicity, subsequent agents are significantly safer. With serum concentrations present within the therapeutic range, renal toxicity and ototoxicity are unusual. The most widely available parenteral agents are gentamicin, tobramycin, and amikacin. Because of the relatively low serum concentrations necessary to prevent toxicity and poor penetration into the spinal fluid, these agents are not used as primary therapy of CNS infections. Direct intrathecal instillation should also not be considered routinely for CNS infections because data collected during a prospective study of aminoglycosides as adjunctive therapy in neonatal gram-negative meningitis revealed higher rates of morbidity.[15] Streptomycin, the most toxic of the aminoglycosides, continues to be used infrequently in the treatment of tuberculosis, plague, and tularemia in children.

Caution should be exercised in the use of these agents in undrained abscess infections, including intraabdominal infections. The acidic and anaerobic conditions present in abscesses produce MICs against aerobic gram-negative organisms that are 10 times higher than those documented under ideal laboratory conditions.[16]

Aminoglycosides have demonstrated excellent clinical efficacy against susceptible organisms. Nevertheless, the toxicity of the antibiotics may preclude the attainment of serum and tissue concentrations that are severalfold higher than the MICs of the pathogens. Synergy between a β-lactam agent and an aminoglycoside in bacterial killing can be demonstrated against many gram-negative pathogens. For the critically ill or immunocompromised child, a combination of agents is often used to obtain the maximal antibiotic killing. In addition, some experts believe that the combination will retard the emergence of antibiotic resistance in gram-negative organisms containing inducible AmpC, chromosomal β-lactamases.

Glycopeptides

Vancomycin is currently the only available glycopeptide in the United States, although teichoplanin is available in other areas of the world and a new generation of glycopeptides is presently in clinical trials in adults. The glycopeptides are primarily active against gram-positive organisms, both aerobic and anaerobic. This class of antibiotic is cell wall active, as are the penicillins, but has a different mechanism of action in prevention of pentapeptide cross-linking in the formation of cell wall peptidoglycan.

Vancomycin is bactericidal against virtually all strains of staphylococci and against most strains of streptococci, although it is bacteriostatic against the enterococci. Resistance to vancomycin is noted to occur in strains of *Enterococcus faecium* (vancomycin-resistant enterococcus [VRE])[17] and has now been described in *S. aureus*.[18]

The tissue distribution of vancomycin is extensive, with elimination of unchanged antibiotic by the kidney. Dosage adjustment is required in renal insufficiency. Penetration into the cerebrospinal fluid (CSF) is not well studied and is erratic. Serum concentrations of approximately 40 μg/mL are thought to be necessary to achieve CSF concentrations sufficiently high enough to achieve a reliable microbiologic cure in meningitis or ventriculitis. The toxicities of vancomycin are primarily nephrotoxicity and ototoxicity. As with the aminoglycosides, close attention to serum antibiotic concentrations will avoid clinically significant toxicity.

The new generation glycopeptides, dalbavancin, telavancin, and oritavancin, are undergoing clinical trials. Telavancin, a lipoglycopeptide, was recently FDA approved in adults for the treatment of complicated skin or skin structure infections caused by gram-positive organisms.

Macrolides

Although erythromycin and related macrolides have been primarily used in the outpatient arena, they may be required in the PICU for children with severe pertussis or atypical pneumonia, or in children with extensive drug allergy precluding the use of standard anti-infective agents. The macrolides bind to the 50S ribosomal subunit of susceptible bacteria to prevent the formation of peptide chains, thereby inhibiting protein synthesis. Macrolides are primarily bacteriostatic at achievable tissue concentrations. Erythromycin is available for parenteral use as a lactobionate salt, whereas clarithromycin is only available as an oral agent. Azithromycin is composed of a 15-member ring structure and is considered an azalide. It is available in both oral and parenteral forms. In general, both clarithromycin and azithromycin are better tolerated than erythromycin because of the lack of degradation products seen with erythromycin that stimulate motilin receptors and lead to nausea, vomiting, and abdominal cramps. The macrolides have traditionally been used in the treatment of nonserious infections caused by group A streptococci, *S. aureus*, and *Streptococcus pneumoniae*. Both clarithromycin and azithromycin exhibit enhanced activity against respiratory gram-negative pathogens (e.g., *H. influenzae*). In addition, azithromycin has potential efficacy as a modulator of airway hyperresponsiveness,[19] even in the absence of overt infection,[20] that may have a role for children in the ICU with community-aquired pneumonia and exacerbation of underlying chronic lung disease or asthma.

Ketolides are a new class of antibiotics structurally similar to macrolides with enhanced bacterial ribosomal binding. Telithromycin is the first FDA-approved ketolide for treatment of community-acquired pneumonia in adults, including some multidrug-resistant strains of *S. pneumoniae* and group A streptococcus.[21] Reports of significant hepatotoxicity with telithromycin[22] use may limit further investigation in children. In addition, there is a "black box" warning for patients with myasthenia gravis.

All the macrolides demonstrate activity against *Mycoplasma pneumoniae*, *Chlamydia, Legionella,* and *Bordetella pertussis*. Macrolides are metabolized by cytochrome P450 enzymes, which cause potential drug-drug interactions (see Chapter 118). These interactions have been well documented with erythromycin and clarithromycin but appear to be absent with azithromycin. Clarithromycin and azithromycin achieve high intracellular concentrations, with demonstrated efficacy against intracellular pathogens. Clarithromycin and azithromycin also demonstrate activity against a number of nontuberculous mycobacteria.

Fluoroquinolones

This class of broad-spectrum agents has been extremely successful in adults over the past 20 years. Because of concerns regarding cartilage toxicity in weight-bearing joints of

experimental animals, however, pediatric studies were not undertaken. With the emergence of resistance to β-lactam agents in *S. pneumoniae,* increasing resistance in gram-negative pathogens, and the need for an oral agent in the treatment of *P. aeruginosa* and other resistant gram-negative pathogens, pediatric studies began in earnest in 1998. Ciprofloxacin, the first of the agents approved for use in adults, shows outstanding activity against *P. aeruginosa*, as well as many enteric bacilli causing both nosocomial infections (*E. coli*, *Klebsiella, Enterobacter, Serratia, Citrobacter*) and gastrointestinal infections (*Salmonella, Shigella, Campylobacter, Yersinia,* and *Aeromonas*). Although resistance to ciprofloxacin in *P. aeruginosa* and other bacilli has been increasing, susceptibility in pediatric inpatient units has remained reasonable. Ciprofloxacin is FDA approved in children older than 1 year for the treatment of complicated urinary tract infections, pyelonephritis, and postexposure treatment of inhalational anthrax. Subsequent chemical modifications of fluoroquinolones have resulted in a set of agents with good to excellent activity against gram-positive cocci, including group A streptococcus, *S. pneumoniae*, and *S. aureus*. These agents—levofloxacin, gatifloxacin, trovafloxacin, and moxifloxacin—are effective in both gram-positive and gram-negative infections. Successful pediatric investigations have been performed in pediatric bacterial meningitis (trovafloxacin), community-acquired pneumonia (levofloxacin), and otitis media (gatifloxacin and levofloxacin). Because of concerns for possible hepatotoxicity, trovafloxacin is used for serious infections only. After reports of an association with dysglycemia in adults, gatifloxacin is no longer being manufactured. Although case reports of possible cartilage toxicity exist, no documented case unequivocally caused by fluoroquinolones in children has been published in any prospective study.[23] A policy statement by the American Academy of Pediatrics Committee on Infectious Diseases states that "fluoroquinolone use should be restricted to situations in which there is no safe and effective alternative to treat an infection caused by multidrug-resistant bacteria or to provide oral therapy when parenteral therapy is not feasible and no other effective oral agent is available."

The mechanism of action of quinolones involves inhibition of DNA synthesis by interference with two bacterial enzymes. The activity of each specific quinolone and the rapidity of the development of resistance to the specific quinolone depend on the relative activity of the quinolone against these enzymes.[24]

Miscellaneous

Clindamycin

A member of the lincosamide family, clindamycin, as with erythromycin, inhibits the growth of bacteria by binding to the 50S subunit of the ribosome. Clindamycin is active against gram-positive organisms and many anaerobes, including most strains of *B. fragilis*. Activity against β-lactam–resistant strains of *S. pneumoniae* and *S. aureus* (MRSA) has led to increased use of clindamycin in children.[25]

In children with infection caused by strains of *S. aureus* or group A streptococcus that are suspected to produce toxin-mediated disease (e.g., toxic-shock syndrome, necrotizing fasciitis), clindamycin is often used (in conjunction with a β-lactam agent) to stop toxin production as quickly as possible. Retrospectively collected data suggest improved outcomes in patients treated with the combination.[26] Clindamycin may be used for treatment of MRSA skin infections and pneumonia; however, it is not recommended as the sole agent for critically ill patients with MRSA infections. In necrotizing infections, the addition of clindamycin to the treatment regimen may decrease the production of the Panton-Valentine leukocidin and other exotoxins.[27,28] Although diarrhea is relatively common with clindamycin (10% to 20%), *Clostridium difficile*–mediated pseudomembranous colitis occurs infrequently (approximately 0.1%) in children.

Linezolid

Linezolid is the first in a class of new antibiotics, the oxazolidinones. These antibiotics are protein synthesis inhibitors that interfere with mRNA binding at the 30S ribosome subunit. Linezolid is a bacteriostatic agent useful in the treatment of infections caused by gram-positive organisms, including MRSA and coagulase-negative staphylococci, VRE, as well as β-lactam and macrolide-resistant strains of *S. pneumoniae*. Linezolid has been studied and has received FDA approval for use in pediatric patients, including the neonatal age group. Linezolid is approved for the treatment of comminity- and hospital-acquired pneumonia, complicated and uncomplicated skin and soft tissue infections, and bacteremia caused by vancomycin-resistant organisms.

Linezolid is excreted by nonrenal mechanisms, although the oxidative metabolites are eliminated by the kidney. No dosage adjustment is recommended in renal insufficiency or in mild to moderate hepatic insufficiency. A concern that appears to have little clinical relevance in healthy children treated under controlled conditions is the drug's nonselective, reversible inhibition of monamine oxidase. Nevertheless, this drug interaction profile has potential impact on the patient in the PICU who is receiving adrenergic or serotonergic drugs. Linezolid has been reported to be associated with hematologic side effects and rarely with optic neuritis and peripheral neuropathy.

Metronidazole

A nitroimidazole derivative first available in 1957, metronidazole has remained a safe and effective antibiotic for parasitic and anaerobic bacterial infections. The primary use of metronidazole in the PICU includes infections caused by β-lactamase–positive strains of *B. fragilis* (intra-abdominal infections) and those caused by *C. difficile* (pseudomembranous colitis). Resistance to metronidazole has not been a clinical problem despite significant clinical use. Little is known about the mechanism of action. The distribution of drug in tissues is extensive, including CNS penetration. It has been a standard component of therapy for anaerobic deep tissue space infections and has been used in the treatment of anaerobic brain abscesses. It is the agent of choice (by the oral route, if possible) for the therapy of *C. difficile* colitis. It is metabolized by hepatic mechanisms and eliminated by renal pathways; therefore some dosing adjustments are required in patients with hepatic insufficiency. Less is known about dosing adjustments required in renal insufficiency.

Colistin

With antibiotic resistance increasing dramatically in gram-negative pathogens, colistin has returned to clinical use and now represents therapy of last resort for organisms resistant to all other available antibiotic therapy.[29]

Colistin (colistimethate), or polymixin E, has broad-spectrum bactericidal activity against gram-negative organisms by acting as a cationic detergent, destroying the bacterial cytoplasmic membrane. This agent may have a role in treatment of infections caused by gram-negative pathogens (e.g., *P. aeruginosa*, *Acinetobacter, Enterobacter, Klebsiella*) that are resistant to all other agents. Colistin has no activity against gram-positive organisms or against *B. fragilis*. The renal toxicity may manifest as decreased urine output, increasing blood urea nitrogen and creatinine, proteinuria, hematuria, and acute tubular necrosis. Peripheral neuropathy, confusion, coma, and seizures may occur. The drug is renally eliminated, and dosage adjustment is required with renal insufficiency. Current adult data suggests less toxicity than originally reported. Limited data in pediatric burn and critical care patients also suggest colistin is effective and safe for multidrug-resistant gram-negative infections.[30,31] In addition, aoerosolized colistin has been used as an adjunctive or monotherapy for gram-negative pulmonary infections. Clinically significant bronchospasm may occur.

Tigecycline

Tigecycline is the first in a new class of antibiotics, the glycylcyclines. Tigecycline inhibits protein synthesis and is generally considered a bacteriostatic agent. It is a derivative of minocycline, although not classified as a tetracycline. It has broad-spectrum antibacterial activity against gram-positive and gram-negative aerobes and anaerobes, including MRSA and multidrug-resistant gram-negative bacteria. It is not effective against *Pseudomonas, Provedentia,* and *Proteus* species. Tigecycline is approved for use in adult patients with complicated skin and SSIs, complicated intraabdominal infections, and community-acquired pneumonia. It is not approved for the treatment on hospital-acquired pneumonia, having demonstrating inferior efficacy in a study of ventilator-associated pneumonia. Tigecycline is mainly excreted unchanged into bile, with only 10% to 15% excreted unchanged in the urine. No dosage adjustment is necessary with renal insufficiency. Dose adjustment is necessary for patients with severe hepatic impairment.

Anaphylaxis and anaphylactoid reactions in patients allergic to tetracyclines have been reported. Similar to tetracyclines, permanent discoloration of teeth when used in patients younger than 8 years can occur. The role of tigecycline in the pediatric population has yet to be defined.

Daptomycin

Daptomycin belongs to a new class of antibiotics, the lipopeptides. Daptomycin disrupts the cell membrane and is rapidly bacteriocidal. It has a broad range of activity against all gram-positive bacteria including methicillin, vancomycin, and linezolid resistant organisms. It should not be used to treat pulmonary infections because surfactant inhibits its activity. Daptomycin is currently approved for use in adults with complicated skin and skin structure infections as well as right-sided endocarditis and staphylococcal bacteremia. A recent review of daptomycin therapy in invasive gram-positive infections in children showed its addition to the treatment regimen resulted in bacteriologic cure in six of seven patients with persistent bacteremia and was well tolerated.[32]

Daptomycin is excreted by the kidney and dosage adjustment must be made with renal insufficiency. The primary toxicity seen is a dose-dependent, reversible myopathy that can be monitored by elevation in serum creatinine phosphokinase.

Antibiotic Resistance

In the PICU, the clinician will encounter both community-acquired and hospital-acquired infections. Community-acquired infections caused by *S. aureus* and *S. pneumoniae* are increasingly problematic because of antibiotic resistance. Nosocomial infections may be caused by antibiotic-resistant gram-positive cocci (*Staphylococcus* spp., *Enterococcus* spp.) or gram-negative bacilli (enteric bacilli, *P. aeruginosa*, *Acinetobacter* spp., and other nonfermenting gram-negative rods). Antibiotic resistance may lead to increased morbidity and mortality as well as increased health care costs.[33]

Antibiotic Resistance Mechanisms

In the ICU, antibiotic use is extensive, resulting in selective pressure for antibiotic-resistant pathogens. Antibiotic resistance is not a new phenomenon. Bacteria are capable of surviving in an environment containing antibiotics by the expression of one or more of many different potential antibiotic resistance mechanisms. The basic mechanisms of resistance can be divided into two broad categories.[34] The first is by accumulation of multiple genes, each coding for resistance, that occur typically on resistance (R) plasmids and include (1) alteration of the antibiotic structure by bacterial enzymes, (2) alteration of the antibiotic's target site within the pathogen (by mutation at the binding site or enzymatic alterations of the binding site), or (3) changes in the cell wall that prevent movement of the antibiotic into the organism. The second basic mechanism may occur by extrusion of the antibiotic from within the organism by efflux pumps. Although community-acquired pathogens most often express only one mechanism of resistance, nosocomial pathogens may express many of these mechanisms simultaneously, and the result is a high degree of antibiotic resistance. In addition, the regulation of resistance gene expression may be altered to allow increased production of the gene product that leads to resistance.

Genes encoding antibiotic resistance may be shared between organisms within a species or between species. The transfer of antibiotic resistance genes by plasmids is a common method by which resistance is shared between bacteria. The description of mobile genetic elements helps explain the rapid development and spread of antibiotic resistance within the pathogens responsible for nosocomial infections.[35] Antibiotic resistance gene cassettes have the ability to assemble on integrons, that in turn may be associated with transposons, that are capable of "jumping" from plasmids to chromosomes, or vice versa, and from one segment of nucleic acid to another.[36] Antibiotic resistant mutants normally exist at low frequencies in any given population of bacteria. Antibiotic exposure is often the selection pressure allowing these otherwise silent mutants to achieve significant numbers, leading to treatment failure.

The clinical expression of antibiotic resistance may involve several different mechanisms operating simultaneously within a pathogen, with each mechanism expressed to a different degree on the basis of the regulation of resistance at a molecular level. For example, an organism with a weak β-lactamase that appears susceptible to an antibiotic in vitro may acquire an efflux pump, may develop porin deficiency, or both.

Either of these additional mechanisms will lead to a much lower concentration of antibiotic intracellularly, allowing the weak β-lactamase the opportunity to degrade the antibiotic before significant cell injury can occur. Most often, when a laboratory tests for susceptibility of a pathogen to an antibiotic, the sum of all resistance mechanisms (except those that may require induction) leads to an in vitro determination of susceptibility that the clinician must use to determine the best agent(s) for treatment.

Antibiotic Resistance and Infections in the Pediatric Intensive Care Unit

Current clinical challenges relate to pathogens that display newer resistance patterns. The ESBL-producing gram-negative pathogens are resistant to extended-spectrum penicillins, third-generation and some fourth-generation cephalosporins, with a proportion of these organisms also demonstrating decreased susceptibility to aminoglycosides, carbapenems, and fluoroquinolones. Some of these organisms are susceptible to β-lactam/β-lactamase inhibitor combinations. Outbreaks caused by ESBL-producing *Klebsiella* and *E. coli* have been widely reported.[51] Outbreaks by enteric gram-negative bacilli that carry chromosomal AmpC β-lactamases (present in *Enterobacter, Serratia,* and *Citrobacter*) have been occurring for several years and continue to present challenges.[52] *Acinetobacter baumannii* has caused recent reported outbreaks, primarily from Asia and Europe. The most critical aspect of *Acinetobacter* for the clinician is the ability of the organism to acquire resistance to all classes of antibiotics. *P. aeruginosa* has always been a nosocomial problem in neonatal ICUs and PICUs.[53] The nonfermenting gram-negative bacteria, including *Stenotrophomonas, Comamonas, Chryseobacteria* spp. (previously known as *strains of Flavobacteria*), and *Acinetobacter* spp. may also cause antibiotic-resistant organism infections, particularly in the immunocompromised child.

Community-acquired MRSA is increasingly a significant pathogen in children.[54] VRE strains have been reported in pediatric hospitals, particularly in neonatal ICUs, in oncology wards, and in patients with gastrointestinal disease.[17,55]

An Approach to Therapy in the Pediatric Intensive Care Unit

General Considerations for Antibiotic Therapy

After an infection is suspected on the basis of the clinical, laboratory, and imaging characteristics of the child, appropriate cultures should be obtained. Broad-spectrum antibiotics should be administered empirically, according to the local susceptibility patterns. Data suggest that using active antibiotics in the appropriate dose without delay decreases morbidity and mortality, the overall costs of treating the infection, and the emergence of resistance. The relative activity of antimicrobial agents against gram-negative (Table 94-1) and gram-positive pathogens (Table 94-2) is provided, although clinicians should consult the local antibiogram. Published data on resistance patterns come from a variety of sources. Each collection of isolates on which resistance is reported may include information for different geographic regions, different population groups (mostly adult based), different patient comorbidities, different tissue sites of infection, and different previous antibiotic exposures.[56-58] Because few published data collections have specific information on children, it is critical that the conclusions reached in these reports be taken with caution when they are applied to pediatric patients.

On the basis of the overall clinical assessment, supported by laboratory and imaging data and the response to empiric therapy, the physician needs to decide whether to continue therapy for a complete treatment course or to stop the antibiotics if data do not support an infection as the cause of the child's clinical state. Optimal duration of antibiotic therapy for infections in the PICU is poorly defined. Monitoring serum inflammatory markers such as procalcitonin may allow optimization of both the antibiotic regimen and duration of treatment.[59]

When culture results are available, antibiotic choice can be tailored to a more narrow spectrum for completion of therapy. If a child has a multidrug-resistant infection, the risk-benefit analysis may well favor the use of an antibiotic that does not have a favorable safety profile if no other alternative exists.

Antibiotic Therapy for Specific Pathogens

MRSA is a frequently isolated nosocomial and community-acquired pathogen in PICUs. Concern about the rate of hospital-acquired MRSA infection has prompted implementation of mandatory screening and reporting in many areas.[60] Almost 60% of catheter-related blood stream infections in the PICU are caused by gram-positive bacteria.[61] Vancomycin has been considered to be a mainstay of treatment for serious staphylococcal infections. Because of a growing concern for treatment failures, and increasing MICs to vancomycin, this tenet is being questioned. Some data in the adult population suggest that the use of high-dose vancomycin (target serum concentration/minimum inhibitory concentration of ≥400 μg/hr/mL) is associated with favorable clinical outcomes. Few pediatric clinical trials have looked at the question of whether alternative antibiotics are superior to vancomycin for MRSA. A pediatric study compared vancomycin to linezolid for the treatment of nosocomial pneumonia, bacteremia, or skin and soft tissue infections; the cure rates were similar.[62] Other newer agents, including daptomycin, tigecycline, and ceftobiprole, are available. Further study is needed to evaluate the effects of combination therapy for MRSA. Nonetheless, the addition of gentamicin or rifampin should be considered for severe infections, such as endocarditis. As previously noted, the addition of clindamycin to the treatment regimen may decrease the production of the Panton-Valentine leukocidin and other exotoxins.

Vancomycin-intermediately susceptible *S. aureus* and vancomycin-resistant *S. aureus* infections are rare in children. Treatment options include linezolid or alternative agents not approved in children (e.g., daptomycin, tigecycline, ceftobiprole, telavancin). In vitro susceptibility testing should guide definitive therapy.

The incidence of vancomycin resistant enterococcal infections is increasing and has been reported to be as high as 75% for *Enterococcus faecium* in adult ICUs. Linezolid is a mainstay of treatment; however, resistance to linezolid has been reported. Daptomycin and tigecycline both have excellent activity against VRE, although there is limited pediatric experience to date. A review of pediatric patients with multidrug–resistant gram-positive infection showed that the addition

Table 94–1 Antibiotic Activity for Gram-Negative Pathogens (0 to +++++)

Organism	Ticarcillin-Clavulanate	Piperacillin-Tazobactam	Ceftazidime	Ceftriaxone	Cefepime	Tobramycin	Ciprofloxacin	Meropenem
E. coli	++++	++++	++++	++++	++++	++++	++++	+++++
Klebsiella spp.	++++	++++	++++	++++	++++	++++	++++	+++++
Enterobacter spp.	+++	+++	++++	++++	++	+++	++++	+++++
Pseudomonas aeruginosa†	+++	+	++++	++++	+++	++++	+++	++++
Acinetobacter spp.*	++	++	+++	+++	+++	++	++	++++
Stenotrophomonas†	+++	+	++	+	+++	++	++	+

Susceptibility data are averaged,[44-46,48,49] with local hospital data potentially much different than these values.
*Colistin may be effective in vitro against organisms resistant to all available agents, with limited data on efficacy and significant toxicities.[21]
†Trimethoprim-sulfamethoxazole is the most active antibiotic against *Stenotrophomonas* in vitro.

Table 94–2 Antibiotic Activity for Gram-Positive Pathogens (0 to +++++)

Organism	Ampicillin	Oxacillin	Cefazolin	Vancomycin	Linezolid
Methicillin-susceptible *Staphylococcus* spp. (*Staphylococcus aureus* or coagulase-negative staphylococci)	0	+++++	+++++	+++++	++++
Methicillin-resistant *Staphylococcus* spp.	0	0	0	+++++	++++
*Enterococcus faecalis**	++++	0	0	++++	++++
*Enterococcus faecium**	++	0	0	++++	++++

Susceptibility data are averaged,[40,44,50] with local hospital data potentially much different than these values.
*For vancomycin-susceptible strains.

of daptomycin to the treatment regimen resulted in clinical improvement in the majority of patients, and in six of seven patients with persistent bacteremia it resulted in bacteriologic cure.[63]

Antibiotic resistance is increasing in gram-negative organisms. These organisms include extended-spectrum β-lactamase producing enteric gram-negative bacteria (*Enterobacter, Serratia*, and *Citrobacter*) and multidrug–resistant *Pseudomonas, Stenotrophomonas*, and *Acinetobacter*. Treatment for patients potentially infected with these organisms should be guided by local resistance patterns and antibiograms. For nonresistant *P. aeruginosa*, ceftazidime (or an extended-spectrum penicillin) and an aminoglycoside (tobramycin or amikacin) represent effective therapy to achieve synergy and to retard the development of β-lactam resistance. Alternatives for resistant organisms include piperacillin/tazobactam, meropenem or imipenem (with or without an added aminoglycoside), or a fluoroquinolone such as ciprofloxacin if resistance is present for β-lactams and aminoglycosides. Extended- or continuous-infusion dosing strategies with β-lactams such as Zosyn, cefepime, or meropenem for treatment of susceptible *Pseudomonas* strains in critically ill patients optimizes bactericidal exposure[64] and have been associated with improved outcomes.[65] Colistin is also an option for multidrug–resistant gram-negative infections.

S. pneumoniae has developed increasing resistance to β-lactam antibiotics, macrolides, and trimethoprim-sulfamethoxazole. For children with suspected pneumococcal meningitis or other life-threatening pneumococcal infections, the addition of vancomycin to either ceftriaxone or cefotaxime has been the standard of care until susceptibility data are available and therapy can be narrowed if appropriate. Other options for therapy of non-CNS infections caused by resistant strains include a newer generation fluoroquinolone or linezolid.

Antimicrobial Stewardship

Antibiotic resistance is a challenge in the ICU setting, where there is a constant struggle to maintain balance between appropriate treatment of known life-threatening infection and broad empiric coverage of possible life-threatening infection. Principles have been established and stewardship guidelines for optimizing antimicrobial therapy have been published by a number of organizations, including the Infectious Diseases Society of America, the Centers for Disease Control and Prevention, and the World Health Organization. It is essential for hospitals to implement oversight and accountability over antimicrobial use as a matter of patient safety. Two broad interventional strategies for antimicrobial stewardship programs (ASPs) exist. One is the prospective audit and feedback program whereby ongoing review of antibiotic utilization and recommendations for adjustments are made to providers. A second strategy uses preauthorization in which antimicrobials are restricted by the intstitution and must be justified and approved at the time of use. Many ASPs are a blend of both strategies with an integration of supplemental programs such as formulary interventions, dose optimization, educational efforts, computer-assisted decision suppport, and adaptation of local published guidelines.[66]

With the move toward computerized provider order entry as the standard of care, there are ways to leverage computerized decision support for appropriate antimicrobial selection based on diagnosis and local susceptibility profiles and dose optimization integrating patient characteristics such as renal function, allergies, and potential drug interactions while preserving clinical judgment and physician autonomy.

Ideally, outcomes should be measured such as antimicrobial consumption (defined daily dose) or antimicrobial days of therapy to assess safety and cost effectiveness of ASPs. The ICU is an ideal environment for implementation of antimicrobial stewardship because of the intense use of antimicrobials and the existence of significant drug resistance.

Summary

As medical care becomes more sophisticated and children are hospitalized for longer periods, the risk of development of complicated infections caused by multi-drug–resistant pathogens increases. The physician is constantly being challenged to deliver effective antibiotic therapy, while at the same time preventing the selection of antibiotic resistance. Knowledge of the pathogens most likely to be present and the potential resistance mechanisms in these organisms is important in selecting empiric antibiotic therapy. An appropriate collection of cultures to obtain susceptibility information on the pathogens is crucial to optimize subsequent therapy and minimize antibiotic resistance.

References are available online at http://www.expertconsult.com.

VI Chapter 95

Life-Threatening Viral Diseases and Their Treatment

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PEARLS

- Obtain serum to store for future serologic testing when viral pathogens are considered as the potential cause of a critical illness.
- Diagnostic sensitivity is generally enhanced when samples for viral culture and staining are sent as early as possible in the course of illness.
- Samples that are obtained for fluorescent antibody, whether for a herpesvirus or a respiratory pathogen, should contain adequate cells.
- Initiate empiric treatment with acyclovir rapidly when herpes simplex virus encephalitis or neonatal disease is suspected.
- Rapid antigen and fluorescent antibody tests are potentially unreliable for new pandemic viruses such as novel influenza A (H1N1); molecular testing and empiric treatment for patients at elevated risk of influenza complications may be warranted.
- Initiate appropriate infection control precautions early to prevent spread of infection to staff and other patients when viral pathogens are suspected.

Viral infections are a frequent cause of disease in individuals of all ages. In general, the spectrum of illness is varied; however, young children and those with suppressed or deficient immune systems are at higher risk of having severe disease. This chapter covers viral causes of entities commonly seen in the intensive care unit: myocarditis, hepatitis, pneumonitis, and meningitis/encephalitis. The content is focused on cause, diagnosis, and treatment, in an attempt to provide the reader with guidance for the initial management of patients with serious viral diseases in terms of diagnosis and specific antiviral therapy.

Myocarditis

Background

Although many infectious and noninfectious causes have been identified, viruses account for most cases of myocarditis.[1] The spectrum of disease ranges from asymptomatic, with only minimal changes on the electrocardiogram, to fulminant, with rapid onset of severe disease. Likewise, myocardial involvement may be focal or diffuse.[2] Most patients have an indolent illness that may progress to dilated cardiomyopathy. Because of the varied presentations and the difficulty in the establishment of a definitive diagnosis, the true incidence of myocarditis is unknown. In a large series from Sweden, 1% of myocardial biopsies from autopsies conducted over a 10-year period fulfilled the Dallas criteria[3] for myocarditis.[4]

Pathogenesis

Although the pathogenesis of viral myocarditis is not well understood, viruses appear to enter cardiac myocytes or macrophages through specific receptors and coreceptors.[5] Viral virulence is likely modified by differential coreceptor binding[6] and variations in the viral genome.[7] Myocardial damage is thought to occur at least in part as a direct result of viral infection, with active viral replication leading to myocardial necrosis.[8] Coxsackie virus protease 2A cleaves dystrophin in cultured myocytes and in infected mouse hearts. The results are impaired dystrophin function and poor myocyte contractility.[9] In addition, both humoral and cellular immune responses contribute to the pathogenesis of myocarditis,[10,11] through postinfectious autoimmune processes,[11] cytotoxic T lymphocytes, and antibody-dependent cell-mediated cytotoxicity.[12] Cytokines[13] may also cause direct myocardial injury and affect cardiac function.

Cause

The viruses most frequently associated with myocarditis are enteroviruses, particularly Coxsackie virus B, and adenoviruses (serotypes 2 and 5).[14] Many other viruses have caused myocarditis in children, including influenza A, herpes simplex virus (HSV); human immunodeficiency virus (HIV); cytomegalovirus (CMV); respiratory syncytial virus (RSV); and the mumps and measles viruses, before the widespread use of the measles-mumps-rubella (MMR) vaccine (Table 95-1). Polymerase chain reaction (PCR) of cardiac tissue from endomyocardial biopsy specimens in 34 children with a clinical diagnosis of myocarditis identified adenovirus in 44%, enterovirus in 24%, and HSV in 6%.[15] In addition to enteroviruses, adenovirus,[14] CMV, human herpesvirus 6 (HHV-6) and parvovirus B19[16] are increasingly recognized as important causes of myocarditis in adolescents and adults. Adenoviruses and enteroviruses are the viruses most frequently identified in patients with dilated cardiomyopathy.

Table 95–1 Viral Etiologies of Myocarditis, Fulminant Hepatitis, Pneumonia, Meningitis, Encephalitis, and Myelitis

	Myocarditis	Liver Failure	Pneumonia	Meningitis	Encephalitis	Myelitis
Adenovirus	XXX	X*	XX	X	X	X
Arboviruses (arthropod-borne viruses):				XX	XX	
• **Western equine encephalitis virus**				X	X	
• **Eastern equine encephalitis virus**					X	
• **St. Louis encephalitis virus**				X	X	
• **California encephalitis virus (La Crosse)**				X	X	
• **Colorado tick fever**				X	X	
• **West Nile encephalitis virus**					X	
Coronaviruses (OC43, 229E, HKU1, NL63, and SARS)			XX			
Enteroviruses	XXX	X	X	XXX	XX	XX
Hantavirus			X			
Hepatitis A		XXX				X
Hepatitis B		X				
Hepatitis C		X				
Hepatitis D		X				
Hepatitis E		X				
Herpesviruses:						
• **CMV**	X	X	XXX*		X	XX
• **EBV**	X	XX		X	X	XX
• **HSV I and II**	X	X†	X*	XX	XX	X
• **HHV-6**	X	X			X	
• **VZV**		X*	XX*	X	X	X
HIV	X				X	
HTLV					X	
Influenza A	X		XXX		X	X
Influenza B			X			
JC virus					X*	
Lymphocytic choriomeningitis virus				X	X	X
Measles	X		X		X	
Metapneumovirus			XX			
Mumps	X			X	X	X
Parechoviruses†	X	X		XXX	XXX	
Parainfluenza virus types 1, 2, 3			XXX			
Parvovirus B19‡	XX					
Rabies					X	
RSV	X		XXX			
Rhinovirus			X			
Rubella					X	X

XXX, Most frequent; XX, frequent; X, less common or rare.
*Primarily in immunocompromised hosts.
†Primarily neonates and young infants.
‡Viruses detected in endomyocardial biopsies appear to have shifted over the past few decades.[2]

Clinical Presentation

Infants with myocarditis usually have symptoms that include poor feeding, fever, irritability, and listlessness. Physical findings are consistent with congestive heart failure. Enteroviral myocarditis in infancy frequently occurs in conjunction with severe hepatitis, pneumonitis, or both and can be difficult to distinguish from bacterial sepsis.[17] The death rate may be as high as 75%. Severe dysrhythmias have been described in infants with myocardial involvement from RSV,[18] and viral myocarditis has been implicated in some cases of sudden death.[19,20] Older children and adolescents are more likely to appear for examination after a prodromal viral illness. Early symptoms include lethargy, low-grade temperature, and decreased appetite. They may have diaphoresis, dyspnea on exertion, malaise, chest pain, and palpitations. Resting tachycardia disproportionate to the amount of fever is common, and an apical systolic murmur may be heard. A subset of children and adults have fulminant myocarditis, characterized by rapid onset of symptoms, severe hemodynamic compromise, and fever.[21]

Laboratory abnormalities may include elevated white blood cell count and erythrocyte sedimentation rate.[22] Serum aspartate aminotransferase (AST) levels are often elevated,[23] as are creatinine kinase-MB levels. Cardiac troponin I may be a more sensitive measure of cardiac muscle injury in myocarditis.[24]

Electrocardiographic abnormalities are almost always present in acute myocarditis, with findings of low-voltage QRS complexes and nonspecific ST and T wave changes. Both atrial and ventricular arrhythmias may be present, including supraventricular and ventricular tachycardia, as well as conduction abnormalities. Echocardiography reveals left ventricular dysfunction, in most cases with either segmental wall motion abnormalities or global hypokinesis. Pericardial effusions are common. In one series, nondilated, thickened, and hypocontractile left ventricles (LVs) were seen in subjects with fulminant myocarditis compared with significant LV dilation and normal LV thickness in subjects with a more insidious onset. Subjects with fulminant myocarditis had more evidence of inflammation on endomyocardial biopsy and were more likely to recover ventricular function.[25] Pulmonary edema, enlarged cardiac silhouette, and prominent pulmonary vasculature may be seen on a chest radiograph. Contrast-enhanced cardiac magnetic resonance imaging (MRI) can document the location and extent of inflammation and can be used to assist in diagnosis or to guide endomyocardial biopsy [26,27]

Acute Liver Failure

Background

Acute liver failure (ALF) is a rare condition, which prior to the availability of orthotopic liver transplantation, carried a mortality of 70% to 80% (see Chapter 88). Early studies of ALF in children used the adult definition that required rapid development of severe hepatic dysfunction with the development of hepatic encephalopathy within 8 weeks of clinical jaundice in a person without a prior history of liver disease. However, due to the difficulty in assessing encephalopathy in young children and the recognition that terminal liver failure can occur in the absence of clinical encephalopathy, the Pediatric Acute Liver Failure Study (PALF) group has accepted the diagnosis of ALF in children with no history of chronic liver disease who present with biochemical evidence of acute liver injury and severe hepatic-based coagulopathy regardless of the presence or absence of hepatic encephalopathy.[28] The causes of ALF in children can be metabolic, toxic, drug-related, immune-mediated or infectious. The percentage of ALF caused by viral infections varies significantly by age group and geographic location, with infections causing only 6% of ALF in a large pediatric series from North America and Great Britain[28,29] but 50% in a series from South America.[30]

Cause

While less than 1% of infections with these viruses result in ALF, the hepatotropic viruses, hepatitis A and B, comprise the majority of cases with a definitive viral diagnosis, particularly in endemic areas.[30-34] Infection with hepatitis C rarely causes ALF; however, there are case reports of ALF with both postnatally and perinatally acquired hepatitis C in children.[28,35,36] In 2006, PALF published a report of the first 348 children presenting with ALF to the study sites throughout North America and Great Britain. Only 6% of the cases in this series had definitive viral causes, with the viruses identified being adenovirus, CMV, hepatitis A, enterovirus, HSV, Epstein-Barr virus (EBV), and hepatitis C. However, both in this series and in a later series of 703 children published by the same group, almost 50% of all the cases were indeterminate, due at least in part to lack of a complete diagnostic workup.[29] It is likely that some of these indeterminate cases were also due to undiagnosed infectious causes. Additional viruses that have been implicated in ALF include hepatitis D and E, parvovirus,[37,38] varicella-zoster virus (VZV),[39] and HHV-6.[40,41] ALF in infants is most likely to be associated with systemic illness due to enterovirus, echovirus, HSV, HHV-6, or CMV.[28,42-44] While most perinatally acquired infections with hepatitis B are asymptomatic, infants born to women with both HBsAg and anti-HBeAb appear to be at greater risk for ALF due to perinatally acquired hepatitis B.[45]

Risk factors for HSV hepatitis outside of the neonatal period include pregnancy and immune suppression.[46,47] Immune suppression is also a risk factor for CMV-, adenovirus-, and VZV-associated ALF. Hepatitis E virus (HEV) is an enterically transmitted virus that causes epidemic hepatitis in many areas of the world, particularly the Indian subcontinent and Southeast Asia.[34] ALF can also occur in severe dengue[48,49] and yellow fever infection.[48-50] HEV, dengue, and yellow fever are not endemic in Western countries.

Clinical Presentation

Symptoms of acute hepatitis include jaundice, anorexia, fatigue, nausea, and vomiting.[32,51,52] In fulminant disease, there is rapid progression to hepatic failure and encephalopathy. Physical examination may demonstrate fever, hepatosplenomegaly with liver tenderness, scleral or cutaneous icterus, and mucosal bleeding. Patients with severe vomiting may have significant dehydration. Laboratory studies include elevated hepatic enzymes (10- to 100-fold increases in AST and alanine aminotransferase), hyperbilirubinemia, prolonged prothrombin time, and elevated ammonia levels. As hepatocyte necrosis progresses, hepatic enzyme levels and

liver size may decrease. Cerebral edema is common in patients with severe encephalopathy[32,52] and renal failure is a common complication.[51,52]

Viral Pneumonia/Pneumonitis

Background

Influenza and pneumonia combined are a leading cause of death of children in developing countries and the eighth leading cause of death in the United States for patients of all ages. A greater burden of disease is present in infants, young children, and older individuals.[53] Although only 20% to 50% of community-acquired pneumonias in adults are associated with viral pathogens,[54-58] viruses account for the majority of the causes of lower respiratory infection in children. It is estimated that more than 500,000 hospitalizations occur each year in the United States for lower respiratory tract infections among children younger than 18 years old,[59,60] and an estimated 80% of these hospitalizations are attributable to viral etiologies, with the majority in children aged less than 5 years.[59,61] The peak season is from midwinter to early spring.

Cause

The etiologic agents of viral pneumonia are varied (see Table 95-1), and recent studies using PCR for diagnosis have considerably improved the ability to detect viruses. RSV is the primary cause of hospitalization for respiratory tract illness in young children, with average annual hospitalization rates in the United States of 17 per 1000 children under 6 months of age and 3 per 1000 children younger than 5 years.[62] In a recent national surveillance study, most children with RSV infection had no coexisting medical conditions or characteristics that significantly identified them as being at greater risk for severe RSV disease, except for being younger than 2 years.[62] Among children, RSV infection is the cause of 50% to 90% of hospitalizations for bronchiolitis, 5% to 40% of those for pneumonia, and 10% to 30% of those for tracheobronchitis.[63] Repeat infections are common; in the healthy host, they are localized to the upper respiratory tract. Among immunocompromised patients, RSV upper respiratory infections can progress to fatal pneumonia, with the greatest mortality risk in patients with severe lower tract disease and in those in whom treatment is significantly delayed.[64,65]

Influenza epidemics occur annually with significant morbidity and death in young children and older individuals. In a national surveillance study, an average of 0.9 per 1000 children aged 0 to 59 months were hospitalized with laboratory-confirmed influenza, with the highest rate of 4.5 per 1000 children in the 0 to 5-month age group.[66] During the four influenza seasons from 2003 to 2007, the total number of reported pediatric influenza deaths ranged from 46 to 153, with an average of 82 deaths each year.[67] Infected infants younger than 2 months may have symptoms mimicking bacterial sepsis, commonly including apnea. In children younger than 5 years, influenza can cause symptoms of laryngotracheobronchitis, whereas pneumonia occurs in 10% to 15% of those younger than 3 years. Finally, older children generally exhibit the classic flulike symptoms of fever, headache, myalgia, and malaise with upper respiratory tract symptoms. Bacterial superinfection is a common and potentially severe complication of influenza. Among immunocompromised patients, risk factors for more severe disease and progression to the lower respiratory tract include lymphopenia and infection early after hematopoietic stem cell transplant.[65, 68] With earlier antiviral treatment, progression to the lower tract and mortality have been markedly reduced.

In 2009, the emergence of a pandemic strain of influenza A, termed *novel H1N1,* led to a greatly increased burden of influenza disease worldwide. Children and young adults were at a disproportionate risk for infection and hospitalization, with 60% of infections occurring among those 18 years of age or younger, and 95% in those younger than 50 years.[69-71] The overall attack rate was highest among children aged 5 to 14 years (147 per 100,000 population),[69] but infants had the highest hospitalization rates and persons aged 50 years or older had the highest mortality rates once hospitalized.[69,71] This differs from seasonal influenza, where about 60 percent of influenza-related hospitalizations and 90 percent of influenza-related deaths occur in people 65 years and older. From April to October of 2009, the Centers for Disease Control and Prevention (CDC) received reports of 145 pediatric deaths associated with influenza infection.[67] Correcting for underascertainment, the CDC estimates the actual count may be three to four times greater than reported (http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm). The majority of hospitalized cases had underlying medical conditions associated with severe seasonal influenza; secondary bacterial infections were observed in 15% to 30% of fatal cases.[71,72]

In a typical influenza season, parainfluenza viruses (PIVs) are generally second only to RSV as important viral causes of lower respiratory infection in children and immunocompromised patients.[73-77] The average annual PIV hospitalization rate is 1.02 per 1000 children 0 to 59 months of age, with the highest rate of 3.01 per 1000 in children 0 to 5 months of age.[77] PIVs account for 50% of hospitalizations for acute laryngotracheitis (croup) and at least 15% of cases of bronchiolitis and pneumonia. PIVs types 1 and 2 cause more cases of croup whereas PIV type 3 is more likely to infect the small air passages and cause pneumonia or bronchiolitis. However, any PIV can cause lower respiratory tract disease, particularly during primary infection or in immunosuppressed patients. In immunocompromised hosts, virologically confirmed PIV pneumonia has a 30-day attributable mortality rate of at least 30% to 35%.[75,78,79] Unlike RSV lower tract disease, in which RSV is usually the single pathogen, copathogens may be identified with PIV pneumonia more than 50% of the time,[75] and management of PIV pneumonia should include workup and treatment for copathogens.

Other respiratory viruses that can cause pneumonia, particularly in young children and immunocompromised hosts, include human metapneumovirus, adenovirus, human rhinoviruses (HRVs), and human coronaviruses (HCoVs). Since it was first described in 2001,[80] human metapneumovirus has been shown to be a common cause of croup, bronchiolitis, and pneumonia in children, the elderly, and immunocompromised patients.[81-89] The clinical manifestations of human metapneumovirus are indistinguishable from RSV. Adenovirus pneumonia can occur as an isolated event or as part of disseminated disease. Risk factors for adenovirus pneumonia include a compromised immune function, chronic underlying respiratory or cardiac disease, and age younger than 7 years.[90] Adenovirus pneumonia due to specific serotypes has been associated with outbreaks among young children (types 3 and 7),[91] high school students (type 11),[92]and a recent community-based outbreak that included children (type 14).[93] HRVs

occasionally cause lower respiratory tract disease requiring admission to intensive care among pediatric and immunosuppressed patients, although a causative role is sometimes difficult to define because HRVs frequently occur in association with copathogens.[94-98] Among pediatric patients, a new species of rhinovirus (HRV-C) has been discovered that may cause more severe disease than HRV-A or HRV-B, although this association is not yet clearly elucidated.[99-104]

The HCoV family currently includes five viruses that are known to infect humans: HCoV-229E, HCoV-OC43, the severe acute respiratory syndrome-associated CoV (SARS-CoV), and the recently described HCoV-NL63 and HCoV-HKU1. The SARS outbreak originated in Guangdong Province in China in the fall of 2002 and was characterized by a life-threatening, atypical pneumonia caused by a novel coronavirus most likely derived from masked palm civets.[105] SARS-CoV was spread by close contact with infected humans, mostly to household contacts and health care workers. Death from progressive respiratory failure occurred in approximately 10% to 15% of adult patients[106-110]; in children, morbidity was less and no deaths occurred.[111-113] SARS-CoV is not currently circulating in the world. The most recent human cases of SARS-CoV infection were reported in China in April 2004 in an outbreak resulting from laboratory-acquired infections.[114] Should SARS-CoV re-emerge, updates to the case definition, including clinical criteria for moderate or severe respiratory illness of unknown cause and epidemiologic criteria for exposure, can be found at www.cdc.gov/SARS. Other HCoVs have been reported to cause pneumonia in children and immunocompromised patients treated for hematologic malignancies.[115-119]

Additional information about respiratory viruses including RSV, influenza, PIV, and adenovirus is available in Chapter 47.

Although CMV usually causes relatively benign disease in immunocompetent hosts, it is frequently severe and often fatal in immunocompromised hosts, including patients with acquired immunodeficiency syndrome (AIDS), malignancy, congenital immune deficiencies, and transplant recipients. CMV is a herpesvirus and, like other herpesviruses, it can cause latent infection in vascular endothelial cells, monocytes and macrophages, polymorphonuclear neutrophils, and renal and pulmonary epithelial cells. Cellular damage is caused directly by the viral lytic infection or indirectly by the immune response of the host. Among allogeneic stem cell transplant recipients, the risk of CMV pneumonia is high; historically, treatment of CMV pneumonia with ganciclovir and intravenous immunoglobulin (IVIG) in the late 1980s dramatically reduced mortality from 80% to 100% without therapy to approximately 50%.[120] The spectrum of CMV pneumonia has changed with the introduction of routine antiviral prophylaxis and preemptive therapy strategies.[121] As a result, CMV disease during the first 3 months after hematopoietic cell transplantation has been reduced from 20% to 30% to less than 5% in most studies.[122] CMV disease now primarily occurs late after transplant. Risk factors for late CMV disease include reactivation of (or primary infection with) CMV during the early period after transplant, and therapy for acute or chronic graft-versus-host disease.[120] Among solid organ transplant recipients, the risk of CMV disease is greatest for lung transplant recipients, followed by liver, heart, and renal transplant recipients.[120,123]

Hantaviruses are known for causing hemorrhagic fevers and acute severe respiratory infection in young adults. Hantaviruses can spread from mammal to mammal, including humans, by exposure to aerosolized feces, infected urine, or other secretions. In the United States, the Sin Nombre virus, which causes the pulmonary syndrome, is found in 10% to 80% of deer mice in rural areas of North America, although the overall seroprevalence rates in the western United States are less than 0.1%.[124] In the United States, hantaviral infections are rare in children under the age of 10 years; however, severe cases resulting in death have been described in children as young as 5 years old in South America.[124,125] Hantaviruses cause disease by creating leakage of plasma and erythrocytes through the vascular endothelium in the lung (hantavirus pulmonary syndrome [HPS]) or the kidneys (hemorrhagic fever with renal syndrome). The differential diagnosis includes influenza A, rickettsial disease, borreliosis, tularemia, *Legionella pneumophila, Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Pneumocystis jiroveci*. HPS is fatal in 35% to 40% of cases across the Americas.[124,126] Supportive care, including early consideration of extracorporeal membrane oxygenation, is key to treatment of patients with HPS.

Clinical Presentation

The clinical presentation of viral pneumonia/pneumonitis usually consists of fever, increased respiratory rate, cough, and increased work of breathing, with grunting, flaring, retracting, and use of accessory muscles in infants and young children. Decreased oral intake with increased insensible loss due to the increased respiratory rate is often present and may lead to dehydration. Some patients have centrally mediated apnea, and other patients have an overwhelming sepsislike syndrome with increased peripheral pulses, decreased central blood pressure, and lethargy. A history or examination findings of certain symptoms, including rhinorrhea, conjunctivitis, otitis media, and previous exposure to an ill child or adult, should immediately raise suspicion of a viral cause. However, many patients with influenza, and most adults and adolescents with SARS-CoV, have no preceding upper respiratory illness. Radiographic findings generally include evidence of hyperinflation and peribronchial cuffing, and a focal or diffuse infiltrate may or may not be present. Bacterial coinfection may appear after, or concomitantly with, the viral infection.

Clinical features of HPS include a noncardiogenic pulmonary edema and a prodrome of fever, headache, and myalgia, usually with nausea and diarrhea, for 4 to 5 days before the onset of cough and dyspnea. There is a lack of upper respiratory symptoms. Tachycardia and tachypnea with hypotension then develop and rapidly progress to acute respiratory distress syndrome. Laboratory findings include leukocytosis, elevated hematocrit, and thrombocytopenia in the early cardiopulmonary phase; prolonged partial thromboplastin time may occur in severe cases. Rapidly evolving diffuse bilateral interstitial infiltrates are seen on chest radiograph.

Central Nervous System Infections

Background

Aseptic meningitis, encephalitis, and myelitis are inflammatory conditions of the central nervous system (CNS), involving meninges, brain, and spinal cord, respectively. Disease is caused by a variety of infectious pathogens, but viruses cause

most disease. Viruses gain entry to the CNS via the bloodstream (enteroviruses and arboviruses) or by direct neuronal spread (HSV and rabies). Pathogenesis may involve direct viral invasion or a vigorous virus-specific immune response resulting in damage to the neurons and supporting cells. Alternatively, infection may trigger activation of an immune response specific for the oligodendroglia or the myelin components themselves. In the latter case, disease may follow an upper respiratory tract or other infection and primarily take the form of a demyelinating process. This disease is commonly termed postinfectious encephalomyelitis or acute disseminated encephalomyelitis.

Individuals of all ages are at risk for CNS viral infections. However, neonates, older individuals, and those with immune deficiencies are prone to more frequent and more serious CNS viral infections.

Cause

The potential viral causes are multiple; however, enteroviruses, herpesviruses, and arboviruses are responsible for most disease (see Table 95-1). Enteroviruses account for up to 99% of cases of aseptic meningitis when a cause is identified.[127] Enterovirus meningitis in older children and adults is typically self-limited and associated with few complications. In contrast, enteroviral infections in neonates may mimic bacterial sepsis, and CNS involvement is often manifested as encephalitis. Parechovirus, another cause of meningoencephalitis in neonates, is a close relative of enteroviruses and clinically very similar.[128]

HSV is a common cause of CNS infection in individuals of all ages. During the neonatal period, HSV type 2, and to a lesser extent type 1, cause encephalitis because of the vertical transmission of the virus.[129] In contrast, in older children and adults, most HSV encephalitis is caused by type 1. HSV-2, however, can cause benign aseptic meningitis in association with primary and recurrent genital infections.[130] Other members of the herpesvirus family (CMV, EBV, VZV, and HHV-6) can also cause aseptic meningitis and encephalitis, albeit less commonly. CMV encephalitis occurs mostly in immunosuppressed individuals but may occasionally appear in otherwise healthy individuals.[131,132] EBV aseptic meningitis and encephalitis present with or without the classic findings of infectious mononucleosis.[133] Acute cerebellar ataxia is a common and usually benign complication of chickenpox. VZV encephalitis can sometimes occur in immunocompetent individuals,[134,135] but more frequently occurs in immunocompromised individuals following days, weeks, or months after a case of varicella or zoster. Zoster encephalitis can be complicated by small- or large-vessel vasculitis (granulomatous arteritis), which carries the potentially serious consequences of infarction.[134,136] HHV-6 has only rarely been reported to cause encephalitis in healthy children during primary infection,[137] whereas it appears to be a more common problem for immunosuppressed patients, such as those receiving stem cell transplants.[138,139]

Arboviruses (arthropod-spread viruses) are important causes of aseptic meningitis and encephalitis. The specific arbovirus determines the epidemiology, morbidity, and risk of death of associated disease. The La Crosse and St. Louis encephalitis viruses account for most arboviral CNS infections in the United States. The La Crosse virus is found mainly in the Midwest, typically occurs in the summer and early fall, and is associated with a relatively low death rate. The St. Louis encephalitis virus occurs in every state but is more common in the Midwest, Florida, and Texas and has been responsible for large urban outbreaks.[140,141] Eastern equine virus occurs less frequently, and mainly in the Northeast and Southeast, but carries a high rate of morbidity (70% to 80%) and death (20% to 80%).[142,143] West Nile virus encephalitis first appeared in the United States in the summer of 1999 in New York state.[144] Over the following summers, the West Nile virus moved southward and westward across the United States, infecting both animals and humans. Most individuals infected with the West Nile virus are symptom free or experience flulike illness; however, older individuals and those with underlying immune deficiency can experience encephalitis that may result in death. In addition to the more typical presentation of encephalitis, an acute flaccid paralysis has also been associated with West Nile virus infection.[145]

A number of viruses are infrequent causes of encephalitis, including mumps, influenza, and lymphocytic choriomeningitis viruses (LCMVs). Historically, mumps virus accounted for a large proportion of aseptic meningitis and encephalitis cases in the United States.[146] Currently, because of the widespread use of the trivalent MMR vaccine, meningitis and encephalitis due to mumps are extremely rare.[147] Influenza has been associated with encephalitis/encephalopathy, especially in Japan. In a national survey representing the 1998-1999 season, 142 cases, most occurring in children younger than 5 years, are reported.[148] LCMV is an infrequently recognized cause of meningoencephalitis. This virus is found in the urine, droppings, and saliva of infected mice, guinea pigs, and hamsters, and disease in humans arises after exposure to these substances.

Postinfectious encephalomyelitis refers to an acute self-limited demyelinating process most commonly following viral respiratory infections and varicella. In contrast, subacute sclerosing panencephalitis (SSPE) and progressive multifocal leukoencephalopathy (PML) are two chronic, usually fatal, demyelinating diseases due to measles and JC virus, respectively. SSPE most commonly follows 5 to 10 years after natural measles infection. SSPE is extremely rare in the United States; however, it may occur as often as one case per a population of 10,000 in areas of the world where the MMR vaccine is not widely used.[149] PML is also rare, usually affecting those with AIDS or, rarely, those with other serious immunodeficiencies. Transverse myelitis has been most frequently associated with enteroviruses; however, VZV,[150,151] CMV, influenza A,[152] and hepatitis A[153] have been reported causes, even in immunologically normal individuals.

Clinical Presentation

Historic clues and physical findings can be helpful in focusing the search for an etiologic agent. Travel or residence in areas where arboviruses are endemic during the appropriate season for arthropod transmission (typically summer months) and a history or evidence of insect bites should raise suspicion for arboviruses. Seasonality also plays a role in enteroviral diseases, because in temperate climates enteroviruses are more prevalent during summer and fall months. History of a mother with recent symptoms consistent with viral illness (fever, sore throat, gastroenteritis, rash) should raise suspicion of enterovirus in a neonate with encephalitis or sepsis-like illness. VZV encephalitis and myelitis typically follow chickenpox or zoster by weeks to months and commonly

occur in older individuals or those with immunosuppression, such as transplant recipients.[154] VZV encephalitis may be complicated by CNS vasculopathy and resulting infarctions. Chronic encephalitis/meningitis due to enteroviruses occurs in individuals with agammaglobulinemia. Chronic or relapsing encephalitis may also be due to VZV, measles (SSPE), or rubella (progressive rubella panencephalitis), though the latter two are extremely rare with the current widespread use of the MMR vaccine. HIV itself may cause encephalopathy/encephalitis or may also be associated with certain opportunistic infections such as PML. Significant exposure to rodent droppings should raise concern for LCMV. Finally, history of exposure to a bat should raise the concern for rabies.

The classic clinical presentation of viral meningitis is characterized by acute onset of fever, headache, photophobia, vomiting, and nuchal rigidity. A more chronic presentation might indicate enteroviral disease in an immunosuppressed host, whereas recurrent aseptic meningitis can be associated with HSV-2. Encephalitis is characterized by acute onset of fever, signs of encephalopathy such as depressed consciousness, focal neurologic findings, and seizures. A chronic progressive presentation might indicate more unusual causes, such as PML and SSPE. Transverse myelitis is characterized by an abrupt onset of weakness of the limbs progressing to flaccid paralysis. Diminished deep tendon reflexes progress to nonexistent, and there is associated sensory deficit. VZV myelitis usually follows varicella or zoster by 1 to 2 weeks.

Cerebrospinal fluid (CSF) findings in aseptic meningitis typically include a normal glucose level, a normal to slightly elevated protein level, and a pleocytosis of up to 1000 cells/μL. The pleocytosis is classically monocytic (>80%); however, there can be an initial predominance of polymorphonuclear cells in the first 48 hours of illness.[155] CSF findings in encephalitis can be normal, or there may be pleocytosis and elevated protein levels. The results of brain computed tomography (CT) and MRI studies are usually normal in viral meningitis, whereas disease is often seen in the setting of viral encephalitides. In general, CT scan is relatively insensitive for detecting acute encephalitis. MRI is the more sensitive study for detecting disease because of its ability to detect altered water content (see Chapter 56).[156] In acute viral encephalitis, early findings include edema with minimal contrast enhancement. As disease progresses, edema and enhancement become more obvious and may be accompanied by mass effect, hemorrhagic changes, and necrosis. As the inflammation resolves, atrophy may become prominent. In HSV, imaging studies may reveal edema and enhancement, often first involving the temporal lobes with subsequent spread to other areas of the brain. Changes can ultimately progress to atrophy, multicystic encephalomalacia, and gyriform high attenuation, especially in children.[157,158] In postinfectious encephalomyelitis, the lesions may be seen throughout the CNS. The lesions are more readily elucidated by MRI and primarily involve the white matter, although gray matter may also be involved.

Exotic Viral Diseases

With both the increase in foreign travel and the threat of bioterrorism, the potential to treat a child with an exotic viral disease exists. Although discussion of these infections, which include Andes virus, B virus, monkeypox, and the hemorrhagic fever viruses (Ebola virus, Marburg virus, Lassa virus, Crimean-Congo hemorrhagic fever virus, Argentine hemorrhagic fever virus, Bolivian hemorrhagic fever virus) is beyond the scope of this chapter, these infections should be kept in mind. If one of these agents is suspected, then the patient and patient garments should be contained in a single room, and infection control, infectious disease specialists, or the public health department should be called immediately.[159-161]

Diagnosing Viral Disease

The key to diagnosis of viral pathogens is high-quality specimens obtained early in the course of disease. There are five main ways to diagnose a viral infection: (1) identification of the virus in cell culture through observation of characteristic cytopathic effect; (2) identification of the virus by assays that link specific antibodies to the viral antigens (complement fixation, neutralization, immunofluorescence assays, enzyme-linked immunosorbent assay); (3) microscopic identification of characteristic viral inclusion bodies; (4) serologic procedures that show either an early antibody (immunoglobulin M [IgM]) or a fourfold or higher rise in IgG antibody titers between an acute phase and (at least 10 to 14 days later) convalescent phase serum; and (5) molecular techniques that amplify target viral DNA or RNA.

If a viral cause is suspected, a few diagnostic studies can be performed immediately. Acute-phase serum should be held for later interpretation. It is critical that this specimen is drawn before administration of IVIG or blood products. Samples for viral cultures and PCR testing should be collected from the appropriate sites with Dacron or rayon swabs with plastic shafts (or other specific swabs appropriate for testing by PCR). Both cotton and wood inhibit viral growth and may contain substances that inhibit the enzymes used in PCR. The virology laboratory should be informed of the diagnosis or suspected pathogens because the cell lines chosen for inoculation vary by what virus is suspected. Nasal washes/swabs and swabs of the base of a vesicle or ulcer (for VZV, HSV) should include good cellular content, because fluorescent antibody assays stain cells and the more cells available, the more sensitive the assay. Table 95-2 outlines appropriate samples and testing for a number of specific viral pathogens.

Myocarditis

Isolation of virus from the myocardium provides a definite viral diagnosis of myocarditis; however, recovery of viruses from the myocardium by culture is rarely possible, even in cases of histologically proven myocarditis. Controversy now exists as to whether endomyocardial biopsy and histologic confirmation will continue to be recommended in myocarditis given the availability of cardiac MRI and the risks associated with biopsy.[162] Viral culture of peripheral specimens such as stool and nasopharyngeal secretions or the demonstration of a fourfold rise in specific viral antibody titers provides an indirect determination of causality; however, the sensitivity is also low, 16% to 26%[15,163] and 30% to 40%, respectively. Molecular biologic techniques such as PCR and in situ hybridization have expanded the number of viruses implicated in the etiology of myocarditis. In addition, because of the increased sensitivity of PCR, the application of PCR for viral nucleic acid in myocardial tissue provides a virologic diagnosis in up to 60% of cases.[15]

Table 95–2 Potential Diagnostic Tests and Corresponding Specimens for Diagnosis of Viral Pathogens

Viral Agent	Specimen	Recommended Diagnostic Tests*
Adenovirus	NP, pharynx, BAL fluid Tissue Serum/plasma†	FA, culture, shell vial or rapid culture, PCR FA, culture, PCR, histology PCR
Arboviruses (California encephalitis, Colorado tick fever, EEE, SLE, WEE, West Nile)‡	Serum (acute and convalescent)/plasma CSF	IgM and IgG antibody,§ PCR and immunohistochemistry for some IgM‖ and IgG antibody,§ PCR
Coronaviruses (OC43, 229E, HKU1, NL63, and SARS)¶‡	NP aspirate (preferred for SARS) or swab, OP swab, BAL, serum/plasma (SARS), stool (SARS), tissues (SARS) Serum	PCR IgM and IgG antibody§
Enteroviruses (echoviruses, coxsackie viruses, enteroviruses)‡	CSF, pharynx Stool** Serum (acute and convalescent)	PCR, culture Culture IgM and IgG antibody available for some
Hantavirus‡	Serum Tissue (lung, kidney, spleen preferred; ante-mortem: lung or bone marrow)	PCR, IgM and IgG antibody§ PCR, culture and immunohistochemistry
Hepatitis viruses	Serum	Serology for all
• **HAV**	Serum	Anti-HAV IgM
• **HBV**	Serum/plasma Liver	HBsAg, anti-HBcAb IgM, PCR PCR
• **HCV**	Serum/plasma Liver	Anti-HCV, PCR PCR
• **HDV**	Serum Liver	Anti-HDV PCR
• **HEV**	Serum Liver	Anti-HEV IgM PCR
HERPES VIRUSES		
• **CMV**	NP or BAL Blood Serum Plasma Tissue Urine	FA, culture, shell vial or rapid culture PCR§§ Buffy coat antigen, PCR IgM and IgG antibody§ PCR FA, culture, histology, PCR Culture, shell vial or rapid culture
• **EBV**	Serum Plasma, CSF Tissue	IgM antibody or slide agglutination test (monospot) PCR PCR, Immunohistochemistry
• **HHV-6**	Serum/plasma, CSF Tissue	PCR PCR, immunohistochemistry
• **HSV I and II**	CSF, plasma Base of lesion, NP, conjunctiva, tissue Serum Stool (neonates)	PCR, culture FA, culture, PCR IgG antibody (differentiation between type 1 and type 2 requires special lab)§ Culture
• **VZV**	Base of lesion, tissue Serum Plasma, CSF	FA and culture, PCR IgM and IgG antibody§ PCR
Influenza A and B	NP, pharynx, BAL fluid Tissue	FA, culture, IA (rapid), PCR‡‡ FA, culture, PCR
JCV‡	Brain CSF	Brain biopsy,†† PCR PCR
LCM‡	Serum CSF	IgM and IgG antibody§ IgM
Measles (Rubeola)‡	Serum Urine, blood, NP	IgM and IgG antibody§ culture
• SSPE	CSF	Oligoclonal bands, IgG, measles titer

Continued

Table 95–2 Potential Diagnostic Tests and Corresponding Specimens for Diagnosis of Viral Pathogens—cont'd

Viral Agent	Specimen	Recommended Diagnostic Tests*
Metapneumovirus	NP, BAL fluid	FA, PCR
Mumps‡	Buccal swab Serum, CSF Pharynx, urine	PCR, culture IgM and IgG antibody§ Culture (rarely grows)
Parechoviruses	CSF, serum/plasma, NP, pharynx, stool	PCR (not widely available), culture (not diagnostic because CPE same as enteroviruses)
Parainfluenza viruses	NP, BAL fluid, tissue	FA, culture, PCR
Parvovirus	Plasma Serum	PCR IgM and IgG antibody§
Rabies virus‡	Serum, CSF Saliva, brain, tissues, urine Punch biopsy (nape of neck), brain	Rabies-specific antibody by neutralization assay Virus isolation/culture (rarely helpful), Fluorescent microscopy (consult ID)
RETROVIRIDAE		
• **HIV**	Serum/plasma, CSF	Screening HIV EIA, DNA PCR RNA PCR (viral load)
• **HTLV**	Serum Tissue	PCR, HTLV EIA PCR
Rotavirus	Stool	EIA or latex particle agglutination assays (commercially available); electron microscopy, culture, polyacrylamide gel electrophoresis, PCR (research labs)
RSV	NP, BAL fluid, tissue	FA, culture, shell vial culture, IA (rapid), PCR
Rubella‡	Serum, NP, pharynx, CSF, blood, urine	IgM and IgG antibody§ Culture

Choice of test depends on clinical setting, including organ system involved and immune status of host.
NP, Nasopharyngeal secretions; *OP,* oropharyngeal; *CSF,* cerebrospinal fluid; *BAL,* bronchoalveolar lavage; *FA,* fluorescence assay; *EIA,* enzyme immunoassay; *IA,* immunoassay; *ID,* infectious disease; *CPE,* cytopathic effect; *EEE,* Eastern equine encephalitis; *SLE,* St. Louis encephalitis; *WEE,* Western equine encephalitis.
*Multiple diagnostic tests are available for each pathogen. Commonly recommended diagnostic tests are listed; however, if results are negative or specimens are not available, infectious disease consultation may be helpful for additional or special testing.
†PCR is usually run on plasma, though some laboratories may run serum samples.
‡Pathogen may have significant public health implications and testing should be performed in consultation with infectious disease and/or local public health department (for enteroviruses, if enterovirus 71 suspected). Testing is often not available without assistance of the Public Health Department, and recommended specimens and tests are frequently evolving; see www.cdc.gov/ for updates.
§IgM and IgG antibody may also be referred to as "serology" on laboratory request forms. For all viral pathogens, when testing for IgG it is optimal to collect acute and convalescent sera approximately 4 weeks apart.
‖IgM antibody does not cross the blood-brain barrier. If found in CSF, IgM antibody denotes central nervous system infection.
¶For suspected SARS, patients should also be evaluated with respiratory FA for influenza A, B, and RSV, sputum Gram stain and culture, blood culture, and urine for *Legionella* and pneumococcal antigen. Blood, serum, and respiratory specimens should be saved. See www.cdc.gov/ncidod/sars/diagnosis.htm for updated diagnostic information.
**Enteroviruses are shed in the stool for weeks and may not be diagnostic.
††Gold standard.
‡‡FA and rapid testing have low sensitivity for 2009 novel influenza A (H1N1); PCR testing is the most sensitive and is necessary for subtyping.
§§Because shedding of CMV occurs in the lungs of seropositive stem cell transplant recipients without overt CMV disease, the recovery of CMV DNA by PCR from BAL fluid (which is considerably more sensitive than culture) without shell vial or culture positivity is of uncertain significance. PCR for CMV DNA in BAL or biopsy fluid should thus not be ordered routinely.

Acute Liver Failure

Viral diagnosis relies on serology, detection of viral nucleic acid in serum, and detection of viral antigens or nucleic acids in tissue obtained from liver biopsy. Hepatitis A infection is confirmed by demonstrating anti-HAV IgM antibodies. In patients with acute hepatitis A, anti-HAV IgM antibodies are detectable in the serum at the onset of symptoms, peak 1 week after onset of symptoms, and become undetectable by 3 to 6 months postinfection. The presence of HBsAg (hepatitis B surface antigen) in serum indicates active HBV replication and is present in acute and chronic HBV infection. Due to the destruction of actively infected hepatocytes, HBsAg may be absent in ALF and the only marker of acute HBV infection may be anti-HBcAb (anti-HBV core) IgM antibodies. Hepatitis B DNA can also be demonstrated in serum and liver tissue by PCR. Absence of HBsAg or HBV-DNA in the serum does not rule out HBV as the cause of ALF, as HBV DNA has been demonstrated in liver tissue of patients with non-A and non-B ALF in whom serologic markers did not suggest HBV infection.[164] Hepatitis D, a hepatotropic virus that causes infection only in the presence of active hepatitis B infection, should be looked for in patients with acute HBV hepatitis, as coinfection or superinfection with HDV may result in more severe disease.[165] Hepatitis D coinfection can be determined by demonstrating anti-HDV antibodies or HDV-RNA in serum.[166]

Although the newer generation antibody assays for hepatitis C are more sensitive than past assays, anti-HCV antibodies may not be detectable early in disease. Therefore, when the epidemiology suggests possible infection with HCV, serum and liver tissue should be analyzed for HCV-RNA by PCR.

HSV hepatitis is frequently a result of newly acquired infection, thus serology may not be helpful. Skin or mucosal lesions, if present, should be cultured for HSV. Liver tissue should be sent for viral culture and PCR for HSV. HSV may also be demonstrated in blood by PCR. Both serology and tissue or blood PCR can be used to diagnose infection with EBV, CMV, HHV-6, HEV, and parvovirus. Diagnosis of adenovirus and enterovirus generally requires PCR of blood and tissue or culture of infected secretions.

Pneumonia/Pneumonitis

If available, fluorescence assays or PCR testing on nasal wash specimens are the initial diagnostic tests of choice for respiratory viruses, because most of these pathogens are concentrated in the nasopharynx. However, by the time the patient has developed lower respiratory tract disease, a lower respiratory sample by bronchoscopy may provide the best yield and may be positive even with a negative nasopharyngeal sample. The sensitivity of indirect immunofluorescence assays is generally as high as 90% to 95% for RSV, influenza A and B, and PIV 1, 2, and 3; if a rapid result is needed, this may be the best approach. However, PCR may be used if the results can be provided in an expedited fashion, as this is a more sensitive assay albeit more expensive. A rapid antigen test for RSV and influenza is also available. However, for the pandemic 2009 influenza A (H1N1) virus, in particular, FA and rapid testing have shown low sensitivity and a negative test result is not reliable.[167-170] PCR testing is most sensitive and necessary for correct virus subtype identification. Adenovirus immunofluorescence assays are available in some laboratories, but sensitivity is generally lower (around 50% to 70%). Shell vial assays can increase sensitivity, and although they are usually performed for CMV, they can also be performed for RSV and adenovirus. The same samples can be sent for culture in addition to immunofluorescence studies; this should be considered for immunocompromised and severely ill children with respiratory distress/failure of unclear etiology if PCR testing is not available. The diagnosis of hantavirus can be made by culture of the virus (which is difficult), PCR for viral RNA from serum, plasma, or tissues, or serologic testing. Antibodies to hantaviruses are usually detectable in serum on the first day of symptoms.[124] A review of diagnostic testing options for etiologies of viral pneumonia is provided in Table 95-2.

Meningitis/Encephalitis

CSF, blood, and throat swabs should be collected for evaluation. One can make a diagnosis of enterovirus by culturing the virus from CSF or by detecting virus in CSF using reverse transcriptase PCR. Because of the greater sensitivity of PCR, compared with culture,[171,172] it should be used whenever possible. Viral culture of a throat swab may also reveal enterovirus and is indicative of a current or recent infection. Rectal or stool viral cultures are less helpful because enteroviruses may be shed in the stool for weeks after infection. DNA PCR of CSF offers relatively sensitive and specific diagnosis of herpesviruses.[132] Detection of viral-specific antibodies in the CSF can add supporting evidence. Additionally, the detection of HHV-6 DNA in plasma or serum by PCR confirms active systemic viral replication. Arboviruses are typically diagnosed through detection of antibodies in acute and convalescent serum specimens. CSF may also be tested for antibodies. PCR and immunohistochemistry have also been used to diagnose arboviral infections and are available in some settings. Diagnosis of LCMV is made through serologic testing. The JC virus can be detected in CSF with PCR, and this appears to be a relatively sensitive and specific method for diagnosing PML.[173,174] Definitive diagnosis, however, is usually made with brain biopsy. Diagnosis of SSPE is made with the evaluation of CSF for oligoclonal bands, IgG level, and specific measles antibody titer.

Treatment for Viral Infections

In general, for most life-threatening viral infections the primary treatment is supportive. Because of improvements in intensive medical care, death from these illnesses has decreased even without the availability of specific antiviral therapy. Despite recent advances, there are no effective antiviral medications for many viral infections. There are, however, antivirals for most of the herpes group viruses and many of the respiratory viruses. For most infections, the efficacy of antiviral therapy is decreased if therapy is delayed, so early diagnosis and rapid initiation of therapy are essential. Consultation with an infectious disease specialist is recommended because some antiviral agents are not commercially available and new treatment modalities continue to be identified. A listing of antiviral agents, indications, and dosages is provided in Table 95-3.

Myocarditis

Mechanical circulatory support should be considered for children with fulminant myocarditis unresponsive to standard management (see Chapter 27). Aggressive therapy is warranted because both adults and children who survive their illness have a good prognosis for return to normal ventricular function.[175-177] Cardiac transplantation may be necessary for those children refractory to other management. Current recommendations do not support the use of immunosuppressive therapy[22,178] or nonsteroidal antiinflammatory agents,[179,180] particularly early in the course of myocarditis. Treatment with high-dose IVIG has been associated with improved left ventricular function in several small studies in children[181,182] and warrants investigation in larger, controlled studies. In adults, a controlled study found IVIG to be no better than placebo for acute dilated cardiomyopathy[182] and a Cochrane Review found no role for the routine use of IVIG in presumed viral myocarditis.[183] Several immune modulators are being investigated for use in treatment of myocarditis.[179,184] Specific antiviral therapy is indicated when the inciting viral agent has been identified.

Acute Liver Failure

The role of antiviral therapy in ALF is limited. Acyclovir should be initiated if HSV is suspected or confirmed, and there are reports of the successful use of lamivudine for treatment of severe acute hepatitis B.[185,186]

Trials using plasma exchange and plasmapheresis have demonstrated improved hemodynamic parameters, decreased intracranial pressure, and improved survival.[187,188]

Table 95–3 Antiviral Agents and Indications for Use

Virus	Drug of Choice/Dose†	Alternate Agents/Dose
Adenovirus	There is no currently approved therapy for the treatment of adenoviral infections.	Both ribavirin and cidofovir have in vitro activity against adenovirus, and cidofovir appears to be more clinically active.[201] Antiviral therapy may be considered for immunocompromised patients with severe adenoviral pneumonia. Small case series in immunocompromised children have suggested potential efficacy with intravenous ribavirin (25 mg/kg loading dose then 10 mg/kg/day; available on compassionate use basis)[202] or cidofovir (5 mg/kg once weekly[203,204] or 1 mg/kg three times a week).[205]
Coronavirus	There is no currently approved therapy for the treatment of coronaviral infections.	The sudden and severe nature of the SARS outbreak in 2002–2003 necessitated the use of empiric treatment strategies. A number of agents have been used to treat SARS-CoV, including ribavirin, lopinavir-ritonavir, oseltamivir, and corticosteroids; however, none was given in a controlled fashion, and the efficacy of these drugs has not been established.[201,206]
Enterovirus	There is no currently approved therapy for the treatment of enteroviral infections.	
Hantavirus	There is no currently approved therapy for the treatment of hantaviral infections.	Intravenous ribavirin has shown benefit in hantavirus renal syndrome,[207,208] but not in hantavirus pulmonary syndrome at the cardiopulmonary stage.[209,210] There is an ongoing NIH/NIAID-sponsored controlled trial of intravenous methylprednisolone for hantavirus pulmonary syndrome in Chile.[126]
HERPES VIRUSES		
• **CMV**	Ganciclovir (5 mg/kg q12h × 2–3 weeks, then 5 mg/kg q24h) is primary therapy for CMV disease. IVIG (500 mg/kg qod × 2 wk then once weekly) or CMV-IG (150 mg/kg, same schedule) should be given concurrently for CMV pneumonia in immunocompromised patients.	Foscarnet (90 mg/kg q12h × 2–3 weeks, then 90 mg/kg q24h), cidofovir (5 mg/kg/wk; high risk of renal toxicity, use with probenecid and saline hydration). Increased efficacy of cidofovir as second-line therapy suggested in allogeneic stem cell transplant recipients with CMV pneumonia in one small study.[211]
• **HSV**	Acyclovir (20 mg/kg/dose IV q8h) for encephalitis in neonates and children <12 years and for neonates with disseminated disease; 10 mg/kg/dose IV q8h for children >12 years.	No specific dosing recommendations are available for HSV-associated hepatitis and pneumonitis. At least 10 mg/kg/dose should be considered outside the neonatal period.
• **HHV-6**	There is no currently approved therapy for the treatment of HHV-6 infections.	Foscarnet and ganciclovir have in vitro activity. Case reports and series show variable clinical response with one or both drugs in combination.
• **VZV**	Acyclovir (10-12 mg/kg/dose IV q8h); high-dose acyclovir (20 mg/kg/dose) should be used for VZV encephalitis or for disease in immunocompromised children.	
Influenza A/B	Oseltamivir (2 mg/kg q12h × 5 days; max 75 mg bid)* or zanamivir (≥7 years) 10 mg (2 oral inhalations) q12h × 5 days. There may be benefit of using higher than approved doses of oseltamivir in immunosuppressed patients as licensing studies showed a trend to more rapid clearance of virus with the higher dose; this is under investigation.[65,212]	Rimantidine or amantidine (5 mg/kg/day div bid; max 75 mg bid), influenza A only. Local circulating influenza viruses must be considered. Combination therapy as empiric treatment may be indicated during periods of concomitant circulating viruses or for severely ill immunosuppressed patients.[65,194] The use of investigational agents such as IV zanamivir or IV peramivir may also be considered.[195-198]
JCV	No effective therapy.	In HIV infection, treatment with combination antiretroviral therapy may improve survival. Potential role for cidofovir.[213]
Metapneumovirus	There is no currently approved therapy for the treatment of metapneumoviral infections.	Ribavirin has in vitro activity against human metapneumovirus and has been shown to decrease viral load and lung inflammation in mouse models.[214,215] Case reports suggest ribavirin and IVIG may be used successfully in immunosuppressed patients.[216-218]

Continued

Table 95–3 Antiviral Agents and Indications for Use—cont'd

Virus	Drug of Choice/Dose†	Alternate Agents/Dose
Parechoviruses	There is no currently approved therapy for the treatment of parechoviral infections.	
Parainfluenza virus	There is no currently approved therapy for the treatment of parainfluenza viral infections.	Treatment for parainfluenza pneumonia should include coverage for copathogens.[75] Ribavirin is active in vitro and in animal models and has thus been used for treatment of parainfluenza pneumonia in immunocompromised hosts. Anecdotal reports of the benefit of aerosolized or systemic ribavirin have shown responses to be highly variable, and a retrospective series of stem cell transplant recipients showed no benefit.[75,201]
RSV	Aerosolized ribavirin (6 g reconstituted in 100 mL tid or 6 g in 300 mL administered over 12–18 hours daily) × 5 days has been used with modest efficacy in patients with severe RSV pneumonia and in immunocompromised patients[201,219]; not recommended for uncomplicated disease.	Combination therapy with aerosolized ribavirin and palivizumab (RSV monoclonal antibody, 15 mg/kg given once) may improve outcome of RSV pneumonia in immunocompromised and high-risk patients and may be used in combination for treatment of documented RSV pneumonia in these populations.[65,219,220]

IVIG, Intravenous immunoglobulin.
*Care should be taken when dosing children <1 year, with doses of 3 to 3.5 mg/kg recommended. In an influenza pandemic or some outbreak situations, treatment should not wait for laboratory confirmation of influenza because laboratory testing can delay treatment and because a negative rapid test for influenza does not rule out influenza. The sensitivity of rapid tests in detecting 2009 H1N1 ranged from 10% to 70%.
†These agents are generally recommended with infectious disease consultation for the infection listed. However, please note that not all these agents are FDA approved for the indicated use.

Experimental therapies such as *N*-acetylcysteine for non–acetaminophen-induced ALF, hepatocyte transplantation, and artificial hepatic support systems have shown promise in early studies.[188-190] For a detailed discussion of the management of ALF,[52] see Chapter 88.

Pneumonitis

The cornerstone of treatment remains supportive with supplemental oxygen, fluids, bronchodilators, and mechanical ventilation. Corticosteroids are generally of no proven benefit in viral-mediated pneumonia, and the data regarding systemic glucocorticoids among infants and young children with bronchiolitis show no benefit compared with placebo.[191,192] The use of empiric broad-spectrum antibiotics may be important until a diagnosis can be established, and because some viral infections such as PIVs, HRVs, and coronaviruses may occur in the context of a bacterial coinfection. For certain immunocompromised patients, fungal copathogens must also be considered. Early isolation and infection control measures for suspected viral infections should be implemented.

A number of antiviral strategies have been investigated or employed on an anecdotal basis to treat viral pneumonia, but the only FDA-approved agents include ribavirin for RSV and antivirals for influenza (oseltamivir, zanamavir, amantadine, and rimantadine). For influenza, the strain of local circulating viruses must be considered when planning a treatment regimen. Seasonal H3N2 viruses have shown almost universal resistance to adamantanes since the 2005–2006 season, and seasonal H1N1 viruses have shown rising oseltamivir resistance since 2008–2009.[193] Seasonal H1N1 viruses typically remain sensitive to adamantanes and zanamavir. The reader is encouraged to consult http://www.cdc.gov/flu/ for national surveillance data on influenza viruses circulating in the United States. Combination therapy as empiric treatment may be indicated during periods of concomitant circulating viruses or for severely ill immunosuppressed patients.[65,194] The use of investigational agents such as IV zanamivir or IV peramivir may also be considered.[195-198] Table 95-3 provides a detailed summary of antiviral agents for various causes of viral pneumonia.

Encephalitis

Untreated, HSV encephalitis carries a death rate in excess of 70%[199] and, even treated, death and complications for those who survive remain on the order of 15% and 20%, respectively.[200] Similarly, despite treatment, neonatal HSV CNS disease carries significant risk of death and morbidity, ranging from 0% to 15% and 43% to 68%, respectively.[129] Early identification of patients and rapid initiation of acyclovir have been associated with better outcome.[199,200] Unless an alternative cause is clear, high-dose acyclovir should be initiated in all children with encephalitis until HSV can be ruled out. Other specific antiviral therapy may be directed as outlined in Table 95-3.

References are available online at http://www.expertconsult.com.

VI

Chapter 96

Infectious Syndromes in the Pediatric Intensive Care Unit

Sonny Dhanani and Peter N. Cox

PEARLS

- Because of the rapid progression of septicemia from meningococcus and variability of markers of infection such as white blood cell count and C-reactive protein, clinical diagnosis is imperative.
- Negative blood cultures do not rule out *Staphylococcus*; accordingly, clinical suspicion must often be relied on.
- Invasive group A β-hemolytic *Streptococcus* is commonly associated with toxic shock syndrome and necrotizing fasciitis.
- *Streptococcus pneumoniae* is the most common cause of otitis media and is a frequent cause of sinusitis. With regard to invasive disease in the critical care setting, pneumococcus most commonly presents as bacteremia, pneumonia, arthritis, and meningitis.
- Relying on serologic tests alone rather that clinical suspicion of Lyme disease can lead to missed diagnoses and overtreatment; markers should be ordered only to confirm objective clinical signs.
- Empiric therapy for Rocky Mountain spotted fever is essential early in the course of illness because fatal outcomes have been linked to missed or delayed diagnosis and treatment.
- Infectious syndromes with multiorgan involvement are often caused by nonbacterial etiologies, including viruses; a broad differential diagnosis should be considered.

The pediatric critical care unit is the epicenter of severe infection in most children's hospitals. Many of these infectious processes are nosocomial and are associated with either patient (e.g., immunocompromised) or procedural issues. Other infectious processes affect specific organs (bronchiolitis and meningitis). These specific infections and the general principles of sepsis management are described in Chapters 29, 47, 65, and 103. In this chapter, the authors describe some of the bacterial, viral, and other infections that may precipitate a systemic response and multiorgan involvement requiring intensive care unit admission. Salient and identifying features are highlighted and, where appropriate, specific comments are provided regarding therapeutic strategies.

Meningococcus

Etiology and Epidemiology

Neisseria meningitidis is a gram-negative diplococcus that is a common cause of bacterial meningitis. It also is responsible for 500,000 cases of a severe sepsis syndrome reported worldwide annually. It is estimated that 1.5 cases per 100,000 persons occur, with 1077 cases reported in 2007 in the United States. The case fatality rate is 10% to 14%.[1,2] Of the 13 serogroups, strains A, B, C, Y, and W-135 are implicated most often.[3] Most cases are isolated or sporadic, with less than 5% associated with outbreaks.[4,5] In the United States, serogroup B accounts for 30% to 70% of sporadic cases, whereas serogroup C is much less common but is often associated with small outbreaks.[6-8] Serogroup A is a common cause of cyclic epidemics in Sub-Saharan Africa ("meningitis belt") and Asia, with increasing outbreaks of W-135 notably in Saudi Arabia in 2001 and in Burkina Faso in 2002.[3,9] There were an estimated 700,000 cases in Africa over the past 10 years with an estimated 10% mortality rate.[10]

The disease most often occurs in children younger than 5 years, with the peak attack rate between the ages of 3 and 5 months. Children with complement C5-9 deficiency and asplenia are at increased risk.[3-5,11] Asymptomatic carriage state has been recognized, and pathogenesis is thought to begin on the nasopharyngeal surface.[12] Patients are considered capable of transmitting the organism for up to 24 hours after initiation of treatment.[2,5,12]

Clinical Presentation

Most invasive meningococcal infections present as meningitis, approximately 10% present as sepsis alone and about 40% present as both systemic and central nervous system (CNS) disease.[3,11,13] Since the introduction of the *H. influenzae* vaccine, *N. meningitidis* has become the second most common cause of bacterial meningitis in North America after pneumococcus.[14] With meningitis alone, the classic signs of headache and meningismus are present but their severity can be variable. Onset of septicemia often is abrupt with fever, chills, malaise, and rash. Rash is the hallmark sign presenting in up to 80% of cases.[6,15] Although petechial rash appearing in clusters at pressure sites is classic, urticarial or maculopapular

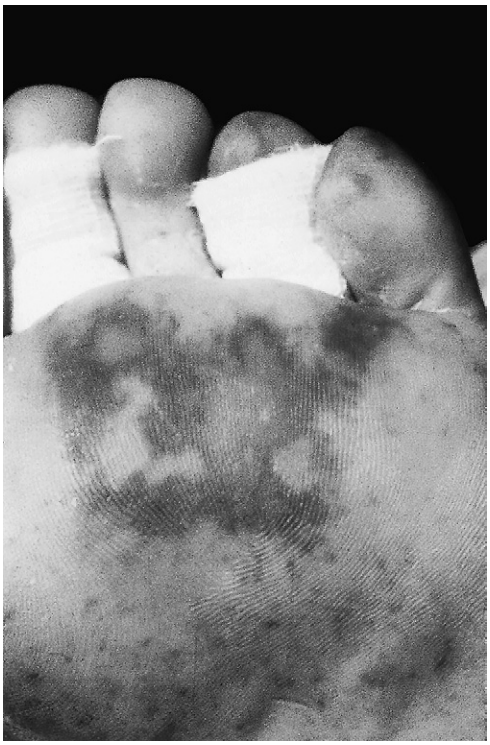

Figure 96–1. Ecchymosis of a sole with meningococcal sepsis. *(From Apicella MA: Neisseria meningitides. In Mandell GL, Bennett JE, Dolin R, editors:* Mandell: principles and practice of infectious diseases, *ed 5, New York, 2000, Churchill Livingstone.)*

rashes may also be present (Figure 96-1).[5] The shock state is mediated by endotoxin (lipopolysaccharide) release with subsequent complement activation and release of numerous inflammatory mediators.[12,16,17] Subsequently, rapid endothelial cell injury occurs, leading to capillary leakage, microvascular thrombosis, refractory peripheral vasoconstriction, and acute myocardial failure.[16] Septicemia can rapidly progress within hours to disseminated intravascular coagulopathy (DIC), shock, and death. Invasive disease can be complicated by an immune-mediated arthritis, pancarditis, endophthalmitis, pneumonia, and adrenal insufficiency from Waterhouse-Friderichsen syndrome.[12,18]

Diagnosis

Because of the rapid progression of septicemia and the variability of markers of infection such as white blood cell count and C-reactive protein, clinical diagnosis is imperative.[15] Clinical suspicion should be based on the characteristic rash and symptoms and signs of hypoperfusion, such as tachycardia, cool peripheral extremities, decreased urine output, and altered mental state. Aggressive treatment should be instituted prior to the onset of overt hypotension, that usually occurs before culture results are available.[19,20]

Confirmation may be difficult, particularly when patients have received early antibiotics. Positive cerebrospinal fluid (CSF) and blood cultures range from 50% to 80% in various series.[21] Nevertheless, cultures from blood and CSF are indicated. Lumbar puncture should be delayed if evidence of increased intracranial pressure, coagulopathy, or cardiovascular instability is present. Cultures from petechial scrapings and other body fluids such as synovial fluid can be helpful. Because *N. meningitidis* may be a part of normal flora, nasopharyngeal cultures are not helpful.[12] Latex agglutination is helpful for CSF but unreliable for urine and blood specimens. Polymerase chain reaction (PCR) for bacterial protein is being used in various centers, with sensitivity and specificity near 90%.[22,23]

Management

Conventional Therapy

Experience and epidemiologic data support rapid early intervention in the peripheral center and aggressive treatment in a tertiary care pediatric intensive care unit.[19,20,24] Rapid administration of antibiotics prior to transfer has been shown to improve prognosis.[25-27] Ceftriaxone 100 mg/kg/day divided once or twice daily is recommended as initial empiric therapy. After *N. meningitidis* is confirmed, then penicillin G 500,000 U/kg/day divided in six doses can be used based on sensitivities. Chloramphenicol is an alternative if the patient is allergic to penicillin.[5,12]

Significant capillary leakage is the hallmark feature in meningococcal sepsis. Thus the prominent problem faced in the early stages is maintenance of adequate circulating volume. Early and aggressive volume resuscitation is vital and has been shown to improve outcome.[28,29] Normal saline or 5% albumin solutions have been the standard fluids; no evidence indicates that other colloids, such as blood, change outcome. Ongoing need for continued volume resuscitation should be based on clinical signs of shock and may be as high as twice the child's circulating volume (e.g., 120 mL/kg).[11,19,30] Myocardial depression should be assumed and inotropes such as dopamine should be used early concomitantly with fluid to ensure adequate cardiac output. Epinephrine, norepinephrine, or vasopressin may be necessary. However, the need for high-dose α-adrenergic agents and vasopressin to maintain blood pressure may need to be balanced against the risk for distal extremity ischemia and necrosis. To ensure appropriate and rapid volume resuscitation and inotropic delivery, central venous access should be established as soon as meningococcal sepsis is suspected; however, volume resuscitation should not be delayed and should be started with peripheral or intraosseous access if central access is not yet available.[30,31]

Respiratory support often is necessary when fluid requirements greater than 40 mL/kg are required. Even if the patient is alert and oriented, early intubation and ventilation is beneficial for resuscitation and transport when meningococcus is suspected in order to ensure adequate oxygenation, reduce the patient's work of breathing, decrease metabolic demands, and maintain stability for transport. More importantly, there is a significant risk of pulmonary edema after aggressive fluid resuscitation in the face of myocardial depression.[31]

Numerous metabolic derangements often present because of cellular fluid shifts. Abnormal potassium, calcium, and magnesium concentrations can affect myocardial function and should be monitored and managed aggressively. Hypoglycemia is a common finding, and accordingly serum glucose concentration should be monitored closely. Metabolic acidosis is common and usually corrects with adequate perfusion and lactate clearance. Replacement of bicarbonate is reserved for pH less than 7.2 assuming adequate ventilation is present. [28,30,31]

DIC is common because of factor loss from capillary leak and clotting factor consumption. Derangements are treated with fresh-frozen plasma and cryoprecipitate as needed to prevent life-threatening hemorrhage. This process is associated with anemia and thrombocytopenia, for which packed red blood cells and platelet transfusions may be necessary, especially if spontaneous bleeding from mucous membranes and venipuncture sites occurs.[31]

Plastic surgical interventions may be necessary for amputations and skin grafting. Consultation with other services may be necessary for renal failure, secondary infections, and neurologic complications.[20,31]

Novel Therapy

In addition to standard cardiovascular and respiratory support, multiple specific treatment strategies for meningococcus have been proposed. They have been aimed at altering the inflammatory cascade, treating hemostatic abnormalities, and inducing vasodilation and perfusion.

The role of steroid therapy remains unclear. Exogenous steroids in the septic setting have been thought to enhance upregulation of adrenergic receptors and improve the response to catecholamines, such as exogenous inotropes. No evidence supports the routine use of steroids in meningococcal sepsis specifically but it is indicated in undiagnosed bacterial meningitis.[31] Adrenal replacement doses of hydrocortisone 1 to 2 mg/kg have been suggested for fluid and vasopressor recalcitrant septic shock.[28,30,32]

Immunotherapy, such as antiserum to *Escherichia coli*, that was thought to halt the immune cascade if given early enough, has not been shown to be beneficial in several trials.[33] Likewise, antiendotoxin HA-1A, a human monoclonal immunoglobulin (Ig)M antibody, had no significant benefit.[34] The overall limitation of antiendotoxin therapy is that it must be given very early in the disease process in order to halt the inflammatory response. An alternative to antiendotoxins may be bacteriocidal/permeability increasing proteins (BPIs). BPIs are found in neutrophils and neutralize endotoxins after their release. The results of a large multicenter trial were promising but underpowered.[35] Anticytokine therapy such as interleukin-1 receptor antagonists and anti–tumor necrosis factor antibodies have been studied for sepsis but not specifically for meningococcus. Plasmapheresis to remove cytokines and other mediators are being studied, but no difference in plasma concentrations or overall outcomes has been reported. Hemofiltration and plasma exchange to remove inflammatory mediators have been performed safely. However, the results are mixed, so they are not currently standard therapy.[36]

As mentioned, several hemostatic abnormalities are related to meningococcal disease, and it is postulated they are key to pathogenesis and severity of disease. Potential therapies to combat DIC include antithrombin-III (AT-III), tissue plasminogen activator (tPA), activated protein C, and heparin, as reviewed by Leclerc et al.[32] Case reports are encouraging, but adequate trials are pending. AT-III infusion may promote return of peripheral perfusion and salvage of limbs.[37] Tissue plasminogen activator was associated with an improvement in shock and a decrease in amputations.[38] In the largest pediatric sepsis interventional trial (RESOLVE) conducted to date, activated protein C was not superior to placebo in terms of shortening duration of organ dysfunction or decreasing mortality. Similarly, adjunctive treatment with activated protein C does not prevent other morbidity, such as significant loss of limbs and was associated with neonatal bleeding.[39,40] Many case reports have supported heparin infusions, but the benefits have not been reproduced in controlled studies.[41] Because of the significant risk of intracerebral bleeding, cost of therapy, and lack of prospective randomized studies, the impact of these adjunct therapies on morbidity and mortality are still being debated and investigated.[39]

Vasodilators to improve peripheral and end-organ perfusion have been studied in small populations, and results are variable. Prostacyclin has been reported to improve distal perfusion, whereas nitroprusside infusions and topical nitroglycerin also have been attempted, with some anecdotal success.[42]

Prevention and Vaccines

Prophylaxis of meningococcal disease is detailed in the American Academy of Pediatrics' Red Book and includes the use of rifampin or ceftriaxone for high-risk contacts. These include household contacts especially less than 2 years old, preschool exposures, and those with direct exposure to body fluids. Routine prophylaxis to health care professionals is not recommended.[5,31] Quadrivalent polysaccharide vaccine to serogroups A, C, Y, and W-135 have been available since the early 1980s but are largely ineffective. More recently, protein conjugate vaccines have been developed and have shown a strong primary response and has lead to a reduction in nasal carriage.[11] Following the introduction of protein conjugate serogroup C vaccine in the United Kingdom, the attack rate decreased by 94% in the immunized population.[43] A quadrivalent conjugate vaccine is now available in North America and further interest in the development of a vaccine to serogroup B, that causes approximately 50% of invasive disease worldwide, is ongoing.[44]

Prognosis

Morbidity and mortality with meningococcus has been difficult to estimate because of multiple serotypes, regional differences, and seasonal variations.[45] Fatalities have been reported as high as 75% in epidemic regions in Africa.[10] The case fatality ratio in the United States is 10% to 14%, with 11% to 19% morbidity in survivors including complications such as need for skin grafting, loss of limbs/digits, and neurologic disability.[44] Several prognostic scores have been developed using multiple clinical and laboratory values. A widely used and validated system is the Glasgow Meningococcal Septicemia Prognostic Score developed by Sinclair and validated by Thomson et al.[15,46] Data suggest that early recognition, early antibiotic administration, aggressive resuscitation, and transfer to a pediatric intensive care unit have reduced mortality of severely ill children from the previously reported rate of 35% down to 2% to 13%.[14,47,48]

Staphylococcus Toxic Shock Syndrome

Etiology and Epidemiology

Staphylococcus aureus is a gram-positive coccus grouped typically in clusters. It is responsible for a wide spectrum of clinical manifestations, including sepsis, pneumonia, cellulitis, arthritis, meningitis, and endocarditis. Staphylococcal

toxic shock syndrome (TSS) came into prominence in the early 1980s with the use of super-absorbent tampons and was named *menstrual-associated toxic shock*.[49,50] Thus this form of TSS had a particular predilection for adolescent and young women.[51] Now, approximately, half of cases in children are hospital acquired.[52,53] Most nonmenstrual cases have been associated with localized musculoskeletal infections, surgery, or insect bites.[54-56]

Staphylococci produce various toxins. These exotoxins are superantigens causing the activation of large number of T cells. In particular, TSS is linked to an enterotoxin named toxic shock syndrome toxin-1 (TSST-1). TSST-1 accounts for approximately 90% of cases of menstrual toxic shock. Other enterotoxins are responsible for up to 50% of nonmenstrual cases.[49,57] TSST-1 acts as a stimulating factor for the release of inflammatory mediators such as interleukin-1β, tumor necrosis factor-α, interleukin-2, and γ-interferon from macrophages and lymphocytes. This massive inflammatory mediator release causes generalized lymphocytic perivasculitis and interstitial edema. This capillary leak syndrome is characteristic of TSS and results in multiorgan dysfunction, including heart, lung, kidney, and brain involvement.[58]

Clinical Presentation

The Centers for Disease Control and Prevention (CDC) has defined TSS as fever, rash, hypotension, multiorgan involvement, and desquamation with specific criteria (Box 96-1).

Box 96–1 Staphylococcus TSS Case Definition

Fever: temperature ≥38.9° C
Rash: diffuse macular erythroderma
Desquamation: 1–2 weeks after onset of illness; involvement of palms, soles, fingers, and toes
Hypotension: systolic blood pressure ≤90 mm Hg for adults, ≤5th percentile for age in children, or orthostatic syncope
and
Involvement of ≥3 of the following organ systems:

- Central nervous system: disorientation or alteration in consciousness, without focal neurologic signs, when fever and hypotension are absent
- Gastrointestinal: vomiting or diarrhea at onset of illness
- Hematological: platelets ≤100,000
- Hepatic: total bilirubin or transaminase concentrations greater than twice the upper limit of normal
- Muscular: severe myalgia or CPK level greater than twice the upper limit of normal
- Mucus membrane: vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: blood urea nitrogen or creatinine concentration greater than twice the upper limit of normal or at least five white blood cells per high-power field in the absence of urinary tract infection

and
Negative results on the following test:

- Blood, throat, or cerebrospinal fluid cultures for other organisms
- Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Modified from Centers for Disease Control and Prevention. Toxic-shock syndrome—United States, *MMWR* 32:201, 1982.

Onset usually is abrupt, with fever, chills, malaise, and diffuse macular erythroderma. Fever often is remarkably high and resistant, occurring with intense myalgias, vomiting, and diarrhea. The rash is described as a generalized erythematous, deep-red "sunburn" and can be accompanied by conjunctival erythema.[59-61] Within 24 hours, cardiovascular depression becomes prominent, with hypotension and decreasing systemic perfusion leading to severe shock and multiorgan dysfunction. Most cases do not cause infective endocarditis unless associated with congenital heart disease. Progressive liver and renal failure are common. The patient may manifest symptoms of diffuse toxic encephalopathy, usually without meningeal signs. Renal failure can be oliguric or nonoliguric. Scaling and desquamation, that are included in the diagnostic criteria, occur with resolution of fever and usually are prominent on the palms and soles.[62-63]

Diagnosis

Differential diagnosis for syndromes that include fever, rash, and multiorgan involvement are numerous and are summarized in Box 96-2. Diagnosis is mainly clinical, but can be supported with inflammatory markers associated with sepsis. The degree of leukocytosis often is not impressive but the percentage of immature cells usually is markedly high.[50] Metabolic derangements can support the diagnosis; for example, hypocalcemia and hypophosphatemia are not unique to TSS but can be profound.[64] Liver function abnormalities are common. Elevated urea and creatinine concentrations result from prerenal causes initially but also may involve acute tubular necrosis. Persistent lactic acidosis even with restoration of hemodynamics may reflect decreased tissue perfusion and end-organ ischemia.[61]

Negative blood cultures do not rule out staphylococcus; accordingly, clinical suspicion often must be relied on.

Box 96–2 Differential Diagnosis of Staphylococcus TSS

Bacterial
Meningococcemia
Invasive group A β-hemolytic *Streptococcus* toxic shock
Group A β-hemolytic streptococcus scarlet fever
Staphylococcus scalded skin syndrome
Salmonella infection

Viral
Measles
Enterovirus syndrome with myocarditis

Tick-Borne
Rocky Mountain spotted fever
Leptospirosis
Ehrlichiosis

Other
Stevens-Johnson syndrome and toxic epidermal necrolysis (drug reaction)
Kawasaki disease
Systemic lupus erythematosus

Modified from Chesney PJ: Pediatric infectious disease-associated syndromes. In Fuhrman BP, Zimmerman JJ, editors: *Pediatric critical care,* St Louis, 1992, Mosby.

Lumbar puncture is not warranted because CSF usually is benign in TSS. Swabs of the primary infection site, such as the postsurgical or vaginal sites can be helpful. TSST-1 antibody assays have been developed but are not recommended, especially because many of the nonmenstrual cases may have other causative endotoxins.[63,65]

Management

Because the course can be variable and unpredictable, close monitoring and observation are essential when TSS is suspected. Rapid and aggressive fluid administration is required because the severity of end-organ involvement is related to the degree of hypotension and duration of decreased perfusion. Volume requirements may be exceptionally high because of the massive capillary leak characteristic of TSS.[66] As a result, acute respiratory distress syndrome (ARDS), myocardial failure, and generalized edema are common. Fluid administration should be guided by close monitoring of blood pressure, central venous pressure, perfusion, and urine output. Other management issues include correction of acid-base abnormalities, electrolyte disorders including hypocalcemia, coagulopathies, renal failure, and fluid overload.[67] Mechanical ventilation, renal replacement therapy, and administration of blood products are often necessary.

Two premises to antibiotic therapy for TSS exist. The first is to kill the organism with a bacteriocidal antistaphylococcal β-lactamase–resistant agent such as cloxacillin or vancomycin. The second is to stop enzyme, toxin, and cytokine production with a protein synthesis inhibitor such as clindamycin. Of note, vancomycin is less effective against staphylococcus and should be limited to resistant organisms or allergic patients.[49,51,67]

Vaginal examination should be performed as soon as possible and foreign bodies removed and sent for cultures. Other possible foci for infection should be drained and irrigated, especially postsurgical sites.

Intravenous gammaglobulin (IVIG) has been shown to prevent T-cell stimulation by enterotoxin and may have a role in modulating the inflammatory response.[68] No systematically studied trials in humans have described benefits of IVIG, but numerous animal models exist. There are anecdotal examples of its effectiveness, especially in refractory cases.[58,69-71] Doses of 150 to 600 mg/kg/day for 5 days or a single dose of 1 to 2 g/kg have been used. In theory, the IVIG must be given early in the course of illness because its role is to prevent rather than treat the systemic inflammatory response.[51]

Corticosteroids have been used after retrospective studies reported beneficial effects on severity and duration of illness.[67,72] However, no further prospective studies have shown specific benefits against the TSST-1 enterotoxin. Therefore steroids usually are reserved for refractory cases where hypotension does not respond to fluids and inotropes. The development of specific antibodies to superantigens is a rapidly developing field.

Prognosis

With aggressive therapy, prognosis is good, with a mortality rate of less than 5%.[53,73] Death usually is related to ARDS or refractory arrhythmias. Mortality is higher in nonmenstrual cases.[74] Other specific risk factors for higher mortality have not been identified, although increasing age has been linked to poorer outcome.[75] Recurrent cases have been noted for both menstrual and nonmenstrual causation.[58,61]

Invasive Group A β-Hemolytic Streptococcus

Etiology and Epidemiology

Invasive group A β-hemolytic streptococcus (GABHS) is a gram-positive coccus often grouped as chains. GABHS accounts for 3.3% of bacteremia in children.[76] Infections resulting from GABHS have become more common, presenting with the two overlapping syndromes of TSS and necrotizing fasciitis.[77-79] The CDC has defined TSS caused by GABHS as having prominent features of shock and multiorgan failure (Box 96-3). TSS caused by GABHS is similar to the clinical entity described for *Staphylococcus* TSS. However, GABHS TSS is more commonly associated with bacteremia and underlying soft-tissue infection compared with staphylococcal TSS.[80-82] Necrotizing fasciitis is characterized by extensive local necrosis of soft tissue and skin. GABHS TSS is associated with necrotizing fasciitis in 50% of cases.[80,83] Apart from these two entities, invasive GABHS can present with more localized infections such as meningitis, pneumonia, osteomyelitis, septic arthritis, and surgical wound infections. It is important to note that severe invasive GABHS rarely occurs following isolated pharyngitis or scarlet fever; rather, most infections reflect the skin or soft tissue as the portal of entry.[84]

The CDC estimates the incidence is 4 to 5 cases per 100,000, with approximately 10,000 cases occurring yearly.[81,85] Overall mortality in the pediatric population is approximately 5% to 10% but is much higher in adults.[86,87] Approximately 10% of cases are hospital-acquired infections. Infections in clusters or outbreaks, even with close contacts, are uncommon.[77]

Box 96–3 Case Definition for Streptococcal TSS

1. Isolation of group A β-hemolytic streptococci:
   - From a normally sterile site: blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy, etc.

   and
2. Clinical signs of severity:
   a. Hypotension:
      - Systolic blood pressure <90 mm Hg for adults; <5th percentile for age in children

      and

   b. Multiorgan involvement with ≥2 of the following:
      - Acute respiratory distress syndrome
      - Coagulopathy: platelets <100,000 or disseminated intravascular coagulopathy
      - Hepatic: total bilirubin or transaminases greater than twice the upper limit of normal
      - Rash: generalized macular erythroderma that may desquamate
      - Renal: creatinine twice the upper limit for age
      - Soft tissue necrosis: necrotizing fasciitis, myositis, or gangrene

If group A β-hemolytic streptococcus is isolated from a *nonsterile* site but other criteria are still fulfilled, then the case is defined as *probable*.

Modified from The Working Group on Severe Streptococcal Infections: Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition, *JAMA* 209:390-391, 1993.

Streptococcal necrotizing fasciitis can occur in otherwise healthy people at any age, but the incidence is higher in young children and the elderly. Risk factors include age younger than 2 years, diabetes mellitus, chronic cardiac or pulmonary disease, immunodeficiency syndromes, intravenous drug use, and malignancy.[88] In children, varicella seems to be an increasing risk factor in recent years. GABHS should be suspected as a secondary infection in children with recurrence of fever especially after day 3 of varicella illness or when lesions are more painful.[89] Several reports have implicated nonsteroidal antiinflammatory drugs as a risk factor for GABHS infection; however, a causal relationship has not been established.[78,90]

The pathogenic mechanism is unknown but is thought to be associated with a streptococcal pyrogenic exotoxin, which may act as a superantigen. This stimulates intense activation and proliferation of T lymphocytes and macrophages, resulting in a massive production of cytokines that, in turn, mediate tissue injury, and shock.[91]

Clinical Presentation

With TSS, most cases present initially with nonspecific flulike symptoms that include fever, chills, and myalgias. Half of the patients develop hypotension within the first 4 hours.[92] Multiorgan failure including ARDS and acute renal failure occurs in up to 55% of patients. Mechanical ventilation is necessary in 90% of patients who develop TSS.[93] Otherwise, presentation includes myositis, perihepatitis, peritonitis, myocarditis, DIC, and generalized septic shock.[86,94]

With fasciitis, severe localized pain is the most common initial symptom, usually without correlating physical signs.[92] It usually is an acute process with rapid progression. The legs are the most common site of infection, but the abdominal wall, groin, and perianal areas also are frequently affected. In newborns, the site most commonly affected is the umbilicus.[85]

Approximately 80% of infants eventually develop obvious signs of soft tissue infection, and of these 70% progress to deeper infections requiring surgical debridement. Over the first 24 to 48 hours, the area becomes erythematous and swollen without sharp margins. Skin vesicles and bullae may be bluish and may appear by days 4 to 5, heralding fasciitis. By this time, the area often becomes anesthetic and gangrenous secondary to thrombosis of small blood vessels. Marked swelling and edema may lead to compartment syndrome requiring urgent fasciotomies.[85,95]

Diagnosis

Signs and symptoms may not be specific for group A streptococcus; thus empiric treatment is initiated before diagnosis is confirmed. Invasive GABHS should be suspected especially when a risk factor such as varicella coinfection or diabetes mellitus is present. Swabbed gram stain and cultures taken from focal lesions probably are the most useful diagnostic tool. Bacteremia is present in 60%, but pending blood culture results should not delay treatment. Often only mild leukocytosis is present, but a left shift is striking.[96] Rising serum creatinine kinase concentration has correlated well with deeper soft tissue infections. When necrotizing fasciitis is suspected, magnetic resonance imaging can be helpful in confirming the diagnosis by identifying muscle and underlying fascia inflammation and necrosis.[97,98] GABHS was identified in 71% of necrotizing fasciitis cases.[99] However, one study in children found GABHS as a single organism in only 25% of the cases; the rest were polymicrobial.[61] Other organisms implicated in necrotizing fasciitis are listed in Table 96-1. Approximately half of necrotizing fasciitis cases involve mixed aerobic and anaerobic flora.[100]

Management

When invasive GABHS (TSS or necrotizing fasciitis) is suspected, aggressive hemodynamic support and prompt antibiotic therapy are essential. A high index of suspicion should encourage initiation of antibiotics specific to GABHS. Frequently, massive amounts of intravenous fluids are required because of the extensive capillary leak.[92] Inotropic agents such as dopamine are needed early in order to support adequate cardiac output. Vasoconstrictors such as epinephrine, norepinephrine, and vasopressin should be used with caution because impaired perfusion to necrotic areas may lead to loss of limbs. Milrinone may be a useful adjunct when vasodilation is necessary.[95]

With TSS, both GABHS and *S. aureus* should be covered with broad-spectrum antibiotics. With a microbiologic diagnosis, the antibiotics can be tailored later. Group A streptococci in general are extremely sensitive to β-lactam antibiotics, but invasive GABHS infections seem to respond less well to the penicillins alone.[101,102] With GABHS identified, penicillin G 200,000 to 400,000 U/kg/day in four to six divided doses can be administered. Clindamycin as an adjunct has proved effective at doses of 25 to 40 mg/kg/day in three to four divided doses.[95,103] Clindamycin works by inhibiting protein synthesis, thus suppressing bacterial toxin production and decreasing penicillin-binding protein synthesis. Clindamycin also has been shown to modulate the immune response.[101] Though no controlled clinical trials have demonstrated improved outcome with the addition of clindamycin, it is recommended in combination with a third generation cephalosporin as initial therapy.[90]

With necrotizing fasciitis, prompt surgical exploration and aggressive debridement are critical, with involvement of general, orthopedic, and plastic surgeons. By the time clinical signs are present, saving viable tissue may not be possible, but debridement is necessary to prevent the progression of inflammation and necrosis.[98] The patient often is returned to the operating room daily for inspection until the infection is adequately

Table 96–1 List of Common Organisms Causing Necrotizing Fasciitis

Gram-Positive Organisms (Percent)	Gram-Negative Organisms (Percent)
Group A streptococci (18–46)	*Escherichia coli* (8–28)
Enterococci (16–34)	*Enterobacter* (2–12)
Coagulase-negative *Staphylococcus* (15–37)	*Pseudomonas* (9–20)
Staphylococcus aureus (9–37)	*Proteus* (6–12)
Staphylococcus epidermidis (18)	Serratia (2–6)
Clostridia (5–21)	*Bacteroides* (18–48)
Mixed gram positives (10)	Mixed gram negatives (16)

Modified from Cunningham JD, Silver L, Rudikoff D: Necrotizing fasciitis: a plea for early diagnosis and treatment, *Mt Sinai J Med* 68:258, 2001.

controlled. Fasciotomies often are needed in the presence of compartment syndrome in order to facilitate adequate perfusion.[102] Amputation may be necessary and should be undertaken early if necessary. Then, daily dressing changes can continue with close monitoring of surgical margins. Often daily magnetic resonance imaging is warranted.[98,100]

Antibodies specific for the toxin do not exist, but use of IVIG 1 to 2 g/kg in a single dose has been effective in case reports in both TSS and necrotizing fasciitis.[69-71,104,105] The possible mechanism may involve prevention of T-cell proliferation and reduction of cytokine release. Some anecdotal reports of the benefits of hyperbaric oxygen also exist but are inconclusive.[106] No controlled trials have demonstrated the efficacy of either of these therapies.

Prognosis

Though incidence of fasciitis may be declining with the use of varicella vaccination, mortality rates for TSS still vary from 30% to 70%.[85,86,107,108] For necrotizing fasciitis, mortality rates range from 6% to 36%.[100] Morbidity is high, including surgical intervention in greater than 50% of suspected fasciitis cases.[84] Irreversible renal impairment is seen in up to 10%. The CDC estimated 1350 deaths related to GABHS in 2007.[81] Unfavorable outcome has been shown to be affected by delayed diagnosis and by the presence of organ failure at the time of admission.[109]

Invasive Pneumococcus

Etiology and Epidemiology

Streptococcus pneumoniae is the most common cause of otitis media and a frequent cause of sinusitis. With regard to invasive disease in the critical care setting, pneumococcus most commonly presents as bacteremia, pneumonia, arthritis, and meningitis. Meningitis is discussed in Chapter 65. This chapter focuses on bacteremia and pneumonia. Other less common pneumococcal infections include endocarditis, soft tissue cellulitis, pericarditis, peritonitis, and salpingitis.

S. pneumoniae is an encapsulated gram-positive diplococcus organized in chains. It is a nasopharyngeal colonizer and is found in up to 40% of healthy children.[110] Transmission via secretions and respiratory droplets increase in environments of close contacts, such as day care centers. Infection from *S. pneumoniae* may be secondary to mucosal barrier changes from other viral infections. In the Northern Hemisphere, invasive disease in children is more prevalent between September and May and can be associated with other viral illnesses such as influenza.[111,112] There are more than 90 serotypes of *S. pneumoniae,* with only a few identified as causing invasive disease. After host cells are invaded, the organism is resistant to phagocytosis because of its capsule and subsequently causes tissue damage.[113] The incidence is higher and the severity of invasive illness greater in children with congenital or acquired humoral immunodeficiencies, including HIV. Patients with deficient splenic function are susceptible (Box 96-4).[112,114]

The overall rate of invasive disease has dropped from 23 to 13 cases per 100,000 persons per year in 2002 in the United States.[115-117] It is relatively more common in newborns and infants up to age 2 years and much less in older children and teenagers.[116,118] Most younger cases result from bacteremia alone.[115] Older children are more likely to develop pneumonia. Per annum, an estimated 500,000 cases of pneumonia, 60,000 cases of bacteremia, and 3000 cases of meningitis related to streptococcus occur in the United States.[81,117] Meningitis occurs most commonly between the ages of 6 and 18 months, bacteremia occurs between 6 and 36 months, and pneumonia presents between 3 and 60 months.[119-121] Of the many children in the Third World who die of lower respiratory tract infection, *Streptococcus* is the primary agent.[122] Globally, *S. pneumoniae* is the most common cause of bacterial pneumonia, accounting for up to 70% of cases.[123] In a Canadian study, the overall incidence of bacterial pneumococcal pneumonia was 9.7 cases per 100,000.[124]

Clinical Presentation

Invasive pneumococcal disease is defined as the isolation of *S. pneumoniae* from normally sterile sites such as blood, pleural fluid, joint fluid, and CSF. Approximately 3% to 5% of febrile children between 3 and 36 months old are at risk for occult or asymptomatic bacteremia, of which 90% are caused by *S. pneumoniae*.[125] In most cases, occult bacteremia resolves without sequelae. However, persistent bacteremia may lead to septic shock with hypotension and end-organ involvement, spreading to the meninges, pleura, bones, and joints.

Pneumococcal pneumonia is associated with bacteremia in 40% of cases.[113,126] Presentation can be quite nonspecific,

Box 96–4 Risk Factors for Invasive Pneumococcal Disease

Organism Factors

Invasive properties of the pneumococcal serotype

Host Factors

Serotype-specific humoral immunity
Age <2 years
Specific ethnic background:
- African American
- Native American
- Alaskan Eskimo
- Micronesian
- Aboriginal (Australia and New Zealand)

Presence of viral respiratory infection
Not breast-fed
Underlying illness:
- Congenital or acquired antibody deficiency
- HIV infection
- Complement deficiency
- Congenital or acquired splenic dysfunction:
  - + Sickle cell disease
  - + Other hemoglobinopathies
  - + Surgical splenectomy
- Malignancy
- Nephrotic syndrome

Environmental Factors

Daycare attendance
Recent antibiotic use
Season of year
Smoke exposure
Overcrowding

Modified from Tan TQ: Pneumococcal infections in children, *Pediatr Ann* 31:242, 2002.

especially in infants. Symptoms range from those managed as an outpatient to those requiring mechanical ventilatory support. Most commonly, symptoms include fever, cough, tachypnea, malaise, and emesis.[126] On physical examination, hypoxia is associated with localized crepitations and decreased breath sounds that correlate with lobar infiltration on chest radiographs. Almost 50% of cases present with multilobar involvement and 40% with pleural effusions.[127] Although rare, necrotizing pneumonia, pneumatoceles, and lung abscesses can be seen. Pleural empyema occurs in up to 14% of pneumococcal pneumonia. Interestingly, lower lobe pneumonia may present with abdominal symptoms and signs, whereas upper lobe pneumonia may be associated with nuchal rigidity.[113]

Diagnosis

Diagnosis depends mostly on clinical suspicion. Initially, *S. pneumoniae* bacteremia should be suspected when the white blood cell count (WBC) is greater than 15,000 and absolute neutrophil count is greater than 10,000. Isolation from blood or sterile fluid confirms the diagnosis but should not delay treatment if pneumococcus is suspected.[128] Pneumococcal rapid antigen testing and PCR can aid in making the diagnosis, especially if antibiotics have already been started.[114,121] Sputum samples are rarely helpful in children; nasopharyngeal cultures may reflect only colonization rather than infection. However, if intubated, samples obtained via bronchioalveolar lavage are beneficial. Ultrasound or computed tomography (CT) can help identify effusions or empyema, which subsequently can be aspirated.[129]

Management

For critically ill patients potentially infected with invasive *S. pneumoniae*, a third-generation cephalosporin such as ceftriaxone or cefotaxime (25 to 100 mg/kg/dose every 8 hours) is recommended. Cefuroxime, a second-generation agent, is also an appropriate choice for non-meningitic cases.[112,130] If the patient is toxic, immunodeficient, or antibiotic resistance is suspected, then vancomycin 10 mg/kg/dose every 6 hours should be added. However, even when nonsusceptible strains were identified, complications, recovery, and mortality were no different than when penicillin alone was used.[114,131,132] Thus vancomycin should not be used routinely but is suggested when meningitis, severe multilobar pneumonia, carditis, meningitis, or hypoxia and hypotension are present. When pneumococcus is confirmed and sensitivities are determined, then antibiotics should be reevaluated and penicillin G 400,000 U every 4 to 6 hours started if susceptible. Clindamycin can be used for patients with penicillin hypersensitivity.[112,130]

During the past 2 decades, antibiotic resistance among pneumococcal strains has continued to increase and has complicated the management of invasive infections. Resistance stems from the alteration of penicillin-binding proteins, which are enzymes that are important in the production of bacterial cell walls. As a result of these alterations, there is a decreased affinity for β-lactam antibiotics and thus decreased susceptibility.[130] In the United States, 34% of strains were nonsusceptible to β-lactams, with 21% showing full resistance and 13% showing intermediate resistance. Similarly, full resistance to ceftriaxone also increased to 14%.[122] Resistance to other classes of antibiotics occurs by other mechanisms and is summarized by Kaplan.[130] Although resistance to vancomycin is not yet described, tolerance such that *S. pneumoniae* is inhibited but not killed has been reported.[133,134]

Treatment should continue for 7 days for bacteremia alone and 10 to 14 days for pneumonia. Symptoms such as fever and tachypnea may persist for 3 to 4 days after initiation of treatment. If fever persists, then further investigations for infectious collections or resistance are necessary.[114,134] If empyema is suspected, then the etiology should be established definitively with immediate thoracocentesis and empyema drainage. These procedures have been shown to decrease the severity and duration of illness. If only effusions are present, then draining is not imperative unless loculations develop or symptoms persist.[129] Dexamethasone as an adjunctive therapy is only warranted for meningitis cases in children 6 weeks of age and older.[112]

Prevention and Vaccination

Pneumococcal conjugate vaccine was licensed in the United States in 2000 for use in children younger than 2 years of age and older children at increased risk for pneumococcal disease. As a result, by 2006 the incidence of invasive pneumococcal infections had decreased by 77% in children less than 5 years old.[112,121] This vaccine targets the seven strains of pneumococcus that, in 2000, were the most common among children. Disease caused by pneumococcal strains not covered by the vaccine formulation has increased, and this increase was primarily driven by serotype 19A; however, new conjugate vaccines should provide protection against serotype 19A disease in the future.[121]

Prognosis

In most children, occult pneumococcal bacteremia resolves spontaneously without apparent sequelae. Overall mortality from documented bacteremia was reported to be 0.4% in one review.[135] The possibility of persistent bacteremia and spread to sterile site results in significant morbidity. Ten percent of patients with bacteremia develop focal complications. The case/fatality rate for pneumococcal pneumonia is 1% in children but up to 20% in adults.[135,136] Pleural empyema and chronic lung changes may occur in up to 14%.[113] The impact of penicillin resistance on the clinical presentation and outcome of invasive pneumococcus is still unclear[137,138] The role of new heptavalent conjugate vaccines on morbidity and mortality is evolving.[121]

Lyme Disease

Etiology and Epidemiology

Lyme disease is a multiorgan system disease caused by the spirochete *Borrelia burgdorferi*. Endemic to many parts of the United States, Lyme disease is transmitted by deer tick bites.[139] It has become the most common reported tick-borne disease in the United States, with almost 20,000 cases reported by the CDC in 2006.[140] The number of cases has been increasing yearly since 1992 (Figure 96-2).[141] Incidence is greatest in the northeastern, mid-Atlantic, and north-central

regions of the United States, although the incidence is rising in the northwest and California (Figure 96-3).[1,142,143] *B. burgdorferi* has also been reported in Asian countries including China.[144] Cases are highest in children between 5 to 14 years old. Two-thirds of cases have onset of symptoms in June and July. Numerous reports have commented on the overdiagnosis of Lyme disease as a result of misinterpretation of serologic tests, that may account for the inflated numbers.[145]

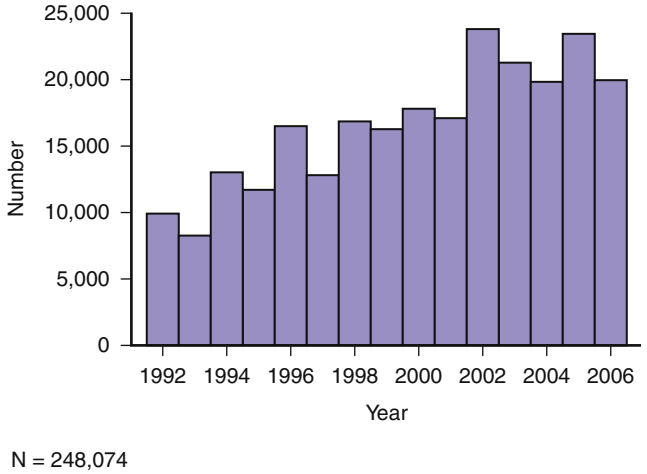

Figure 96–2. Number of reported cases of Lyme disease by year—United States, 1992–2006. *(From Centers for Disease Control and Prevention: Surveillance for Lyme disease—United States 1992-2006,* MMWR *57: 1–9, 2008.)*

Clinical Presentation

The classic infection was well described by Steere[146] and outlined by the CDC in 1995.[139] The clinical manifestations are divided into three stages: early localized (7 to 14 days after tick bite), early disseminated (3 to 10 weeks), and late disease (months). In 80% of patients, Lyme disease in so-called stage 1 starts as a slowly expanding erythema migrans rash with central clearing. The lesion begins as a red macule or papule at the site of the bite, which usually is in the head and neck region. The rash expands over days to a diameter greater than 5 cm. Only one third of cases presents with the classic central clearing lesion. This characteristic "bull's eye" or "target" lesion often is accompanied by nonspecific, intermittent flu-like symptoms such as fever, malaise, fatigue, headache, myalgias, and arthralgias. The incubation period from infection to onset of erythema migrans typically is 7 to 14 days but may be as short as 3 days and as long as 30 days.[142,147-149] Gerber et al.[143] described initial presentations in children with a single migrans lesion in 66%, multiple lesions in 23%, arthritis in 7%, meningitis in 1%, and carditis in 0.5%.[150] Symptoms in children included seventh nerve palsy in 14%, fever in 24%, fatigue in 58%, arthralgias in 33%, and headache in 42%.[143,149,151,152] Some infected individuals have no recognized illness and have only serologic evidence of infection. The initial rash usually fades within 3 weeks.[142]

After a few weeks the disease enters stage 2 and becomes disseminated. The first sign often is multiple smaller erythema migrans lesions and frank arthritis in up to 80% of cases. Approximately 15% of untreated patients develop neurologic symptoms such as a lymphocytic meningitis, encephalitis,

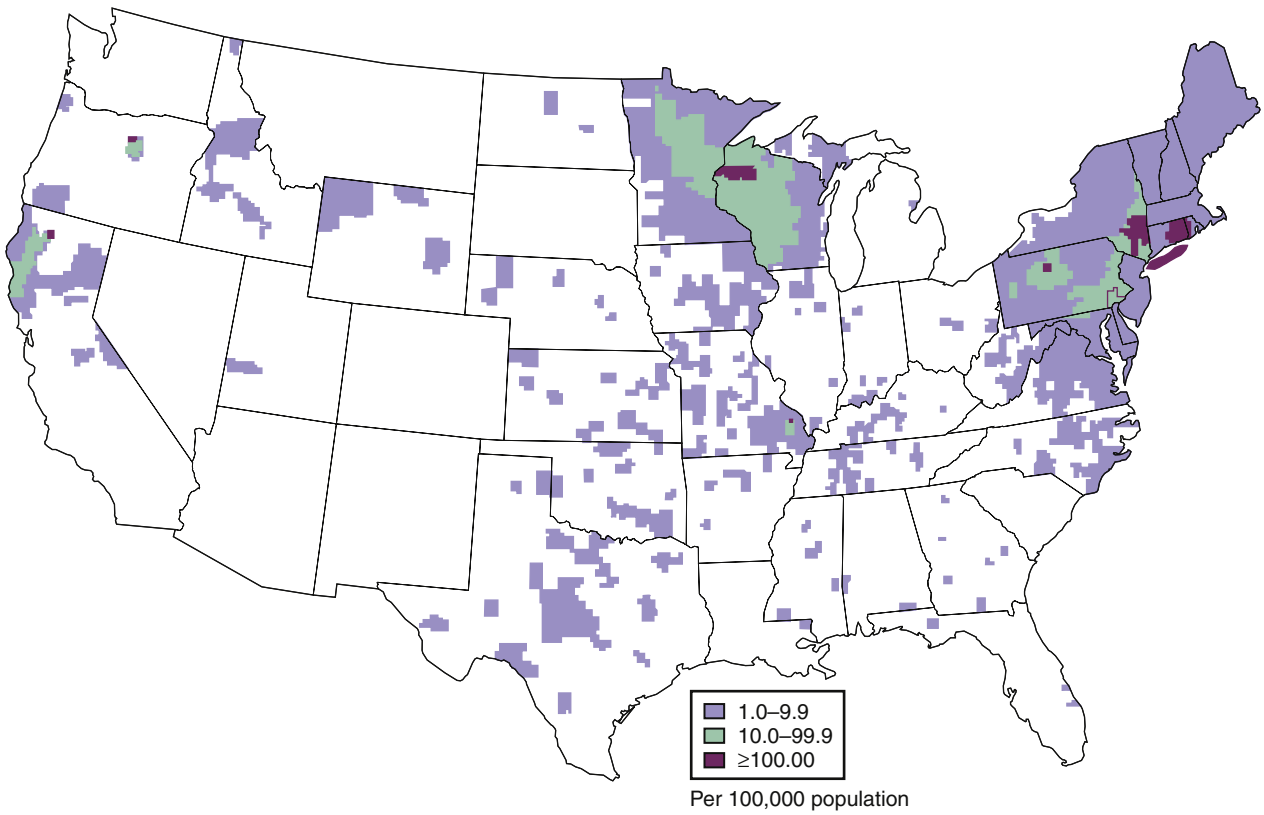

Figure 96–3. Number of reported cases of Lyme disease by county—United States, 1992–2006. *(From Centers for Disease Control and Prevention: Surveillance for Lyme disease—United States 1992-2006,* MMWR *57:1–9, 2008.)*

pseudotumor cerebri, cerebellar ataxia, radiculoneuritis, and focal neuropathies, particularly seventh nerve facial palsies and optic nerve deficits.[153,154] The neurologic abnormalities typically improve even without treatment. Approximately 5% of patients develop acute cardiac manifestations, most commonly atrioventricular block of varying degrees but also myocarditis and dilated cardiomyopathy. Carditis from Lyme disease is rare in children and is usually transient.[149,155] Arthritis of the knee and hip is the most common late presentation of Lyme disease, especially in children.[155] However, the diagnosis is often missed because of assumption of septic arthritis from other bacterial etiologies.[156]

In stage 3, late manifestations of damage to major organ systems may persist, particularly to joints and the neurologic system. In 5%, chronic symptoms of encephalitis, polyneuropathy, and cognitive impairment may persist. However, late neurologic disease is rare in children.[157-159] In 90% of patients, the arthritis is single joint and involves the knee; it can last up to 2 years.[160] Typically, the arthritis involves swelling rather than pain and redness; thus it presents as a less "septic" picture. Chronic arthritis now is rare with antibiotic treatment, but arthralgia symptoms persist in up to 33%.[142,148,161]

Diagnosis

Laboratory testing is neither required nor recommended.[155] Although the diagnosis usually is based on clinical suspicion, serologic assays can help confirm the diagnosis. Patients are frequently seronegative on early presentation, so clinical suspicion remains imperative. Because of the many false-positive results, especially in areas of low prevalence, the diagnosis should not be made solely on the basis of serologic tests.[162] Relying on serologic tests alone rather than clinical suspicion has led to missed diagnoses and overtreatment.[145] Thus markers should be ordered only to confirm objective clinical signs.

Borrelia is often found on culture from skin aspirates from migrans lesions or from blood culture in early, disseminated disease. Blood cultures usually are negative in the early, localized stage.[149,163] Serologic confirmation has improved with use of enzyme immunoassays, but again false-positive results are obtained for other spirochetal infections, viral infections (varicella), and autoimmune diseases. Because of difficulties with serologic assays, ELISA and Western blot testing are used to confirm the diagnosis.[1,151] Serology was positive in 80% of cases with neurologic or joint involvement and in 50% of cases with rash alone.[155] IgM-specific antibodies arise between 3 to 6 weeks, and IgG rises slowly and peaks months after the onset. Antibodies persist for years and should not be used to follow treatment success. PCR is more widely used but has low sensitivity and is prone to false-positive results, so is not recommended as the sole method for diagnosis.[162]

Overall, laboratory findings are nonspecific, with mild elevation in white cell count. Hepatic and renal functions are usually not affected. With arthritis, neutrophil predominant pleocytosis in synovial fluid can be associated with an elevated erythrocyte sedimentation rate. Lumbar puncture is recommended if neurologic symptoms are present and is especially useful for the confirmation of pseudotumor cerebri. Imaging is recommended before lumbar puncture in these cases.[151] However, the need for lumbar puncture is controversial when facial palsies present in isolation.

Management

The drug of choice for early, localized disease in children older than 8 years is doxycycline 100 mg twice daily. The American Academy of Pediatrics also recommends amoxicillin 50 mg/kg/day for younger children. Treatment with antibiotics is recommended for 14 to 21 days.[151] For early disseminated disease with mild migrans, isolated facial palsies, or mild arthritis, the same oral regimens are warranted. Some evidence shows that only 10 to 14 days treatment may be sufficient.[164] Treatment at the erythema migrans stage almost always prevents the development of later stages of the disease. Although the rash subsides within days, other symptoms may take several weeks before resolving. Treatment does not affect the resolution of nerve palsies but prevents the late disease.[154] Lyme arthritis alone can be treated with oral doxycycline or amoxicillin. Nonsteroidal antiinflammatory agents may be helpful. If severe or persistent arthritis, neurologic, or cardiac manifestations occur, then ceftriaxone 100 mg/kg/day intravenously for 21 days is recommended.[142,148,151,161] Children with prolonged PR intervals or heart block should be hospitalized with cardiac telemetry and treated with parental antibiotics.[155] Corticosteroids have not shown to be effective therapy for neurologic or arthritic symptoms.[165] Repeat courses of antibiotics have not shown benefit for chronic or severe cases.[166]

Prognosis

Although Lyme disease is rarely fatal, the morbidity, especially related to neurocognitive effects, can be severe if untreated.[149,155] Behavioral and sleep changes and auditory and visual deficits have been identified.[159] However, children treated appropriately have shown no cognitive deficits on long-term neuropsychological testing in prospective studies.[167] Almost half of children report recurrence of symptoms, usually arthralgias, but almost none have residual true arthritis.[168] Lyme disease may be linked to chronic fatigue and fibromyalgia.[169] Approximately 10% have recurrence of erythema migrans. Overall the success rate of treatment is approximately 95% with equivalent neurologic, cardiac, and daily functioning compared with matched controls.[149,170-172]

Rocky Mountain Spotted Fever

Etiology and Epidemiology

Rocky Mountain spotted fever (RMSF) is a tick-borne bacterial infection resulting in a diffuse small-vessel vasculitis with the potential for causing multisystem disease. It is among the most virulent and potentially fatal pathogens because it often presents as a diagnostic dilemma for clinicians.[173] RMSF is caused by *Rickettsia rickettsii*, small gram-negative coccobacilli carried by dog or wood ticks. Other rickettsial groups may also be responsible for spotted fever illnesses.[174] RMSF is transmitted while the tick feeds on blood during bites.[175] RMSF is endemic to the United States, Canada, Mexico, and Central and South America. The disease occurs mostly in the spring and early summer months, with almost half of cases occurring during May and June.[176,177] The incidence is particularly high in the southeastern, south central, and south Atlantic regions. Different rickettsial strains have higher prevalence in these different regions.[178,179]

In the United States, approximately 2.2 cases per 1 million per year are reported, with the highest incidence in children between 5 and 9 years old.[180,181] In 2007, 2221 cases were identified in the United States. The number of cases continues to rise each year (Figure 96-4).[141] Approximately 20% of these cases and almost 15% of the deaths were in children younger than 10 years.[1,182] Serologic infection with rickettsii is much more common than indicated by disease incidence reports, suggesting the existence of subclinical disease.[183] Rickettsiae invade and multiply in the endothelial cells of the vasculature, resulting in cytopathic vascular injury and leading to morbidity and mortality.[184]

Clinical Presentation

The incubation period after a tick bite is 2 to 14 days (mean, 7 days).[175] The classic triad consists of fever, rash, and headache with a history of a tick bite. The classic triad is present in only 60% and in less than 20% during the first 3 days.[185,186] Approximately 30% to 40% of patients do not recall receiving a tick bite.[187] Initial symptoms often are nonspecific, with malaise and myalgias.[188] The fever is observed in two thirds of patients by day 3. Other common presenting symptoms are nausea, vomiting, and abdominal pain, especially in younger children.[189,190] The rash often begins by day 4, with blanching maculopapules classically starting at the wrists and ankles and then appearing on the palms, soles, and trunk (Figure 96-5).[189] Later, in up to 50% of patients the rash may become petechial, purpuric, or even gangrenous.[182,191] Younger patients tend to develop the rash earlier.[192] Importantly, the absence of the pathognomonic rash does not exclude RMSF; an estimated 10% of cases are "spotless."[193] Headache is present in almost all adults and in most older children.[177] Encephalitis, focal neurologic deficits, and meningismus have been described in some patients.[189,194,195]

Rickettsiae invade and multiply in the endothelial cells of the vasculature, resulting in cytopathic vascular injury that is responsible for morbidity and mortality. Endothelial damage results in the activation of the clotting cascade, extravasation of fluid, and reduced perfusion. The increased vascular permeability leads to the major complications of edema, hypovolemia, and hypotension, with end-organ failure such as shock, coma, myocarditis, liver dysfunction, and renal failure.[182,190,195,196] Renal insufficiency on presentation is secondary to glomerular and tubular damage and has been shown to have prognostic implications with increased fatal outcomes.[197] On autopsy, rickettsial vasculitis has been found in the brain, spinal cord, cardiac tissue, and lungs.[195,196] Other complications include cardiac arrhythmias, gastrointestinal bleeding, and skin necrosis.[182]

Diagnosis

The WBC count often is quite variable and usually is not helpful. Most patients, however, develop thrombocytopenia as the disease progresses. Approximately 30% of patients also are anemic. Liver and renal function abnormalities are common.[175,177,198,199] Approximately 20% of patients have hyponatremia and hypoalbuminemia from massive capillary leak and fluid shift.[195] CSF shows mononuclear pleocytosis in one third of samples, with an elevated protein concentration in 20%.[185]

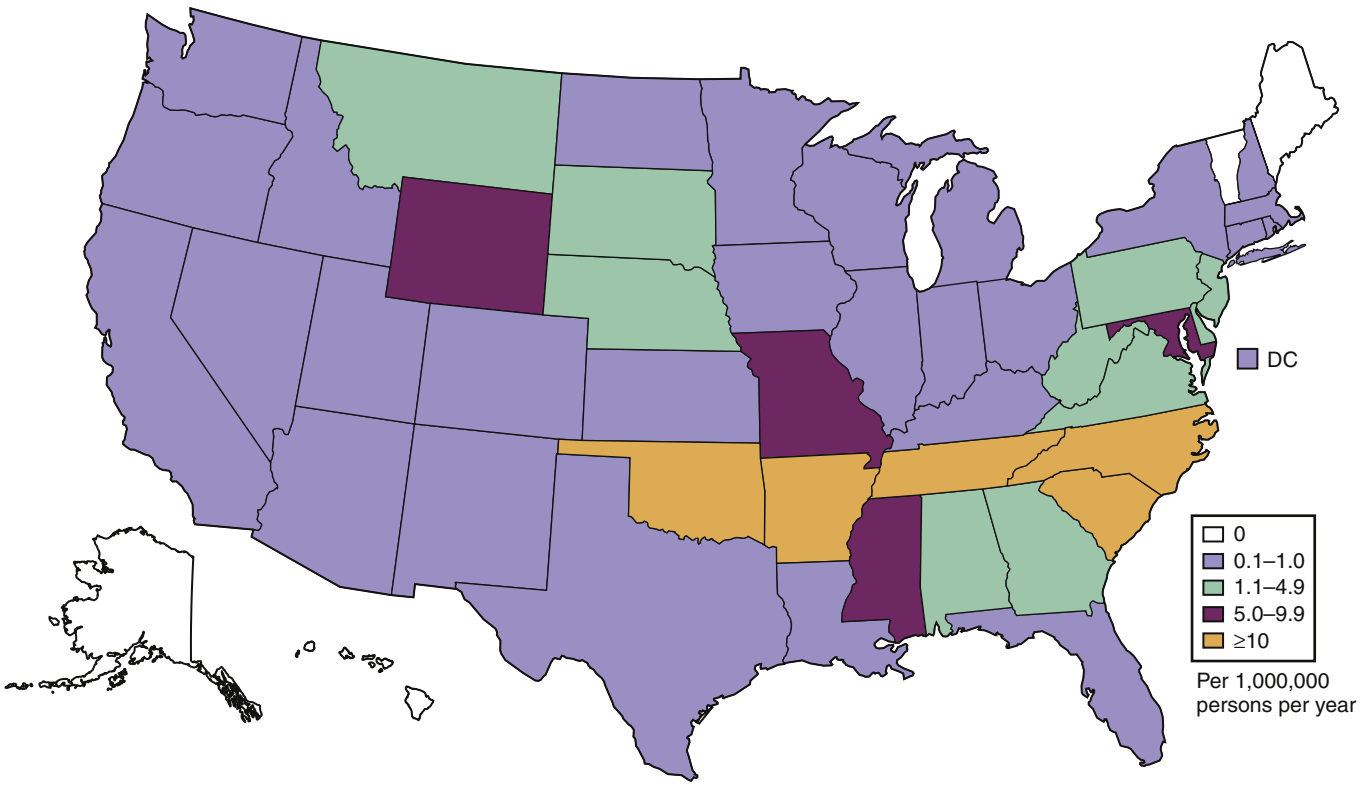

Figure 96–4. Distribution of average reported cases of Rocky Mountain Spotted Fever—United States 1997–2002. *(From Chapman AS, Bakken JS, Folk SM, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichiosis, and anaplasmosis—United States: a practical guide for physicians and other health care and public health professionals,* MMWR Recomm Rep *55:1-27, 2006.)*

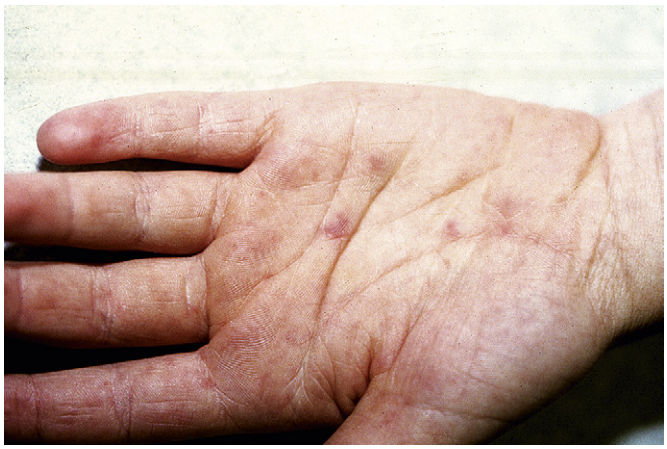

Figure 96–5. Palmar rash associated with Rocky Mountain spotted fever. *(From Walker DH, Raoult D:* Rickettsia rickettsii *and other spotted fever group rickettsiae (Rocky Mountain spotted fever and other spotted fevers). In Mandell GL, Bennett JE, Dolin R, editors:* Mandell: principles and practice of infectious diseases, *ed 5, New York, 2000, Churchill Livingstone.)*

Because *R. rickettsii* often is not cultured, the diagnosis usually is clinical. For confirming the diagnosis, serotyping by direct immunofluorescence and immunoperoxidase staining are up to 90% sensitive and 100% specific on skin biopsies if a rash is present.[183,200] If available, PCR can reliably confirm the diagnosis early in blood or biopsy.[190,199] Serum antibodies using indirect immunofluorescence, complement fixation, and latex agglutination can be obtained but do not become positive until 7 to 10 days into the illness.[177,180] Thus these tests are impractical in the acute setting, and pending results should not delay treatment.

A differential diagnosis of enterovirus, measles, Epstein-Barr virus, cytomegalovirus, mycoplasma, scarlet fever, TSS, meningococcus, ehrlichiosis, and Kawasaki disease should be considered.[189]

Management

Empiric therapy is essential early in the course of illness because fatal outcomes have been linked to missed or delayed diagnosis and treatment.[178,201] The drug of choice for treatment of RMSF is doxycycline. Until recently, chloramphenicol was recommended by the American Academy of Pediatrics and CDC for children younger than 9 years because of the risk of teeth staining with tetracycline usage.[199] However, because of the risk of aplastic anemia and retrospective evidence of higher case/fatality rates with chloramphenicol, doxycycline now is first-choice therapy even in young patients.[202] In fact, the risk of staining is limited with a short course of therapy.[192,203] The fluoroquinolones also have activity against rickettsiae but have not been well studied in humans.

Doxycycline can be administered orally but should be used intravenously in the critical care setting when the patients are vomiting, obtunded, or have multiorgan involvement. Doses of 2 to 4 mg/kg/day divided every 12 hours are given for a minimum of 5 to 7 days and until the patient has been afebrile for at least 2 days.[177,199] Because initial therapy is empiric, other broad-spectrum antibiotics such as third-generation cephalosporins also should be started to cover other infections in the differential diagnosis.

Along with antibiotic therapy, aggressive supportive measures must be instituted. Restoration of massive fluid imbalances and cardiovascular support may be necessary. Correction of electrolyte abnormalities and coagulopathy are essential, and close monitoring of liver and renal dysfunction is indicated.[176,189]

Prognosis

Prior to antirickettsial therapy and aggressive supportive care, case fatality rates were higher than 30%, and approximately 13% of children with RMSF died. Even with treatment and the supportive care now available, the case/fatality ratio is 2% to 3%.[181,182,196] Geographic variations in case fatality have been recognized.[179] Some cases are not diagnosed until postmortem.[178] Delayed diagnosis and late initiation of specific therapy, especially after day 5 of illness, have the most significant association with higher mortality, emphasizing the need for empiric doxycycline as soon as RMSF is suspected.[177] Other risk factors for fatal outcomes include nonwhite race, male, age older than 40 years, absence of headache, no history of tick bite, gastrointestinal symptoms, and renal dysfunction.[186,192,194,195]

Hantavirus

Etiology and Epidemiology

Invasive infections for sepsis syndromes can be caused by non-bacterial causes including enterovirus and influenza virus species. These are discussed in other chapters. This chapter will focus on rarer viruses with specific cardiopulmonary syndromes; a classic example is Hantavirus. Hantavirus was first recognized in 1993 in the southwest United States and subsequently was named Hantavirus pulmonary syndrome (HPS).[204-206] In Europe and Asia, hantavirus species have been linked to a group of diseases with varying severity of hemorrhagic fever with renal syndrome (HFRS).[207,208] Since then, HPS has been recorded throughout North and South America and the clinical picture has been broadened to a cardiopulmonary syndrome.[209,210] Between initial cases in 1993 and 2006, a total of 438 cases with 20 to 50 new cases annually have been identified in 31 states.[1] There were 32 cases reported in North America in 2007.[141] The average age was 35 years old, with the youngest 11 years old (eight patients younger than 16 years old).[207] Ten cases in adolescents and five cases younger than 12 years old (youngest 5 years old) were reported in Argentina.[211]

Hantavirus has been linked to mice and rat species endemic to many areas in both urban and rural environments. The deer mouse is the main vector in rural areas throughout the United States and Canada. Infection occurs most commonly via inhalation of aerosolized saliva or excreta of infected rodents. The virus subsequently invades the pulmonary mucosa after inhalation with typically a 2-week incubation period, causing direct cellular damage that leads to increased vascular permeability.[212]

Clinical Presentation

HPS initially presents with a nonspecific illness manifested as fever, myalgia, headache, and gastrointestinal symptoms. When reviewed by Duchin et al.[204] in 1994, myalgia seemed to be the most frequently observed initial symptom. Shortness

of breath and cough occurred in 76%. Gastrointestinal symptoms varied from abdominal pain, nausea, vomiting, and diarrhea in up to 76%. The hallmark feature is rapidly progressive, noncardiogenic, pulmonary edema, and ARDS. The most common physical findings were tachypnea, tachycardia, and significant hypoxemia but otherwise were nonspecific (i.e., fever, malaise, anorexia).[204,210] In the cardiopulmonary syndrome, a dry cough then signals the onset of the cardiogenic phase with progression to shock and DIC.[213] Myocardial depression may be related to direct infiltration of cardiac endothelium resulting in atypical myocarditis. [214,215]

Hallmarks of the HFRS are prominent vascular permeability with subsequent petechiae and frank hemorrhages as well as severe renal involvement. Usually five stages are present, including febrile, hypotensive, oliguric, diuretic, and convalescent phases.[216] Up to 30% present with moderate-to-severe disease. Most often patients have severe abdominal and back pain. Pulmonary involvement does not seem to be a feature in Europe and Asia.[217,218] Although this serotype has been found, the HFRS clinical picture is rare in the United States, for reasons that are still unclear.

Diagnosis

Almost all patients had an elevated WBC count, with significant left shift, neutrophilia, myeloid precursors, and sometimes atypical lymphocytes.[204] Leukopenia and thrombocytopenia are also common features.[219] PTT was elevated in two thirds of patients with elevated D-dimers and abnormal fibrinogen levels. Hematocrit levels are elevated due to ultrafiltration of fluid in the lungs. On urinalysis, 40% had proteinuria and almost 60% had hematuria, although renal function abnormalities were uncommon in cases occurring in the United States.[214] The diagnosis is confirmed by PCR or by serology using enzyme-linked immunosorbent assay techniques. Chest radiographs show mostly rapidly progressive bilateral, diffuse infiltrates and developing pleural effusions.[214]

Differential diagnosis includes other sepsis syndromes such as meningococcus and other infectious causes of acute respiratory failure, such as pneumonic plague, leptospirosis, rickettsial infections, legionellosis, and atypical viral or bacterial pneumonias.

Management

Treatment is mainly supportive, especially of the respiratory system. Early intensive care management with prompt correction of pulmonary, cardiovascular, and electrolyte abnormalities is critical.[220,221] Cardiovascular support for hypotension and subsequent arrhythmias may be necessary.[215] However, fluid administration for hypotension must be balanced in the face of massive vascular leakage and significant pulmonary edema. Thus early use of vasopressors is recommended.[214] Extracorporeal membrane oxygenation support has improved survival.[222] Intravenous ribavirin has been used but has not shown a benefit in reducing mortality in HPS.[223,224]

Prognosis

Mortality rate is 35% with Hantavirus infection and usually is secondary to severe hypotension and arrhythmias secondary to vascular leakage and progressive hypoxemia.[225] The CDC reports the case fatality rate is 37% but was as high as 76% in some reviews of HPS.[204,226] Case/fatality rates in adolescents were up to 60% in patients younger than 12 years in an Argentinian review.[211]

References are available online at http://www.expertconsult.com.

Health Care–Associated Infection in the Pediatric Intensive Care Unit: Epidemiology and Control—Keeping Patients Safe

Tracie Northway, Joanne M Langley, and Peter Skippen

PEARLS

- Handwashing is the most important means of preventing nosocomial infection. Each pediatric intensive care unit should develop programs to increase compliance with hand hygiene.
- Nonessential invasive devices should be removed. Establish routines that require individual patient evaluation of device use daily.
- Antimicrobial stewardship aims to minimize overexposure and unnecessary use of broad-spectrum antibiotics. Antibiotic-resistant bacteria are an increasing concern as a cause of hospital-acquired infection, requiring a multipronged approach to control that includes adherence to isolation procedures, appropriate use of antibiotics, educational interventions, prescribing guidelines, and restriction of the use of some antibiotics.
- A comprehensive infection prevention and control program allied with organizational quality and patient safety programs is an essential strategy for minimizing hospital-acquired infections. Critical care teams should establish strong collaborative partnerships with the infection prevention and control service.
- Parents and visitors should be made partners of the infection control team to help prevent infection in their children.

Burden of Illness and Scope of the Problem

Children ill enough to require admission to a critical care unit are among the most vulnerable to infection in the hospital. Normal physical defenses such as skin integrity, the cough reflex, and gastric motility are interrupted in the critically ill child. Innate and adaptive immunity are compromised during high-acuity acute illness. Broad-spectrum antibiotics used as empiric therapy for suspected sepsis may disrupt normal protective flora and permit overgrowth by pathogenic bacteria and fungi. Younger children are more likely to require intensive care unit (ICU) admission than older children; this age group has a maturing immune system and may not have completed the full series of all routine childhood vaccines.

The most common health care–associated infections (HAIs) in the pediatric ICU (PICU) are primary bloodstream infections (BSIs) (28%), ventilator-associated pneumonia (21%), and catheter-associated urinary tract infections (15%). HAIs increase length of stay and morbidity and mortality rates for both adult and pediatric critically ill patients. This translates to an economic burden on the system as a whole.[1]

There has been renewed emphasis in the last decade on systematic strategies for preventing HAIs, both from a patient safety perspective and in an effort to reduce the cost of health care. In a public health care system, it is often argued that money is not saved by improving efficiency because each patient discharged is replaced by a new patient with comparable overall costs. In this context, the incentive to reduce HAIs is perhaps more on the ability to help decrease ICU and hospital length of stay and therefore improve access to the system. Infection prevention and control, patient safety, patient advocates, and health care providers alike see the value of improved health outcomes associated with reduction in nosocomial infections.

This chapter reviews the epidemiologic principles underlying infection prevention and control measures and recommends interventions to prevent the most common HAIs in the PICU.

Epidemiologic Principles of Infection Prevention and Control

Chain of Infection

The transmissibility of microorganisms between infected or colonized persons and susceptible hosts was perhaps most convincingly demonstrated in the 1847 observations of Ignaz Semmelweis, who introduced handwashing to the obstetric

wards of an Austrian maternity hospital and subsequently observed a reduction in the rates of puerperal fever.[2] In this instance, the initiation of hand hygiene after patient contact (cadavers) interrupted the spread of the infectious agent (group A *Streptococcus*) via the route of transmission (hands). Over time the epidemiologic roles of the susceptible host, the infected person, and the route of infection were more clearly elucidated and came to be known as the *chain of infection.* The interaction among these three components is dynamic, and infection may be favored when the host is more susceptible, the infectious agent is more virulent, and the route of transmission is more facilitating.

Children, long recognized as not just "little adults," are unique hosts because of their continuing physical, neurodevelopmental, and immunologic change and development from infancy through adolescence. Children, especially infants, lack immunity to many pathogens because they have not been exposed through infection or immunization. They are prone to multiple viral infections during any year and naturally share them. Young children are not developmentally capable of understanding or performing good self-hygiene.

The nature of a children's hospital can also put children at risk of developing an HAI. Open design wards and critical care units rather than single-room design, shared toys, pet visiting, and communal play areas provide many opportunities for transmission of infection.

Once admitted to the ICU, children become more vulnerable to infection because of the interventions needed to provide life-sustaining care as well as the close contact of multiple care providers. An infectious agent that is a harmless or helpful commensal in a normal host can become a life-threatening pathogen in the ICU patient. Because of frequent antibiotic use, the spectrum of infecting microorganisms in the hospital, particularly the ICU, are usually more pathogenic that those acquired in the community setting. Finally, the route of transmission of infection in the ICU is facilitated through frequent patient contact by health care workers, use of mechanical devices and medical therapies that disrupt natural defenses, and inadequate attention to infection prevention and control measures that prevent spread of infection to and between patients (Box 97-1).

BOX 97–1 Factors that Influence Risk of Infection in the PICU

Factors that Influence Exposure

Host Factors
- Loss of skin integrity (e.g., intravascular devices)
- Loss of respiratory defenses such as cough, cilia propulsion (e.g., intubation, sedation)
- Loss of gastrointestinal defenses such as low pH, motility (e.g., use of H2 blockers, nasogastric tubes)
- Anatomic defect (e.g., surgical site)

Environmental Features
- Crowding in the ICU
- High patient/health care worker ratios (decreased time for infection prevention measures)
- Use of prophylactic antibiotics (alters colonizing normal flora, allows overgrowth of pathogens)
- Infection prevention and control practices of ICU health care workers
- Immunization status of health care workers
- Visitor policies
- Reservoirs of infectious organisms in the ICU (e.g., health care workers who are carriers, environmental reservoirs)

Factors that Influence Likelihood of Infection if Exposed

Host Factors
- Age
- Gender
- Genetic makeup
- Coexisting infection
- Nutritional status
- Use of immunosuppressive agents, including systemic steroids
- Immunization status
- Immune deficiency

Infectious Agent
- Virulence
- Antimicrobial resistance

Routes of Infectious Disease Transmission

Infectious diseases, whether bacterial, viral, protozoal, fungal, or helminthic, are transmitted via one or more of three routes, usually categorized for infection control purposes as contact (direct or indirect), droplet, or airborne (Table 97-1).[3]

Contact transmission includes direct contact and indirect contact. *Direct contact* transmission occurs when organisms are transferred through physical contact from an infected or colonized person to a susceptible host. *Indirect contact* transmission occurs when microorganisms are passively transferred to a susceptible host via an intermediate object, such as a contaminated medical device, inanimate objects in the patient's physical environment, or contaminated hands.

Droplet transmission is the transfer of microorganisms through large droplets (≥5 μm in diameter) generated from the respiratory tract of an infected or colonized person (the source) that are propelled 1 to 2 meters from the source and land on the nasal or oral mucosa of the susceptible host or in the immediate environment. The droplets can be propelled from the respiratory tract in the course of coughing, sneezing, vomiting, or singing or during procedures such as suctioning. These large droplets are propelled a distance of less than 2 meters through the air but do not remain suspended in the air; that is, they do not become aerosolized.

Airborne transmission refers to the spread of microorganisms in particles that are very small (<5 μm) and can therefore remain suspended in the air and widely dispersed by currents to places far from the host. Airborne particles are created through the evaporation of large droplets or may exist in dust particles containing skin squames and other debris.

Infection Prevention and Control Measures

The Infection Prevention and Control team

Prevention of infection in patients receiving health care is the responsibility of all health care providers. Although Infection Prevention and Control Professionals (ICP) provide an essential expertise,[4] it is important that the PICU team establish ongoing multidisciplinary processes to reduce infection risk. Among the activities the multidisciplinary team will address are the integration of surveillance data into formal plans for

Table 97–1 Modes of Transmission of Microorganisms in the ICU

Mode of Transmission	How Organisms Are Transmitted	Example
Direct	Direct physical contact between an infected or colonized individual and a susceptible host.	Visitor asymptomatically shedding herpes simplex virus kisses postoperative transplant patient.
Indirect	Passive transfer of microorganisms to a susceptible host via an intermediate object such as contaminated hands that are not washed between patients or contaminated instruments or other inanimate objects in the patient's immediate environment.	Health care worker provides care to patient with *Clostridium difficile* diarrhea, does not perform adequate hand hygiene, then enters room of a noncolonized patient and handles bedding and bedrails, leaving *C. difficile* spores in susceptible patient's environment.
Droplet	Large droplets (≥5 μm in diameter) generated from the respiratory tract of the source (infected individual) during coughing or sneezing or during procedures such as suctioning or bronchoscopy. These droplets are propelled a distance of <1 m through the air and are deposited on the nasal or oral mucosa of the new host (newly infected individual) or in the immediate environment. These large droplets do not remain suspended in the air; therefore special ventilation is not required since true aerosolization (see below) does not occur.	Health care worker with influenza virus infection sheds respiratory secretions on the face of a PICU patient.
Airborne	Dissemination of microorganisms by aerosolization. Organisms are contained in droplet nuclei, airborne particles <5 μm in size that result from evaporation of large droplets, or in dust particles containing skin squames and other debris that remain suspended in the air for long periods. Such microorganisms are widely dispersed by air currents and inhaled by susceptible hosts who may be some distance away from the source patients or individuals, even in different rooms or hospital wards.	Patient with measles is housed on an open ward in the emergency department; airborne virus particles are carried throughout the department and inhaled by susceptible hosts.

improvement of patient care at regular intervals and designing and implementing quality improvement initiatives. The collaborators in these initiatives can be infection control practitioners, the hospital epidemiologist or medical director of infection control, a clinical pharmacist, members of quality and patient safety departments, and representatives from nursing, ICU physicians, and respiratory therapy. Others may be needed depending on the issue at hand, such as housekeeping or information technology.

Isolation Practices: Standard Precautions and Additional (Transmission-Based) Precautions

Schema to classify infection prevention and control techniques have evolved over time from systems in which a microbiologic laboratory isolate was required (e.g., disease-specific *Salmonella* diarrhea isolation), to systems focused on preventing transmission of blood-borne diseases to health care workers (Universal Precautions), to the present system in which certain practices are followed continuously with all patients and supplemented based on syndromic presentation and/or specific laboratory diagnoses. In Canada and the United States, the procedures and practices that should be continuously practiced in health care settings are termed *Standard Precautions* and *Routine Practices,* respectively, and are briefly outlined in Table 97-1. The concept of Standard Precautions, in which the health care worker has a responsibility to practice certain behaviors (e.g., hand hygiene) or use certain interventions (e.g., wear a mask when face-to-face with a coughing patient) based on a recognition of the need to do so rather than because they were asked to do so, has not yet been universally adopted in health care settings. Training in these skills should be considered an essential component of health care worker competency.

Types of isolation practices (routine, additional) are based on the scientific understanding of how infectious diseases are transmitted from a host or inanimate reservoir to a susceptible host and aim to control or eliminate the reservoir or infectious agent, interrupt transmission, and protect susceptible persons.

If a patient has symptoms that could be caused by an infection (e.g., cough, diarrhea, rash) or diagnosis of a communicable infectious disease, then Additional Precautions may be required in addition to Standard Precautions.[3] The three types of Additional Precautions are contact, droplet, and airborne. A full description of the rationale for these precautions and the specific information needed to apply them is beyond the scope of this chapter; readers are referred to comprehensive guidelines available from public health agencies such as the U.S. Centers for Disease Control and Prevention (CDC)[3] or from the relevant agency in the jurisdiction in which they practice. A useful guide when deciding which type of precautions to use for an individual patient is the "Red Book" of the Infectious Diseases Committee of the American Academy of Pediatrics[5]; each institution will also have its own infection control manual.

The basic components of Standard Precautions are hand hygiene, use of personal protective equipment (PPE) (e.g., gowns, gloves, masks, face shields) based on the nature of the health care worker-patient interaction and the extent of anticipated body fluid exposure, respiratory/cough etiquette, and safe injection practices. As previously emphasized, Standard Precautions are to be integrated into all patient care activities, regardless of the clinical status of the patient. Additional, or transmission-based, precautions are used when the route(s) of transmission are not completely interrupted by using Standard Precautions alone.[3]

Respiratory Etiquette/Cough Hygiene are measures to contain respiratory secretions and include covering one's cough (e.g., coughing into a tissue or the elbow), promptly disposing of tissues, and performing hand hygiene after touching respiratory secretions.

Safe Injection Practices are basic principles of aseptic technique in the preparation and delivery of parenteral medication that limit the risk of infectious disease transmission for both the health care provider and the patient. They include preferential use of single-dose over multidose vials and use of sterile, single-use, disposable needles (needleless access devices) and syringes.

Infection Control Practices for special lumbar puncture procedures are the donning of a face mask and sterile gloves by the health care worker when placing a catheter or injecting material into the spinal space. These recommendations were made after a number of postmyelography meningitis cases occurred without such precautions.

Contact Precautions are intended to prevent transmission of infectious agents, including epidemiologically important microorganisms, that are spread by direct or indirect contact with the patient or the patient's environment. In addition to Standard Precautions, for example, gloves are required for all entries to a patient's room rather than just when patient interaction will occur.

Droplet Precautions are intended to prevent transmission of pathogens through close respiratory or mucous membrane contact with respiratory secretions. In addition to Standard Precautions, for example, health care workers and others coming within 3 to 6 feet of a patient on Droplet Precautions would be required to wear facial protection (mask, goggles, and/or face shield), a gown, and gloves. A child on Droplet Precautions would generally be placed in a room alone to avoid contact with other children. (Note: Some guidelines refer to a 3-foot perimeter of an infectious person on Droplet Precautions, and others refer to a 6-foot distance. The worldwide experience with the severe acute respiratory syndrome (SARS) virus, in which droplet transmission may have occurred up to 6 feet from the source, has led some jurisdictions to implement a 6-foot perimeter for droplet precautions.)

Airborne Precautions prevent transmission of infectious agents that remain infectious over long distances when suspended in the air. A patient on Airborne Precautions must be placed in a room alone with special air handling and ventilation capacity. PPE that should be donned by health care workers entering the room of a patient on Airborne Precautions includes a gown, gloves, and a surgical (procedure) mask or respirator depending on the disease encountered.

Patient placement is the determination of which physical setting is safest for the child while minimizing risk of transmission of infectious disease from a potentially or definitely infected patient. Within Additional Precautions recommendations include guidance about the need for a single room (e.g., whether shared rooms are acceptable) or whether a room with special air handling is required.

There are inherent safety risks associated with isolation practices. Isolation practices such as single rooms and PPE may limit the number and type of encounters health care workers have with patients because of the cumbersome nature of entering a room, breaking coverage, the discomfort of certain PPE, and the need to come and go to bring equipment, documentation, and other materials.[6] Limited encounters may inhibit the critical care team's ability to access and assess accurately the child and family. Adult studies have demonstrated a negative correlation between patient safety and isolation[7] as well as increased HAI with lower nurse/patient ratios.[8] Although no conclusions can be drawn regarding recommended staffing levels for isolated patients in the PICU, this evidence suggests that increased vigilance is warranted for these critically ill children.

Hand Hygiene

Contaminated hands of health care workers have been shown in many studies to transmit health care–associated pathogens.[2,9] The World Health Organization Patient Safety initiative on hand hygiene emphasizes five moments for hand hygiene: before touching a patient, before clean/aseptic procedures, after body fluid exposure/risk, after touching a patient, and after touching patient surroundings.[9]

The advent of waterless hand hygiene agents has been a particularly important development for the critical care setting because of superior antimicrobial killing, time saved compared with water-based handwashing, rapid action, no risk of antimicrobial resistance, and the ease with which waterless agents can be stationed close to the point of patient care. Alcohol-based hand rubs are in general the preferred hand hygiene product for all health care settings.[2,9] When hands have visible dirt or organic matter (e.g., blood) they must be cleaned with water and soap.

Although the benefits of proper hand hygiene far outweigh the risks, skin irritation and health care worker attitudes about hand hygiene products can be an impediment to compliance and satisfaction with hand hygiene agents and must be considered when choosing a particular product in a specific health care setting.[9,10]

Personal Protective Equipment

PPE consists of clothing or devices donned by health care workers for their safety or protection while performing potentially hazardous patient care activity. To interrupt infectious disease transmission, eye protection (goggles or face shield), masks, gowns, and gloves may be worn as a part of Standard Precautions and Transmission-Based Precautions.

A surgical (procedure) mask provides adequate facial protection against droplets generated from the respiratory tract. Surgical masks are also used for source control (e.g., on a coughing patient) as a part of respiratory hygiene/cough etiquette. To protect against airborne particles, a particulate filtering face piece respirator is required because it is thought to filter at least 95% of the smaller airborne particles.[11] Airborne particles are known to be produced in certain infectious diseases (e.g., tuberculosis, varicella, measles) or may be produced during aerosol-generating procedures in the ICU (e.g., intubation) in patients with respiratory infections (e.g. influenza, SARS). The choice of mask type became a controversial topic during the influenza A H1N1 pandemic that began in 2009, with different jurisdictions recommending procedure masks for health care worker protection during non–aerosol-generating procedures in patients with suspected influenza and others recommending respirators. There is little evidence to suggest that influenza is transmitted through the airborne route; in a recent randomized controlled trial surgical masks

were not inferior to respirators in preventing influenza transmission.[12] Readers are referred to local public health and infection control authorities for jurisdiction-specific guidance.

Surveillance

Surveillance for HAIs in a PICU is a process in which information about infections acquired after admission are summarized and given back to the care team in a timely manner so that problems can be identified for action. Surveillance has been defined as "a systematic method of collecting, consolidating, and analyzing data concerning the distribution and determinants of a given disease or event, followed by the dissemination of that information to those who can improve outcomes."[13]

Although an HAI could occur in any body system to a patient admitted anywhere in the hospital, historical systems of total hospital surveillance are no longer seen as wise use of scarce resources. Surveillance "by objective" was introduced in the 1980s and has led to systems focused on "targets" that cause the most morbidity or mortality, are frequent, or are remediable.[14] In the PICU, the most important are BSIs and ventilator-associated pneumonia.[15,16] Other important surveillance targets in the PICU are urinary tract infection associated with catheterization, surgical site infections such as mediastinitis, and acquisition of epidemiologically important pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococcus (VRE).

The National Health Safety Network (NHSN) of the CDC is a national surveillance system that collects data from a sample of health care facilities that voluntarily submit data on the occurrence of certain HAIs. Because standardized methodology and definitions and risk-adjusted data are used in the NHSN, the surveillance data permit recognition of trends, identification of practices associated with prevention of HAIs, and comparison of rates within and between facilities.[17] Relevant to the PICU setting, NHSN reports central line–associated BSI (CLA-BSI) rates (number of infections per central line days), central line utilization ratio (central line days per patient days), urinary catheter–associated infection (UTI) rate and utilization ratios, and ventilator-associated pneumonia (VAP) rate (VAP days per ventilator days) and utilization. It is important to note that these rates are device specific and therefore incorporate the effect of exposure to an important risk factor. Surveillance results from the NHSN are updated periodically and published in medical journals and on the CDC website.

Standard surveillance definitions have been developed by the CDC (Table 97-2).[18] The CDC definitions incorporate subcategories for children younger than 1 year in recognition of the variable clinical presentation of infection by age. However, CDC definitions may be difficult to apply in children, and alternative approaches have been explored.[19-23] Surveillance definitions fulfill a different purpose than inclusion/exclusion criteria for clinical trial enrollment, or than the diagnosis of illness by a clinician. Surveillance definitions consistently identify indicators of HAI over time and between settings.

Identification, synthesis, interpretation, and report generation of HAI surveillance data in the health care setting are performed by infection control professionals.[4] These professionals have completed certification requirements, have achieved competence in infection prevention and control practice,[24] and have been shown to perform HAI surveillance more accurately than do quality assurance personnel.[25]

Screening

Patient Screening

Screening of patients for colonization with certain antibiotic-resistant organisms (AROs) such as MRSA has been proposed as a method to contain spread of these organisms in colonized or infected patients. Several types of ARO screening programs have been described, including admission screening based on risk factors (e.g., hospitalization in the last 6 months, patient from a long-term care facility), universal screening on admission, and weekly point prevalence screening surveys. The pretest likelihood of colonization, the cost of the test, the timeliness of test reporting, the ability to isolate screened patients, and the degree to which MRSA transmission is occurring are all factors that influence the feasibility and usability of the type of screening program chosen.[26] Although increased frequency of screening will identify more colonized patients, it is not clear if this practice reduces the frequency of transmission in the PICU setting.[27] An active MRSA surveillance testing program is recommended when MRSA transmission continues to occur despite the implementation of basic practices for prevention and monitoring of transmission.[28]

Visitor Screening

The importance of family-centered care and visitation by siblings as well as parents means that PICUs must establish mechanisms to identify visitors who may have communicable infections before they enter patient care areas. Education of visitors regarding signs and symptoms of illness and recommendations to remain away are used in many PICUs. Visitor self-screening was widely used during the 2009 H1N1 influenza pandemic. Brochures, posters, telephone messages, and videos may be used to communicate these messages.

Occupational Health

Occupational health programs play an essential role in the protection of health care workers from infectious diseases through prevention and management of unintended communicable disease exposures. These interventions reduce the risk of infectious occupational hazards to health care workers as well as opportunities for health care workers to spread infectious diseases to patients. Occupational health programs ensure health care workers are offered immunization against vaccine-preventable infectious diseases of importance in the health care setting, perform fitness-to-work assessments, assist in educational programs so that health care workers can protect themselves and their families from acquiring infectious diseases while at work (e.g., respiratory protection programs, respirator fit testing), and provide postexposure counseling and care (e.g., blood exposures during phlebotomy; unprotected intubation of a patient with meningococcemia or group A *Streptococcus* toxic shock syndrome). Occupational health programs collaborate closely with infection prevention and control programs.[29]

Table 97–2 Summary of CDC/NHSN Definitions for HIA (2008)

Bloodstream infection	Laboratory confirmed *(infections must be primary)*	*Regardless of age:* • Recognized pathogen from ≥1 blood culture, *or* • Common skin contaminant in ≥2 blood cultures associated with symptoms (fever, chills, hypotension)
		≤1 Year of age: • Common skin contaminant in ≥2 blood cultures, *and* • Associated with symptoms (fever >38° or <37° C, apnea, bradycardia)
	Clinical sepsis	*Applies only to ≤1 year of age:* • Symptoms (fever >38° or <37° C, apnea, bradycardia), *and* • Negative or no blood culture done, *and* • Physician initiates sepsis treatment *and* • No primary infection elsewhere
Systemic infection	Disseminated infection	• Infections, usually of viral origin, without an apparent single site of infection and involving multiple organs and systems (e.g., varicella)
UTI	Symptomatic	• $\geq 10^5$ Microorganisms/mL urine, not >2 species, and symptoms (at least one of the following: fever >38° C, urgency, frequency, dysuria, suprapublic tenderness)
		• Symptoms (at least two of the following: fever >38° C, urgency, frequency, dysuria, suprapublic tenderness) *and* at least 1 of 5 urinary laboratory criteria *or* physician diagnosis *or* treatment for UTI • Separate criteria are available for children ≤1 year without nonspecific symptoms (not referent to the urinary tract) *and* 1 of 7 laboratory criteria
	Asymptomatic	• Indwelling urinary catheter within 7 days before urine culture, *and* • $\geq 10^5$ Microorganisms/mL urine, not >2 species, *and* • Asymptomatic, *or* • No indwelling urinary catheter within 7 days of urine culture, *and* • $\geq 10^5$ Microorganisms/mL urine, not >2 species in two urine cultures with same organism(s)
Pneumonia *(Alternate criteria are used for the diagnosis of pneumonia in adults.)*	Clinically defined (infants and children)	• Serial chest radiographs (one or more for patients without underlying disease and two or more for patient with underlying disease) with new or progressive and persistent infiltrate or consolidation or cavitation, or pneumatocoeles (in ≤1 year old), *and* • Clinical signs and symptoms (vary according to the patient age: ≤1 year or ≥1 year and ≤12 years)
Lower respiratory tract, not pneumonia	Bronchitis, tracheobronchitis, other lung infection	• No clinical or radiographic evidence of pneumonia, *and* • Two or more symptoms or signs (fever >38° C, cough, new or increased sputum production, rhonchi, wheezing), *and* • One or more positive cultures from deep tracheal aspirate or bronchoscopy *or* positive antigen test on respiratory secretions, *or* • Child ≤1 year with no clinical or radiographic evidence of pneumonia, *and* • Two or more symptoms or signs (fever >38° C, cough, new or increased sputum production, rhonchi, wheezing, respiratory distress, apnea or bradycardia), *and* • One or more of the following: positive culture from deep tracheal aspirate or bronchoscopy *or* positive antigen test on respiratory secretions, *or* serologic diagnosis
Ear, eye, nose, throat, mouth	Conjunctivitis	• Pathogen cultured from purulent exudate from conjunctiva or contiguous tissues, *or* • Patient has redness or swelling of conjunctiva or periorbital area and white blood cells and organisms on gram stain *or* purulent exudate, positive antigen test on exudate, *or* conjunctival scraping, positive viral culture, serologic diagnosis, or multinucleated giant cells on microscopic examination of conjunctival exudate
	Sinusitis (Separate criteria exist for oral cavity, ear and mastoid infections, eye infections other than conjunctivitis, and pharyngitis, laryngitis, and epiglottitis.)	At least one of the following: • Organism cultured from purulent material from sinus cavity, *or* • One or more of the following signs or symptoms with no other recognized cause: fever >38° C, pain or tenderness over the involved sinus, headache, purulent exudate, or nasal obstruction, *and/or* • Positive transillumination or positive radiographic examination
Central nervous system	Intracranial infection	At least one of the following: • Organisms cultured from brain tissue, *or* • Abscess or intracranial infection seen during surgical operation, *or* • Selected central nervous system symptoms without another cause *and* 1 of 4 laboratory criteria, *or* • Patient ≤1 year with at least 1of 5 selected symptoms *and* 1 of 5 laboratory criteria

Continued

Table 97–2 Summary of CDC/NHSN Definitions for HIA (2008)—Cont'd

	Meningitis or ventriculitis	• Organisms cultured from cerebrospinal fluid, *or* • At least one of the following symptoms: fever, headache, stiff neck, meningeal signs, cranial nerve signs, irritability, *and* • 1 of 5 laboratory criteria, *or* • Patient ≤1 year with at least of 1 of 5 selected symptoms *and* 1 of 5 laboratory criteria
	Spinal abscess without meningitis	• Organisms cultured from abscess in the spinal epidural or subdural space, *or* • Abscess in spinal epidural or subdural space seen during surgery, autopsy, or in histopathologic examination
SSI	Superficial incisional, primary or secondary	• Occurs within 30 days of operative procedure, *and* • Involves only skin and subcutaneous tissue of the incision, *and* • At least one of the following: purulent drainage from incision, organisms isolated from aseptically obtained incisional fluid or tissue, one sign or symptom (pain, tenderness, redness, swelling, heat), *and* • Surgeon opens incision and incision is not cultured or is culture positive
	Deep incisional, primary or secondary	• Occurs within 30 days of operative procedure or within 1 year if an implant is left in place, *and* • Involves deep soft tissues of the incision, *and* • At least one of the following: purulent drainage from the deep incision but not from the organ/space of the surgical site, spontaneous dehiscence of surgical site or symptomatic patient has site opened by surgeon and incision is not cultured or is culture positive, abscess found on direct examination (radiologic, histopathologic, or during operation), or surgeon diagnosis
	Organ space, primary or secondary, indicated specific type (e.g., cardiac)	• Occurs within 30 days of operative procedure or within 1 year if an implant is left in place, *and* • Infection involves any part of the body, excluding superficial or deep incisional areas, opened or manipulated during the operative procedure, *and* • Patient has one of the following: purulent drainage via a drain placed into organ/space; organisms cultured from aseptically obtained specimen from organ/space; abscess found on direct examination, during reoperation, or by radiologic or histologic examination or surgeon diagnosis
Bone and joint infection (Separate criteria exist for joint or bursa infection and disc space infection.)	Bone (osteomyelitis)	*At least one of the following:* • Organisms cultured from bone, diagnosis based on direct examination during surgery or on histopathologic examination, *or* • Two or more symptoms (fever >38° C, localized swelling, tenderness, heat, or drainage at bone site), *and* • One laboratory finding (positive blood culture or blood antigen test or radiographic evidence of infection)
Cardiovascular system	Mediastinitis (Separate criteria exist for endocarditis, myocarditis, pericarditis and vascular infection.)	*At least one of the following*:* • Organisms isolated from mediastinal tissue or fluid obtained by aspirate or during surgery, *or* • Diagnosis during surgical procedure or by histopathologic examination, *or* • Presence of one or more of the following signs or symptoms: fever >38° C, chest pain, or sternal instability, *and* • One or more of the following: mediastinal widening on chest radiograph, purulent drainage, or organism cultured from drainage
Gastrointestinal (Separate criteria exist for hepatitis, sgastrointestinal tract infections and intra-abdominal infection.)	Gastroenteritis	*At least one of the following:* • Acute onset liquid stools for >12 hours with or without vomiting or fever and no likely noninfectious cause, *or* • Two or more of following signs and symptoms: nausea, vomiting, abdominal pain, fever >38° C, or headache, *and* • One or more of the following: enteric pathogen detected in stool or rectal swab (by culture, routine or electron microscopy, or cytopathic change in tissue culture), or enteric pathogen detected by antigen or antibody assay on blood or feces
	Necrotizing enteritis	• In infants, two or more signs and symptoms (vomiting, abdominal distension, prefeeding residuals) and no other recognized cause, *and* • Persistent microscopic or gross blood in stools, *and* • More than one radiologic abnormality (e.g., pneumoperitoneum, pneumatosis intestinalis, unchanging rigid loops of small bowel)

This summary of the CDC/NHSN surveillance definitions for HAIs and criteria is not comprehensive. The reader is referred to Horan TC, Andrus M, Dudeck MA, et al: CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting, *Am J Infect Control* 36:309-332, 2008.

Primary, First infection; *secondary,* infection as a result of another previous infection in the patient.

*For infants ≤1 year of age, the symptoms and signs above are adapted to fever (>38° C rectal), hypothermia (<37° C rectal), apnea, bradycardia, or sternal instability.

Vaccine-preventable diseases of particular importance in the PICU setting are hepatitis B, pertussis, influenza, bacterial agents that cause meningitis and bacteremia *(e.g., Neisseria meningitidis, Haemophilus influenzae),* measles, mumps, rubella, and varicella. Critical care settings may present unique challenges because of the intensity and frequency of health care worker/patient contact and the likelihood of health care worker exposure to body fluids while manipulating invasive devices.

Selected Topics in Policy, Procedure, and Program Development to Prevent Health Care–Associated Infection

Intervention Bundles

Care "bundles" are a group of evidence-based interventions that, when executed together, result in better patient care than when implemented individually[30] and can reduce HAIs or colonization.[31,32] Intervention bundles to prevent BSIs and VAP in the ICU setting have been included in national patient safety campaigns such as the United States' Institute for Healthcare Improvement's "Saving 100,000 Lives" and the Canadian Patient Safety Institute's "Safer Healthcare Now."

Characteristics of care bundles are their scientific grounding, all-or-none implementation (the process is not completed if one step is left out), goal of improved reliability of processes needed for effective care, and potential to contribute to improved teamwork and interprofessional communication in a care area.[30,33] Strategies include team generation of ideas as to how to implement bundle components, development of educational approaches for acquisition of new knowledge and/or sharing of information, and creation of reliable processes and methods of measurement, such as a daily goals sheets incorporated into daily bedside rounds.

Antibiotic Stewardship

Judicious use of antimicrobials is now seen as an essential component of preventing the emergence of multidrug-resistant organisms.[34] The overuse and inappropriate use of antibiotics is associated with the emergence of AROs. Principles of judicious antibiotic use include restriction of antibiotics (e.g., stop orders, restricted hospital formulary, requirement for infectious disease consultation for use of certain drugs), including antimicrobial susceptibility reporting and educational efforts aimed at changing physician prescribing practices.

Antibiotic stewardship begins with empiric treatment of the newly admitted patient. Although a suspected infection should initially be treated with broad-spectrum antibiotics, therapy should be changed to the most narrow spectrum agent once culture results are available or discontinued if there is no further evidence of bacterial infection. The clinical pharmacist is an integral member of PICU daily bedside rounds. They should participate in the one-on-one education of resident and nursing staff, be available for consultation, and assist in the development of evidence-based antibiotic prescribing guidelines for specific hospital acquired infections, updated regularly and combined with regular surveillance knowledge of local offending pathogens and their susceptibilities. Approval of certain antibiotics by an infectious disease consultant reduces antibiotic use, costs, and the emergence of AROs.

Antibiotic Prophylaxis

Some surgical procedures may be performed in the ICU rather than the operating room. Antibiotics given within 2 hours before certain surgical procedures (e.g., implantation of biomedical devices, central nervous system surgeries) and continued for less than 24 hours decrease the incidence of surgical site infection.[35-37] There is no evidence that antibiotic prophylaxis before the placement of central venous catheters (CVCs) or external ventricular drains reduces infection rates. Antibiotic prophylaxis while these devices remain in place only leads to resistant colonizing organisms without reducing infection rates.

Antibiotic Cycling

Antibiotic cycling refers to a scheduled rotation of antibiotics with similar spectrums of bacterial coverage for a specified period, with the aim of limiting the emergence of resistance to any single agent. Although this strategy has been proposed as a potential method to decrease antimicrobial resistance,[34,38] there is insufficient evidence to recommend its widespread application at this time.[39]

Antibiotic Gastric Decontamination

Normal gut flora have an important role in nutrition, metabolism, and immune regulation. The normal balance of organisms is altered when a child becomes ill or receives antibiotics, leading to infection by endogenous flora. Selective decontamination of the digestive tract was first introduced in 1983 and extensively studied in adult ICU patients.[40] Selective decontamination protocols involve a short course of intravenous antimicrobials (e.g., third-generation cephalosporin) and oropharyngeal and enteral nonabsorbable antimicrobials (e.g., colistin, amphotericin B, tobramycin) in addition to routine infection control practices. Variable effectiveness has been demonstrated in clinical studies. In a recent large randomized controlled trial of almost 6000 adults, oral decontamination and selective gut decontamination were associated with decreased mortality rate compared with standard care.[41] There are insufficient data on selective decontamination in children to recommend its use at this time.

An alternate strategy to reduce the development of potential AROs is the oral administration of probiotics (nonpathogenic microorganisms) such as lactobacillus. Their main role appears to be the prevention of pediatric antibiotic-associated diarrhea, the prevention of necrotizing entercolitis in premature infants, and the treatment of *Clostridia difficile*–associated diarrhea. Although apparently not associated with harm, the role of probiotics remains unclear in the critically ill child as an infection control strategy or therapy.[42]

Specific Infection Syndromes in the Pediatric Intensive Care Unit

Bloodstream Infections

BSIs are usually the most common HAI acquired in the PICU setting[43] and are associated with morbidity, excess length of stay, and mortality,[44] with an attributable cost of up to $46,000 per patient.[44,45] Most BSIs are associated with intravascular catheter use and commensal skin flora that gain access to the bloodstream through the device. The scope of intravascular

device–associated infections includes laboratory-confirmed bacteremia, infections of the skin and subcutaneous tissues around the device (exit site and tunnel infections), clinically defined sepsis,[46] septic thrombophlebitis and thrombosis, and right-sided endocarditis.

Epidemiology

The median rate of CLA-BSIs in 71 pediatric medical/surgical ICUs, in the most recent report of the NHSN was 2.1 infections per 1000 central line days, with a 25th percentile of 0.0 and a 90th percentile of 6.0. The pooled mean in these medical/surgical ICUs was 2.9 infections per 1000 line days; in 10 medical PICUs the mean rate was 1.0. The median utilization ratio was 0.41 (central line days per patient days), which is comparable to adult ICUs.[17] In 2007, the Canadian ICU Collaborative reported a cumulative rate of 2.8 CLA-BSIs for six PICUs,[47] with rates ranging from 0 infections per 1000 line days to 10 over the 3-year surveillance period (Figure 97-1).

The most common infecting organism in CLA-BSI is the gram-positive bacteria coagulase-negative *Staphylococcus* (CONS), a group of about 20 species, including *Staphylococcus epidermidis,* that are normal flora of human skin.[48] Gram-negative bacteria, including enterobacteraciae, and nonfermenting gram-negative bacteria such as *Pseudomonas* spp., *Acinetobacter* spp., and *Stenotrophomonas* spp. account for about 25% of infections. *Candida* spp. infections are increasingly recognized.

There are many types of intravascular devices, including CVCs, arterial catheters, and peripherally inserted catheters. Catheters can also be classified according to the site of insertion, the expected duration of placement (e.g., long vs. short term), and the path to the vessel (e.g., tunneled or not).[46] To date, surveillance for HAI associated with these devices has focused on central venous lines. For surveillance purposes, BSIs are categorized as primary (no other identifiable source of infection) or secondary (the BSI occurred as the result of an infection at another site).[18,21] Surveillance definitions used for CLA-BSI can be found in Table 97-2.

Migration of skin flora along the catheter to the blood vessel is thought to be the pathogenesis of most CLA-BSIs.[46] The reduction in rates of CLA-BSI studies using maximal sterile barrier precautions and careful antisepsis[31,49] during catheter insertion and care support this hypothesis. Infection can also result from contamination of the catheter hub with endoluminal migration, be hematogenously seeded from another source, or occur because of contaminated infusate.[46]

Prevention

Successful programs to reduce the incidence of CLA-BSIs have been reported in the last decade; all use multimodal team-based, systematic approaches in which combinations of effective preventive interventions are introduced into a care setting.

The central line bundle is a compilation of eight components broken into two separate bundles for insertion and maintenance. The bundle components described in the following sections are from the Canadian Safer Healthcare Now campaign and align with other improvement bundle packages for reduction of CLA-BSIs. The Canadian ICU Collaborative PICU teams reduced their collective CLA-BSI rate from 5.6 per 1000 line days to 2.8 per 1000 line days.[47] Other PICUs that have implemented the central line bundle have seen dramatic reductions in CLA-BSIs rates of up to 75%.[50]

The insertion bundle components include hand hygiene, maximal barrier precautions, and skin antisepsis. Maximal sterile barrier precautions for the inserter mean strict compliance with hand hygiene, a cap that covers all hair, a mask that covers the mouth and nose securely, a sterile gown, and sterile gloves. The patient is covered from head to toe with a sterile drape except for a small opening for the insertion site and to maintain the airway. Chlorhexidine skin antisepsis is recommended over other antiseptic agents.[46] With regard to the optimal site for a line, practitioners are urged to consider what is best for the patient based on current and future needs, anatomic features, and the inserter's technical competence.

Other components of success include empowering nurses to enforce the use of a central line checklist that incorporates inclusion of all components of the insertion bundle and constraining practice by creating central line insertion kits or carts that include the required equipment needed to maintain asepsis (e.g., only one antiseptic offered: chlorhexidine).

Antibiotic-impregnated CVCs are not recommended for routine use unless the concerted efforts to implement a strategy

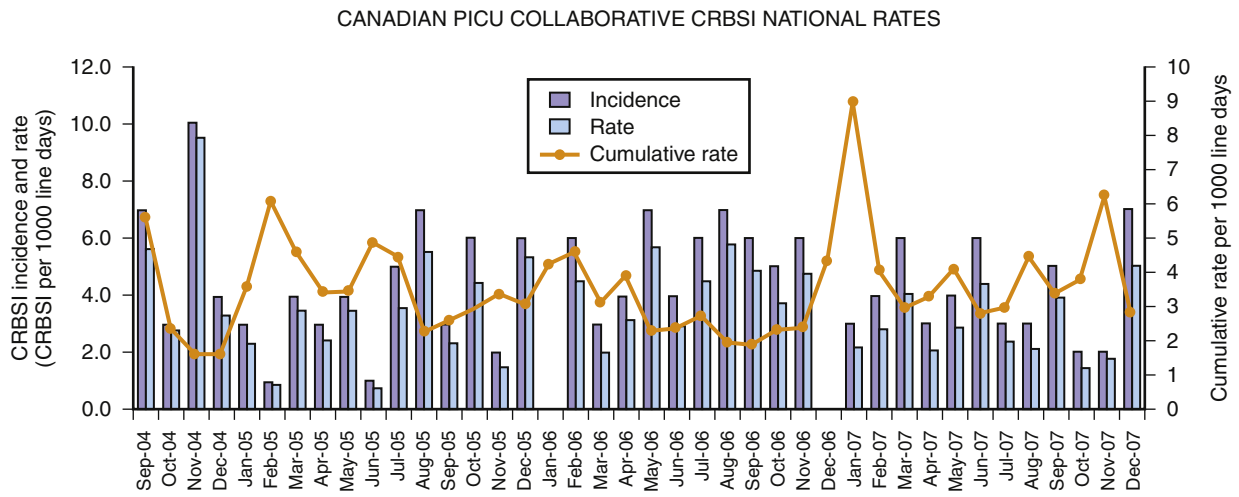

Figure 97–1. Canadian PICU Collaborative catheter-related bloodstream infection national rates. *(From Northway T, Folz E, Gavin S, et al: Success of a national pediatric critical care collaborative in reducing central line blood stream infections: an update of our progress,* Dynamics *19(2):40, 2008.)*

fail to reduce a local institution's infection rates below benchmark levels. They may be considered in specific patient populations such as the immunosuppressed requiring long-term CVC use, although their superiority over standard CVCs in this population has never been proven.

Ultrasound guidance for placement of CVCs to reduce insertion-related complications was identified by the Agency for Healthcare Research and Quality in 2001. In 2002, the National Institute for Clinical Excellence in the United Kingdom issued recommendations for the use of two-dimensional ultrasound guidance for insertion. The associated decrease in insertion-related complications might contribute to a reduction in CLA-BSIs through less-traumatic catheter placement, but this remains to be proven.

The maintenance bundle to prevent CLA-BSIs incorporates, in addition to hand hygiene, multimodal education and training programs, aseptic access to the lumens (scrubbing the hub), regular checks of the entry site for inflammation with each dressing change (at minimum), daily review of line necessity with removal if deemed unnecessary, and a dedicated total parenteral nutrition line.

Emerging trends in maintenance of CVCs include chlorhexidine-impregnated transparent dressings and biodiscs (which hug the catheter at the insertion site) and are intended to reduce the quantity of bacteria at the skin entry site.[51] Evidence of the safety and efficacy of this intervention in children is lacking, and it is not routinely recommended.

Practitioners are urged to check for recent updates in CLA-BSI reduction quality improvement strategies from Safer Healthcare Now (www.saferhealthcarenow.ca) or the Institute for Healthcare Improvement (www.ihi.org) or their national or local equivalents because these strategies change over time based on evolving evidence.

Management

Clinical diagnosis of BSI in the ICU based on clinical signs and symptoms is insensitive and nonspecific.[21] Laboratory confirmation should be sought and broad-spectrum antimicrobial therapy initiated early and targeted at likely pathogens until microbiologic results are available. If the device is suspected to be the source of infection or to have been secondarily infected, the clinician will need to decide if the infection can be eradicated with the device in place. The need for catheter removal will depend on the infecting organism and the availability of another route for parental antibiotic administration. Although CONS infections can often be treated without catheter removal,[52] this is likely not possible or wise if the infection is due to fungal infection or infection with *Pseudomonas* spp. or *S. aureus*. Current Infectious Disease Society of America guidelines recommend at least 10 to 14 days of therapy if the device remains in place along with consideration of antibiotic lock therapy.[53] The possibility of secondary seeding of the heart or thrombophlebitis should also be considered.

Respiratory Infections and Ventilator-Associated Pneumonia

Respiratory Infections

Respiratory tract infections are the most common illness in children in the community as well as the most common reason for admission to hospital, with young healthy children having an average of 6 to 8 infections each year. Respiratory infections acquired during health care encompass a broad range of illness of the upper and lower respiratory tract (see Table 97-2). In the child with high-acuity illness requiring admission to the PICU, some respiratory infections are particularly associated with increased morbidity, mortality, and health care cost. The following section focuses on viral respiratory tract infections, VAP, and sinusitis.

Epidemiology

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in young children in the community and occurs in yearly outbreaks during the winter in temperate climates.[54] Hospital-acquired RSV is associated with prolonged length of stay, increased morbidity and mortality rates,[55] and, if acquired around the time of cardiac surgery, worse postoperative outcomes.[56] Outbreaks of various respiratory virus infections in the PICU have been reported with attack rates of up to 30%.[57] Outbreaks of RSV and influenza provide useful information on the burden of illness associated with this HAI, but rates of HAI-associated respiratory virus infection determined by surveillance programs are infrequently reported.[58]

Like RSV, influenza virus HAI occurs at the same time as the local winter community epidemic. Multiple other respiratory virus infections (e.g., rhinovirus, adenovirus, parainfluenza virus) also spread by large droplets from the respiratory tract, the contaminated hands of care providers, or contact with contaminated nonporous surfaces on which the virus may survive.

Respiratory viral illness can increase the risk of secondary bacterial infection because the normal defensive function of the mucociliary apparatus is impaired and colonizing bacteria in the respiratory tract can invade through the nasopharynx or descend to the lower respiratory tree.

In the past 10 years, three novel respiratory viruses exposed severe gaps in hospital infection control practices. The SARS epidemic in Canada and Asia demonstrated the ability of a novel coronovirus to infect health care workers providing care for critically ill patients.[59] The avian influenza H5N1 virus and H1N1 influenza viruses spread predominately in community settings but forced health care centers to accelerate pandemic readiness and identified severe shortcomings in critical care capacity.[60] Transmission of these agents is thought to be by large droplet, but evidence for optimal occupational health protection is lacking.[12,61]

VAP is the second most common HAI in the PICU, estimated to occur in up to 10% of ventilated children.[62] In the most recent NHSN report pooling data from 50 pediatric medical-surgical ICUs, the median incidence was 0.7 episodes of VAP per 1000 ventilator days, and the mean frequency was 2.1.[17] Notably, the rate of VAP has decreased in the last decade from mean rates of 3.7 per 1000 ventilator days in 1998 in the Pediatric Prevention Network study[63] and 5.7 per 1000 ventilator days (median, 4.2 days) in participating PICUs.[64] VAP is a serious and life-threatening complication of PICU admission and is associated with prolonged ICU stay, need for ventilatory support,[65-67] and excess costs (more than $50,000 in one study[68]). VAP is also associated with increased mortality; in a prospective PICU study, Bigham et al.[69] observed a mortality rate of 19.1% in children with VAP compared with 7.2% in those without VAP ($P = .01$).

The preeminent risk factor for VAP in all age groups is the placement of an endotracheal tube, which provides a ready conduit to the lower respiratory tract and increases the risk of VAP 6-fold to 20-fold.[70] VAP is usually due to endogenous bacteria, and less commonly fungi, from the patient's oropharynx. VAP is often categorized into early (fewer than 5 days after intubation) and late (more than 5 days after intubation). Early VAP is usually caused by normal endogenous flora of the respiratory tract such as *H. influenzae, Moraxella* spp., *Streptococcus pneumoniae,* and alpha-hemolytic *Streptococcus* spp. These organisms are assumed to have gained entry around the time of intubation or to have been aspirated early in the course of treatment. During hospitalization, the normal endogenous flora of the nasopharynx are replaced within days by gram-negative bacteria such as *Pseudomonas* spp., *Escherichia coli, Acinetobacter,* and *Stenotrophomonas* spp., and various *Enterobacteraciae* spp. *S. aureus* is also a cause of HAI lower respiratory tract infection. For practical reasons, many studies base their laboratory diagnosis on specimens obtained from the endotracheal tube rather than invasive sampling of the lower respiratory tract; hence isolated microorganisms could be present in the nasopharynx, colonizing the endotracheal tube, or actually be the cause of infection in the lung.

In addition to its role as a conduit, the endotracheal tube also serves as a foreign body. As with other biomedical devices, an endotracheal tube interferes with normal defense mechanisms (e.g., cough, mucociliary apparatus) and acts as a nidus for adherence of microorganisms, which create a biofilm. Tracheal suctioning can cause mucosal denudation and detachment and aspiration of adherent biofilm aggregates that become a pulmonary inoculum. Not surprisingly, the length of respiratory assistance and endotracheal intubation—and therefore the device-related risk—remain significant risk factors of nosocomial pneumonia.[62,68,71,72]

Other risk factors for HAI pneumonia include immune deficiency, use of neuromuscular blocking agents, reintubation, transport outside the ICU, multiple organ dysfunction, shock, multiple-organ trauma, severe head trauma, and burns.[66,73-75] More rarely, VAP is associated with inhalation of contaminated aerosolized fluids or medications or hematogenous seeding (e.g., right-sided bacterial endocarditis).

Prevention

Respiratory Viruses. Prevention of HAI respiratory virus infection in the PICU can be accomplished through a collaborative effort between the PICU and the organization's infection prevention and control and occupational health programs. The goal of this effort is to avoid contact between persons with probable or definite respiratory infection (including family members) and PICU patients and prompt institution of isolation practices (Standard Precautions and Additional Precautions) in symptomatic patients, regardless of laboratory confirmation.

Occupational health programs assess fitness-to-work in health care workers with possible respiratory illness. An employee with new-onset cough and rhinorrhea, for example, could be deployed to a non–patient care assignment rather than the PICU or sent home. The occupational health program should ensure immunization status for employees is current and offer annual influenza vaccine programs in addition to ensuring access to vaccines against other infections that can be transmitted in the health care setting (hepatitis B, pertussis, measles, mumps, rubella, varicella, diphtheria). Regular education in the use of Standard Precautions/Routine Practices is recommended so that health care workers will use hand hygiene appropriately, understand how to use PPE, implement isolation practices when they suspect a communicable infection in a patient, and be aware of organization-wide and unit-specific infection prevention and control policies and procedures.

As part of the hospital and PICU admission process, screening of the patient for symptoms and signs of infectious illness should be conducted to determine appropriate placement. In the winter respiratory season, screening of all symptomatic children for viral infections and placing them on contact and droplet isolation until results are available have been reported to limit nosocomial spread. Screening admitted children with suspected viral infection is now done, and depending on the local laboratory capabilities, covers RSV, metapneumovirus, influenza A and B, parainfluenza, adenovirus, and rhinoenterovirus.

Ventilator-Associated Pneumonia. Strategies of prevention are directed against the three mechanisms by which VAP is thought to occur: aspiration of secretions, colonization of the aerodigestive tract, and use of contaminated equipment. General recommended measures are to conduct active surveillance for VAP, minimize the duration of ventilation and use noninvasive ventilation whenever possible, perform daily assessments of readiness to wean from ventilation, and educate health care workers who care for ventilated patients about VAP.[71]

Effective individual interventions that prevent VAP have been combined into bundles by the Institute for Healthcare Improvement.[76] Implementation of the bundles has shown documented evidence of a reduction in pediatric VAP; in one center a reduction of 5.6 to 0.3 infections per 1000 ventilator days over a 3-year period was observed.[69]

Recommended practices to prevent VAP are mostly based on studies conducted in adult patients.[71] The strategies to prevent VAP prepared by the Society for Healthcare Epidemiology and the Infectious Disease Society of America[71] highlight practical recommendations focused on this device-specific infection. Comprehensive recommendations published by the CDC provide background scientific rationale and guidance for detecting and preventing HAI pneumonia.[77] The original bundles included general care strategies for critically ill patients not related to VAP prevention (e.g., peptic ulcer prophylaxis and deep venous thrombosis prophylaxis). Oral hygiene protocols may reduce colonization by pathogenic bacteria in the oropharynx and are recommended.[77] Meta-analyses of trials conducted to date in adults indicate reduced risk of VAP in patients treated with oral chlorhexidine.[78] The CDC guidelines make no recommendation for routine use of chlorhexidine or antimicrobials for this purpose.[77]

Most recent pediatric VAP bundles have removed the general care strategies along with the adult-based recommendations of a daily sedation holiday and use of continuous aspiration of secretions above the endotracheal tube cuff.[77] Safety concerns for children (daily sedation) and tube design limitations in pediatrics are the rationale for elimination of the latter strategies. The pediatric bundle has recently been updated and published by Safer Healthcare Now. Specific

precautions of the pediatric VAP bundle are hand hygiene before and after circuit manipulation, elevation of the head of the bed (angle varies based on positioning limitations of the child based on age), proper positioning of the oral or nasogastric tube, elimination of the routine use of instillation before suctioning of the endotracheal tube, changing in-line suctioning catheters only when visibly soiled or malfunctioning, regular oral care for all children,[72] and maintaining the ventilator tubing in a dependent position.

Management

Lower Respiratory Tract Infection: Respiratory Syncytial Virus and Influenza. Management of RSV infection in the PICU is mainly supportive. Inhaled ribavirin has minimal efficacy in altering patient outcomes and is difficult to administer, particularly since particulate drugs may block the endotracheal tube. It may be used in the immunocompromised patient with altered cell mediated immunity who may otherwise be unable to clear infection. Laboratory confirmation is made by isolation of RSV from a nasopharyngeal aspirate or swab using molecular techniques, immunoassay, or viral culture. Monoclonal anti-RSV antibodies provide passive immunization for certain high-risk infants (e.g., hemodynamically significant heart disease, oxygen-dependent bronchopulmonary dysplasia) during the RSV season in the first year or two of life[79] but are not used for treatment of established infection. Evidence regarding cost-effectiveness of RSV passive immunization is conflicting.

Influenza infection can be treated with neuraminidase inhibitors (oseltamivir, zanamavir), which shorten the period of viral shedding and duration of fever. Practitioners are advised to be aware of seasonal public health guidance regarding antiviral susceptibility, which can change over time. The adamantine class of antivirals, for example, has not been used in recent years because of influenza virus resistance to these drugs.

Ventilator-Associated Pneumonia. The surveillance definition of VAP (see Table 97-2) permits comparison of HAI rates over time and between institutions but serves a different purpose than for diagnosis and clinical treatment.[23] VAP is difficult to diagnose accurately because of the inaccessibility of the lower respiratory tract. The gold standard for diagnosis is microbiologic confirmation from a lower respiratory tract specimen, such as lung biopsy.[80] Obtaining uncontaminated lower respiratory tract specimens in children by bronchoalveolar lavage, lung biopsy, or transthoracic biopsy are procedures with inherent risks, but diagnostic criteria have been proposed.[62,81-83] Despite the accepted shortcomings, tracheal aspirates remain the most common specimen for guiding initial empiric antibiotic therapy in a child with suspected VAP.

Aggressive and prompt treatment is required when nosocomial pneumonia is suspected in a critically ill patient because it is a life-threatening illness. Initial empiric therapy for VAP should be broadly based, with consideration of local microbiologic data on antibiotic resistance and a plan to reevaluate and narrow antibiotic selection when results of cultures or other diagnostic information is available. If aspiration is suspected, coverage for anaerobes can be considered (e.g., ticarcillin-clavulanate or clindamycin). If methicillin-resistant *S. aureus* is suspected, vancomycin or linezolid should be used. The appropriate duration of therapy for VAP in children is not known. Most experts recommend a 7- to 14-day course of therapy for VAP.

Sinusitis

Although acute viral rhinosinusitis (inflammation of the nose and paranasal sinuses) is a common infection in childhood,[84] data on its occurrence in the PICU are scarce. Care in the ICU was first associated with increased risk of sinusitis in adult ICU patients in the 1970s, following case reports of sinusitis ipsilateral to the nasotracheal tube.[85] Since that time, observational studies have supported this finding and indicate that prolonged nasal cannulation is associated with increased incidence of sinusitis, that larger nasal cannulae appear to accelerate this process, and that fewer devices in the nose decrease risk of infection.[85]

Epidemiology

There are few reports of sinusitis complicating the care of critically ill children in the ICU setting,[86] and active surveillance for this HAI is not done by most programs.[17,63,67] In one retrospective review, 1 of 98 children ventilated for at least 7 days had sinusitis noted in a follow-up visit that resolved spontaneously.[87]

Sinusitis can be categorized as acute or subacute bacterial, recurrent acute bacterial, chronic, or acute on chronic in nature. Although the ethmoid and maxillary sinuses are present at birth, the sphenoid and frontal sinuses are not pneumatized until age 5 and 7 years, respectively.[84] Diagnosis of sinusitis is challenging in children, particularly in the intubated child. Direct sinus puncture to permit microbiologic identification of infecting organisms is the gold standard for diagnosis, although it is rarely performed because it is invasive, time-consuming, and painful.[84] Normal sinus radiographs and CT scans provide evidence that sinusitis is absent, but mucosal thickening is a nonspecific finding.[88] The surveillance definition of health care–associated sinusitis is seen in Table 97-2.

Acute sinusitis is most commonly caused by respiratory flora such as *S. pneumoniae, H. influenzae,* and *Moraxella* spp. In ventilator-associated sinusitis, *S. aureus, Pseudomonas aeruginosa*, enteric gram-negative bacilli, and streptococcal infection need to be considered.

Prevention

The paranasal sinuses are contiguous with the nasopharynx and mostly lined with pseudostratified ciliated respiratory epithelium.[89] The normal defense of the sinuses against infection is the mucociliary apparatus; secretions capture particulate matter that is then propelled by cilia to the sinus ostia. Factors that would be expected to predispose to sinus obstruction or decreased mucociliary function include foreign bodies in the nasopharynx (e.g., nasogastric or endotracheal tubes), previous viral respiratory infection, preexisting abnormalities such as cilial disorders or cystic fibrosis, and craniofacial anatomic abnormalities or facial trauma. Orotracheal intubation is recommended over nasotracheal intubation because the latter increases the risk of sinusitis, which in turn may increase the risk of VAP.[71,77] Judicious use of antibiotics in the ICU would be expected to decrease the risk of colonization of the respiratory tract with gram-negative and antibiotic-resistant organisms.

Management

Because of their proximity to the brain, bacterial or fungal infection of the sinuses may be complicated by contiguous spread. If microbiologic confirmation obtained by sinus puncture is not possible, systemic antimicrobial therapy should be directed broadly to cover anaerobic respiratory flora, gram-positive and gram-negative bacteria such as *Pseudomonas* spp., and enteric flora. Options for antibacterial coverage include a third-generation cephalosporin or monobactam or an extended-spectrum penicillin–clavulanic acid combination with the addition of vancomycin to cover MRSA or penicillin-resistant pneumococcus, depending on antimicrobial susceptibility and epidemiology.

An otolaryngologist should be consulted in the care of children with complicated sinusitis to determine if surgery is necessary to remediate ostial obstruction or drainage of abscesses. Involvement of the central nervous system requires neurosurgical intervention. The infectious disease team should also be involved to assist in determining optimal antibiotic combinations and duration of therapy in these complicated cases with central nervous system involvement.

Urinary Tract Infections

The spectrum of illness associated with urinary tract infection (UTI) in the PICU can range from asymptomatic bacteruria in the presence of a catheter to a funguria that becomes a source of life-threatening disseminated fungal infection.

Epidemiology

A mean of 5.0 catheter-associated UTIs (CA-UTIs) occurred per 1000 catheter days (median, 3.0 per 1000 catheter days) in the U.S. National Health Safety Network surveillance system, with 37 pediatric medical-surgical ICUs reporting.[17] This rate is very similar to the CA-UTI frequency of 5.4 infections per 1000 urinary catheter days determined 10 years earlier in a survey of 35 PICUs and 33 NICUs.[63] In a recent review, secondary bacteremia occurs in about 3% of catheterized critically ill children.[22]

A urinary catheter is both a foreign body in the urinary tract and a conduit for microorganisms to ascend to the bladder, ureters, and kidney and potentially to the bloodstream. Voiding is an important defense mechanism for the urinary tract in which periurethral flora are flushed out regularly. Because of the urethra's anatomic location in the perineum, the most common organisms causing community and health care–associated UTI are normal periurethral or perirectal flora such as *E. coli* and *Klebsiella pneumoniae.* However, enterobacteriaceae such as *Pseudomonas* spp. and opportunistic organisms such as *S. aureus, S. epidermidis,* and *Candida* spp. also can be involved.

In addition to the general factors that increase risk for HAI in the PICU, children at increased risk for UTI include those with preexisting uropathies, especially neurogenic bladder.

Prevention

Guidelines for the prevention of CA-UTI in acute care hospitals focus on certain key strategies, all related to urinary catheter use: (1) recommendations for which patients should receive indwelling urinary catheters, (2) recommendations for catheter insertion, (3) recommendations for catheter maintenance, and (4) quality improvement programs to achieve appropriate placement, care, and removal of catheters.[90] The most important action that PICU staff can take to prevent CA-UTIs is to limit the use of urinary tract instrumentation, particularly indwelling urinary catheters. Systemic morphine infusions are not a contraindication to the removal of the urinary catheter.

Proper technique for catheter insertion includes hand hygiene before and after any manipulation of the device, use of aseptic technique, use of the smallest bore catheter needed, and proper securement of the catheter after insertion to prevent movement.[90] The catheter should be maintained as a closed drainage system with unobstructed urine flow. The catheter and collecting system should be replaced if the system is disconnected or leaks occur. Standard Precautions should be used for any manipulation of the catheter or collecting system (e.g., use of gloves and gowns as appropriate). Neither systemic antimicrobials, bladder irrigation with antimicrobials, nor complex drainage systems with antiseptics are recommended to prevent CA-UTIs. Special catheter materials (e.g., antimicrobial impregnation) are only recommended if a comprehensive strategy to reduce CA-UTI rates is unsuccessful.

A number of quality improvement resources are available to assist with systemic approaches to the prevention of CA-UTI. The Association for Professionals in Infection Control[91] produced the "Guide to the Elimination of Catheter-Associated Urinary Tract Infection" in 2008, and the Institute for Healthcare Improvement[92] has developed a program for the prevention of CA-UTI. Overall approaches for reduction of CA-UTI rates include the avoidance of unnecessary urinary catheters, use of aseptic technique when inserting urinary catheters, maintenance of urinary catheters based on recommended guidelines, and prompt daily review of urinary catheter necessity.[92]

Management

Surveillance definitions for UTI acquired in the health care setting are found in Table 97-2. Of note, infection may be asymptomatic or symptomatic. In the critically ill PICU patient diagnosis of UTI may be difficult because of inability to determine symptoms and signs; therefore laboratory criteria from aseptically obtained urine specimens are essential.[22]

For CA-UTI, the catheter should be removed as soon as possible because it is an ongoing source of infection. Once removed, intermittent catheterization may be required if spontaneous voiding does not occur. Therapy should be the narrowest spectrum agent that will treat the offending pathogen; appropriate empiric choices before availability of antimicrobial susceptibility should include consideration of common infecting organisms in that PICU, but appropriate initial choices include aminoglycosides, an extended-spectrum penicillin, or a third-generation cephalosporin.

Skin and Surgical Site Infections

Although almost all surgical procedures are performed in the operating room, a substantial component of care in the PICU is postoperative care for critically ill children. Procedures may also need to be performed in the PICU in patients who are too unstable for transport to the surgical suite or do not have primary closure of the surgical wound (e.g., open chest after cardiac surgery). The integument is the largest organ in the human body; it is a barrier to invasion of microorganisms and

plays a role in thermal regulation and fluid homeostasis. Disruption of the skin, whether by surgery, insertion of biomedical devices, or pressure sores, interrupts a key defense against infection.

Epidemiology

In an NNIS study of 61 U.S. PICUs from 1992 to 1999, skin and soft tissue and surgical site infections (SSIs) combined accounted for one quarter to one third of nosocomial infections in PICUs.[43] The NNIS reports SSIs according to operative procedure and risk index category but does not report the ward where the patient was cared for (e.g., ICU or not) or patient age.[17] In a prospective 6-month surveillance project in 17 European PICUs, postsurgical infections accounted for 7% of all HAIs.[67] A national Canadian pediatric point prevalence survey identified approximately 3% of the population with an SSI.[93] Complications of SSIs include contiguous or systemic spread and, in adults, an increased length of stay of 7 to 10 days and increased risk of death.[94] Depending on preexisting comorbidities, site, and severity of infection, the estimated costs of SSIs are between $3000 and $29,000.[94]

Surgical sites have bacterial contamination by the end of the procedure despite appropriate skin antisepsis.[95] Most commonly, the source of infection is the patient's own flora that migrate into the wound, but other sources include the surgical staff and contaminated instruments. The probability of a wound becoming infected is thought to result from the interaction of four key clinical variables: the inoculum of bacteria, the virulence of the infecting organism, the microenvironment of the wound (e.g., foreign body), and the state of host defenses.[95] Given this pathogenesis, it is not surprising that skin flora are the most common infecting organisms. *S. aureus* is the most common pathogen in SSIs without biomedical device placement, but *P. aeruginosa* and other gram-negative bacteria have been found.[72,96,97] Often a single microbiologic cause is not identified because the surgical site is open and contiguous with skin or mucosa. In procedures in which a device is implanted (e.g., neurosurgical cerebrospinal fluid shunts), the most common organism isolated is CONS. Of growing importance are infections caused by multidrug-resistant organisms, such as MRSA, and fungi.

Risk for an SSI can be predicted in adult patients by using the National Nosocomial Infections Surveillance System index, which combines the traditional four-category wound classification system of clean, clean-contaminated, contaminated, and dirty or infected with the American Society of Anesthesiology score and duration of procedure time.[95] An equivalent validated scoring system to identify high-risk children has not been developed. Multiple variables associated with increased risk for SSI in various studies include intrinsic factors (e.g., age, glucose control, obesity/malnutrition, smoking, steroid use, prolonged preoperative hospital stay, preoperative nares colonization with *S. aureus,* perioperative transfusion and immunosuppressive medications, presurgical comorbidity) and extrinsic factors (e.g., preoperative antiseptic showering, preoperative hair removal, patient skin preparation in the operating room, preoperative hand/forearm antisepsis, management of infected or colonized surgical personnel, antimicrobial prophylaxis). In pediatric cardiac surgery patients, an open sternum is a risk factor for SSIs.[96,97] Operative risk factors are surgical scrub by the team, skin preparation of the patient, appropriate and timely antibiotic prophylaxis, surgical drapes and attire, surgeon skill and technique, asepsis, and operative time. Operating room characteristics are also considered extrinsic factors. They include ventilation, traffic, and sterilization of surgical equipment. Postoperative factors incorporate incision care and discharge planning.

Prevention

Prevention of SSIs is directed at addressing the clinical variables that increase the probability of infection, as previously mentioned.[95] For example, patient skin preparation, health care worker hand hygiene, and antimicrobial prophylaxis affect the inoculum of bacteria into the wound. Optimal glucose and temperature control enhance the capacity of the host to deal with invading organisms. CDC recommendations for the prevention of SSIs are available,[36] and a compendium of strategies to prevent SSIs in acute care hospitals has been published.[94]

Surgical Site Infection Bundle

Most SSI bundles include measures to improve timing and choice of antimicrobial prophylaxis, appropriate hair removal, and prospective surgical wound infection surveillance with provision of feedback to individual surgeons. The surveillance definitions for SSI are provided in Table 97-2.

A considerable body of research has demonstrated that perioperative antibiotic prophylaxis is most effective when given 1 hour before the incision to maximize tissue concentration during cut time—when the antibiotic (as narrow spectrum as possible and as short a course as possible) is active against the likely contaminating organisms. Although the duration of administration varies by procedure, the optimal duration ranges from the operative period to the 24 hours after the surgery. Doses beyond this interval do not prevent infection and put the patient at risk of developing infections with resistant bacteria and fungi. The choice and duration of antibiotic prophylaxis depends on the surgical procedure, degree of wound contamination, emergency or elective surgery, and patient allergy.[36] Vancomycin should not be routinely used as prophylaxis but instead reserved for specific clinical situations such as an MRSA-positive patient with a SSI.[94]

Postoperative surgical site care includes regular observations and documentation of the integrity of the site. Recommendations for postoperative incision care include protecting a primary closure incision with a sterile dressing for 24 to 48 hours postoperatively, adhering to hand hygiene principles, applying sterile technique when changing dressings, promoting proper incision care, and identifying complications by educating patients and families.[36]

Management

Recognition of SSIs requires regular wound inspection for the usual signs of inflammation, with or without pus. Microbiologic confirmation of infection is often not possible or definitive because of contamination of the operative site by contiguous external surfaces. Treatment of SSIs includes appropriate empiric antimicrobials directed at the likely infecting organisms and subsequent narrowing of the spectrum when organism identification and susceptibility are available. Drainage of the infected area should be facilitated (e.g., removal of staples), and wound debridement may be required. Foreign bodies may need to be removed.[95] The extent of the infection will determine the wound care requirements, which

may involve packing the wounds or use of a negative-pressure wound therapy.

Ventriculostomy-Related Infections

The incidence of ventriculostomy-associated infection varies widely in the literature and is influenced by both patient characteristics and system factors, such as infection control policies and procedures pertaining to placement and maintenance of external ventricular drains. The risk increases with increasing duration of catheterization and with repeated insertions, but routine replacement is not recommended. The use of local antibiotic irrigation or prophylactic systemic antibiotics is not recommended. Routine surveillance cultures of cerebrospinal fluid are not more likely to detect infection than are cultures obtained when clinically indicated.[98,99]

Hospital-Associated Diarrhea

Clostridium difficile–associated diarrhea is a potentially life-threatening illness that can range in clinical presentation from diarrhea to colitis and megacolon. Although less common in children, it can cause problematic illness in oncology patients. Outbreaks of rotavirus and norovirus can occur in critical care settings, where close health care worker/patient contact can facilitate spread of secretions. Prevention of diarrheal illness is accomplished by prompt isolation of patients with diarrhea before laboratory results are available, careful hand hygiene, and regular and thorough environmental cleaning focusing on high-touch surfaces.

References are available online at http://www.expertconsult.com.

VI Chapter 98

Autoimmune Diseases: Diagnosis, Treatment, and Life-Threatening Complications

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PEARLS

- Approximately 1 child in 250 has a rheumatologic disease.
- Children may present to the intensive care unit with life-threatening manifestations of an undiagnosed rheumatologic disease or life-threatening complications of known rheumatologic diseases.
- A high index of clinical suspicion for rheumatologic disease is necessary when children present with:
  - Persistent fevers of unknown origin and constitutional symptoms
  - Multisystem involvement, including dermatologic, renal, pulmonary, gastrointestinal, cardiac, hematologic, or central nervous system pathology
  - Abnormal joint examination findings (can help decide whether child needs further evaluation for a rheumatic disease)
  - Unexplained elevated inflammatory markers
- Infectious and oncologic processes may mimic rheumatologic diseases and should be considered and/or excluded.
- The diagnosis of rheumatologic diseases requires a high index of clinical suspicion as few diagnostic tests are confirmatory and few clinical features are pathognomonic. While elevated inflammatory markers, abnormal serologies, and pathologic examination of a biopsy from an affected organ can aid in confirming a clinical suspicion, performing a careful history and physical exam, and considering a broad differential provides the basis for making these diagnoses.
- Life-threatening complications of rheumatologic diseases may affect any organ system. These complications include:
  - Severe infections secondary to immunosuppression
  - Adrenal insufficiency secondary to chronic steroid therapy
  - Airway compromise, pneumonitis, interstitial lung disease, pleuritis, pleural effusions, and acute alveolar hemorrhage
  - Pericarditis, myocarditis, valvular disease, arrhythmias, and acute coronary syndromes including myocardial infarction
  - Peritonitis, intestinal perforation, severe pancreatitis, and gastrointestinal hemorrhage
  - Renal insufficiency, severe nephrotic syndrome, and malignant hypertension
  - Cerebral infarction and hemorrhage, seizures, and psychosis
  - Prothrombotic states related to:
    - Antiphospholipid antibody syndrome
    - Thrombotic thrombocytopenic purpura
  - Immune dysregulation causing overwhelming cytokine storm:
    - Macrophage activation syndrome
- Therapies for rheumatologic diseases are often initiated in the intensive care unit, including: high dose corticosteroids; chemotherapeutic agents such as cyclophosphamide; "biologic" agents including tumor necrosis factor blockers and rituximab; intravenous immunoglobulin; and plasma exchange. These often present unique management challenges, given the complexities of potential interactions between the disease processes and complications of treatment.
- While waiting for studies to return and specific treatments to work, intensive support and coverage for alternative etiologies such as infection are critical.

Approximately 1 child in 250 has a rheumatologic condition. In the adult rheumatology patient population, approximately 10% to 25% of all patients who visit emergency departments for a rheumatic disease require hospital admission, and approximately one third of the hospitalized patients need intensive care.[1] Although the number of pediatric patients with rheumatologic diseases who require intensive care management is unknown, early diagnosis and rapid treatment can significantly decrease mortality and morbidity.[2,3] Patients may present to the intensive care unit (ICU) with life-threatening manifestations of new-onset disease, and a high index of suspicion is necessary in patients who present with

constitutional symptoms, unexplained elevated inflammatory markers, and multisystem involvement. Patients with known rheumatologic diseases may be admitted to the ICU with life-threatening complications of the disease process itself or complications secondary to therapies.[4] This chapter provides an overview of the most common pediatric rheumatologic diagnoses followed by a discussion of the most common conditions encountered by the intensivist.

Rheumatologic Diseases: Clinical Presentation, Diagnosis, and Treatment

Rheumatic diseases in children are best diagnosed by careful history and physical examination. Although laboratory changes may be consistent with and confirm clinical suspicions, they are frequently not diagnostic and must always be placed within the context of the patient's clinical picture.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease (Box 98-1).[5] Most children are managed as outpatients, but the disease or its complications occasionally require intensive care.

Systemic juvenile idiopathic arthritis (S-JIA) accounts for only approximately 10% of children with juvenile arthritis; however, it is the type most likely to present with severe extra-articular multisystem disease.

Clinical Presentation

Classic features include fever, which by definition is a temperature higher than 38.5° C in a quotidian pattern for at least 2 weeks. Pleural and pericardial effusions occur in up to two thirds of patients and may compromise respiratory effort and rarely cause cardiac tamponade. Unwillingness to lie down, distant heart sounds, chest dullness to percussion, and reduced air entry are physical findings consistent with effusions. Friction rubs may be absent. Other clinical findings include diffuse lymphadenopathy and hepatosplenomegaly, sometimes so prominent as to lead to the consideration of malignancy and infectious processes, which must always be excluded. One helpful sign is the presence of the rheumatoid rash, which usually occurs with fever spikes, is nonpruritic and rapidly migratory, and often disappears completely when the temperature normalizes. Arthritis may not be the most prominent feature, although there is usually a history of morning stiffness, limp, or avoiding particular activities. A careful joint exam is essential.

Laboratory Studies

No diagnostic studies are specific, but tests consistent with systemic onset juvenile arthritis include anemia (often hemoglobin levels in the range of 6 to 8 g/dL); elevated white blood cell counts, sometimes into the leukemoid range; and platelet counts may rise to 1,000,000/μL or more. Low white blood cell and platelet counts should lead to consideration of macrophage activation syndrome (MAS), which is discussed in the following section, or malignancy. C-reactive protein and erythrocyte sedimentation rate (ESR) are usually markedly elevated, although in the setting of MAS the ESR may drop because of lowered fibrinogen levels. Antinuclear antibodies (ANAs) and rheumatoid factor are typically absent.

Box 98–1 Criteria for Juvenile Idiopathic Arthritis

JIA is a disease of childhood onset characterized primarily by arthritis persisting for at least 6 weeks with no known cause.

Systemic Arthritis

Arthritis with or preceded by daily fever of at least 2 weeks' duration, which is documented to be quotidian for at least 3 days, and accompanied by one or more of the following:

- Evanescent, nonfixed, erythematous rash
- Generalized lymph node enlargement
- Hepatomegaly or splenomegaly
- Serositis

Oligoarthritis or Polyarticular Arthritis

Arthritis affecting one to four joints during the first 6 months of disease. Two subcategories are recognized:

- Persistent oligoarthritis: affects no more than four joints throughout the disease course
- Extended oligoarthritis: affects a cumulative total of five joints or more after the first 6 months of disease

Polyarthritis (Rheumatoid Factor Negative)

Arthritis affecting five or more joints during the first 6 months of disease; tests for rheumatoid factor are negative.

Polyarthritis (Rheumatoid Factor Positive)

Arthritis affecting five or more joints during the first 6 months of disease associated with positive rheumatoid factor tests on two occasions at least 3 months apart.

Psoriatic Arthritis

Arthritis and psoriasis or arthritis and at least two of the following:

1. Dactylitis
2. Nail abnormalities (pitting or onycholysis)
3. Family history of psoriasis confirmed by a dermatologist in at least one first-degree relative

Enthesitis-Related Arthritis

Arthritis and enthesitis or arthritis or enthesitis with at least two of:

- Sacroiliac joint tenderness and/or inflammatory spinal pain
- Presence of HLA-B27
- Family history in at least one first- or second-degree relative of medically confirmed HLA-B27–associated disease
- Anterior uveitis that is usually associated with pain, redness, or photophobia
- Onset of arthritis in a boy after 8 years of age

Other Arthritis

Children with arthritis of unknown cause that persists for at least 6 weeks but that either:

- Do not fulfill criteria for any of the other categories, *or*
- Fulfill criteria for more than one of the other categories

HLA, Human leukocyte antigen.

From Petty RE, Southwood TR, Manners P et al: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, *J Rheumatol* 31:390–392, 2001.

Complications

Chest radiographs may show cardiomegaly or pleural effusions. An echocardiogram may detect subclinical effusions and identify signs of cardiac wall compromise. Most will respond to medical management, but occasionally aspiration and drainage of effusions is necessary.

The cervical spine may be affected, usually in children with systemic or polyarticular disease, and lead to loss of range or instability. Between the odontoid process and the transverse ligament is a synovial bursa that may become inflamed and cause erosions, leading to instability of C1 on C2 with actual or potential neurologic impairment. The facet joints of the lateral spinous processes of the cervical vertebrae are also synovial and inflammation at this site may lead to loss of range of motion or fusion of the c-spine. Limitation and instability may be problematic if hyperextension is attempted for intubation, or has occurred with a whiplash injury, and fracture and paralysis have been reported. Any patient with juvenile arthritis who has a history or findings of cervical spine disease should have careful flexion/extension views taken before intubation is attempted for any reason. If changes are identified, alternate airway management methods such as fiber optic visualization or even tracheostomy should be considered. Temporomandibular joint arthritis causes diminished mouth opening, also leading to difficulty in airway management. Cricoarytenoid arthritis may present as a sore throat with localized tenderness over the joints, or stridor and airway obstruction secondary to limitation of vocal cord mobility.

Rarely, fewer than 10% of children with JIA who exhibit polyarticular rheumatoid factor positive disease have complications such as progressive lung disease or other extra-articular manifestations of their disease.

Many children with previously diagnosed S-JIA are treated with steroids and immunosuppressives such as methotrexate, tumor necrosis factor (TNF) inhibitors, and other biologic agents. Therefore heightened awareness of the risks of adrenal suppression and infection is essential.

Management

Children with complications of active S-JIA should be treated aggressively with pulse methylprednisolone, usually 30 mg/kg/day up to 1 g/day administered over 1 hour for 3 consecutive days, then maintained at 2 to 3 mg/kg/day divided into 2 to 3 doses/day until symptoms resolve or until other steroid sparing agents are introduced with consultation from a pediatric rheumatologist. It is prudent to cover for infections at the same time because these massive doses of steroids compromise neutrophil function. Sodium and fluid retention, hypertension, gastric upset, and hyperglycemia are other short-term complications.[6]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by loss of self-tolerance resulting in development of autoantibodies and formation of immune complexes.[7] The organs targeted by the autoantibodies and sites of immune complex deposition determine the disease presentation. Females in peripubertal and postpubertal years are most likely to be affected; however, both males and younger children can develop the disease. To make a diagnosis of SLE, 4 of 11 criteria must be met (Box 98-2).[8] However, lupus can be regarded as a medical example of Murphy's law—what can go wrong, will—so any organ system may be affected and in ways not always listed in the criteria. Therefore a thorough evaluation of all organ systems and serologic tests for antibodies and other markers commonly found in SLE is essential if this diagnosis is being considered.

Box 98–2 Revised SLE Classification Criteria

For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any of four or more criteria are present, serially or simultaneously, during any interval of observation.

1. Malar rash: Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash: Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring (may occur in older lesions)
3. Photosensitivity: Skin rash as a result of unusual reaction to sunlight, by patient's history or physician's observation
4. Oral ulcers: Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis: Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis
   a. Pleuritis, a convincing history of pleuritic pain, or rub heard by a physician or evidence of pleural effusion *or*
   b. Pericarditis with or without documentation by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder
   a. Persistent proteinuria >0.5 g/day or greater than 3+ if quantitation not performed, *or*
   b. Cellular casts (may be red cell, hemoglobin, granular, tubular, or mixed)
8. Neurologic disorder
   a. Seizures in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance), *or*
   b. Psychosis in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder
   a. Hemolytic anemia with reticulocytosis, *or*
   b. Leukopenia <4000/mm^3 total on two or more occasions, *or*
   c. Lymphopenia <1500/mm^3 on two or more occasions, *or*
   d. Thrombocytopenia <100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder
    a. Anti-DNA: Antibody to native DNA in abnormal titer, *or*
    b. Anti-SM: Presence of antibody to Sm nuclear antigen, *or*
    c. Positive finding of antiphospholipid antibodies based on:
       1. An abnormal serum level of immunoglobulin G or immunoglobulin M anticardiolipin antibodies, *or*
       2. A positive test result for lupus anticoagulant using a standard method, *or*
       3. A false-positive serologic test result for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome.

From Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, *Arthritis Rheum* 40:1725, 1997.

Clinical Presentation

Mucocutaneous Findings. Malar rash, discoid rash, photosensitivity, and oral (especially hard palate) and nasal mucous membrane ulcerations are classically included. However, almost any kind or rash, including bullous lesions, may be seen. Skin biopsy with immunofluorescence to demonstrate immune complex deposition can be helpful.

Central Nervous System Disease. Seizures and psychosis are included in the criteria; however, strokes, severe migraines, and an encephalopathic picture are among other central nervous system (CNS) findings. CNS disease can occur with minimal serologic changes.[9] CNS disease is related to antiphospholipid (APL) antibodies that can cause either thrombotic or embolic phenomena. These findings may be mistaken for or occur concurrently with infections, including opportunists such as nocardia. The eye can be involved in a number of ways (conjunctivitis, scleritis, episcleritis, uveitis, retinal vasculitis), and a careful eye exam is warranted in any possible rheumatic disease.

Pulmonary Involvement. Many patients have pulmonary signs and symptoms.[10] Pleuritis is included in the clinical criteria and may be severe, causing respiratory compromise. Pulmonary hemorrhage is one of the most serious complications of pulmonary involvement in SLE and may be precipitated by vasculitis or infection. Dyspnea, hemoptysis, and an otherwise unexplained drop in hemoglobin make this diagnosis obvious, but are not always present. More subtle hemorrhage may be detected by pulmonary function testing, specifically elevation of the diffusion capacity if the patient is stable and able to cooperate. Radiographs or chest computed tomography (CT) of the lungs will reveal patchy ground glass infiltrates.

Pulmonary embolism maybe related to APL antibodies or other hypercoagulable states such as nephritic syndrome or inborn errors. These may be massive and immediately life-threatening, and are best diagnosed by CT imaging, often at the time of interventions to lyse the clots. Smaller and recurrent emboli are thought to be a major contributor to pulmonary hypertension. Rarely, progressive interstitial disease, and possibly chronic pleural inflammation and fibrosis, lead to a "shrinking lung" syndrome.

Gastrointestinal Involvement. Sterile peritonitis may be present as part of a polyserositis picture. Hepatitis and pancreatitis may be primarily caused by lupus**,** but many commonly used therapies such as corticosteroids, azathioprine, and mycophenolate (MMF) may also cause liver and pancreatic side effects.

Cardiovascular Disease. Any layer of the heart including the pericardium, myocardium, and valves (e.g., Libmann-Sacks endocarditis) may be inflamed. Vasculitis may target the coronary vessels, and the increased risk of myocardial infarction and other premature vascular diseases are related to chronic inflammation, disease and drug-related hyperlipidemia, hypertension, and sometimes steroid-related diabetes. The role of generalized chronic inflammation in premature cardiovascular disease is under study. Vasculitis may affect other organs such as the gastrointestinal (GI) tract and brain with risk of thrombotic and hemorrhagic complications.

Raynaud phenomenon is unusual in children and is often a clue to an underlying rheumatic disease. If the vascular spasm persists, it may cause compromise of digits and require ICU intervention with vasodilating agents such as iloprost.

Renal Involvement. Renal disease is more common and more severe in children with SLE, occurring in about 80% of all cases. The spectrum varies from a silent disease identified only by abnormal urinalysis or by kidney biopsy to renal failure, severe nephrotic syndrome and malignant hypertension. Both nephritic and nephrotic patterns occur, loosely correlating with diffuse proliferative disease and membranous disease, respectively.[11]

Hematologic Involvement. Antibodies against specific cells usually reflect hematologic involvement. Anemia maybe related to Coomb positivity, but blood loss and marrow suppression should also be considered. Leukopenia is one of the criteria for SLE. If the white blood cell count is high in the context of what appears to be active SLE, then infection must be seriously considered. High-dose steroids demarginate neutrophils and therefore may also cause an elevated white cell count. Thrombocytopenia may be profound and life-threatening and may be mediated by antiplatelet antibodies or APL antibodies

Musculoskeletal Manifestations. Arthritis occurs in about 80% of patients with SLE and is a helpful clue to the diagnosis. Although a joint exam is not a regular part of the intensivist's repertoire, it can be very useful in deciding who needs further rheumatologic evaluation. Myositis is less common. Avascular necrosis can result from the disease itself, especially if the patients have APL antibodies, or as a complication of steroids.

Endocrine Issues. Thyroid disease may present as hyperthyroidism or hypothyroidism. Diabetes is usually a complication of steroid treatment, although rarely insulin resistant diabetes related to insulin receptor antibodies causes hyperglycemia refractory to therapy. Adrenal insufficiency is usually iatrogenic secondary to adrenal suppression from exogenous steroids.

Immune Dysfunction. Many factors reduce the immune response in patients with SLE. They are intrinsically immunosuppressed related to: altered B- and T-cell function; low complement levels that impair opsonization encapsulated organisms; and both hypergammaglobulinemia and hypogammaglobulinemia. In addition, immunosuppressive agents used to control their disease increase their risk of handling infections poorly. Furthermore, many patients with immunodeficiency can present with autoimmune phenomena, particularly those with chronic granulomatous disease, common variable immunodeficiency and T-cell abnormalities such as di George syndrome and ataxia telangiectasis.

Laboratory Studies. A hallmark of lupus is a positive test for ANAs in over 95% of cases; however, a positive ANA is found in many other conditions, including other rheumatic diseases and infections. It is therefore essential to support the diagnosis with clinical features and evidence of other autoantibodies

and immune complex formation.[12] Antibodies to double-stranded DNA (ds-DNA) are found in about 40% of patients at onset of their lupus and about 80% during the course of disease. These are quite specific to lupus and correlate with renal disease as the size and charge of the immune complex they form is filtered and deposited in the kidney, triggering an inflammatory response.

Smith antibodies (antiribonucleoprotein antibodies) are not quite as specific but are still part of the diagnostic criteria. Complement levels are low in active disease, reflecting consumption during immune complex formation. A total hemolytic complement should be screened to check the total complement pathway, and if zero, a search for complement component deficiency should be initiated. However, C3 and C4 are relatively quick and convenient screens of both the classic and alternate pathways and are used to monitor disease activity.

Full laboratory and imaging evaluation of all organ systems is essential to establish which organ systems are affected and the severity of the disease. A thorough clinical, laboratory, and radiographic evaluation is necessary to help guide treatment decisions.

Management

In patients ill enough to require intensive care, pulses of corticosteroids (methylprednisolone 30 mg/kg/day administered over 1 hour with careful monitoring of blood pressure, fluid and electrolyte status, and hyperglycemia for 3 days), are often indicated, with subsequent maintenance at 2 to 3 mg/day methylprednisolone divided every 8 hours. Simultaneous coverage for infection is usually advisable. Steroid-sparing agents such as cyclophophosphamide are often initiated, especially in the case of significant renal and CNS disease. Renal failure and dialysis can affect metabolism and clearance of many medications used to treat SLE, and consultation with nephrology and pharmacology services can assist in proper dosing. Careful attention to management of individual organ involvement such as hypertension, seizures, cardiac or pulmonary compromise, and hematologic abnormalities is just as important as overall disease treatment.

Neonatal Lupus Syndromes

Mothers who have autoantibodies, whether or not they are symptomatic, may transmit antibodies to the fetus causing antibody-related disease even before infants have the capacity to make antibodies of their own.[13] usually causes neonatal heart block that is irreversible and requires a pacemaker. Anti-La, which mediates neonatal cutaneous lupus syndrome, usually causes a rash that erupts after light exposure, but is sometimes associated with hepatitis and other organ system involvement. Other maternal antibodies, such as antiplatelet or Coomb antibodies, may cause neonatal thrombocytopenia and hemolytic anemia. As the maternal antibody levels in the infant's circulation decline, the signs usually resolve; however, exchange transfusion can remove antibodies causing serious adverse events.

Juvenile Dermatomyositis

Clinical Presentation. Juvenile dermatomyositis is an inflammatory disease characterized by rashes over the eyelids, face, "shawl" area, and extensor surfaces of the small joints of the hand, knees, and elbows (Gottron papules).[5,14] The inflammation affects striated muscle, proximal more than distal muscle groups, and can cause profound weakness of hip and shoulder girdle groups as well the palate, pharynx and upper third of the esophagus, resulting in dysphagia, dysphonia, and aspiration risk. Respiratory failure may not be obvious as muscle weakness may mask typical signs. Nailfold capillary dilatation and dropout are markers for systemic vasculitis. Vasculitis targets the GI tract and may cause bleeding, necrosis and perforation. Pulmonary hemorrhage is another complication of systemic vasculitis, and the fundi and skin may also be affected. Cardiac muscle may be inflamed, and rarely myocarditis and conduction defects have been reported. The kidneys are not usually a primary target of vasculitis, but rhabdomyolysis with secondary renal impairment rarely occurs. Severely ill patients may also demonstrate findings of MAS. An underlying malignancy is extremely rare, unlike adult-onset dermatomyositis.

Laboratory Studies. A typical rash, muscle weakness, and evidence of vasculitis usually makes this diagnosis obvious. However, laboratory studies can confirm the diagnosis, monitor disease activity, and guide management. Acute phase reactants and muscle enzymes, including creatine phosphokinase, aldolase, and lactate dehydrogenase are usually markedly elevated. A video swallowing study establishes whether aspiration risk is high enough to suggest alternative feeding methods. Electrocardiogram, echocardiogram, chest radiograph, chest CT, and pulmonary function studies establish the extent of cardiopulmonary involvement. Stool should be checked for occult blood and abdominal CT performed if there is any suggestion of GI involvement. A magnetic resonance image of proximal muscles will show muscle edema and inflammation and can be used to identify a site of biopsy if there is concern for other causes of a myositic or myopathic process.

Management. Besides airway and respiratory support and close monitoring for GI complications, an aggressive medical approach is essential. High-dose pulse steroids, methotrexate and intravenous gammaglobulin should be initiated immediately, not only to keep the patient alive, but to prevent permanent muscle destruction and reduce the risk of long term complications such as calcinosis. Other agents, such as cyclosporine, MMF mofetil, and rituximab may be used. Because of GI involvement, medications administered orally may not be reliably absorbed, and accordingly parenteral administration is preferred. Physical therapy should be initiated early to prevent joint contractures. After muscle enzymes start normalizing, physical therapy should emphasize strengthening muscles and regaining function.

Mixed Connective Tissue Disease (Overlap Syndrome)

This condition displays features of more than one rheumatic disease, for example a rash and arthritis like lupus, muscle inflammation like dermatomyositis, and fibrosing lung disease like scleroderma. Serologically, these patients usually have very high titer ANAs and antibodies only to ribonucleoprotein. Management, besides general control of inflammatory features, depends on the clinical features identified and the organs affected.

Antiphospholipid Antibody Syndrome

Catastrophic thrombotic syndromes are caused by hypercoagulable states. Some are related to primary hematologic diseases, such as deficiencies of protein C and protein S, 5,10-methylene tetrahydrofolate reductase polymorphisms and factor V Leiden. However, APL antibody syndrome, either primary or secondary to autoimmune disease, is also a common cause of hypercoagulability.[16] The syndrome is defined by recurrent arterial or venous thrombosis (often deep vein thrombosis and pulmonary emboli), thrombocytopenia, or, in women of child-bearing age, recurrent fetal loss. APL antibody syndrome also should be considered in the setting of severe neurologic manifestations such as stroke, transverse myelitis, seizures, or mononeuritis multiplex.

Laboratory Studies

Laboratory findings include prolongation of the partial thromboplastin time (PTT) that does not correct with a 1:1 mix (the antibody binds to the substrate, and adding normal serum with clotting factors does not affect this), false-positive syphilis test result, and the presence of antibodies to cardiolipin and associated proteins measured by either functional coagulation assays (lupus anticoagulant) or antibody titers (anticardiolipin and β_2-glycoprotein). Sometimes transient APL antibodies can be triggered by intercurrent infectious illnesses, and abnormal values three months apart are required to confirm APL syndrome.[16]

Management

The treatment of thrombotic episodes related to APL is anticoagulation with unfractionated heparin as the agent of choice.[17,18] Heparin acts as an anticoagulant within the clotting cascade in addition to preventing binding of C5a to endothelial cells and inhibiting release of factors triggering clotting at the vascular wall level. Monitoring for therapeutic anticoagulation may be difficult in the context of an already prolonged PTT and therefore, anti-factor Xa levels may be more reliable. If the thrombosis is acute or subacute, tissue plasminogen activator may facilitate breakdown. Use of Greenfield filters is controversial. If APL is identified in the context of a diagnosis such as SLE or vasculitis, additional immunosuppression is indicated.

Vasculitic Syndromes

Vasculitis is a generic term for inflammation of blood vessels, and is classified as either primary, or secondary to another rheumatic disease, such as lupus or dermatomyositis. Primary vasculitis is then classified according to size of affected vessels, although there may be overlap (Table 98-1). Diagnosis is usually made either by biopsy of affected tissue, or imaging showing characteristic changes in medium or large vessels. In some cases, serologic studies are helpful. With current treatment approaches, the prognosis has markedly improved.[19] The most common forms of vasculitis in children are Henoch Schönlein purpura and Kawasaki disease, but children can also develop Wegener granulomatosis (WG), microscopic polyangiitis (MPA), polyarteritis nodosa, and Takayasu arteritis.[20] Occasionally only one organ system is affected, for example, isolated CNS vasculitis.

Small Vessel Vasculitis Syndromes

Henoch-Schönlein Purpura

Clinical Presentation. Henoch-Schönlein purpura is an immunoglobulin A–mediated small vessel vasculitis, often triggered by a preceding infectious illness. Most cases are mild and resolve without treatment. However, rapidly progressive glomerulonephritis and GI complications including intussusception, necrosis and perforation may occur. Rarely pulmonary hemorrhage and CNS involvement have been reported. Classic clinical features include palpable purpura predominantly in the lower extremities, arthritis or arthralgias, abdominal pain, and hematuria.

Laboratory Studies. Laboratory tests are nonspecific, usually showing only mild elevation of inflammatory markers and white blood cell counts. Coagulation studies should be normal. On biopsy, immunoglobulin A may be deposited in the skin and kidney.

Management. Treatment is primarily supportive, but high-dose corticosteroids have been used for serious organ involvement, especially threatened or actual intussusception. Immunosuppression with cyclophosphamide, azathioprine, cyclosporine, intravenous immunoglobulin (IVIG), and plasmapheresis has been described for more severe or unresponsive disease.

Wegener Granulomatosis

Clinical Presentation. WG is a systemic granulomatous vasculitis that targets the head and neck, especially sinuses and middle ear, kidneys, and lungs (both airways and parenchyma).[21] Serious components of this disease include pulmonary hemorrhage, necrotizing cavitating lung lesions, and subglottic stenosis with symptoms of shortness of breath and stridor. The renal disease is a rapidly progressive pauci-immune glomerulonephritis. Table 98-2 lists the clinical syndromes causing severe nephritis and hemoptysis that should be considered in the differential of WG.[22] Neurologic manifestations occur in a significant portion of patients and include peripheral nervous system disease, mononeuritis multiplex, cerebral involvement with seizures, infarction, hemorrhage, (stroke or mass lesions), and transverse myelitis.

Laboratory Studies. Positive antineutrophil cytoplasmic antibodies (p-ANCA) in the setting of a compatible clinical picture are strongly suggestive of WG. Antibodies against proteinase-3 are quite specific for WG and may correlate with disease activity. Complete evaluation of the lungs and airways is essential, including a CT to identify cavitating lung lesions, pulmonary hemorrhage, or narrowing of the trachea, bronchi and bronchioles. Sinus disease may be silent and identified only by imaging. Renal biopsy shows pauci-immune necrotizing glomerulonephritis. Cutaneous vasculitis and thrombotic episodes secondary to APL antibodies are reported.

Management. Immunosuppression with a combination of cyclophosphamide and corticosteroids has been shown to decrease mortality and to induce remission in the majority of patients. Cyclophosphamide is given at 2 mg/kg/day orally or as an intravenous pulse dose of 250 mg/m^2 weekly in the setting

Table 98–1 Autoantibody Profiles for Vasculitis Associated with Various Autoimmune Diseases

	ANA	Ds-DNA	Smith	ANCA	Complements
SLE	+++	+ in 40%–80%	+ 50%–60%	Usually –	Low
WG	– or weakly +	–	–	0% + (PR3)	Normal
MPA	– or weakly +	–	–	90% + (MPO)	Normal
Polyarteritis	–	–	–	Usually –	Normal
Takayasu arteritis	–	–	–	–	Normal
S-JIA	–	–	–	–	Normal–high

+, Positive; –, negative; *MPO,* myeloperoxidase.

Table 98–2 Organ Involvement and Typical Laboratory Findings in Various Autoimmune Diseases

Diagnosis	Pulmonary Findings	Renal Findings	Other Organ System Involvement	Laboratory Findings
WG	Cavitating lung lesions, pulmonary hemorrhage	Pauci-immune necrotizing glomerulonephritis	Sinus, airways	Usually ANCA positive (PR3)
MPA	Pulmonary hemorrhage	Pauci-immune necrotizing glomerulonephritis	Skin, CNS	Usually ANCA positive (MPO)
Goodpasture syndrome	Pulmonary hemorrhage	Anti-GBM positive glomerulonephritis	None	Anti-GBM positive
SLE	Pulmonary hemorrhage	Proliferative or membranous changes; marked immune complex deposition	Multisystem disease	ANA positive, ds-DNA positive, Sm positive, low complements
Scleroderma	Fibrosing lung disease	Sclerosing glomerular and interstitial disease	Skin, GI tract	Scl-70 positive

GBM, Glomerular basement membrane; *MPO,* myeloperoxidase.

of serious, life-threatening disease. Pulse corticosteroids may be given in conjunction with this regimen until the inflammation and clinical setting improve, but steroids alone are not sufficient to maintain long term remission. More recently, rituximab (anti-CD20) has been used to target the B lymphocytes thought to be pathogenic in this disease. Antibiotic coverage for sinusitis and surgical intervention to improve sinus drainage can be helpful. Patients with WG are at increased risk of fungal infections such as aspergillus species, and care must be taken to differentiate infection from flare of disease.

Microscopic Polyangiitis

Clinical Presentation. The kidneys, lungs, GI tract, central and peripheral nervous system, skin and muscles are most frequently affected. Typically the patient exhibits constitutional symptoms such as fever, fatigue, weight loss, and symptoms of affected organs. Clinical presentations include pulmonary hemorrhage, GI bleeding or infarction, strokes, and kidney failure.

Laboratory Studies. Diagnosis of MPA is primarily clinical. Tests for p-ANCAs are often positive, especially for the neutrophil component myeloperoxidase. However, antibody testing is neither sensitive nor specific. It can be positive in other rheumatic diseases and in conditions such as inflammatory bowel disease. A positive biopsy of affected vessels confirms the diagnosis but is negative in almost half of cases. Renal biopsy shows pauci-immune necrotizing glomerulonephritis.

Management. Management includes supportive care and the use of corticosteroids. The addition of cytotoxic agents, such as cyclophosphamide or MMF, is associated with a lower mortality rate. Some cases with pulmonary hemorrhage have required extracorporeal membrane oxygenation treatment in addition to management of the underlying vasculitis. Plasmapheresis may be helpful in severe cases or in the setting of pulmonary hemorrhage.

Medium Vessel Vasculitis

Polyarteritis Nodosa

Clinical Presentation. Classic polyarteritis nodosa affects medium sized vessels. It is a rare disease in childhood but should be considered in any patient who has a combination of hypertension, GI involvement, rash, and fever. As in other forms of vasculitis, nonspecific muscle tenderness, arthritis, arthralgia and constitutional symptoms may occur. CNS signs include psychosis, seizures, strokes, or neuropathy. Skin manifestations can be varied, with painful nodules, purpura, petechiae, or patchy edema. GI vasculitis usually presents with abdominal pain, hemorrhage, necrosis or perforation. Cardiac involvement, including coronary arteritis, is more common in children.

Diagnosis. Diagnosis is confirmed by pathologic findings of medium sized vessels (those with a muscularis layer) on biopsy of affected tissues or angiography, either conventional or by magnetic resonance or CT contrast studies, that demonstrate

aneurysms, post stenotic dilatation and "rat tailing" changes in vessels. These may be patchy and multiple vessels, including renal, cerebral and celiac axes, may need to be studied to identify changes.

Management. Management includes high-dose corticosteroids and cyclophosphamide. *Streptococcus*-associated disease can trigger the disease and flare-ups. Appropriate antibiotic therapy and antibiotic prophylaxis may be warranted.

Large Vessel Vasculitis

Takayasu Arteritis

Clinical Presentation. Takayasu arteritis is an inflammatory disease that affects the aorta and its major branches. Early, in the inflammatory phase, the patient may have fever, fatigue, and weight loss and nonspecific organ findings. Later, after the inflamed vessels have begun to fibrose and stenose, symptoms related to compromised blood flow, such as absent pulses, angina, abdominal pain, visual changes, syncope, or stroke, will occur.

Diagnosis. Diagnosis is made by arteriography of the aorta and adjacent large vessels, although ultrasound, magnetic resonance imaging, or CT may be useful diagnostic procedures.

Management. High-dose corticosteroids are the primary treatment modality, augmented by cyclophosphamide, methotrexate, azathioprine, or in some cases, anti-TNF-α therapy. Surgical interventions may be indicated to bypass tight stenoses or replace a compromised aortic valve.

Primary Vasculitis of the Central Nervous System

Clinical Presentation. Primary vasculitis or angiitis of the CNS is characterized by inflammation of vessels within the CNS and by exclusion of vasculitis in other organ systems. This diagnosis is often considered in a child with unexplained CNS deterioration, especially after other diagnoses such as infections or metabolic conditions have been excluded.[23] Manifestations can be quite variable and include seizures, headache, hemiparesis, vertigo or dizziness, and aphasia.

Diagnosis. Diagnosis may be made by angiography, but small vessel disease may require brain or leptomeningeal biopsy. However, pathologic examination is prone to lower sensitivity if the biopsy sample does not capture an affected vessel area.

Management. Corticosteroids and cyclophosphamide have been shown to improve survival.

Kawasaki Disease

Clinical Presentation

Kawasaki disease is a childhood illness characterized by acute onset of fever at least 5 days, conjunctivitis, cervical lymphadenopathy, enanthem, exanthem, and extremity changes with redness, edema, and later desquamation.[24] Although acute myocarditis may occur during the acute febrile phase, the predominant morbidity results from the risks associated with development of coronary artery aneurysms and thrombosis peaking approximately six weeks after onset. Other peripheral arteries may develop aneurysms. Not all patients fulfill the classic clinical criteria, and so-called *atypical* or *incomplete Kawasaki disease* can include significant coronary artery involvement. The aneurysms of Kawasaki disease are at greater risk for stenosis or obstruction than are unaffected vessels and are prone to thrombosis and resultant morbidity. Furthermore, children with a history of Kawasaki disease have a higher incidence of premature myocardial infarction, even in the absence of known aneurysms.

Laboratory Studies

ESR and CRP are usually markedly elevated. After IVIG is administered, ESR is no longer an accurate marker of inflammation and CRP is a better marker for disease activity. Platelet counts can rise to more than 1,000,000/μL. High platelet counts are a maker of greater risk of thrombosis risk. Anemia and elevation of liver function tests also are common. Serial echocardiograms are the best way of monitoring the coronary vessels for signs of inflammation and development of aneurysms.

Management

Prompt initial diagnosis and treatment with 2 g/kg IVIG and high dose aspirin help prevent aneurysm formation. In the clinical scenario with concomitant myocarditis, supportive care including inotropes, fluid management with diuretics, and/or pacemaker may be necessary. Long-term use of low-dose aspirin is recommended once the acute illness is resolved. For cases refractory to IVIG, the addition of pulse steroids and TNF blockers such as infliximab and etanercept has been effective. Anticoagulants should be considered in the setting of large aneurysms to prevent further cardiovascular sequelae.

Scleroderma (Systemic Sclerosis)

Clinical Presentation

This is a rare condition causing vascular changes and fibrosis in multiple organ systems, especially lungs, kidneys, and GI tract.[25-27] Problems likely to be encountered in the ICU are renin mediated renal crises, which are best managed by use of angiotensin-converting inhibitors. Severe Raynaud phenomenon usually responds to vasodilators, including calcium channel blockers, alpha adrenergic blocking agents such as prazolol, or prostaglandin E agents such as iloprost. Progressive pulmonary fibrosis may result in respiratory failure. Prevention of microaspiration secondary to esophageal dysfunction and proton pump inhibitors to control gastroesophageal reflux may help. Cor pulmonale is a common terminal complication and is thought to be a result of microangiopathy and microthrombi, in which APL antibodies may play a role. Cardiac catheterization may demonstrate elevated pulmonary artery pressures, and trial of agents such as calcium channel blockers and bosentan (an endothelin-1 inhibitor) may result in reduction of right ventricular and pulmonary artery pressures. Pneumothorax from rupture of blebs in sclerodermatous lungs may require sclerosing of the pleura to prevent lung collapse. Rarely, pneumatosis intestinalis can result in intestinal perforation.

Critical Rheumatic Disease–Related Events in the Intensive Care Unit

Infections

Severe Infections

Life-threatening infections account for approximately 50% of ICU admissions in patients with systemic rheumatic disorders. They are the leading cause of mortality for patients with SLE, and affect a significant proportion of patients with other rheumatologic diseases.[28,29] The inflammatory disease process and chronic immunosuppression secondary to corticosteroids, chemotherapeutic agents, and biologic therapies reduce the ability of the innate immune system to fight infection, significantly increasing the risk for severe infections, including pneumonitis, sepsis, and necrotizing fasciitis.[28-35] A high index of suspicion for infection and the early judicious use of broad spectrum antimicrobial therapy are warranted, because many immunosuppressed patients may not be able to manifest the classic signs and symptoms of infection, including leukocytosis, fever, and erythema. Infectious organisms include community acquired bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, gram-negative enteric organisms, and opportunistic agents, such as *Pneumocystis carinii*, *Mycobacterium tuberculosis*, mucormycosis, *Aspergillus* spp., and cytomegalovirus. Common organisms may be found in unusual sites, such as staphylococcal endocarditis, whereas opportunistic organisms may be identified in common locations including sinuses and airways, such as *Aspergillus* pneumonitis. Before the initiation of antimicrobial therapy, body fluids and specimens should be obtained, cultured, and examined for the presence of both common and opportunistic infectious etiologies. In the setting of infectious pulmonary disease processes, high-resolution chest CT scans and bronchoscopy with bronchoalveolar lavage should be considered early in the course of illness while the patient is stable enough to tolerate them, as lung lesions can rapidly progress into severe, acute lung injury without adequate therapy.[1] In addition, soft tissue infections may not be obvious; however, may rapidly progress as necrotizing fasciitis, requiring extensive debridement.[31,33,34] *Pneumocystitis carinii* pneumonia prophylaxis should be considered for patients receiving immunosuppressive agents. In patients with history of *Herpes zoster* or fungal infections, antiviral and antifungal prophylaxis should also be considered.

Endocrine Involvement

Adrenal Insufficiency

Chronic corticosteroid therapy in patients with rheumatologic diseases increases the risk of inability of the adrenal system to respond to states of physiologic stress. Rapid initiation of stress dose corticosteroids in the setting of acute illness or surgery is essential. Chronic corticosteroid therapy may not be the only etiology for adrenal insufficiency, as basal serum cortisol levels were reported to be low in children with active JIA off corticosteroid therapy.[36]

Airway Compromise

Childhood rheumatologic conditions may present with airway problems related to obstruction from inflammation within the airway, compression from outside the airway, or the inability to protect the airway secondary to muscle weakness. This may be indolent or very rapid in onset. Sometimes intubation can be difficult and otolaryngology should be notified early in case a tracheostomy is required.

Disease processes that cause airway obstruction secondary to a pathologic process within the airway include SLE, JIA, WG, and relapsing polychondritis. Oropharyngeal obstruction is uncommon, but rarely occurs in SLE from acute mucosal swelling of the pharyngeal and laryngeal tissues related to an acquired inhibitor causing an angioedema type picture.[37] Cricoarytenoid arthritis and airway obstruction from decreased mobility of the vocal cords can occur in JIA and SLE.[38,39] Subglottic stenosis affects 10% to 20% of patients with WG and is five times more common in pediatric than adult-onset disease. If the patient's condition allows, a conservative approach with medical therapy and topical approaches such as intralesional steroid injections and dilation may be attempted before surgical intervention.[4,39,40] Rarely, relapsing polychondritis, that causes recurrent cartilage inflammation, affects both small and large airways and may cause either upper or lower airway obstruction.[4,39]

Airway compromise secondary to external compression may occur in sarcoidosis. Children may present with dysphagia and dyspnea from enlarged nodes compressing the airway or supraglottic stenosis

Finally, in juvenile dermatomyositis, weakness of muscles in the palate, pharynx, larynx, and upper third of the esophagus leads to dysphagia, dysphonia, inability to manage secretions and airway compromise, requiring intubation.[4] As noted, signs of distress may be absent because of muscle weakness.

Pulmonary Involvement

Although infectious etiologies are the most common cause of lung involvement in pediatric patients with rheumatologic disease, noninfectious pneumonitis, interstitial lung disease, pulmonary fibrosis, acute alveolar hemorrhage, and pleuritis with pleural effusion frequently occur. The severity of these pathologic processes is highly variable; however, patients who suffer from significant respiratory compromise need supportive care with positive pressure ventilation. Patients may require chest tubes while pharmacologic and cytotoxic therapies are initiated.[41-45]

Pneumonitis

In addition to infectious etiologies, patients with rheumatologic diseases may develop pneumonitis with no identifiable infectious agent. In these cases, aggressive immunosuppressive therapy may decrease pulmonary inflammation, leading to improved outcomes. In WG, up to 80% of patients have pulmonary involvement. The most common findings on chest CT include pulmonary nodules, ground-glass appearance, and air opacifications. Plain chest radiographs may not reveal these changes.[19,21] Systemic sclerosis targets the lower third of the esophagus and may result in incompetence of the gastroesophageal junction. Resulting reflux and microaspiration may also contribute to the interstitial lung disease frequently seen in this

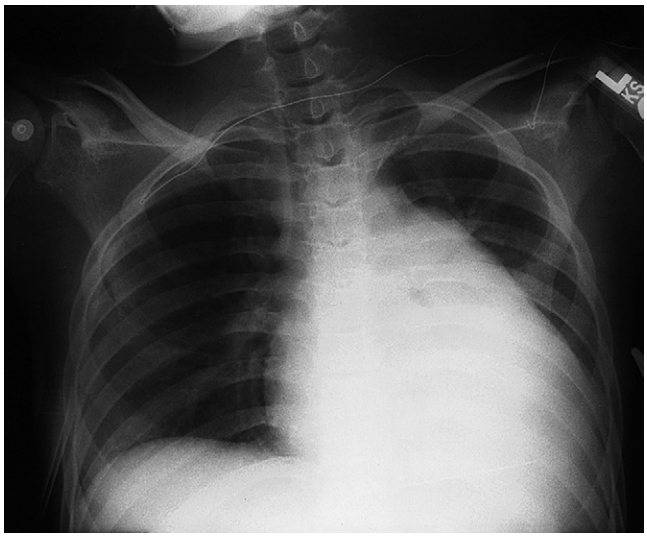

Figure 98–1. Portable chest radiograph of a 12-year-old female patient with scleroderma. The patient arrived at the ICU with sudden onset of orthopnea and thrombocytopenia. Cardiomegaly was observed. Echocardiography revealed pericardial effusion. However, pulmonary vascularity was normal in this patient. Physical examination revealed sclerodactyly. The patient eventually developed cor pulmonale as a result of pulmonary hypertension. Inflammatory changes suggestive of other collagen vascular diseases may be seen in the early course of scleroderma. Use of pulse intravenous methylprednisolone reduced these early inflammatory changes, although as an outpatient the patient maintained stable right-sided heart disease that was not responsive to immunosuppressive medication, consistent with scleroderma.

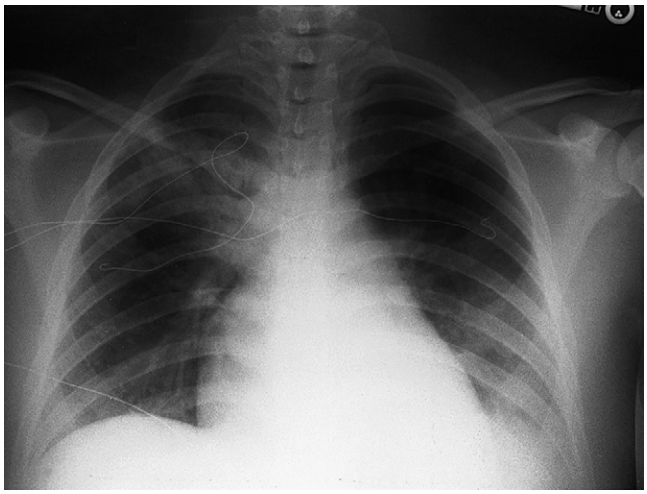

Figure 98–2. Portable chest radiograph of a 16-year-old female patient with SLE. Lupus pneumonitis is reflected by infiltrate in the right upper lobe and bilateral diffuse interstitial changes. Pleural fluid suggested by haziness over the left lower lobe, as well as blunted left costophrenic angle (not shown), was confirmed by bilateral decubitus films.

condition. A range of 40% to 80% of patients with systemic sclerosis exhibit interstitial lung disease based on several case series reports.[26,27] In these patients, pulmonary arterial hypertension can be associated with the interstitial lung disease, requiring pharmacologic vasodilator therapies (see Figure 98-1).[27] Although rare, severe interstitial lung disease has also been reported in juvenile dermatomyositis, requiring intensive immunosuppression and supportive therapy with extracorporeal membrane oxygenation.[25] Similarly, interstitial lung disease is rarely reported in SLE as acute lupus pneumonitis and idiopathic juvenile arthritis (see Figure 98-2).[4] Patients with interstitial lung disease secondary to autoimmune disease are at increased risk for developing pulmonary fibrosis.

Pleuritis and Pleural Effusions

Pleuritis, with or without pleural effusions, is a common manifestation of autoimmune disorders in children. Approximately 30% of patients with SLE and S-JIA demonstrate pleuritis that may cause pleural effusions sufficiently large to compromise pulmonary function.[45] Drainage with chest tubes may be required.

Pulmonary Hemorrhage

Systemic vasculitides, including WG, MPA, Goodpasture syndrome, and SLE place patients at risk for acute alveolar hemorrhage, causing significant morbidity and a mortality rate as high as 90%.[46] Acute pulmonary hemorrhages are not always preceded by hemoptysis and may be catastrophic, leading to acute hypoxemic respiratory failure and hemorrhagic shock. Chest radiographs typically reveal diffuse alveolar airspace filling defects, although patients with milder disease may have only focal abnormalities. Chest CT scans are more sensitive than chest radiographs and typically reveal ground glass opacities.[47] If the patient is able to cooperate with pulmonary function testing, an elevated diffusion capacity value is a good marker for pulmonary hemorrhage. Supportive care includes positive pressure ventilation with high positive end-expiratory pressure to reduce the hemorrhage, rapid blood transfusions, and close monitoring for hemodynamic stability. Although extracorporeal membrane oxygenation requiring anticoagulation therapy may be considered contraindicated in these settings, case reports in the literature demonstrate that extracorporeal membrane oxygenation can be safe and lifesaving.[48,49] Treatment of the cause of acute pulmonary hemorrhage requires high-dose corticosteroids and appropriate immunosuppressive therapies. Plasma exchange has also been shown to improve outcomes in Goodpasture syndrome and possibly other forms of vasculitis.[50] Evaluation for bacterial, viral, and fungal infections and treatment with antimicrobial therapy should be considered, as concurrent pulmonary infections such as mucormycosis may trigger pulmonary hemorrhage. Long term consequences of acute pulmonary hemorrhage include the development of pulmonary fibrosis and rarely, bronchiolitis obliterans, although many children recover without sequelae.[44,47]

Pulmonary Embolism

Patients with APL antibody syndrome, either primary or secondary to conditions such as SLE or vasculitis are at increased risk for the development of thrombotic events, including pulmonary embolism. Pulmonary embolism can also be associated with nephrotic syndrome from multiple conditions including SLE because of the renal loss of anticoagulant factors.[51,52] Patients typically present with pleuritic chest pain, tachypnea, tachycardia, and hypoxia, but some may be silent. Chest CT scans with angiography are the best studies. Treatment requires supportive care and early intervention with systemic thrombolytics, including unfractionated heparin and tissue plasminogen activator, especially for hemodynamically significant pulmonary emboli.[4,53] Occasionally, intrapulmonary thrombolytics are indicated to attempt to dissolve large clots if there is significant hemodynamic compromise.[54]

Cardiovascular Events

Pericarditis and Pericardial Tamponade

Pericarditis affects from 12% to 48% of patients with SLE, who present with positional precordial chest pain, fever, tachycardia, diminished heart sounds, and sometimes a friction rub.[55] Similarly, 8% to 42% of children with JIA are reported to have pericardial involvement.[4] Acute pericarditis with large effusions may lead to tamponade, characterized by tachycardia, a narrow pulse pressure, diminished heart sounds on exam, and clinical signs of poor cardiac output. Emergent pericardiocentesis is indicated when there are clinical signs of poor cardiac output or if there is concern for an infectious etiology.[56]

Chronic pericarditis may cause restrictive cardiac disease. Evaluation for pericarditis includes an echocardiogram and electrocardiogram. Medical management in the setting of systemic inflammatory disease includes nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppression.

Myocarditis

Although rare, patients with rheumatic diseases, including SLE, JIA, dermatomyositis, and vasculitis may present with clinical evidence of poor cardiac output and congestive heart failure secondary to myocarditis.[4,57-59] Patients report fatigue and exercise intolerance and have tachycardia, respiratory distress with bilateral rales, and hepatomegaly on physical exam. The chest radiographs may reveal cardiomegaly with pulmonary edema, whereas the echocardiogram shows diminished ventricular systolic function. Management involves diuresis, inotropic support, and escalation of immunosuppressive therapy. Inflammatory myocarditis may be very sensitive to agents such as digitalis, resulting in arrhythmias, so these should be used judiciously if at all.

Valvular Disease

The most common valve disease associated with autoimmune diseases is verrucous endocarditis, or Libman-Sacks disease, found in up to 10% of patients with SLE.[45] Fibrinoid nodules may form on any of the cardiac valves, with the mitral and aortic valves most commonly involved.[4] Vegetations and valvular thickening may lead to severe regurgitation and occasionally stenosis. In addition to the hemodynamic complications associated with valvular regurgitation and stenosis, Libman-Sacks endocarditis may be complicated by thromboembolism, especially in the presence of APL antibodies, and infective valvulitis. Diagnosis requires an echocardiogram. As transthoracic echocardiograms have been shown to have low sensitivity and specificity, a transesophageal study should be considered. Some patients respond to conservative treatment, but others require valve replacement surgery.[60]

Arrhythmias

SLE is associated with an increased risk for conduction abnormalities. In one case series, approximately 12% of patients with lupus suffered from arrhythmias, including premature atrial beats, supraventricular tachycardia, atrioventricular blocks, and right bundle branch blocks. Diagnosis requires an electrocardiogram and echocardiogram. Patients usually respond to pharmacologic antiarrhythmics. Pacemakers are indicated for complete atrioventricular block, particularly in neonatal lupus.[4,45]

Acute Coronary Syndromes

The increased risk for acute myocardial infarction secondary to premature atherosclerosis, resulting from disease-related dyslipidemia, coronary artery inflammation or arteritis, and side effects of pharmacologic therapies is well recognized in SLE.[61]

Pediatric patients are especially at risk because of increased disease severity and lengthy disease burden. Approximately 60% to 85% of children and adolescents with lupus have dyslipidemia, compared with 5% to 10% of healthy children and adolescents. A randomized clinical controlled trial (APPLE trial) is studying the safety and efficacy of the use of statins to prevent premature atherosclerosis in pediatric patients with lupus.[62,63]

The 15% to 25% of patients with Kawaski disease who have delayed diagnoses, and those resistant to medical therapy are at increased risk for acute myocardial infarction secondary to the development of coronary artery aneurysms. These aneurysms are the site of thrombosis, stenosis, or rupture, causing myocardial ischemia. Giant aneurysms (>8 mm in diameter) have the poorest prognosis. Surgical intervention with bypass grafting is indicated when there is reversible ischemia on stress imaging tests with no coronary disease distal to the planned bypass graft site.[64] Occasionally, an older patient with a history of Kawasaki disease as a child may have a myocardial infarction as an adolescent or young adult.

Gastrointestinal Involvement

Gastrointestinal Hemorrhage

Vascularities and other systemic inflammatory diseases increase the risk for acute or subclinical GI hemorrhage. If GI bleeding is suspected during the initial assessment, large-bore intravenous access should be obtained and blood products should be readily available. Early GI and surgical consultation is advisable. Embolization under radiologic guidance controls the hemorrhage in some occasions. In patients with Henoch-Schönlein purpura, up to 30% of patients develop GI hemorrhage, although severe hemorrhage, irreducible intussusception and perforation are rare.[65]

Acute Surgical Abdomen: Peritonitis and Intestinal Perforation

Patients with autoimmune disease processes and vasculidites are at increased risk of morbidity and mortality from acute abdominal pathology, including intestinal perforation and bacterial peritonitis with abscess formation. Approximately 20% of patients with SLE report recurrent abdominal pain. A high index of suspicion for severe pathology is necessary, because immunosuppression may blunt the clinical signs and symptoms of an acute surgical abdomen.[66,67] Delayed intervention is common and leads to an increased mortality rate from abdominal complications

Pancreatitis

In addition to an acute surgical abdomen, severe acute pancreatitis is reported in SLE. This may be disease related or secondary to the use of high-dose steroids and other immunosuppressive agents.[68-70] Mortality rates secondary to pancreatitis in the setting of systemic disease have been reported as

high as 59%.[4] Children with Henoch-Schönlein purpura and Kawasaki disease have also been reported to suffer from pancreatitis.[4] In patients complaining of nonlocalizing abdominal pain in the setting of autoimmune disease, serum amylase and lipase levels should be obtained. If these enzymes are elevated, imaging studies including ultrasound and abdominal CT should be performed to evaluate for evidence of inflammation, stones and pseudocysts. Treatment involves pain control, non-enteral nutrition, close monitoring of electrolytes, and avoidance of refeeding too early. In cases caused by drug toxicity, inciting drugs should be avoided if possible.

Renal Involvement

Renal Failure and Malignant Hypertension

Most autoimmune disorders, including SLE, WG, microscopic polyarteritis, and Henoch-Schönlein purpura affect the kidneys. Renal findings include oliguria/anuria, hypertension, hematuria, proteinuria, elevated creatinine, low albumin and electrolyte imbalance. These may be present initially or evolve as the disease process progresses.[71,72] Evaluation of the renal status should include a urinalysis, electrolytes, blood urea nitrogen, creatinine, spot urine protein/creatinine ratio, 24-hour urine protein and creatinine collection, complete blood count, ANAs, complement levels including C3 and C4, and antineutrophil cytoplasmic antibodies. If the patient is stable and does not have contraindications such as a bleeding diathesis or severe hypertension, a renal biopsy should be performed early in the course of the disease process to aid in diagnosis and staging of disease. Although specific treatment depends on the etiology of renal insufficiency, all patients require close monitoring for hypertension, electrolyte abnormalities, and volume overload.

Adjunctive therapies with corticosteroids, cyclophosphamide, MMF mofetil or cyclosporine have been shown to improve remission rates.[73] In rapidly progressive glomerulonephritis, management includes high-dose corticosteroids, immunosuppression, and occasionally plasma exchange. Dialysis may be required for renal failure, but some patients will recover from acute renal injury if treated with aggressive medical therapy. However, some will not, and will need management for end-stage renal disease. Renal transplantation can be successful in the context of good control of active disease.[74,75]

Central Nervous System Involvement

Seizures are a feature of several rheumatic diseases, usually a result of small vessel vasculitis. They should be managed with standard agents in conjunction with antiinflammatory agents. Although some anticonvulsants have been associated with induction of a lupuslike picture, there is no evidence that these exacerbate lupus itself. Cerebral infarction is usually result of vasculitis or thrombosis related to APL. Hemorrhage can also result from vasculitis, but thrombocytopenia and anticoagulation for APL can also be factors.

Psychosis is most commonly seen in SLE. Often, markers usually abnormal in active lupus may be normal. An antibody, antiribosomal-p, may be a marker for psychosis in some patients.[76,77] It should be managed with antipsychotic agents as well as control of active disease. Rarely, steroids may cause psychosis, and the choice might be between reducing steroids to see if symptoms improve, or adding stronger immunosuppressants.

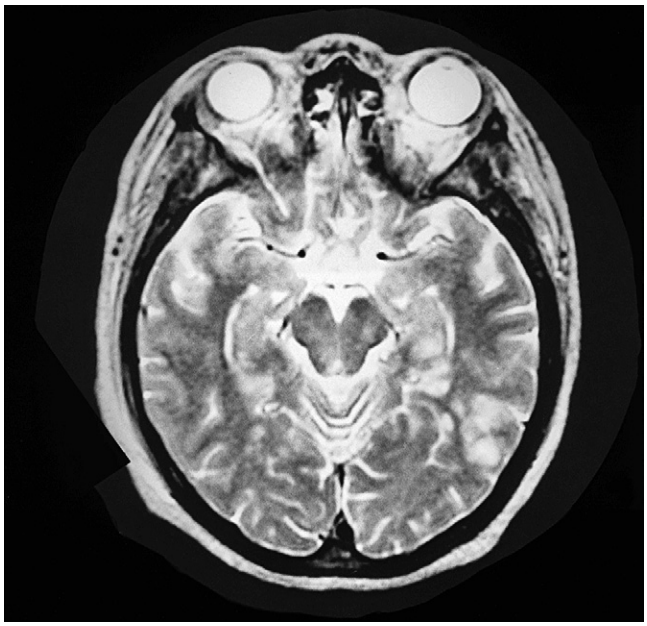

FIGURE 98–3. Magnetic resonance image of the brain of a 16-year-old female patient with SLE. This image was obtained after the patient was stabilized. Multiple areas of increased signal are scattered throughout both cerebral hemispheres, consistent with ischemic infarctions resulting from lupus cerebritis. Other views demonstrated similar infarcts in the brainstem and cerebellar hemisphere. Magnetic resonance angiography obtained at the same time revealed normal vasculature, suggesting pathologic involvement of brain tissue but sparing of vessels. The patient responded well to pulse intravenous methylprednisolone and cyclophosphamide, with no residual neurologic deficit.

Encephalopathy with altered state of consciousness should always raise concerns for infection, however may also be a result of active disease. Standard imaging may demonstrate abnormal findings (Figure 98-3) or may be normal even in the context of what appears to be active disease.

In SLE, lumbar puncture may yield spinal fluid with a mildly elevated white cell count with lymphocyte predominance, elevated protein and low glucose levels. Complement levels in the spinal fluid are difficult to interpret and not recommended.

Hematologic and Immunologic Involvement

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare, life threatening hematologic disorder that can be inherited or acquired. It is associated with SLE, especially in pediatric patients. Diagnosis is based on a clinical pentad: (1) thrombocytopenia and disseminated platelet aggregation, (2) microangiopathic hemolytic anemia, (3) neurologic abnormalities, (4) fever, and (5) renal disease. The reasons for the association between SLE and TTP is unknown; however, up to 50% of pediatric patients diagnosed with TTP also meet criteria for SLE.[78] The pathophysiology is explained by a malfunction of ADAMTS-13, that cleaves von Willebrand multimers. This lack of cleavage leads to binding of von Willebrand multimers to platelets, creating aggregates of platelets that bind to the endothelium, causing hemolysis and ischemia of affected

organs. In hereditary TTP, there is an absence of ADAMTS-13, whereas in secondary TTP, an inhibitory antibody inactivates ADAMTS-13. In patients with clinical TTP, demonstrating reduced levels of ADAMTS-13 activity (<5%) is confirmatory.[79] Treatment for TTP requires plasma exchange, which significantly decreases the mortality rate, and immunosuppression with corticosteroids and cyclophosphamide.[78-82]

Macrophage Activation Syndrome

MAS is a severe, life-threatening complication of childhood systemic inflammatory diseases, primarily S-JIA. It typically occurs during an acute flare of the disease, change in medical therapy, or with a concurrent infection. The diagnosis of MAS can be difficult, as findings can be confused with intercurrent infections, sepsis, and acute exacerbations of the underlying disease process. Therefore, a high index of clinical suspicion is necessary.

Patients typically become acutely ill with unremitting high fevers (different from the quotidian pattern of S-JIA), lymphadenopathy, hepatosplenomegaly, intravascular coagulation abnormalities causing possible purpura, easy bruising, and mucosal bleeding, and neurological changes, including lethargy, irritability, disorientation, headaches, seizures, or coma. Laboratory evaluation typically reveals pancytopenia, elevated liver transaminases, coagulopathy, hyponatremia, elevated triglycerides, elevated lactate hydrogenase, and most importantly, a significantly elevated ferritin level, usually greater than 10,000 ng/mL. The pathognomic feature of the disease is a bone marrow examination that reveals numerous macrophages phagocytosing hematopoietic cells.[83-87]

The pathogenesis of the disease process is not entirely understood; however, MAS is associated with an uncontrolled expansion of T lymphocytes and hemophagocytic macrophages. The hemophagocytic macrophages express CD163, a scavenger receptor that recognizes haptoglobin-hemoglobin complexes. Uptake of these complexes by macrophages leads to an upregulation of heme-oxygenase enzymatic activity that degrades the subunit of hemoglobin into biliverdin, carbon monoxide and free iron and leads to increased synthesis of ferritin. Hence, a significantly elevated ferritin level is typically associated with MAS. In addition to rapid expansion of macrophages, diminished cytotoxicity of CD8 T cells and natural killer cells has been found in MAS. The etiology of this diminished cytotoxicity is not entirely understood, however defects in the function of perforin, a protein expressed in lymphocytes, macrophages, and other bone marrow precursors that forms pores in the cell membranes of target cells, leading to osmotic lysis, has been associated with both familial hemophagocytic lymphohistiocytosis and MAS.[83-87]

Treatment for MAS requires parenteral administration of high doses of corticosteroids. Patients who are refractory to corticosteroids may be managed with cyclosporine A. Although the mechanism of cyclosporine A is not entirely understood, it suppresses the early steps in T-cell activation by inhibiting the activation of transcription for genes encoding for cytokines, decreases macrophage production of interleukin-6, interleukin-1, and TNF-α, and inhibits the expression of cell surface costimulatory molecules, altering the antigen-presenting function of dendritic cells for T cell activation. In addition to corticosteroids and cyclosporine A, etanercept, a TNF-α inhibitor, has been shown to have efficacy.[88] IVIG, plasma exchange, cyclophosphamide, and etoposide may be effective in some patients, but relevant studies have reported conflicting results.[85,86]

Complications of the Treatment of Rheumatologic Diseases

Although aggressive management of rheumatic diseases is necessary to control active inflammation and prevent further organ system damage, therapies have risks of their own.[89] High-dose steroids exacerbate hypertension, cause electrolyte imbalance (particularly sodium and fluid retention, shift of potassium from intracellular matrix to plasma, and transient rise in creatinine) and hyperglycemia. White cell changes include lymphopenia, demargination of neutrophils with elevated peripheral count, and decreased neutrophil function. Increased susceptibility to infection is related to these factors. Long-term effects of steroids include loss of bone density resulting in risk of compression fractures, and striae and thinning of the skin potentiating the risk of breakdown and loss of skin integrity. Several medications cause gastric irritation, liver abnormalities, and pancreatitis. GI prophylaxis with proton pump inhibitors and monitoring pancreatic and liver enzymes is recommended. The newer biologic agents used in managing rheumatic disease may trigger hypersensitivity reactions, and patients receiving them should be monitored. Sometimes a patient may be admitted to the ICU for desensitization to allow them to tolerate a needed treatment.[90]

Managing medications can be very complex in seriously ill patients with rheumatic diseases. Because many medications are cleared through the kidneys or affected by dialysis, metabolized in the liver, or affect protein binding, careful attention to dosing and possible drug interactions is critical (see Chapter 118).

Summary

In summary, rheumatologic diseases manifest themselves in numerous ways and can affect all organ systems. Pediatric intensivists should have a basic understanding of the most commonly diagnosed conditions, including S-JIA, lupus, juvenile dermatomyositis, vasculidities, and scleroderma, as critically ill children may present to the ICU with new onset disease or with complications from previously diagnosed conditions. In addition, many of the therapies for autoimmune diseases have clinically significant side effects or require technical skills (such as plasmapheresis) that may require close monitoring in the intensive care setting. The diagnosis of rheumatic diseases requires a high index of suspicion, a broad differential diagnosis, and a thorough history and physical exam, because there are few tests that are exclusively diagnostic or pathognomonic for the disease processes. Early diagnosis and intervention can significantly reduce morbidity and mortality, and hence the intensivist plays a crucial role in providing life saving therapies to children with rheumatologic diseases.

References are available online at http://www.expertconsult.com.

Genomic and Proteomic Medicine in Critical Care

David Jardine, Mary K. Dahmer, and Michael Quasney

PEARLS

- The DNA of two unrelated humans is more than 99.9% identical.
- Human genetic variation most commonly comes from single-nucleotide polymorphisms or copy number variations. Copy-number variations are stretches of DNA of greater than 1 kb that show differences in the expected number of copies of the DNA in greater than 1% of the human population. One single-nucleotide polymorphism is believed to occur in every 100 to 300 bases.
- Although high-throughput screening technology is not commonly utilized for individual patients, in the future these technologies will likely be used to provide information on an individual patient's disease or response to therapy.
- Gene expression arrays are providing new insights into sepsis and acute lung injury. Studies of genetic variation are helping us to better understand response to medications such as opiates and β-agonists.
- Genomic medicine will provide us with tremendous benefits and challenges. Perhaps one of the greatest benefits will be the understanding that human similarities and differences transcend the racial and ethnic categories that have proved so contentious in the past.

The recently developed disciplines of genomics, proteomics, and metabolomics are producing significant change in the biologic sciences. In the next decade, these disciplines are projected to have a major effect on clinical medicine, both in speeding the development of new therapies and in helping to create individualized therapies that are specifically tailored to the disease and drug metabolism characteristics of each patient.

One of the hallmarks of these new technologies is that they produce enormous quantities of data, so they often are described as "high-throughput" technologies. These data simultaneously reveal details about many components of a biologic system rather than focusing on a single pathway or product. To meet the challenge of extracting meaningful information from such large quantities of data, the new discipline of systems biology is being developed. The goals of systems biology are to integrate information from a variety of sources and to develop a comprehensive picture of the relationships and interactions between the components of a biologic system. This chapter will focus on these disciplines and describe their potential impact on patients in the intensive care unit.

Genomics

From the Discovery of the Double Helix to the Human Genome Project

In 1953, in a manuscript that scarcely exceeded one page,[1] the double helical structure of deoxyribonucleic acid (DNA) was described. This brief report opened the door for a new understanding of heredity and gene function. As a direct result of this discovery, the field of molecular biology emerged and the task of deciphering the genetic code began. Initially, progress was slow, depending mostly on methodical detective work and a certain measure of luck. It was not until 1983, with the localization of the mutation for Huntington's disease to chromosome 4, that a gene was unequivocally linked to a physical location within the human genome (Figure 99-1). Another 10 years would elapse before the sequence of this gene was known and the molecular abnormality causing Huntington disease was identified. The cystic fibrosis gene was among the earliest disease-causing genes to be sequenced in 1989. Among the insights gained was that the disease was genetically heterogenous. Only 70% of patients with this illness had the most common mutation (ΔF508); the remaining patients could have any of hundreds of mutations in the chloride-channel protein encoded by this gene. Knowledge of variation in the gene's sequence helped to explain the tremendous diversity in the clinical manifestations of this disease.

Gene Expression and Microarrays

High-throughput automated DNA sequencing was developed in the late 1980s, allowing rapid determination of DNA sequences. This development has led to new challenges, because managing the large volumes of sequence data demanded new technologies. Fortunately, the rapid increase in computing power in mainframe and desktop computers and the availability of the Internet to link investigators to public databases provided a solution to this problem. A fusion of these technologies greatly accelerated the pace of gene sequencing.

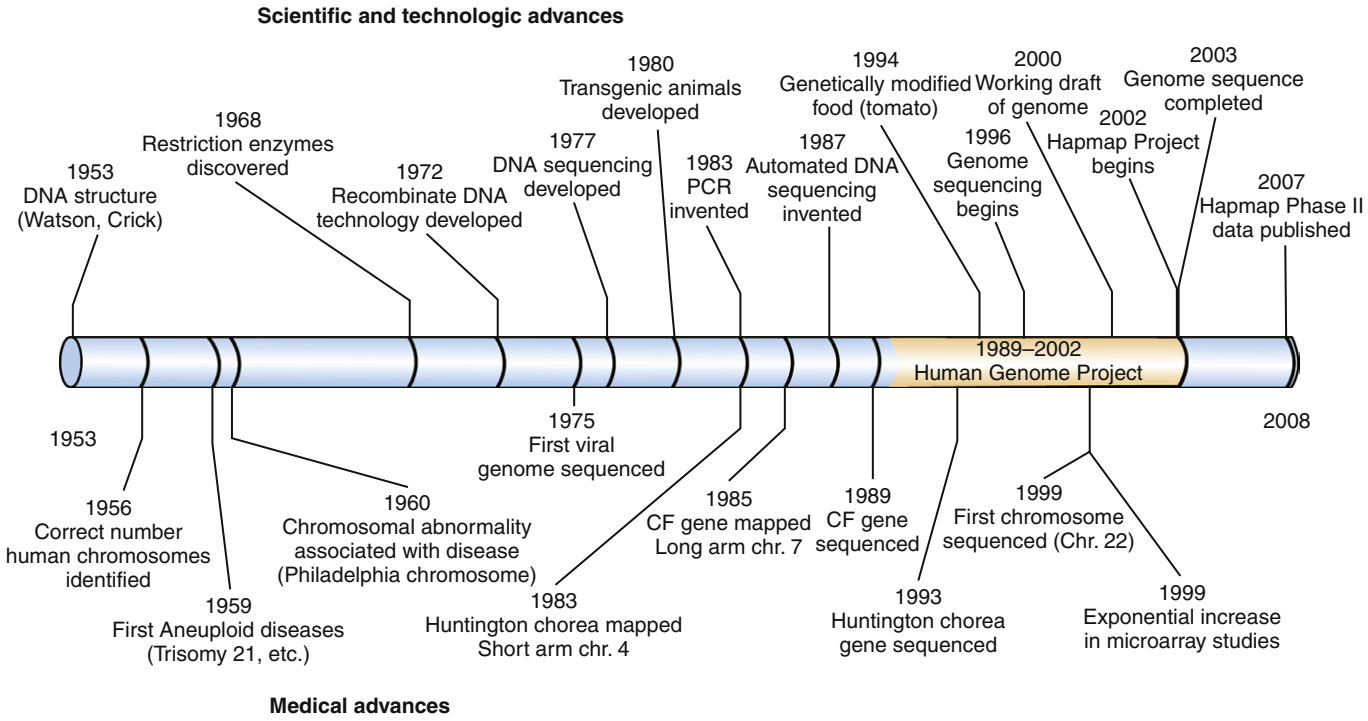

Figure 99–1. Milestones in molecular biology and sequencing of the human genome.

In the late 1980s and early 1990s, leaders from the National Institutes of Health and the Department of Energy began to create the infrastructure necessary for large-scale sequencing of the human genome. Although the Human Genome Project began in the early 1990s, the international effort to sequence the entire genome did not begin until 1998.[2] Remarkably, this massive project was completed just 5 years later.[3] Scientists throughout the world who participated in the human genome project contributed DNA sequence data to public databases so that the entire sequence of the human genome is freely available to the scientific community.

In the early 1990s, as the DNA sequence of an increasing number of genes became available, investigators began to experiment with gene expression microarrays. These investigators made microarrays from slides with a series of spots, in which each spot contained the DNA from a single gene. As the technology improved, the investigators were able to examine the expression of an increasingly larger number of genes in a single experiment. In the earliest published experiments, the investigators examined expression patterns of 45 yeast genes.[4] Less than a decade later, commercially produced gene expression microarrays were available with more than 30,000 human genes on each array.[5] The field of functional genomics emerged when gene expression microarrays made it feasible to study the expression of thousands of genes at once. Gene expression microarray use has increased rapidly since 1995, when the first gene expression microarray publications appeared in the literature. These powerful tools are readily available to laboratory investigators and are beginning to find their way into clinical practice. Within the next few years, gene expression microarrays and other high-throughput technologies will find increasing numbers of applications in clinical medicine.

Gene Expression Microarrays

All gene expression microarrays start with known gene sequences bound to some kind of a platform. These DNA sequences are obtained from public databases. As new information about the sequence and function of genes becomes available, it is added to the database so that the latest information is readily available to investigators who are using microarrays. Gene expression microarrays depend on the property of a single strand of DNA in solution to hybridize (bind) with a complementary strand of DNA that is bound to the microarray slide.

The oligonucleotides chosen for the microarray are selected based upon their ability to bind tightly with the DNA from a single gene, thus making each oligonucleotide highly selective for one gene with little cross-reactivity for other genes. Each oligonucleotide is printed onto a known location (spot) on the surface of the slide such that the various genes are arrayed in rows and columns. This spot is the "address" of the oligonucleotide and is an important piece of information in collecting and interpreting data from microarrays.

Quantifying Gene Expression

Microarray experiments usually are designed so that gene expression from two tissue samples may be compared either directly or indirectly.[6] This allows investigators to learn how different conditions can alter gene expression. For example, much has been learned about the biology of cancer by comparing gene expression from cancer cells to gene expression from normal cells in the same tissue.

When a gene is expressed in a cell, the DNA from that gene is transcribed into messenger ribonucleic acid (mRNA). This is transported out of the nucleus and then used as a template to guide the synthesis of proteins in the cell. At any given

time, the mRNA content of a cell represents a snapshot of the genes being expressed and the proteins being made in the cell. If a gene is turned on (upregulated), more mRNA will be produced from that gene. Conversely, if a gene is turned off (downregulated), less mRNA will be produced from that gene. To quantify gene expression, mRNA is extracted from the cell and reverse transcribed to make cDNA that is labeled with a fluorescent dye. The labeled cDNA is then incubated on a microarray slide to permit the hybridization with complementary DNA oligonucleotide probes that are bound to the surface of the slide (Figure 99-2). The amount of labeled cDNA hybridized to each oligonucleotide spot will be proportional to the quantity of mRNA that was expressed from the target gene.

When hybridization is complete and the labeled target DNA is bound to the oligonucleotide probes, the microarray is ready for analysis. The relative amount of mRNA produced from each gene is quantitated by exposing the microarray to blue laser light and capturing the image. A strong fluorescence signal from an oligonucleotide spot indicates a large quantity of mRNA was present from that gene. The strength of signals can be compared under different experimental conditions to determine how the conditions affect gene regulation. The signal intensity for each spot is quantitated and saved in a database. Because the position of each spot corresponds to a specific oligonucleotide, the database links the information about the image intensity to information about the gene. It now is possible to assemble a profile of the gene expression in the tissue.

Large, high-density microarrays contain thousands of spots, each of which corresponds to a different gene. Managing and analyzing this data would be nearly impossible if not for the substantial power available from desktop computers and the use of specialized software packages designed for microarray data analysis. Using this technology, it is possible to track the expression patterns of sets of genes and observe how these patterns change under different conditions. Analysis of gene expression patterns can provide new insights into how tissues and organs respond to a disease or a therapy.

Knowledge gained from expression microarray studies has greatly enhanced our understanding of the mechanisms organisms employ in response to environmental stresses, diseases, metabolic challenges, and therapeutic interventions. At the cellular level, maintenance of homeostasis often means altering gene expression to compensate for changes in a cell's environment. Learning which genes are activated or suppressed by changes caused by disease can suggest new targets for therapies directed specifically at correcting the molecular changes created by a disease state.

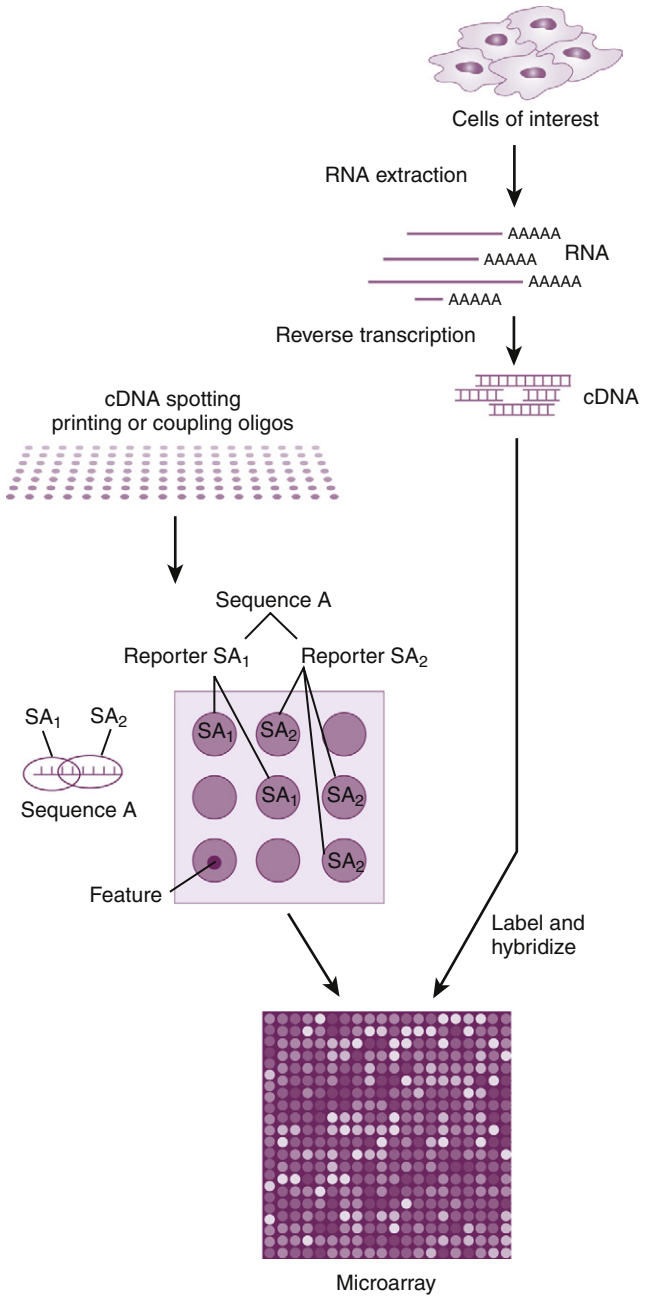

Figure 99–2. Making of a microarray. Ribonucleic acid (RNA) is isolated from a cell and reverse transcribed into labeled complementary deoxyribonucleic acid (cDNA). This is placed on the surface of a slide, which is covered with spots of oligonucleotides that are complementary to the cDNA. Under carefully regulated conditions, the labeled cDNA specifically hybridizes with a complementary oligonucleotide. Under a fluorescent laser, the brightness of each oligonucleotide spot is proportional to the quantity of cDNA bound to it. The brightness is measured to determine the relative amounts of RNA from each gene in the cells.

Genes and Human Variation

When contemplating the great diversity among humans, it is somewhat surprising to realize that the DNA of two unrelated humans is more than 99.9% identical.[7] Although the vast majority of nuclear DNA is identical from one person to the next, a small fraction of DNA sequence (~0.1%) varies between individuals and is responsible for the genetically determined variation in our physical characteristics and physiology. Genetic variability also appears to be involved with susceptibility to some diseases, as well as therapeutic responses to treatment.

The sequencing of the human genome (actually now several individuals' genomes) and the advent of high-throughput sequencing and genotyping technologies has revolutionized the understanding of gene structure and genetic variation. Many genes are polymorphic; that is, there are small differences in DNA sequence between individuals. Polymorphisms are sites in DNA in which variation at a specific nucleotide or DNA region is found in greater than 1% of the general population, and in some instances in as much as 50% of the population. (Mutations are considered to be sites at which

variation occurs in 1% or less of the population.) Polymorphisms may alter protein level or function in several ways. For example, altering a single base can alter an amino acid in a protein, which may lead to a change in protein function. Polymorphisms can also have significant effects without altering proteins. A polymorphism occurring in a promoter region, that controls gene expression through controlling mRNA synthesis, may lead to increased or decreased synthesis of that protein, which may have significant effects. Although polymorphisms are still being mapped and the function of most polymorphisms is still being defined, it is clear that these genetic variations account for the vast majority of inherited human phenotypes, from differences in hair color to differences in response to medications.

Polymorphic sites within a gene do not necessarily affect the expression or the function of the gene product. However, polymorphisms are not only of interest because of the subset which are responsible for genetic variability, but also because they occur fairly frequently in the human genome and can be used as markers to map genes involved with disease to specific regions of the genome. To be used as a marker, a polymorphism does not have to change the expression or function of a protein product but rather only needs to be linked to the gene involved with the disease of interest.

Single-Nucleotide Polymorphisms

Polymorphisms in DNA sequence may exist in several forms with the most common form due to the substitution of one nucleotide for another. These single nucleotide substitutions are called single-nucleotide polymorphisms (SNPs). For example, the sequences GATCACA and GATTACA differ because one of the cytosines (C) in the first sequence has been replaced by a thymine (T) in the second sequence. This example represents the most common human SNP, which involves the substitution of T for C.

Although such substitutions may occur spontaneously and represent a new mutation, the vast majority of the observed substitutions are stable variations in the human gene pool. SNPs are the most common type of polymorphism, and are thought to account for approximately 90% of human variation.[8] One SNP is believed to occur in every 100 to 300 bases. Although most of the SNPs in the human genome remain to be identified, if this figure holds true for the entire genome, then more than 20 million SNPs exist in our genome, and constitute an enormous source of variation.

Copy-Number Variations

In addition, polymorphisms within genes may be due to insertions or deletions of fragments of DNA, or to the presence of a variable number of tandem repeats (VNTRs) of short, repetitive DNA sequences. Some of these insertions or deletions, although submicroscopic, can be relatively large, resulting in gene copy-number variations (CNVs). CNVs are generally defined as stretches of DNA of greater than 1 kb that show differences in the expected number of copies of the DNA (that generally would be two due to the presence of one copy on each chromosome) in greater than 1% of the human population.[9,10] Very recently it has become clear that CNVs are common in human genomes and contribute significantly to human genetic variation.[11,12] In addition, CNVs have been demonstrated to be associated with a number of diseases including Williams-Beuren syndrome, DiGeorge syndrome, mental retardation, and autism.[9,10] It is thought that alterations in phenotypes due to CNVs are due to differences in gene dosage or to gene disruption that may be caused during the duplication or deletion. This is a new and rapidly expanding field and the next 10 years will likely determine how large a role CNVs play in human variation and disease.

Genotyping and Microarrays

DNA microarrays have been designed for both SNP and CNV genotyping. SNP microarrays are similar to those used for gene expression studies, but the oligonucleotides on SNP arrays have each been designed to selectively hybridize with one form of an SNP. Some of these microarrays have probes for almost a million different SNPs from throughout the genome and can quickly reveal the genotypes of an individual at these sites. Many of these same arrays also have the ability to genotype the individual for almost a million CNVs. Such arrays have been used for genome-wide association studies to identify genes associated with complex diseases such as asthma[13-16] and diabetes.[17-19] The ability to define the genetic components of variation with speed and precision is more than a valuable research tool. In the near future, this information will be used to identify disease and to help select therapies for illness, taking into consideration the individual variations that can be predicted on the basis of a patient's SNP and CNV genotype. As more polymorphisms are identified and their function understood, this technology will probably become an integral part of clinical practice. In the future, this new technology likely will permit physicians to plan highly individualized therapy for each patient, taking into account issues such as individual disease susceptibility and variations in drug metabolism.

Proteomics

Genes are the main sites of biologic information, but proteins are the main centers of biologic activity, which gives proteins a unique importance. The discipline of proteomics encompasses the study of all the proteins encoded by the genome present in specific tissues, cells, or fluids. Proteomics encompasses not only the study of differences in protein levels but also the study of the modifications that occur after protein synthesis. Study of the proteome is particularly important because levels of mRNA often do not correspond to levels of the protein product.[20] In addition, it is estimated that there are over a million proteins encoded by only about 30,000 genes, suggesting that there is substantial protein processing and modification involved in generating the proteome.[21] In clinical medicine, proteomic studies often examine differences in proteins between normal and diseased—or between untreated and treated—cells, tissues, or body fluids. Often the goal is to identify biomarkers associated with disease, or to identify novel targets for drug development.

Because the protein complement within a cell can vary widely over time in response to intracellular and extracellular influences, any picture of the proteome must consider these influences. Knowing which genes are expressed or suppressed by a given disease state is important but is only part of the picture. After proteins are synthesized, they can be modified in a number of ways that can dramatically alter their function. Such alterations are generally due to activation of a signaling cascade or enzyme pathway. Because activation of these cascades and pathways can occur without the activation of gene expression,

gaining a full picture of the functioning of a cell, particularly during differentiation, development of disease, or response to extracellular signals or drugs, will require determination of protein levels, protein modifications, and protein interactions.

Unfortunately, proteins are much more complex than DNA and RNA in a variety of ways. Proteins are composed of 20 amino acids rather than the four nucleotides that constitute DNA and RNA. The three-dimensional structure of proteins, which is critical to their function, usually is much more complicated than the three-dimensional structure of DNA. Finally, after proteins are synthesized, they undergo a variety of modifications (e.g., cleavage, phosphorylation, and glycosylation) termed posttranslational modifications. In contrast, DNA undergoes relatively little modification after synthesis. Proteomic methods are being developed to detect and measure posttranslational modifications.[22,23] The complexity of proteins has slowed the development of high-throughput methods for examining large numbers of proteins simultaneously. Nevertheless, great progress has been made in this field and a number of new techniques are being developed to enhance the use of proteomics for studying disease.[21] Some of the techniques bear a resemblance to DNA-based microarrays, except that proteins or ligands rather than oligonucleotides are spotted on a slide.[24,25] Other approaches, including mass spectrometry-based analysis of proteins, are also showing considerable promise.[21,25,26]

Metabolomics

Perhaps the newest of the "omic" fields is metabolomics, the study of all the small molecules, primarily metabolites, within cells, tissues, organs, or biological fluids. The goal is to provide a comprehensive picture of the metabolic state of a cell or tissue by measuring the full suite of metabolites and small molecules. The metabolites produced in a cell can vary widely depending on external influences, including the environment, and can reflect the health of the cell. In a sense, metabolites are at the end of the cellular information chain (because they are dependent on genes, gene expression, and proteins), but the metabolic state of the cell often drives mRNA and protein synthesis through feedback loops.

Because metabolites are a heterogeneous group of small molecules, many of which are structurally unrelated, this field presents great challenges. Substantial progress is being made in measuring the metabolic state of a cell using the technologies of gas and liquid chromatography coupled to mass spectrometry.[27-30] Recently, relatively high-throughput metabolomics approaches have been utilized to identify metabolomic signatures for a number of disease processes including cancer, motor neuron disease, and type 2 diabetes, and have demonstrated that metabolomic signatures are also useful in identifying drug-response phenotypes.[27,29] Metabolomics studies in cancer patients have resulted in the use of this technology for tests for diagnosis of breast and prostate cancer that are paid for by insurance providers.[29] Future metabolomic studies will likely help elucidate disease processes, identify biomarkers, and identify new drug targets.

Systems Biology

Together, the fields of genomics, proteomics, and metabolomics characterize biologic processes at a level of detail that was almost unimaginable 20 years ago. However, amalgamating these details into a meaningful narrative is one of the greatest challenges facing scientists (the genomic data alone can have more than 30,000 data points per experiment). The ambitious goal of systems biologists is to integrate data from all the "omic" disciplines, identify important components, and assemble the knowledge into a meaningful whole that can be validated (Figure 99-3).[31] Integrating information about system structures, system dynamics, the control method, and the design method can lead to a systems-level understanding of an organism.[32] Because of the obvious technical challenges in such an undertaking, this field is still relatively new. Nevertheless, a systems biology approach has already produced novel biologic insights regarding the regulation of innate

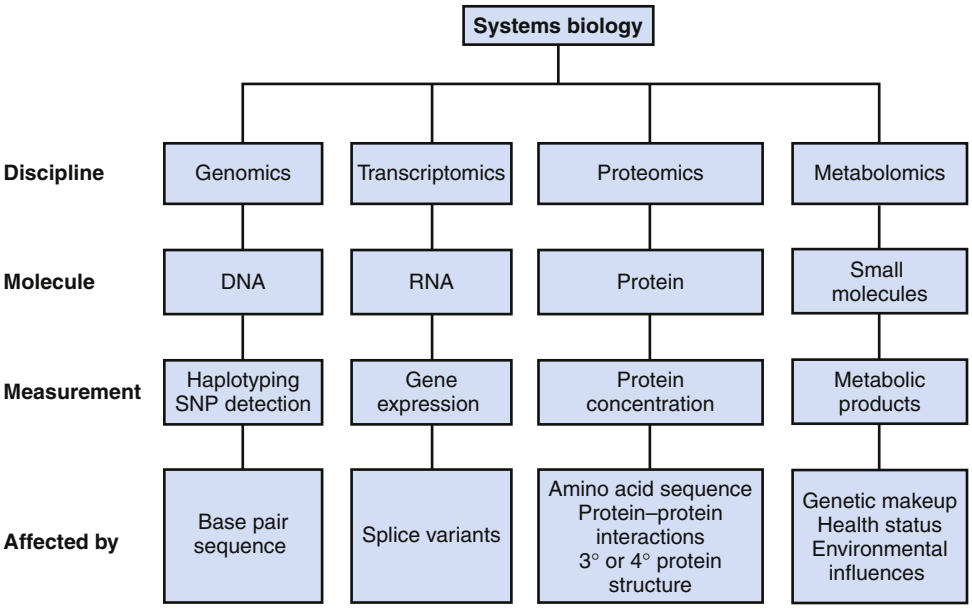

Figure 99–3. The goal of systems biology is to provide an integrated picture of all cellular functions. Each of the "omic" fields provides a comprehensive picture of one aspect of cellular function. *(Modified from Minie ME:* Module 7, expression resources, NCBI Advanced Workshop for Bioinformatics Information Specialists. *Available at http://www.ncbi.nlm.nih.gov/Class/NAWBIS/.)*

immunity[33,34] and protein kinases.[33] As expertise in this field continues to grow, there is optimism that it will lead to new insights in such diverse areas as drug discovery,[35,36] synthetic transgene control networks,[37] and neurologic diseases,[38] to name a few.

Metabolic control analysis is another discipline dedicated to the development of an integrated overview of genetic, enzymatic, and substrate control mechanisms in biologic systems.[38,39] When a metabolic control analysis is fully developed, a control coefficient is assigned to each step in an enzymatic pathway.[40] These coefficients reflect the magnitude of change that is induced in a pathway compared with the change in the state or level of an enzyme. Enzymes with high coefficients are logical targets for therapeutic intervention (drug design). Identification of important regulatory points also can help with the understanding of carcinogenesis and can provide new insights into genetic disorders.

Clinical Applications

The new technologies described above offer great promise for clinical medicine. At the research level, new biologic insights already are becoming available as a result of high-throughput technologies. Clearly, genomic screening of tumors can aid in diagnostic classification, and SNP analysis of enzymes involved in drug metabolism can characterize an individual's response to some drugs. Although high-throughput screening technology has not yet been implemented routinely for individual patients, almost certainly in the near future high-throughput technologies will provide information about an individual patient's disease or response to therapy.

Cancer

Oncologists have made extensive use of gene expression profiling to revise and more accurately classify the prognostic categories of malignancies.[41-44] One of the earliest uses of microarray technology for prognostic purposes was to study lymphomas using a specialized microarray, the "Lymphochip." Using this microarray, investigators were able to identify different histologic classes of lymphoma by their gene expression patterns, indicating that histologically distinguishable tumors differ in their gene expression, so these tumors can be distinguished at a molecular level. More importantly, the investigators found patients with gene expression patterns that permitted them to separate B-cell lymphomas into two groups: one group that resembled germinal center B cells and another that resembled activated B lymphocytes. Although these subgroups had identical histology, patient survival was significantly altered by the gene expression patterns. The lymphomas that exhibited gene expression patterns similar to germinal center B cells had a 5-year survival of 76%, whereas lymphomas that demonstrated gene expression patterns similar to activated B cells had a 5-year survival of 16%.

The promise of expression arrays to help define the prognosis of tumor types has also been used effectively in classifying breast cancers according to risk of metastasis. Use of microarray analysis of gene expression patterns permitted grouping of patients into high- and low-risk groups with greater accuracy than currently used clinical parameters.[45,46] Although these investigations were performed with high-density microarrays containing thousands of genes, the investigators found that expression levels of just 70 genes were sufficient to distinguish risk groups.[45] The authors believed that these results indicate the propensity to metastasize was an inherent genetic property of certain tumors and that this was not necessarily something that developed late in tumorigenesis. In the near future, these tools may be used to select patients who will require adjuvant therapy and to spare patients in the low-risk group who will not benefit from therapy.

Proteomic and metabolomic studies have also been utilized to characterize cancers. As described earlier (in the Metabolomic section), a specific metabolomic signature has been identified that is now used diagnostically to identify patients with breast and prostate cancer. Proteomic approaches have also been utilized in cancer research. Such studies have generally focused either on better understanding the cancer process with the goal of identifying novel therapeutic targets or on identifying biomarkers that can be used clinically. Proteomics studies have provided significant insight into understanding the mechanism of cancer development and currently much effort is targeting the use of proteomics to identify biomarkers that can be utilized in clinical oncology.[47,48]

Pharmacology

High-throughput genomic and proteomic technologies are currently being used in the field of pharmacology to speed the discovery of new drug targets, learn more about the mechanisms of drug action, and identify genetic polymorphisms that alter efficacy or increase risk of toxicity (see Chapter 117).[49] Gene expression arrays have identified genes that are differentially regulated in disease and provided clues about possible pathways and proteins that may be targets for drug therapy.[50,51] The combination of genomic technology with pharmacology has led to the new field of *pharmacogenomics,* a term that is often used interchangeably with *pharmacogenetics,* to refer to studies examining the contribution of genetic variation to drug response.[52,53]

The goal of pharmacogenomics/pharmacogenetics has been individualization of drug therapy to optimize therapeutic effect and minimize toxicity. Historically, attaining these goals has been difficult because it has often been impossible to predict an individual's response to therapy before treatment was initiated. Instead, using pharmacodynamic data (drug levels), optimization was attempted after therapy was started. It was clear that inheritance played an important role in individual responses to drug therapy; however, until recently it has been impossible to easily identify variations in an individual's genetic makeup that would determine therapeutic responses. Pharmacogenomics uses genetic markers (specific variants such as SNPs or CNVs) that determine a patient's course and/or response to therapy to tailor therapy according to an individual's genetic makeup.[54] Current examples where this new paradigm is utilized is in determining safe and effective therapeutic doses when treating with thiopurines or warfarin.[55-59] The new paradigm will allow optimal individualization of therapy on the basis of a patient's genetic profile and will be useful for improving outcomes and risk stratifying patients.[55]

Are there examples in the critical care environment in which genetic variations influence the pharmacologic treatment of critically ill children? Variations in genes coding for drug transporters, receptors, components of signal transduction pathways, and proteins involved in the metabolism

of drugs can alter the overall response to a given drug. The following discussion highlights some drugs used relatively frequently in the ICU for which genetic variations may potentially be involved in response, yet much more research is needed to support the widespread use of pharmacogenetics in this patient population.

The use of opiates, the mainstay for treating pain in the ICU, is an example of an instance where the influence of genetic variations on the efficacy of drug therapies is well documented. The mechanism of action of opioids involves a number of processes, including enzymatic conversion to active metabolites, transport across various barriers including the blood-brain barrier, binding to various receptors, and secondary involvement of catecholamines, such as dopamine and norepinephrine. Genetic variations in a number of the proteins involved in these processes have been demonstrated to influence the clinical efficacy of opiates.[60,61] For example, many opiates are metabolized by the CYP2D6 enzyme encoded for by the highly polymorphic *CYP2D6* gene. This metabolic step is required to convert the prodrug to the active metabolite. Genetic variations in *CYP2D6* contribute to four general phenotypes characterized by the rate of opiate metabolism: poor, intermediate, extensive, and ultrarapid. Individuals with one or two copies of the wild type *CYP2D6* gene are phenotypically classified as extensive metabolizers and tend to have better responses to opioids than poor metabolizers. Individuals who are poor metabolizers are at greatest risk for treatment failure.

Another example of a step in opiate response that is subject to genetic variability is opioid receptors. Of the three opioid receptors the primary target for the opioid drugs is the mu (μ) receptor encoded for by the opioid receptor mu-1 (*OPRM1*) gene. *OPRM1* has a SNP at position 118 (adenine to guanine substitution) found in 10% to 15% of Caucasians that results in a substitution of an asparagine for aspartate at amino acid position[40] in the extracellular domain of the μ receptor.[62] Individuals with the wild-type μ receptor (A allele) who have cancer or are in the perioperative period have significantly reduced requirements for analgesia compared with those individuals with the less common G allele.[62-65]

In addition to receptor binding and CYP2D6 activity to generate active metabolites, opiates such as methadone are a substrate for the P-glycoprotein 170 (P-gp 170) that transports drugs from the intracellular to the extracellular compartments in tissues that act as barriers such as the blood-brain barrier. P-gp 170 is encoded for by the highly polymorphic ATP-binding cassette sub-family B member 1 (*ABCB1*) gene in which over 100 SNPs have been identified. Many studies have been performed examining the role of ABCB1 genetic variations on function, including one in which a three SNP haplotype in the *ABCB1* gene was shown to be associated with the need for a higher methadone requirement in a cohort of heroin-dependent adults; however, the field has not yet reached a consensus on the contribution of variation in *ABCB1* on drug opioid effects.[61,66]

Finally, catecholamines are also involved in the mechanism of opioid action, and thus, catecholamine metabolism can affect opiate efficacy. Variability in the gene coding for catechol-*O*-methyltransferase enzyme (COMT) has also been demonstrated to be associated with the need for lower morphine dose in a cohort of adults receiving morphine for cancer-associated pain.[67]

Thus, individual genetic variability appears to influence the efficacy of opiate use, but studies involving children in the ICU setting have yet to be done. While the response to opiates is likely the best-characterized example of the role pharmacogenomics may play in the ICU setting, there are other studies that suggest that genetic variations influence the response to drugs commonly used in the ICU. For example, genetic polymorphisms in the gene coding for butyrylcholinesterase, an enzyme involved in hydrolysis of succinylcholine to its inert form, result in decreased enzyme activity. Individuals with these genetic polymorphisms exhibit a prolonged paralytic effect of succinylcholine.[68] Another example is the use of β_2-adrenergic receptor (β_2-AR) agonists, particularly in children with severe acute asthma exacerbations. Variability in response to inhaled β-agonist treatment between individuals is well documented and approximately 60% of such variability is estimated to be due to genetic differences.[69] A number of studies indicate that polymorphisms in the gene for the β_2-AR, the target of β-agonists, may affect response,[70-74] although there are conflicting reports. Future studies will clarify the contribution of genetic variation in the β_2-AR in variable response to treatment in children. Lastly, genetic variations have been described in the genes coding for the family of cytochrome P450s, which are involved in the metabolism of a large number of drugs that are commonly used in the ICU setting. Such drugs include proton pump inhibitors, antiepileptics, angiotensin II blockers, β-blockers, and nonsteroidal anti-inflammatory agents. Clearly the above described examples demonstrate that pharmacogenomics and pharmacogenetics will provide opportunities to refine treatment strategies and enhance medication efficacy and safety. However, much work is still needed to identify the optimal use of pharmacogenomics and pharmacogenetics data in critically ill children.

Drug Discovery

The pharmaceutical research industry has already been changed by the technologies discussed in this chapter. Drug discovery has been enhanced by the application of gene expression arrays, which have revealed previously unsuspected therapeutic targets. Gene expression array and other high-throughput technologies have proved invaluable in the screening of novel compounds for activity against disease. High-throughput technologies have also revealed new biomarkers of disease that can be used for diagnosis, or to monitor response to therapy. The recent discovery of a genetic variant that is highly associated with the development of age-related macular degeneration[75] illustrates the power of these technologies to identify potential new targets of therapy as well as to aid in the molecular diagnosis of diseases. Recently, a new technique that is capable of identifying extremely rare genetic variants has been developed.[76] It is only a matter of time before these technologies shed light on the diseases that we commonly encounter in pediatric critical care. It is reasonable to anticipate that we may begin to see these discoveries in the relatively near future.

These new technologies are also reshaping our perception of certain diseases, in much the same way that sequencing of the cystic fibrosis gene led to the realization that the cystic fibrosis phenotype could be caused by any one of a large group of genetic variations within the cystic fibrosis gene. For example, although a single gene causing schizophrenia

has yet to be identified, a recent investigation indicates that schizophrenic patients have an unusually high proportion of genetic abnormalities within a group of genes known to be involved in signaling networks that control neurodevelopment.[77] This suggests that the schizophrenia phenotype, like the cystic fibrosis phenotype, may be caused by any one of a group of genetic abnormalities rather than by a single flaw in one gene. Consequently, it is possible that rather than a single therapeutic target for schizophrenia treatment, there may be multiple targets, each of which may show a different response to a given therapeutic agent. If this concept is found to be correct, it may help to explain why the response to therapy is so variable in this illness. Novel insights such as this may ultimately contribute to better diagnosis and therapy for a variety of illnesses.

Biomarkers

A biomarker is a biologically derived indicator of the presence or progression of a process or condition such as an illness. Many genomic, proteomic, and metabolomic studies are designed to identify biomarkers of disease or response to treatment for a variety of illnesses. These markers should enable physicians to better identify the presence and progression of various conditions. In turn, this should help in targeting the optimal therapy, and/or the optimal time point for delivery of therapy, during the course of an illness.

Historically, proteins have been used as biomarkers. In the past, protein biomarkers were usually proteins which were known to be elevated during the disease process and studies were performed to determine whether the protein could be used as a prognostic marker of disease. Protein biomarkers have been identified for a number of disease processes including sepsis (procalcitonin[78]), pneumonia (soluble triggering receptor on myeloid cells-1 [sTREM-1][79-82]), and neurologic outcomes after cardiac arrest (neuron specific enolase and S-100B).[83,84] Currently a substantial body of research is focusing on disease-related functional proteomics in the hopes of developing novel protein biomarkers or protein biomarker signatures.[22]

Microarray technology has also been utilized for identification of biomarkers. In breast cancer treatment, expression array analysis has led to the identification of new prognostic biomarkers, given novel insights into the biology of the tumors, and suggested new therapeutic targets.[85] A similar approach has been used to identify new potential biomarkers for hepatocellular carcinoma[44] and bladder cancer.[86] Investigators seeking to identify novel biomarkers for low doses of radiation have used microarray technology to identify a set of genes whose regulation is altered by exposure to sublethal levels of radiation.[87]

In addition to single biomarkers, genomic and proteomic technologies open the possibility of using multiple biomarkers as a "molecular signature." One example of such an application is the development of pathogen chips, which are microarrays containing genes from viral or bacterial pathogens. These chips can be used to identify genes and gene expression patterns that will identify a pathogen and tell us about the drug sensitivity of the organism.[88] Another example is that results from expression arrays can be used as a molecular signature of a disease state. This is probably best exemplified by the use of expression arrays in typing cancers as described above under the section on Cancer.[41-44] It is likely that in the future, genomic, proteomic, and metabolomic studies will generate biomarker profiles indicative of many disease processes.

Critical Care

The above sections provide a framework for understanding of how the new "omic" fields of study are relevant in the pediatric intensive care unit. Currently, in the field of critical care these types of studies have been utilized primarily for research. Some of these studies are described in more detail below to highlight their relevance to critical care and the potential for use in diagnostics.

Gene Expression Microarrays

Gene expression studies in the PICU setting have primarily been utilized to examine expression profiles in children with sepsis. The value of such studies is twofold; first, they provide a better understanding of the host response to severe infection by indicating what genes are turned on and off in sepsis; and second, they may be useful for predicting which children are at risk of developing more severe disease or stratifying children into groups most likely to benefit from specific treatments. Wong and colleagues have pioneered this field and have studied the largest cohort of children with sepsis in whom gene expression profiles have been generated.[89-91] Several important observations have been made; first, many genes involved in zinc homeostasis are downregulated in children with septic shock; however, metallothionein, a metal-binding protein, is upregulated in nonsurvivors.[91] Nonsurvivors of sepsis demonstrated lower serum levels of zinc, which is consistent with the ability of metallothionein to sequester zinc intracellularly. Further support for the importance of metallothionein in sepsis is the observation that metallothionein knockout mice demonstrate a survival advantage over wild-type mice in a sepsis model.[91] In addition, similar studies examining longitudinal expression of signaling pathways in children with septic shock indicated that expression profiles of genes involved in immunity and inflammation appear to change over time, and gene networks involved with T cell and major histocompatibility complex (MHC) antigen-related biology are persistently downregulated.[89,90] Other gene networks are also differentially regulated in those children with septic shock compared with those with systemic inflammatory response syndrome or sepsis (see Chapter 103). For example, genes in the human leukocyte family are repressed in children with septic shock, while those involved in the signaling pathway for transforming growth factor-beta (TGF-β) are upregulated.[90] Recently a genomic signature related to repression in genes related to zinc homeostasis and lymphocyte function has been validated for pediatric septic shock.[92]

Gene expression profiles have also been used to identify expression patterns that are associated with the development of ventilator-associated pneumonia (VAP) using transcriptional profiles of circulating leukocytes in a cohort of severely injured adults.[93] Using these profiles, patients who developed VAP could be identified several days prior to the actual confirmatory diagnosis of VAP. If these results are confirmed, the use of gene expression profiling could help eliminate the use of antibiotics in those patients that are only colonized.

Genetic Variation

Recent studies in both critically ill adults and children have suggested that the clinical presentation, treatment, and outcome from critical illnesses are influenced in part by the

genetic makeup of the patient. Sepsis and acute lung injury (ALI) have been two areas of intense research, with the primary objective in both areas being to investigate whether new or previously identified genetic variations are associated with the susceptibility to, or outcome from, disease (sepsis or ALI). These studies have the potential to impact of clinical practice because they (1) may help identify those patients who have an increased susceptibility to, or an increased risk of worse outcome from, critical illnesses, thereby allowing tailoring of treatment or monitoring in the ICU to the specific risk of the individual; and (2) may identify novel genes or pathways involved in a specific illness, thereby generating the potential for novel therapies. This section will briefly highlight some of the studies supporting the concept that genetic variations influence the susceptibility to or outcome from critical illnesses. These studies are generally designed to determine whether specific genetic variants are associated with susceptibility or outcome of critical illness. In the last 10 years, many genetic-association studies have been reported, and often, such studies fail to replicate previously reported results. There are many reasons for this lack of consistent results including inadequate power (resulting from small cohorts and/or examination of multiple polymorphisms), population stratification (resulting from inclusion of multiple races and/or ethnicities in the study group), different study populations, and different definitions of response.[94,95] Currently, most journals are requiring that the authors demonstrate that their study does not suffer from such weaknesses. In addition, replication of any association is important to document that any observed association is not spurious.

The ability of the host to recognize a pathogen and respond with a well-measured and balanced response is crucial in the clinical course of patients with sepsis. However, individuals vary in the ability to recognize a pathogen and mount a response. Some of this variability may be accounted for by genetic variations. This idea is supported by the observation that an early death of a biologic parent from infection is associated with a much greater risk of death of a child from infection than the death of an adoptive parent from infection on the risk of death from a similar infection of an adoptee.[96] Identification of genetic variations which contribute to the susceptibility to and outcome from sepsis is important given the major impact of sepsis on the morbidity and mortality in neonatal, pediatric, and adult ICUs.

The innate immune response enables the host to recognize pathogens and provide a rapid inflammatory response. This response includes the production of cytokines, chemokines, and effector molecules allowing for the interaction with the adaptive immune response.[97] These two components of the innate immune system, recognition and response, utilize a large number of receptors and accessory proteins, signaling molecules, and transcription factors and proteins involved in protein synthesis. Any part of the recognition and response components that is altered in quantity or functional activity by the presence of genetic variations in the genes coding for them may ultimately influence the final response to a pathogen. Thus, the number of possible genes in which variation might influence the innate immune response, and, thereby, the susceptibility to and outcome from sepsis is quite large. The recognition component of the innate immune system consists of a large repertoire of receptors and binding proteins that recognize pathogen-associated molecular patterns. These include such proteins as the family of cell surface toll-like receptors, intracellular accessory proteins CD14 and MD-2, and circulating mannose-binding lectin (MBL). Discussed below are studies examining whether genetic variations in MBL are associated with susceptibility to, or severity of, infection as an example of how genetic variation may be important in individuals with critical illnesses.

Several genetic variations in the gene coding for MBL (*MBL2*) or its regulatory region have been described, and three are noted for resulting in changes in amino acids at positions 52, 54, and 57 (referred to as variants D, B, and C, respectively). These amino acid changes diminish the ability of the helical tails to polymerize, resulting in an increased degradation of MBL and reduced serum levels of MBL.[98] Studies have demonstrated associations between the three MBL structural variants D, B, and C and susceptibility to or outcome from infections in humans. These include associations with an increased risk for meningococcal infections,[99,100] with pneumonia and sepsis in neonates,[101] with acute respiratory infections in children,[102] with hospitalizations due to infections in children,[103] and with viral coinfections in adults with pneumococcal pneumonia.[104]

The influence of genetic variation on the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is another area of intense research in the intensive care unit (hereafter, the term ALI will be used to reflect both ALI and ARDS). Genetic variations in over a dozen genes have been shown to be associated with either the development of ALI or the outcome from ALI.[105] The pathophysiology of ALI involves a number of critical processes that occur during various stages[106,107] and include inflammation, breakdown of the vascular endothelial cell barrier, impairment of normal surfactant function, alveolar fibrin deposition, interstitial fibrosis, and matrix deposition, to name just a few. The strategy utilized thus far in the study of genetic variation and ALI has been to select candidate genes whose gene products are thought to play a central role in the development of ALI. These include genes involved in innate immunity and inflammation, surfactant proteins, vascular barrier integrity, and regulation of lung endothelial and epithelial cell death, and oxidative stress. To date, the strongest evidence for the association of genetic variations with ALI exists for the genes encoding surfactant protein B,[108-111] angiotensin converting enzyme,[112-114] and interleukin-6.[115-118] Although considerable progress has been made in identifying genetic variants associated with ALI, further studies are warranted.

The above discussion demonstrates that these new technologies have great promise for critical care medicine. These technologies may help us to diagnose disease and to select appropriate medications and doses for our patients. Some of the earliest benefits to critical care patients likely will come from a systems biology approach to understanding inflammation. As the effects of genomic and proteomic components of the inflammatory cascade are understood in an integrated fashion, researchers/physicians should be able to identify critical points in selected pathways that will permit favorable alteration of the inflammatory response. Multigene studies should provide new insights into the mechanisms and prognosis of diseases such as sepsis, ALI, and hypoxic injury. Intriguing examples of potential applications of this technology to the field of critical care are already appearing.

Patients in critical care units are extensively monitored. In the future, this monitoring probably will include genomic, proteomic, and even metabolomic monitoring of responses to therapy as well as the previously mentioned pharmacogenomic monitoring.[119] Using genomic, proteomic, and metabolomic markers of disease, physicians will have a powerful set of tools to identify who is at risk for developing an illness or complication before clinical signs become apparent and will allow the use of therapies to minimize the disease burden, delay the onset of clinical symptoms, or decrease the risk of complications. Managing the volumes of information that will result from these tests will be a challenge to physicians, but these challenges will provide us with an opportunity to optimize our patients' therapies in ways that could not have been imagined a decade ago.

Ethical Issues

The technologies discussed in this chapter have prompted a wide public discussion about the ethics of genetic testing. In the past, genetic testing was infrequently performed and was usually limited to the identification of a very limited number of genetic variants. With the current high-throughput technologies, it is feasible and increasingly inexpensive to sequence an individual's entire genome. This feat can easily be performed on a tiny amount of DNA; theoretically, the DNA content of a single cell is sufficient for this purpose. A sufficient quantity of DNA for genotyping an individual can be obtained from a small amount of blood, sputum, or epithelial cells lining the mouth. There are several ways that an individual's genetic makeup may be characterized. The most commonly employed analysis is to perform SNP genotyping utilizing efficient high-throughput methods. The ease with which such information can be generated has led to concern about misuse of this information, especially with regard to genetic discrimination, particularly in regard to employment or insurance. In the 1970s, a well-documented example of genetic discrimination was the denial of health insurance to some African-Americans who carried the sickle cell trait.[120]

It has been argued that genetic information is special or "exceptional" for several reasons[121]: (1) Such information can be used for eugenic purposes. In theory, this information could be used to select for or against certain traits. (2) An individual's genetic information may provide the individual with unique and perhaps unwelcome insights with regard to his/her parents or siblings. For example, nonpaternity may be revealed. (3) Genetic information is immutable. The test, if correctly done, provides one with information about one's genetic status forever. This is unlike other medical information, which often changes with age or disease status. (4) For many conditions, genetic information is probabilistic and provides ambiguous risk assessments. Such information may be unnecessarily frightening to individuals and if revealed to employers or insurers could lead to genetic discrimination. Although these arguments for genetic exceptionalism may appear to be compelling, most authorities feel that genetic information is not clearly and distinctly different from nongenetic medical information.[122,123]

Legislation passed prior to 2000 provided limited protection with regard to genetic discrimination. The Americans with Disabilities Act (1990) prohibits discrimination against symptomatic disabilities, but it does not protect against discrimination based on unexpressed abnormalities. This left open the possibility that an individual could be discriminated against based upon an as-yet-unexpressed genetic trait. HIPAA legislation (1996) protected an individual's right to enroll in a health insurance plan without discrimination based upon expressed or unexpressed abnormalities. This legislation, however, did not address these issues in employer-provided health plans. In response to the public's concern regarding the potential misuse of genetic information, almost every state has issued legislation regarding genetic privacy.[124,125] Despite opposition from the National Association of Manufacturers, the National Retail Federation, the Society for Human Resource Management, and United States Chamber of Commerce, the Genetic Information Nondiscrimination Act of 2008 easily passed the United States House and Senate. This law (H.R. 493) prohibits insurers from denying coverage to individuals based solely upon a genetic predisposition to develop a disease in the future. Employers are prohibited from making decisions about hiring, firing, or promotion based upon such information.

The protection provided by both state and federal legislation has addressed some of the concerns raised by arguments for genetic exceptionalism. Increasingly, genetic information is being treated in the same manner as other medical information. Institutional review boards are finding it easier to craft policies regarding the use of genetic information in investigations, as these boards are increasingly guided by federal and state legislation as well as by precedents from other institutional review boards. Much work remains to be done in this area and we must remain vigilant to protect the rights of individuals. Nevertheless, the protections and precedents that have been established are already serving to facilitate appropriate use of genetic information in clinical care and research.

References are available online at http://www.expertconsult.com.

Molecular Foundations of Cellular Injury: Necrosis, Apoptosis, and Autophagy

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PEARLS

- As an "accidental" form of death, necrosis is an uncontrolled process.
- Apoptosis is a controlled, evolutionarily conserved process.
- Alterations in the balance between cellular proliferation and death can lead to disease.
- Altered apoptosis is estimated to play a role in half of all medical illness for which prevention is lacking.
- Apoptosis appears to play a role in critical illness, both in septic and noninfectious inflammatory states.
- Autophagy is a reversible form of cell death used to recycle intracellular organelles and is increased in states of starvation, inflammation, and infection.

Cell Death

Each day, the human body produces and eradicates 60×10^9 cells, a rate of cell death of nearly 1 million per second.[1] Cells die by one of three mechanistically distinct processes: apoptosis, autophagy, or necrosis (Table 100-1).[2,3] These three forms of cell death can be distinguished by both morphologic and molecular biologic criteria.

In necrosis, an overwhelming acute injury is followed by cell and organelle swelling, with early dissolution of the plasma membrane and subsequent cell lysis. As the cell bursts, its contents enter the interstitial space, leading to an accompanying inflammatory response to the toxic enzymes and proteases released. Morphologically, cells undergoing necrosis show swelling of the entire cell and its internal organelles. Deoxyribonucleic acid (DNA) fragmentation has no characteristic pattern and exhibits a random pattern on electrophoretic gel analysis. As an "accidental" form of death, necrosis has always been described as an uncontrolled process. However, more recent evidence suggests that necrosis may be more controlled than previously thought.[3]

In contrast, apoptosis (also known as *programmed cell death type I* or *cell suicide*) is a well-controlled, evolutionarily conserved process.[4,5] Following an appropriate trigger, a cell's apoptotic machinery leads to orderly death of the cell. This is characterized by cell and organelle shrinkage (pyknosis), nuclear fragmentation (karyorrhexis), and cytoplasmic blebbing with retention of plasma membrane integrity. Ultimately, there is fragmentation of the cell into small apoptotic bodies that are phagocytosed by neighboring cells. Orderly DNA fragmentation is identifiable on electrophoretic gels as a characteristic "ladder" pattern. Because cytosolic contents are not released into the interstitial space, there is no accompanying inflammatory response.

Apoptosis is critical to the existence of virtually all multicellular organisms and is involved in widely divergent physiologic processes, including embryonic development, maturation, immunity, repair, and cellular homeostasis. However, alterations in the balance between cellular proliferation and death have been proposed to be involved in the etiology of cancer and autoimmunity[6,7] and excessive apoptosis has been noted in the origins of neurodegenerative disease, osteoarthritis, allograft infection, graft-versus-host disease, type 1 diabetes, and heart failure.[1,8] Importantly, apoptosis is increasingly recognized as playing a role in critical illness, in both septic and noninfectious inflammatory states. Because of the importance of apoptosis in multiple disease states, a number of ongoing phase II and phase III trials targeting apoptotic pathways are currently ongoing.[1,9]

Autophagy (also known as *programmed cell death type II*), is the only cell death process thought to be reversible and functions to allow cells to degrade cytoplasmic contents, including dysfunctional intracellular components, for either recycling or removal.[10] Autophagy is characterized by formation of autophagosomes or large double-membrane vesicles that engulf intracellular organelles. Autophagosomes subsequently are trafficked to the lysosomal system for degradation. In times of starvation or stress, the breakdown of intracellular components provides the cell with a much-needed energy source. Autophagy, much like apoptosis, has been shown to be involved in a diverse number of physiologic processes, including embryonic development and immunity.[11] Furthermore, over the last 5 years increases in autophagy have been associated with several disease states, including sepsis, cancer, heart disease, and Alzheimer disease.[10] Finally, autophagy has been

closely linked to apoptosis by the fact that both forms of cell death use many of the same signaling mechanisms and are induced by overlapping stimuli.[12]

Pathways of Apoptosis and Autophagy

Apoptosis is initiated by two main pathways: a receptor-mediated pathway and a mitochondrial-mediated pathway (Figure 100-1).[13-16] The receptor-mediated pathway can be activated by a number of ligands, including Fas and tumor necrosis factor (TNF)-α. The mitochondrial pathway can be activated by a number of different stimuli following DNA damage, including reactive oxygen species, radiation therapy, and chemotherapy. Within the mitochondrial pathway, the Bcl-2 family of molecules plays a critical role. This group of proteins includes more than 20 proapoptotic and antiapoptotic molecules, many of which physically interact with each other.[1,15,17,18] Their primary function appears to be regulation of cytochrome c release from the mitochondria, with proapoptotic family members promoting and antiapoptotic family members suppressing its release. The prototypical antiapoptotic proteins are Bcl-2, Bcl-xL, and Mcl-1, whereas the prototypical proapoptotic family members are Bax and Bak.

Both receptor-mediated and mitochondrial-mediated pathways activate specific members of the cysteine aspartyl-specific protease (caspase) family.[19] Produced as inactive precursors, caspases are triggered by proteolytic processing as part of a cascade that produces their active counterparts. Depending on their location in the apoptosis cascade, caspases can be either upstream "initiators" or downstream "effectors" of cell death. Although several pathways for inducing these molecules exist, the receptor-mediated pathway acts by inducing caspase-8. In the mitochondrial pathway, cytochrome c binds to apoptotic protease-activating factor-1 (APAF-1), which in turn induces caspase-9. Both caspase-8 and caspase-9 converge on the final common pathway of apoptosis via induction of the death effector caspase-3, leading to the ultimate death of the cell.[18] Crosstalk between the mitochondrial and receptor-mediated pathways of death can occur via the molecule Bid.

The pathways and regulation of autophagy are much less understood, but ongoing research is beginning to unravel some of the complex signals that lead to autophagy. Autophagy is known to occur at basal levels and is important in the maintenance of cellular homeostasis.[10] Importantly, like apoptosis, autophagy can be a double-edged sword, in that too little or exaggerated levels can lead to unwanted consequences to the host. Key regulators of autophagy include ATG proteins and beclin-1, which are important in both formation of autophagosomes and autophagy signaling. It is important to note that many of the same genes that regulate apoptosis also regulate autophagy, the most studied of these being the Bcl-2 family and beclin-1. Antiapoptotic members of the Bcl-2 family inhibit beclin-1 function and proapoptotic family members disrupt this inhibition, thus promoting autophagy.[20,21] Although a complete understanding of the relationship between these two forms of cellular death is not yet clear, there is growing evidence that both are important in a multitude of human diseases.

Table 100–1 Differences Between Necrosis and Apoptosis

Autophagy	Necrosis	Apoptosis
Cell shrinkage	Cell and organelle swelling	Cell shrinkage
Double-membrane vesicles	Early loss of membrane	Preservation of membrane integrity until late
Organelle degradation	Organelle swelling Random DNA fragmentation Accompanied by inflammation	Organelle shrinkage (pyknosis) Nuclear fragmentation (laddering) No accompanying inflammation

Modified from Hotchkiss RS, Tinsley KW, Swanson PE, et al: Endothelial cell apoptosis in sepsis, *Crit Care Med* 30(5 suppl):S225–S228, 2002.

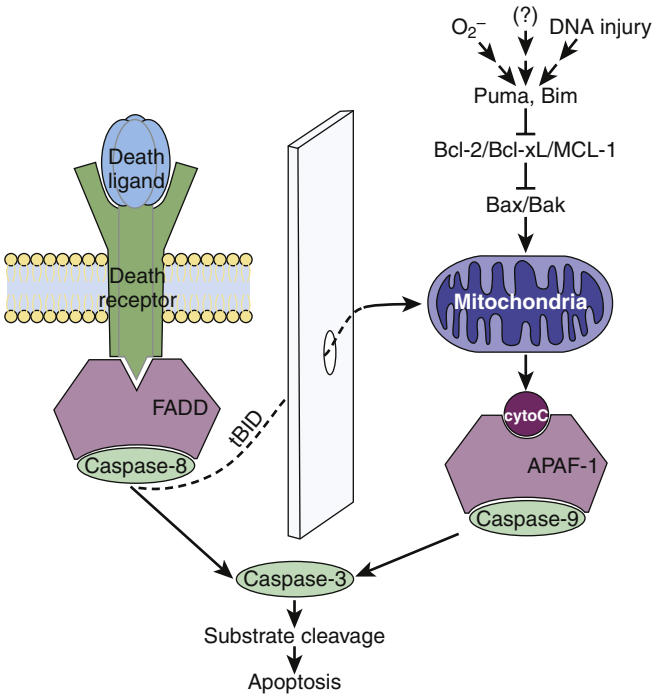

Figure 100–1. Schematic representation of major pathways of apoptosis and their convergence in a final common pathway leading to cellular death. *APAF-1*, Apoptotic protease-activating factor-1. *(Adapted From Chang KC, Unsinger J, Davis CG, et al: Multiple triggers of cell death in sepsis: death receptor and mitochondrial-mediated apoptosis, FASEB 21:708–719, 2007.)*

Human Studies

Several human studies have shown alterations in apoptosis, necrosis, and autophagy in critical illness. The potential functional importance of these alterations has led to the development of agents aimed at manipulating cell death for therapeutic benefit currently undergoing preclinical and clinical trials.[1,9]

Sepsis

A prospective analysis by Hotchkiss et al.[22] of 37 patients who died in a surgical intensive care unit and underwent immediate autopsy demonstrated increased lymphocytic and gut

epithelial apoptosis in approximately 50% of septic patients with multiple organ dysfunction syndrome compared with essentially no alterations of cell death in critically ill, nonseptic patients (Figure 100-2). In addition, necrosis was detectable in 35% of patient livers but was minimal or absent in all other tissues examined. Similar findings have been shown in both neonates and pediatric patients with sepsis.[23,24] Increased apoptosis in septic patients has been demonstrated to be associated with an increase in active caspase-3 activity. Further studies from this same group showed that B and $CD4^+$ T lymphocytes are disproportionately lost in septic patients.[25] B and $CD4^+$ T-lymphocyte apoptosis is caspase-9 dependent, with the degree of cell death greater the longer the patient is septic. Antigen-presenting dendritic cells are also decreased in the spleens of septic patients.[26] Apoptosis is significantly decreased, however, in macrophages obtained by bronchoalveolar lavage (BAL) in septic patients compared with nonseptic controls.[27] This decrease in apoptosis is associated with lower levels of Bcl-2 than in control patients. An inverse correlation appears to exist between the severity of sepsis and the percentage of apoptotic alveolar macrophages. Minimal macrophage necrosis has been detected in BAL fluid.

Apoptosis is also decreased in neutrophils in patients who become septic after an initial traumatic insult, through upregulation of tyrosine phosphorylation by circulating mediators.[28] This appears to be related to the septic insult because neutrophil apoptosis is not significantly different between noninfected trauma patients and healthy volunteers.[28] In addition, circulating neutrophil apoptosis is decreased in infected patients with the systemic inflammatory response syndrome compared with controls. The decrease in neutrophil death is not associated with alterations in caspase-3 levels. Of note, however, levels of apoptosis are similar to those seen in patients who underwent elective abdominal aortic aneurysmectomy.[29]

Although there are few studies evaluating the role of autophagy in patients with sepsis, a recent study by Watanabe et al.[30] showed a significant increase in autophagy in patients with sepsis. In this study, liver sections from six patients who died from sepsis were compared with four control patients. The patients who died from sepsis showed a threefold increase in autophagic vacuoles compared with controls.[30] The significance of this finding is not entirely understood, and further studies are needed to determine the pathologic significance of increased autophagy in sepsis.

Noninfectious Inflammation

Similar to sepsis, tissue lymphocyte and intestinal epithelial apoptosis are increased in patients who have undergone shock and trauma. Intestinal specimens resected from 10 patients following motor vehicle collisions or gunshot wounds revealed extensive crypt epithelial and gut lymphocytic apoptosis, whereas control patients who underwent elective bowel resections had no obvious change in levels of cell death.[31] Apoptosis was detectable within 2 hours of traumatic injury, and patients with the highest injury severity score had the most severe apoptosis. Importantly, patients with high apoptosis on initial evaluation following trauma had no evidence of increased cell death at follow-up elective laparotomy.

Increased apoptosis has also been demonstrated to be present in circulating T lymphocytes of patients following blunt trauma or burn injury.[32,33] Although increased apoptosis of lymphocytes in the bloodstream was not directly associated with a negative outcome in the 30 individuals studied, patients with very high levels of apoptosis prior to complete activation

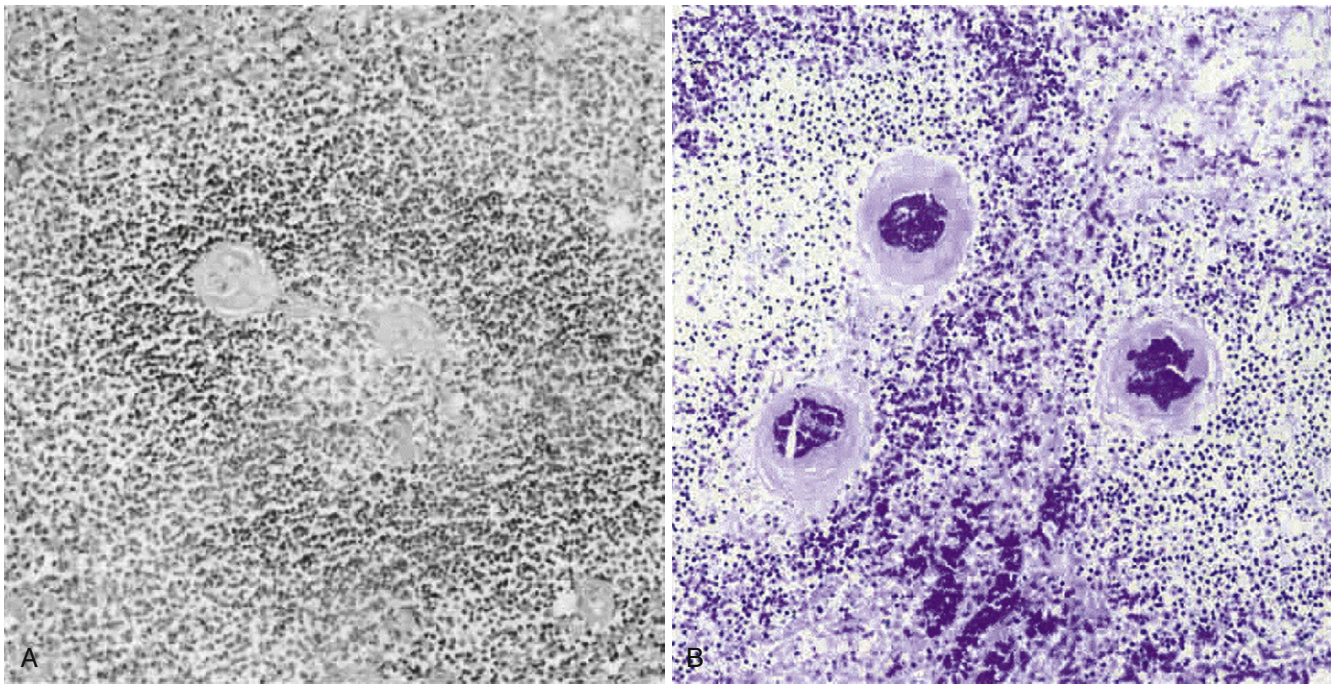

Figure 100–2. Spleen from a control patient (**A**) demonstrating a normal lymphoid follicle and from a septic patient (**B**) with substantial depletion in the lymphoid follicle. *(From Hotchkiss RS, Swanson PE, Freeman BD, et al: Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction,* Crit Care Med *27:1230–1251, 1999.)*

and expansion of the T-cell response appear to be predisposed to anergy and organ failure. T-cell anergy leading to immunosuppression is further supported by Miller-Graziano et al.,[34] who recently showed increased apoptosis in circulating T cells of trauma patients and that high levels of T-cell apoptosis correlated with T-cell anergy.

The apoptotic response of polymorphonuclear leukocytes to trauma has not been fully elucidated. Ogura et al.[35] reported that apoptosis is decreased in this cell type for as long as 3 weeks following trauma. This contrasts with data showing that neutrophil apoptosis is decreased in septic trauma patients but is not significantly different between patients 24 hours after traumatic injury and control volunteers.[28]

Neutrophil apoptosis is low in BAL fluid from patients with acute respiratory distress syndrome (ARDS) as well as those at risk for ARDS.[36,37] Levels of apoptosis did not correlate with patient survival. Interestingly, in vitro human polymorphonuclear leukocytes from healthy volunteers have less apoptosis when incubated with BAL fluid from ARDS patients compared with BAL fluid from healthy controls.

Further evaluation of this antiapoptotic effect on normal neutrophils showed it to be highest during the early stages of ARDS, with subsequent decreases over time. This change in apoptotic response to BAL fluid from ARDS patients correlates with levels of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor.[38]

Soluble Fas ligand is present in BAL fluid before and after onset of ARDS.[39] However, its concentration is higher at the onset of ARDS in patients who eventually die. Of note, BAL fluid from patients with ARDS induces a Fas-dependent apoptosis in distal lung epithelial cells, whereas BAL fluid from patients at risk for ARDS but without the disease does not have an effect on distal lung epithelial cell death. BAL fluid also has elevated concentrations of the apoptosis-related molecules perforin, granzyme A, and granzyme B in critically ill patients with early ARDS compared with those not having lung injury or late ARDS.[40]

Although autophagy is thought to play a role in the human response to trauma and hemorrhage, there are currently no studies showing autophagy in humans. However, there is extensive literature on the role of autophagy in other noninfectious inflammatory conditions. Several groups have now shown a correlation between genetic mutation in autophagy genes and the development of inflammatory bowel disease.[40,41] The exact mechanisms by which these specific mutations lead to inflammatory bowel disease are not known, but the role these autophagy genes play in inflammation is thought to be at least partially responsible.[41] There is also growing evidence that autophagy is increased in atherosclerotic heart disease; however, it is unclear if this increase is detrimental or protective.[43-45]

Animal Studies

Although human studies demonstrate that apoptosis, autophagy, and necrosis are altered in critical illness, the functional importance of these descriptive associations has not yet been studied in patients. Animal models of sepsis and noninfectious inflammation can help determine whether altered cell death is harmful in critical illness and offer mechanistic insights into the pathways underlying changes in cell death.

Sepsis

Similar to human autopsy studies, apoptosis is primarily localized to lymphocytes, dendritic cells, and the gut epithelium in animal models of sepsis. In cecal ligation and puncture (CLP), a murine model of ruptured appendicitis, as well as in overwhelming infection from *Pseudomonas aeruginosa* pneumonia, sampling of multiple cell and tissue types shows that maximal lymphocytic and intestinal apoptosis occurs 24 hours after onset of septic insult without substantial necrosis reported (Figure 100-3).[46-51]

As outlined above, apoptosis occurs via two main pathways: a receptor-mediated pathway and a mitochondrial-mediated pathway. In animal models, it appears that both pathways play a role in sepsis-induced apoptosis. Animals with gene-specific knockouts of proapoptotic Bcl-2 family members (mitochondrial pathway) or Fas-associated death domain transgenic mice (receptor-mediated) demonstrate significant decreases in sepsis-induced splenocyte apoptosis.[17,52] Intestinal epithelial lymphocytes and lamina B lymphocytes undergo Fas ligand-dependent (receptor), endotoxin-independent apoptosis.[53,54] However, thymic apoptosis is mainly Fas independent (mitochondrial) and is related to release of endogenous steroids, potentially acting via Bcl-2 expression.[55] Sepsis-induced apoptosis, whether initiated by the mitochondrial or the receptor-mediated pathway, converges into a single common pathway mediated by caspase-3. It should be noted that there are likely alternate pathways that are independent of caspase-3, given that caspase-3 knockout mice exhibit only a small degree of apoptosis.[56]

Increased lymphocytic apoptosis appears to be detrimental to survival in sepsis. Overexpression of Bcl-2 in transgenic mice overexpressing either T lymphocytes or B lymphocytes improves survival twofold to fourfold in three different strains of inbred mice subjected to CLP.[56,57] Similar increases in survival have been shown in mice where the proapoptotic Bcl-2 family member Bim has been knocked out.[17] Administration of the polycaspase inhibitor N-benzyloxycarbonyl-Val-Ala-Asp(O-methyl) fluoromethyl ketone (z-VAD) or the caspase-3 specific inhibitor M-971 result in similar improvements in outcome.[57,58] The beneficial effects of caspase inhibitors on survival in murine sepsis require the presence of lymphocytes; there is no survival benefit conferred to Rag-1 mice treated with caspase inhibitors. Adoptive transfer of T lymphocytes that overexpress Bcl-2 into Rag-1 animals improves survival similar to that seen in transgenic mice that overexpress Bcl-2 in their lymphocytes.[57]

The mechanisms that account for worse outcomes with increasing lymphocytic apoptosis appear to involve immunosuppression. Although immunosuppression in sepsis is multifactorial, the ongoing loss of immune effector cells in both the innate and adaptive compartments likely plays a significant role. In addition to the loss of cells, there is an upregulation of T regulatory cells and myeloid-derived suppressor cells.[58] This upregulation of immunosuppressive cells is driven in part by the production of interleukin (IL)-10, an antiinflammatory, immunosuppressive cytokine. IL-10 has been shown by several researchers to be an important mediator of immune function and is known to downregulate monocyte and neutrophil function as well as decrease inflammatory cytokine production by T cells.[59-62]

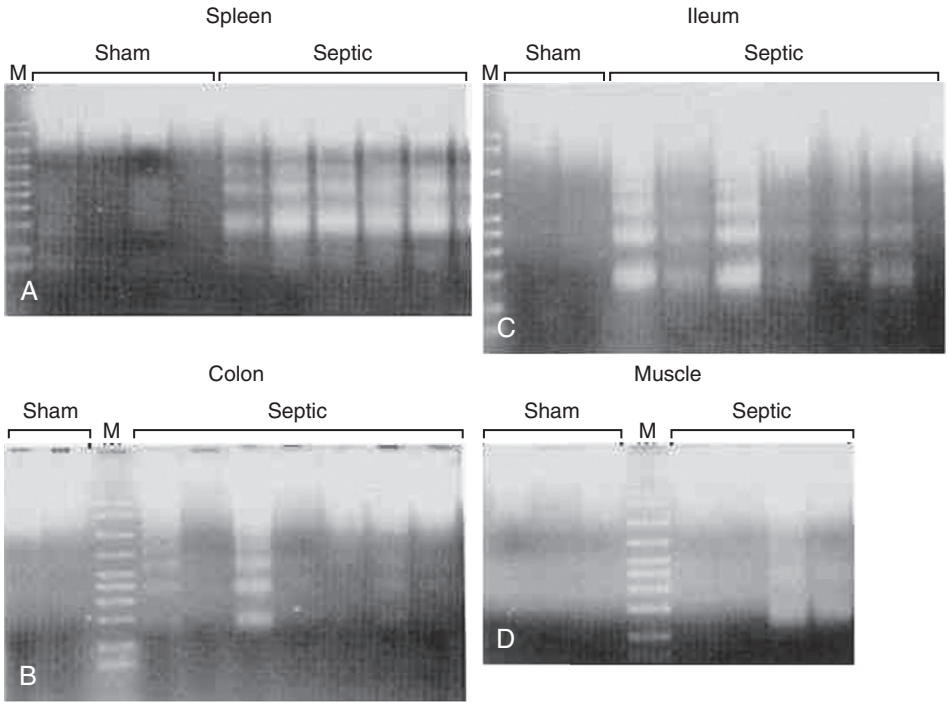

Figure 100–3. DNA agarose gel showing characteristic "laddering" pattern in spleen (**A**) and colon (**B**) in septic but not sham mice. *(From Hotchkiss RS, Swanson PE, Cobb JP, Jacobson A, et al: Apoptosis in lymphoid and parenchymal cells during sepsis: findings in normal and T- and B-cell-deficient mice,* Crit Care Med *25:1298–1307, 1997.)*

Gut epithelial apoptosis is increased in CLP, *P. aeruginosa* pneumonia,[49] and in vitro after infection with invasive enteric pathogens *Salmonella dublin* and *Escherichia coli*.[63] Intestinal cell death appears to be detrimental in polymicrobial or monomicrobial sepsis originating in the peritoneal space or the lungs because overexpression of Bcl-2 in the gut epithelium of transgenic mice confers a twofold survival advantage in CLP[51] and a tenfold survival advantage in *P. aeruginosa* pneumonia (Figures 100-4 and 100-5).[49] The mechanism underlying the improvement in survival caused by decreasing gut epithelial apoptosis is unclear, although it appears to be related to crosstalk with lymphocytes. However, bacterial translocation is similar between transgenic and nontransgenic animals with sepsis-induced pneumonia despite widely varying survival, and there are no statistically significant differences in cytokine levels between septic mice that overexpress Bcl-2 in their gut epithelium and their nontransgenic littermates.

Understanding of the role of lung apoptosis in sepsis is evolving. Respiratory epithelial cells are highly resistant to apoptosis when exposed to *P. aeruginosa*, undergoing cell death in vitro only under culture-specific conditions when treated with virulent bacteria capable of expressing both adhesins and cytotoxins.[64] In addition, lung epithelial apoptosis reportedly is absent in *P. aeruginosa* pneumonia in mice.[47] However, Grassme et al.[65] reported that *P. aeruginosa* pneumonia induces respiratory epithelial apoptosis in mice through activation of the Fas/Fas ligand system. Respiratory apoptosis appeared to be essential for survival in this study, with rapid sepsis-induced mortality in Fas or Fas ligand-deficient mice that lacked bronchial apoptosis. Alveolar and bronchiolar apoptosis were present in rats 8 hours after pneumonia was induced with *Streptococcus sanguis* (which resolves after 1 week) or *Streptococcus pneumoniae* type 25 (which progresses to pulmonary fibrosis).[66,67] Apoptosis was widespread for the first 4 days following either type of pneumonia. Eight days following *S. sanguis* pneumonia, apoptosis was localized to lung abscesses, implying a role for cell death in the resolution of injury.[66] By contrast, apoptosis was widespread and actually increased in intensity after *S. pneumoniae* type 25 pneumonia. Lung apoptosis has also been demonstrated following CLP in multiple mouse strains.[46,47]

Few animal studies demonstrate sepsis-induced apoptosis in other cell types. One exception is an increase in murine hepatocyte apoptosis following infection with *Listeria monocytogenes*.[68] Liver apoptosis is greatest at the edge of microabscesses and is independent of endotoxin, Fas, and nitric oxide. Apoptosis is also increased in murine granulocytes after CLP through a TNF-dependent pathway.[69] In contrast, blood leukocyte apoptosis is decreased in mice 24 hours after the same insult.[69]

Despite the paucity of literature supporting the role of autophagy in human sepsis, there is a growing body of literature characterizing the role of autophagy in animal models of infection. Liver autophagy in mice following cecal ligation and puncture.[30] Multiple researchers have also shown the importance of autophagy in the response to infection to a variety of bacteria and viruses including *S. pyogenes*, *M. tuberculosis*, *S. flexneri*, and Herpes simplex virus 1.[42] To date, autophagy has been shown to be important in both innate and adaptive immunity, inflammation, and immune homeostasis.[11,12,42] Some of these functions include degrading intracellular pathogens, delivering foreign material to MHC class II compartments, regulating T-cell homeostasis and directing viral genetic material to cell surface receptors.[70]

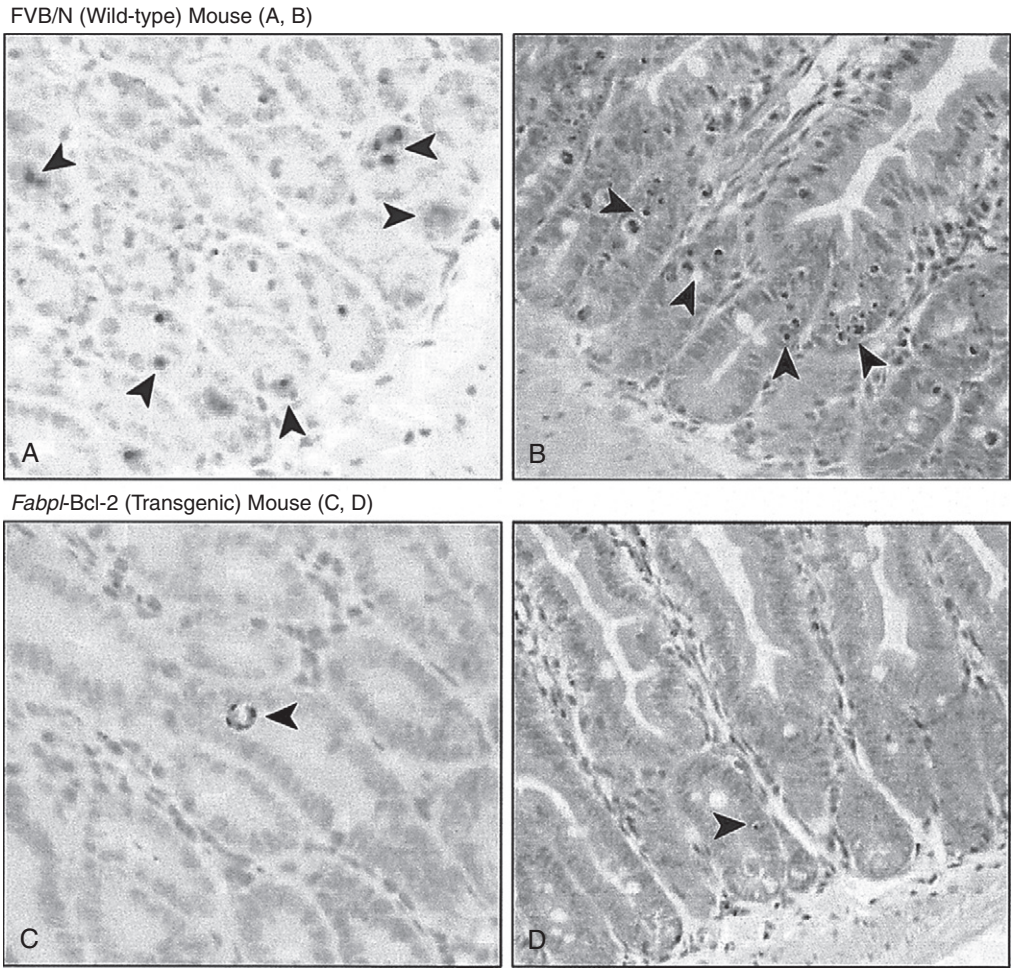

Figure 100–4. Intestinal epithelial sections from wild-type (**A** and **B**) and Bcl-2 transgenic (**C** and **D**) mice with sepsis from *Pseudomonas aeruginosa* pneumonia. Bcl-2 decreases apoptosis when assessed by active caspase-3 (**A** and **C**) or hematoxylin and eosin (**B** and **D**). *(From Coopersmith CM, Stromberg PE, Dunne WM, et al: Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis,* JAMA *287:1716–1721, 2002.)*

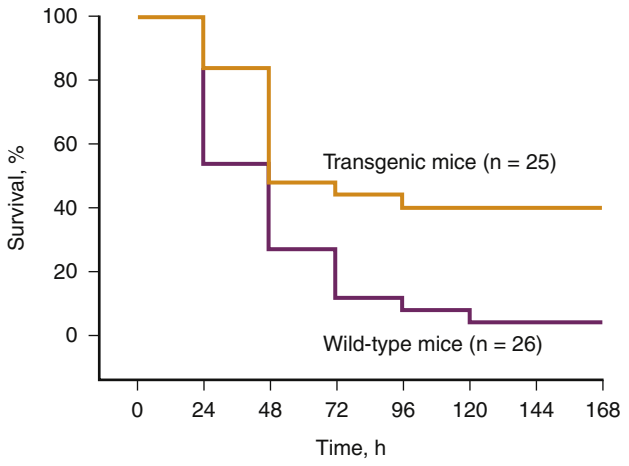

Figure 100–5. Survival 7 days after sepsis from *Pseudomonas aeruginosa* pneumonia in transgenic mice that overexpress Bcl-2 in their intestinal epithelium and wild-type mice. *(From Coopersmith CM, Stromberg PE, Dunne WM, et al: Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis,* JAMA *287:1716–1721, 2002.)*

Noninfectious Inflammation

Similar to sepsis, significant lymphocyte and intestinal epithelial apoptosis are present in human and animal studies of noninfectious inflammation; however, in noninfectious inflammation, cell death is also increased in a number of other tissues. Both thymocyte apoptosis[71,72] and B-cell Peyer patch apoptosis[73] are increased following either trauma/hemorrhage or hemorrhage alone. Both injuries decrease the release of the myeloid stimulating cytokine IL-3 from thymocytes,[71] whereas increased thymus-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) is only seen following hemorrhage alone. Lymphocyte apoptosis in Peyer patches also occurs following either trauma/hemorrhage or hemorrhage alone and is associated with elevated Fas expression, consistent with the Fas-dependent apoptosis seen in animal models of sepsis.[73] Thymocyte, splenocyte, Peyer patch, and intraepithelial lymphocyte apoptosis are all increased following thermal injury.[74-79] Thymocyte and splenocyte apoptosis are associated with increased levels of active caspase-3 but are independent of endotoxin as evidenced by high levels of apoptosis in lipopolysaccharide-nonresponsive transgenic mice.[75,76] Cell death is also dependent upon corticosteroids, as pretreatment with the glucocorticoid receptor antagonist

mifepristone significantly reduced both apoptosis and active caspase-3 activity following burn injury.[76] Mifepristone also reduces apoptosis in intraepithelial lymphocytes.[78] The roles of both TNF-α and Fas ligand in burn-induced lymphocyte apoptosis are more complicated. TNF-α levels are elevated following thermal injury in both thymus and spleen in C57BLK6/J mice; however, TNF-α protein levels are disproportionately elevated in thymic tissue, which is associated with elevated thymic but not splenic apoptosis.[79] The finding of elevated thymus and spleen apoptosis in TNF-α knock-out mice further complicates its role in burn-induced apoptosis.[75] Thymocyte, splenocyte, and $CD8^+$ T-cell Peyer patch apoptosis all are Fas ligand independent,[76,78] whereas B-cell Peyer patch cell death depends on the presence of this molecule because burn-induced apoptosis is eliminated in C3H/HeJ-FasL(gld) mice that lack functional Fas ligand.[78]

As in human studies, gut epithelial apoptosis is increased in multiple animal models of noninfectious inflammation including trauma, LPS administration, ischemia reperfusion, and thermal injury.[80-87] Gut epithelial apoptosis appears to be in large part induced through the mitochondrial-mediated pathway. Apoptosis is suppressible in murine ischemia reperfusion by overexpression of Bcl-280 in gut epithelia cells. In addition, the administration of the poly (ADP-ribose) synthetase inhibitor 3-aminobenzamide decreases LPS-induced apoptosis and is associated with a preservation of Bcl-2 expression by gut epithelial cells.[82] In contrast, thermal injury–induced gut epithelial apoptosis appears to be in part regulated through the receptor-mediated pathway because treatment with insulin-like growth factor 1, in combination with its binding protein, decreases apoptosis by downregulation of the Fas pathway.[88]

Acute lung injury (ALI) causes increased death in multiple cells within the lung.[67,89] Intratracheal injection of LPS induces apoptosis in alveolar cells, neutrophils, and macrophages.[89] This process is associated with upregulation of Fas in alveolar and inflammatory cells, and lung injury can be blocked by administration of an anti-Fas antibody. Respiratory apoptosis is also increased in a diffuse fashion in a hyperoxia model of ALI and in a patchy distribution in ALI caused by intravenous injection of oleic acid.[65] ALI has been shown to cause both epithelial and endothelial apoptosis in the lung.[90,91] Recent work by Barlos et al.[91] showed in a rat trauma-hemorrhagic shock model that both epithelial and endothelial apoptosis occur in the lung and that epithelial apoptosis occurs in a caspase-3–dependent fashion, whereas endothelial apoptosis is caspase-3 independent. The endothelium also plays a role in influencing neutrophil apoptosis.[92] Rat lung neutrophil apoptosis shows a significant delay following intratracheal LPS instillation. The mechanism underlying the delay is unrelated to LPS; a similar delay is seen following the addition of the potent apoptosis-inducer TNF-α. The process of endothelial transmigration appears to play a major regulatory role in regulating neutrophil apoptosis. Adhesion molecules from the integrin and selectin families also have a role in modulating neutrophil cell death.[93]

Extensive hepatocyte apoptosis is seen in animal models of trauma/hemorrhage and depends on the severity of shock induced with increasing apoptosis correlating with duration of shock.[94,95] In addition, apoptosis is only seen following resuscitation, and the introduction of IL-6 at the time of resuscitation completely prevents trauma/hemorrhage-induced apoptosis.[95] Apoptosis of hepatocytes is also seen in animal models of thermal injury.[96]

Other organ tissues susceptible to apoptosis, particularly through thermal injury, include cardiac and skeletal muscle.[85,97] Cardiac apoptosis appears to be predominantly located in the subendocardial region of the left ventricle.[85] Increased skeletal muscle apoptosis is seen up to 7 days after thermal injury and was found in muscle tissue below the site of injury as well as in remote areas.[97] Similar to infectious models, increasing mortality in noninfectious inflammation is related to host immunosuppression. Apoptosis of immune effector cells, epithelial cells, and endothelial cells is a likely contributor to the overall immune status of the host.

Autophagy has also been implicated in the pathophysiology of noninfectious inflammation, most notably in animal models of cardiac ischemia and reperfusion. Increased autophagy has been found in multiple animal models of cardiac ischemia and reperfusion with mixed results. Matsui et al.[98] evaluated autophagy in mice with a defect in a key autophagy genes and found decreased autophagy in these mice was associated with decreased cell death and decreased infarct size. Alternatively, Hamacher-Brady et al.[99] found that increased autophagy in mice leads to decreased ischemia/reperfusion-induced myocyte death and protects the myocardium.

References are available online at http://www.expertconsult.com.

VI

Chapter 101

Endotheliopathy

Yves Ouellette and Jan A. Hazelzet

PEARLS

- Because of their location, endothelial cells have the ability to interact with blood components, such as flow, soluble factors, and other cells. Endothelial cells integrate these signals into a cohesive regulation of vascular responses.
- The endothelium controls the vascular tone of the underlying smooth muscle cells through the production of vasodilator and vasoconstrictor mediators.
- Endothelial cell activation in response to inflammation changes endothelial cellular physiology and results in altered vascular function.

Until recently, scientists and clinicians considered the endothelium, the cell layer that lines the blood vessels, as an inert barrier separating the various components of blood and the surrounding tissues. The vascular endothelium is now recognized as a highly specialized and metabolically active organ performing a number of critical physiologic, immunologic, and synthetic functions. These functions include regulation of vascular permeability, fluid and solute exchange between the blood and interstitial space, vascular tone, cell adhesion, homostasis, and vasculogenesis.[1]

The normal vascular endothelium is only one cell layer thick, separating the blood and vascular smooth muscle. The endothelium responds to physical and biochemical stimuli by releasing regulatory substances affecting vascular tone and growth, thrombosis and thrombolysis, and platelet and leukocyte interactions with the endothelium. Normal endothelial functions include control over thrombosis and thrombolysis, platelet and leukocyte interactions with the vessel wall and regulation of vascular tone and growth. Of particular interest to intensivists is the fact that the endothelium secretes both powerful vasorelaxing (e.g., nitric oxide [NO]) and vasoconstricting substances (e.g., endothelin-1 [ET-1]). Since normal endothelial function plays a central role in vascular homeostasis, it is logical to conclude that endothelial dysfunction contributes to disease states characterized by vasomotor dysfunction, abnormal thrombosis, or abnormal vascular proliferation.

The endothelium lies between the lumen and the vascular smooth muscle, where it is uniquely positioned to "sense" changes in hemodynamic forces or blood-borne signals by membrane receptor mechanisms. The endothelial cells can respond to physical and chemical stimuli by synthesis or release of a variety of vasoactive and thromboregulatory molecules and growth factors. Substances released by the endothelium include prostacyclin, NO, endothelins, endothelial cell growth factors, interleukins, plasminogen inhibitors, and von Willebrand factor (vWF). The vascular endothelium possesses numerous enzymes, receptors, and transduction molecules, and it interacts with other vessel wall constituents and circulating blood cells. In addition to these universal functions, the endothelium may have organ-specific roles that are differentiated for various parts of the body, such as gas exchange in the lungs, control of myocardial function in the heart, or phagocytosis in the liver and spleen. From a structural perspective, endothelial cells from different sites of the vascular tree differ in size, shape, thickness, and nuclear orientation. For example, endothelial cells that line the pulmonary artery of the rat are larger and more rectangular than those lining the aorta, whereas endothelial cells in the aorta are thicker than their counterparts in capillaries or veins.[2]

Studies of endothelial structure and function have been accomplished by a variety of techniques, including ultrastructural studies, in vitro experiments for endothelial cell isolation and culture, physiologic studies in animals, and, most recently, clinical studies in humans. This knowledge has facilitated the development of treatment strategies based on administration of endothelial products, such as prostacyclin and NO, or their antagonists.

Normal Endothelial Function

Endothelial Cell Heterogeneity

Many vascular diseases appear to be restricted to specific vascular beds. For example, thrombotic events are often localized to single vessels. It is also common for certain vasculitides to specifically affect certain arteries, veins, or capillaries, or to affect certain organs. Tumor cells will often metastasize more commonly within particular vascular beds. The basis for this variability in vascular disease is poorly understood, but may be explained in the heterogeneity of endothelial cells. Recently, there has been a greater understanding of how endothelial cell heterogeneity may contribute both to the maintenance of organ-specific function and to the development of disorders restricted to specific vascular beds.[1-3]

The morphological appearance of capillary endothelium from different vascular beds may explain differences in tissue function. For example, the brain microcirculation is lined by endothelial cells connected by tight junctions that maintain the blood-brain barrier. By contrast, sinusoids found in the liver, spleen, and bone marrow are lined by endothelial cells that allow transcellular trafficking between intercellular gaps. Similarly, fenestrated endothelial cells found in the intestinal villi, endocrine glands, and kidneys facilitate selective permeability, which is required for efficient absorption, secretion, and filtering. [4]

Another example of endothelial cell heterogeneity lies in the expression of cell surface receptors involved in cell-to-cell signaling and cell trafficking. For example, in the mouse, lung-specific endothelial cell adhesion molecules are exclusively expressed by pulmonary postcapillary endothelial cells and some splenic venules. Similarly, specific mucosal cell adhesion molecules are expressed primarily on endothelial venules in the Peyer patches of the small intestine.[5,6] Tumor cells may show clear preferential adhesion to the endothelium of specific organs paralleling their in vivo metastatic propensities.[7] Distinct subsets of endothelial cells often exist within a single organ. In in situ studies, two distinct sinusoidal endothelial cell phenotypes can be recognized in the adult human liver: hepatic periportal vessels express specific cell surface molecules such as PECAM-1 and CD34, whereas sinusoidal intrahepatic endothelial cells do not.

Cultured microvascular endothelial cells express surface markers, protein transporters, and intracellular enzymes specific to their tissue of origin such as brain, liver, or other organs. These tissue-specific phenotypic differences can be maintained for some time under identical tissue culture conditions. Endothelial phenotype can be manipulated by changing the microenvironment, a phenomenon that has been referred to as transdifferentiation. For example, aortic endothelial cells cultured on lung-derived extracellular matrix are induced to express lung-specific endothelial cell adhesion molecules, whereas the same cells develop fenestrae when cultured on matrix derived from the kidney-derived MDCK cells. Similarly, endothelial cells grown on extracts of basement membrane from different organs have been observed to develop preferential adhesivity for tumor cells prone to metastasize to that organ.

Endothelial Progenitor Cells

In the last decade, a significant amount of literature has shown that maintenance and repair of vasculature in ischemic diseases may be at least partially mediated through recruitment of endothelial progenitor cells (EPCs) from the bone marrow to areas of vascular injury.

EPCs are a specific subtype of hematopoietic stem cells that have been isolated from circulating mononuclear cells, bone marrow, and cord blood. EPCs migrate from the bone marrow to the peripheral circulation, where they contribute to vascular repair.[8,9] When injected into animal models of ischemia, EPCs are incorporated into sites of neovascularization,[8,10,11] and have contributed to improved outcomes in patients with ischemic vascular disorders.[12] In addition, there has been accumulating evidence for the function of EPCs in critical illnesses such as sepsis.

Recruitment of EPCs to areas of endothelial and vascular damage may have prognostic implications and be associated with clinical outcome. The pathophysiologic changes associated with critical illness, notably sepsis and sepsis-related organ dysfunction, may lead to apoptosis and necrosis of endothelial cells from the vasculature and recruitment of EPCs from the bone marrow. Whether recruitment and mobilization of EPCs is associated with clinical outcomes in critically ill patients, thus serving as a prognostic biomarker, remains uncertain.

In various models of vascular injury and organ dysfunction, only a few studies have emerged regarding EPCs in particular as a therapeutic strategy. Transplanted EPCs have been shown to improve survival of mice following liver injury.[13] Infusion of EPCs also restored blood flow in a mouse model of hindlimb ischemia.[9] A recent prospective randomized trial compared the effects of EPC transplantation in patients with idiopathic pulmonary arterial hypertension versus conventional therapy and showed that after 12 weeks, patients who had received EPCs had a significant improvement in their 6-minute walk test, mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output.[14]

Coagulation and Fibrinolysis

A normal physiological function of the endothelium is to provide an antithrombotic surface inhibiting platelet adhesion and clotting, thus facilitating normal blood flow. Under pathophysiological conditions, the endothelium transforms into a prothrombotic surface. A dynamic equilibrium exists between both states that permits a rapid response to an insult and a rapid recovery.[15]

Anticoagulant Mechanisms

The endothelium has anticoagulant, antiplatelet, and fibrinolytic properties.[16] Endothelial cells are the major site for anticoagulant reactions involving thrombin. Thrombin plays a key role in coagulation, including activation of platelets, activation of several coagulation enzymes and cofactors, and stimulation of procoagulation pathways on the endothelial cell surface. In the normal state, there is little thrombin enzyme activity. The surrounding endothelial cell matrix contains heparin sulfate and related glycosaminoglycans that activate antithrombin III. In addition, the subendothelial cell matrix contains dermatan sulfate which promotes the antithrombin activity of heparin cofactor II. Furthermore, microvascular endothelial cells release tissue-factor pathway inhibitor that inhibits the factor VIIa/tissue factor complex, and further contributes to anticoagulation (Figure 101-1).

Thrombin activity is also modulated by endothelial cell synthesis of thrombomodulin.[17,18] The binding of thrombin to thrombomodulin facilitates the enzyme's activation of the anticoagulant protein C. Activated protein C (APC) activity is enhanced by cofactor C, also called protein S, which is synthesized by endothelial cells as well as by other cells (see Figure 101-1). APC inhibits factor Va and factor VIIIa. Thrombomodulin (TM) also inhibits prothrombinase activity indirectly by binding factor Xa (Figure 101-2). Protein C has a special receptor on the endothelial cells: endothelial protein C receptor (EPCR). EPCR augments protein C activation approximately twentyfold in vivo by binding protein C and presenting it to the thrombin-TM activation complex. Both EPCR and TM can be found in plasma as soluble proteins. Activated protein C retains its ability to bind EPCR, and this complex appears to be involved in some of the cellular signaling mechanisms

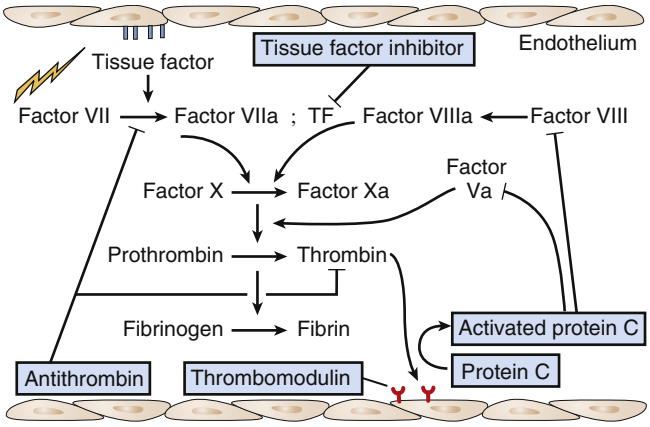

Figure 101–1. Endothelium control of the coagulation cascade. An inflammatory stimulus upregulates the interaction of tissue factor (TF) with factor VII, which generates activated factor VII (factor VIIa). The TF–factor VIIa complex then leads to the conversion of factor X to factor Xa. The interaction of factors Xa and Va results in the conversion of prothrombin to thrombin, and the conversion of fibrinogen to fibrin. Three key anticoagulant pathways can inhibit this process. Protein C is activated through its interaction with cell-surface thrombomodulin, and inhibits the activities of factors Va and VIIIa. Antithrombin blocks the activation of multiple factors including factor X and thrombin. Tissue factor pathway inhibitor interferes directly with the tissue factor–factor VIIa complex.

that downregulate inflammatory cytokine formation (tumor necrosis factor, interleukin-6). Activated protein C has a variety of antiinflammatory activities. As said, it suppresses inflammatory cytokine during sepsis, inhibits leukocyte adhesion, decreases leukocyte chemotaxis, reduces endothelial cell apoptosis, helps maintain endothelial cell barrier function through activation of the sphingosine-1 phosphate receptor, and minimizes the decrease in blood pressure associated with severe sepsis.[19] Another interesting effect of APC is its PAI-1 neutralizing effect. PAI-1 (plasminogen activator inhibitor-1) is a glycoprotein that acts as an acute-phase protein during acute inflammation. Its primary role in vivo is the inhibition of both tissue- and urokinase-type plasminogen activators. PAI-1 is the most efficient inhibitor of activated protein C and thrombin in the absence of heparin. PAI-1 competes with TM for binding with thrombin, which, in combination with its inhibition of activated protein C, makes it a strong local procoagulant by a combined action of displacing and inactivating anticoagulant thrombin from thrombomodulin. In this way PAI-1 has important pathophysiological effects in acute and chronic diseases.[20] The thrombin-TM complex also activates thrombin-activatable fibrinolysis inhibitor, a procarboxypeptidase that renders fibrin resistant to clot lysis and neutralizes vasoactive molecules such as complement C5a.[21]

In addition, platelet adhesion to endothelial cells is markedly inhibited by endothelium-derived prostacyclin.[22] The same stimuli that activate platelets, such as thrombin and adenosine diphosphate and adenosine triphosphate (ATP), also act to release prostacyclin from the endothelium, which allows the endothelium to limit the extent of platelet plug formation. The interactions between platelets and endothelium regulate platelet function, coagulation cascades, and local vascular tone.

Microvascular endothelial cells may secrete tissue-type plasminogen activator (t-PA), the powerful thrombolytic agent in frequent clinical use for treatment of coronary thrombotic occlusion.[23] t-PA release is stimulated in vivo by norepinephrine, vasopressin, or stasis within the vessel lumen. Thrombin may also stimulate t-PA release, providing a further endothelium-mediated safeguard against uncontrolled coagulation.

Procoagulant Mechanisms

The expression and release of tissue factor is the pivotal step in transforming the endothelium from an anticoagulant to a procoagulant surface.[24,25] Tissue factor accelerates factor VIIa-dependent activation of factors X and IX (see Figure 101-1). The synthesis of tissue factor is induced by a number of agonists, including thrombin, endotoxin, several cytokines, shear stress, hypoxia, oxidized lipoproteins, and other endothelial insults. Once endothelial cells expressing tissue factor are exposed to plasma, prothrombinase activity is generated and fibrin is formed on the surface of the cells. Tissue factor can also be found in plasma as a soluble protein. Its role there is not well understood, but it probably plays a role in the initiation of coagulation.

Endothelium-Derived Vasodilators

The important role that the endothelium plays in controlling vascular tone has only recently been appreciated. Clinicians and researchers have come to appreciate that the endothelium controls underlying smooth muscle tone in response to certain pharmacological and physiological stimuli. This response involves a number of luminal membrane receptors and complex intracellular pathways and the synthesis and release of a variety of relaxing and constricting substances, described in the following sections.

Nitric Oxide

Furchgott and Zawadzki first postulated the existence of an endothelial derived relaxing factor (EDRF) in 1980, when they noticed that the presence of endothelium was essential for rabbit aortic rings to relax in response to acetylcholine.[24] Later, it was determined that the biologic effects of EDRF are mediated by NO.[26]

NO is generated from the conversion of L-arginine to NO and L-citrulline by the enzyme nitric oxide synthase (NOS).[27] There are two general forms of NOS: constitutive and inducible. In the unstimulated state, NO is continuously produced by constitutive NO synthase (cNOS). The activity of cNOS is modulated by calcium that is released from endoplasmic stores in response to the activation of certain receptors. Substances such as acetylcholine, bradykinin, histamine, insulin, and substance P stimulate NO production through this mechanism. Similarly, shearing forces acting on the endothelium are another important mechanism regulating the release of NO. The inducible form of NOS (iNOS) is not calcium-dependent, but instead is stimulated by the actions of cytokines (e.g., tumor necrosis factor-α [TNFα], interleukins) and/or bacterial endotoxins (e.g., lipopolysaccharide). Induction of iNOS occurs over several hours and results in NO production that may be more than a thousandfold greater than that produced by cNOS. This is an important mechanism in the pathogenesis of inflammation (see Figure 101-2). Inhibition of NOS using competitive analogs of L-arginine drastically reduces endothelium-dependent relaxation in vitro, particularly in large conduit arteries, thereby evoking vasoconstriction.

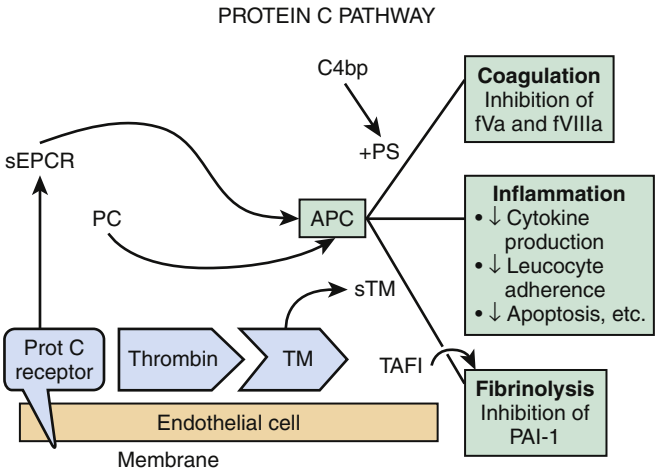

Figure 101–2. The interaction of the protein C system with the endothelium: thrombin bound to thrombomodulin (TM) modifies protein C bound to the endothelial protein C receptor on the cell surface to generate activated protein C (APC). APC acts as a natural anticoagulant by inactivating activated factors V (fVa) and VIII (fVIIIa), modulating inflammation by downregulating the synthesis of proinflammatory cytokines, leukocyte adherence, and apoptosis, and enhancing fibrinolysis by inhibiting thrombin-activatable fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor type-1 (PAI-1). *C4Bbp,* C4b binding protein (binds protein S); *+PS*, in the presence of protein S; *sTM,* soluble thrombomodulin; *sEPCR*, soluble endothelial cell protein C receptor. *(Modified from Hazelzet J: Pathophysiology of pediatric sepsis. In Nadel S:* Infectious diseases in the pediatric intensive care unit, *London, 2008, Springer.)*

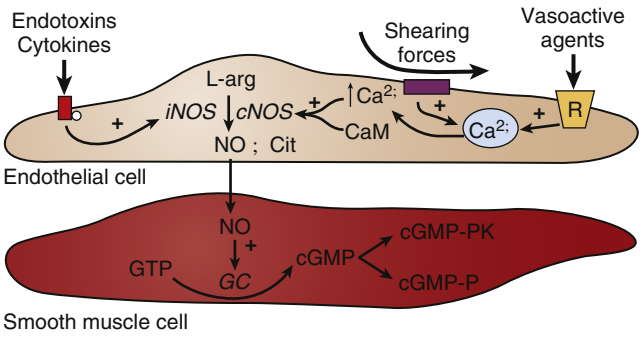

Figure 101–3. Nitric oxide (NO) is generated from L-arginine (L-arg) by the action of nitric oxide synthase (NOS). In the resting state, constitutive NOS (cNOS) is modulated by intracellular Ca^{2+} and calmodulin (CaM). Stored Ca^{2+} is released in response to vasoactive agents (acetylcholine and bradykinin, for example) and other external stimuli such as shearing forces. Cytokines' and endotoxins' activation of endothelial cells results in increased expression of inducible NOS (iNOS). Citrulline (Cit) is a byproduct of NO production. NO has a half-life of only a few seconds in vivo and quickly diffuses to surrounding cells such as smooth muscle cells. NO stimulates the production of the intracellular mediator cyclic GMP (cGMP). Increased cGMP activates a series of cGMP-dependent protein kinases (cGMP-PK) and cGMP-dependent phosphatases (cGMP-P).

Chronic treatment of animals with NOS inhibitors or suppression of the cNOS gene is reported to induce hypertension.[28-30]

Once NO is formed by an endothelial cell, it readily diffuses out of the cell and into adjacent smooth muscle cells where it binds and activates the soluble form of guanylyl cyclase, resulting in the production of cyclic guanosine-monophosphate (cGMP) from guanosine-triphosphate.[31] cGMP in turn activates a number of cGMP-modulated enzymes (Figure 101-3). Increased cGMP activates a kinase that subsequently leads to the inhibition of calcium influx into the smooth muscle cell, and decreased calcium-calmodulin stimulation of myosin light-chain kinase. This, in turn, decreases the phosphorylation of myosin light chains, thereby decreasing smooth muscle tension development and causing vasodilation. There is also some evidence that increases in cGMP can lead to myosin light chain dephosphorylation by activating the phosphatase. In addition, cGMP-dependent protein kinase phosphorylates K^+ channels to induce hyperpolarization and thereby inhibits vasoconstriction.[32,33] Interestingly, NO inhibition of platelet aggregation is also related to the increase in cGMP. Drugs that inhibit the breakdown of cGMP such as inhibitors of cGMP-dependent phosphodiesterase (for example, sildenafil) potentiate the effects of NO-mediated actions on the target cell.

NO therefore contributes to the balance between vasodilator and vasoconstrictor influences that determine vascular tone.[34] The exogenous nitrovasodilators sodium nitroprusside and nitroglycerin use the same pathways. The generation of NO from L-arginine can also be specifically blocked by arginine analogues, such as N^G-monomethyl-L-arginine (L-NMMA), which has recently proven to be a useful tool in clinical research, allowing investigation of the biologic distribution and role of NO.

Prostacyclin

Another major endothelium-derived vasodilator is the prostaglandin prostacyclin (PGI_2), a derivative of arachidonic acid synthesized through the action of the enzyme cyclooxygenase. Endothelium cells are capable of producing a variety of vasoactive substances that are products of arachidonic acid metabolism. Among these are prostaglandins, PGI_2, leukotrienes, and thromboxanes. These substances act as either vasodilators or vasoconstrictors, amongst their other biological activities. PGI_2 is a potent vasodilator and is active in both the pulmonary and systemic circulations. In addition to its vasodilatory effects, prostacyclin also has antithrombotic and antiplatelet activity. Its release may be stimulated by bradykinin and adenine nucleotides. Like NO, it is chemically unstable with a short half-life.[35] However, unlike NO, PGI_2 activity in arterial beds depends on its ability to bind to specific receptors in vascular smooth muscle. Its vasodilator activity is therefore determined by the expression of such receptors. PGI_2 receptors are coupled to adenylate cyclase to elevate cyclic AMP levels in vascular smooth muscle.[36] The increase in cAMP results in (1) stimulation of ATP-sensitive K^+ channels resulting in hyperpolarization of the cell membrane and inhibition of the development of contraction; and (2) increase efflux of Ca^{2+} from the smooth muscle cell and inhibition of the contractile machinery.

In addition, PGI_2 facilitates the release of NO by endothelial cells and the action of PGI_2 in vascular smooth muscle is potentiated by NO. Interestingly, NO may also potentiate the effects of prostacyclin. The NO-mediated increase in cGMP in smooth muscle cells inhibits a phosphodiesterase that breaks down cAMP, and therefore indirectly prolongs the half-life of the second messenger of PGI_2.[37]

Endothelium-Derived Hyperpolarizing Factor

Endothelium stimulation by acetylcholine also produces hyperpolarization of the underlying smooth muscle and thereby induces vasorelaxation. This process is not mediated

by NO, but is instead mediated by another endothelium-derived factor. This factor acts by increasing K^+-channel conductance in smooth muscle cells, resulting in smooth muscle cell relaxation. The resulting vasodilation is not inhibited by L-NMMA, the specific antagonist of NO, but is inhibited by ouabain, a Na^+/K^+-ATPase inhibitor. In addition, in most medium- to resistance-sized arteries, electrophysiological studies have established that endothelium-dependent hyperpolarization of vascular smooth muscle is resistant to the combined inhibition of both NOS and cyclooxygenases. Accordingly, a component of the endothelium-dependent relaxation in these arteries is mediated by a substance different from NO and PGI_2. This component of endothelium-dependent vasodilatation has been attributed to a yet unidentified diffusible endothelium-derived hyperpolarizing factor (EDHF).[38]

EDHF acts by opening K^+ channels in vascular smooth muscle. Hyperpolarization inhibits vasoconstriction by closing voltage-sensitive Ca^{2+} channels, impairing the receptor-dependent activation of phospholipase C and the subsequent release of Ca^{2+} from intracellular stores, as well as by reducing the Ca^{2+} sensitivity of the contractile proteins. Of significant clinical importance is the fact that EDHF-mediated effect increases as the arterial diameter decreases, such as in resistance arteries. EDHF likely plays a significant role in the regulation of peripheral vascular resistance and local hemodynamics. Unfortunately, in the absence of selective inhibitors of the EDHF pathway, it is not possible to evaluate the relevance of EDHF in vivo.[38]

Endothelium-Derived Vasoconstrictors

Endothelins (Endothelium-Derived Contracting Factors)

Endothelin is a 21-amino-acid peptide and is one of the most potent vasoconstrictors yet identified. Endothelial cells synthesize the prohormone big endothelin and express endothelin-converting enzymes to generate endothelin. There are three isoforms of endothelin, but only one (ET-1) has been shown to be released from human endothelial cells. ET-1 is synthesized in the endothelial cells and its release is mediated by a variety of stimuli. ET-1 release is stimulated by angiotensin II, antidiuretic hormone, thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. ET-1 release is inhibited by nitric oxide as well as by PGI_2 and atrial natriuretic peptide.[39,40]

ET-1 has a short half-life, suggesting that similarly to NO, ET-1 is mainly a locally active vasoregulator. Once released by endothelial cells, ET-1 binds to a membrane receptor (ET_A) found on adjacent vascular smooth muscle cells. This binding leads to calcium mobilization and smooth muscle contraction. The ET_A receptor is coupled with a G-protein linked to phospholipase-C, resulting in the formation of IP_3. Interestingly, ET-1 can also bind to an ET_B receptor located on the vascular endothelium, which stimulates the formation of NO by the endothelium. This release of NO appears to modulate the ET_A receptor-mediated contraction of the vascular smooth muscle. Its physiological role includes maintenance of basal vascular resistance, and it is present in healthy subjects in low concentrations. Elevated endothelin levels have been found in systemic and pulmonary hypertension, coronary artery disease, and heart failure, although the role of ET-1 in the pathophysiology of these conditions has been postulated but not proven.[39,40]

Reactive Oxygen Species

Endothelial cells secrete oxygen-derived free radicals and hydrogen peroxide in response to shear stress and endothelial agonists such as bradykinin. Such reactive oxygen species are reported to inactivate NO, resulting in vasoconstriction. Reactive oxygen species may also facilitate the mobilization of cytosolic Ca^{2+} in vascular smooth muscle cells and promote Ca^{2+} sensitization of the contractile elements. Endothelium-derived superoxide anion, under conditions of hyperoxia, may combine with NO with diffusion-limited kinetics to generate peroxinitrite, negating NO-mediated vasodilation, an effect inhibited by superoxide dismutase, which metabolizes superoxide anion to hydrogen peroxide.[41]

Vasoconstrictor Prostaglandins

The metabolism of arachidonic acid by cyclooxygenase in endothelial cells may lead to the secretion of precursors of thromboxanes and leukotrienes. These prostaglandins act on receptors in vascular smooth muscle to induce vasoconstriction. PGI_2, however, is the major endothelial metabolite of arachidonic acid that is generated through the cyclooxygenase pathway. Thus, under normal circumstances, the influence of the small amounts of vasoconstrictor prostanoids released by endothelial cells is masked by the production of PGI_2, NO, and EDHF.[42,43]

Endothelium and Blood Cell Interactions

In addition to the interactions of the endothelium with blood coagulation factors, endothelial cells also express cell-surface molecules that orchestrate the trafficking of circulating blood cells. These cell-associated molecules help direct the migration of leukocytes into specific organs under physiologic conditions and accelerate migration towards sites of inflammation. They have also been implicated in the adhesion of platelets and erythrocytes in several common disorders associated with homeostasis.

Interactions of Leukocytes with the Vessel Wall

It is now well established that flowing leukocytes may adhere to specific regions of the endothelium in response to tissue injury or infection. These multicellular interactions are essential precursors of physiologic inflammation. Leukocytes interact with vessel surfaces through a multistep process that includes (1) initial formation of usually reversible attachments; (2) activation of the attached cells; (3) development of stronger, shear-resistant adhesion; and (4) spreading, emigration, and other sequelae.[44] (Figure 101-4)

Selectins are key molecules in the interaction of leukocytes and endothelial cells. They are transmembrane glycoproteins that recognize cell-surface carbohydrate ligands found on leukocytes, and initiate and mediate tethering and rolling of leukocytes on the endothelial cell surface. Selectins constitute a family of three known molecules. L-selectin is expressed on most leukocytes and binds to ligands constitutively expressed

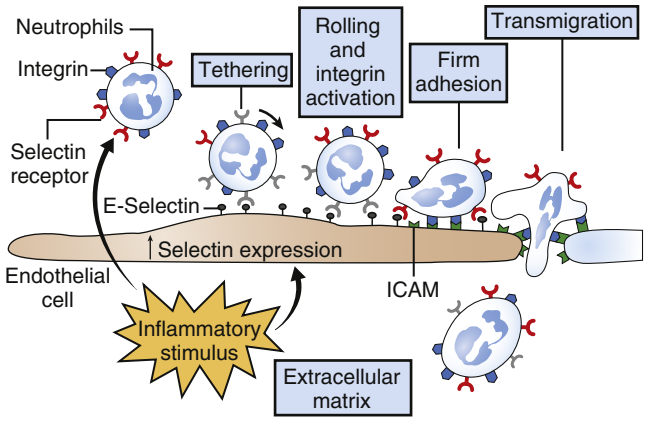

Figure 101–4. Leukocyte recruitment process and transmigration. The multistep model for leukocyte recruitment at sites of inflammation begins with the activation of neutrophils and endothelial cells. Once activated, endothelial cells express selectins, whose binding to neutrophils initiates rolling and adhesion of neutrophils to the endothelium. Activated integrins on the surface of neutrophils bind to endothelial cell ICAMs, facilitating a firm adhesion. Transmigration through the endothelium further involves interactions with other molecules such as PECAMs and cadherins on the surface of endothelial cells.

on endothelial cells found in venules of lymphoid tissues. Its expression is induced on endothelium at sites of inflammation. E-selectin is expressed on activated endothelial cells and leukocytes. P-selectin is rapidly redistributed from secretory granules to the surface of platelets and endothelial cells stimulated with thrombin. Both endothelial cells E-selectin and P-selectin bind to ligands on leukocytes.[45]

With stimulation, leukocytes usually attach to postcapillary venule endothelial cells, where shear stresses are lowest. Leukocytes adherent to the endothelium can make contact with flowing leukocytes through the L-selectin molecule, resulting in amplification of leukocyte recruitment to sites of inflammation. It is generally understood that selectins initiate inflammatory, immune, and hemostatic responses by promoting transient multicellular interactions.[46]

Proinflammatory molecules presented on the surface of the endothelium proceed to activate a second family of adhesion molecules, the integrins, and cause cells to firmly adhere. After the initial tethering of leukocytes to endothelial cells, leukocytes then must roll prior to transmigrating through the endothelium. Inhibition of leukocyte adhesion does not reduce leukocyte rolling, suggesting that rolling and adhesion are distinct molecular events. In addition, inhibiting rolling reduces adhesion, suggesting that rolling is a prerequisite of leukocyte adhesion/recruitment and ultimately the inflammatory response.

Leukocytes subsequently migrate between endothelial cells into tissues by mechanisms that are not completely understood but which we know are affected by gradients of chemokines, integrins activation states, and interactions with PECAM-1, an Ig-like receptor. This migration requires disruption of endothelial-cell-to-endothelial-cell interaction of cadherins at tight junctions. Leukocyte recruitment to lymphoid tissues or inflammatory sites requires the coordinated expression of specific combinations of adhesion and signaling molecules. Diversity at each step of the cascade ensures that the appropriate leukocytes accumulate for a restricted period in response to a specific challenge.[4,46]

Platelet Adhesion

Endothelial cells and circulating platelets normally do not interact with each other due to the release of PGI_2, the release of NO, and the expression of CD39 on the surface of endothelial cells.[47] During vascular injury and inflammation, platelets adhere to exposed subendothelial components, and are rapidly activated. Circulating platelets interact with the adherent platelets, producing a hemostatic plug that promotes thrombin generation and development of a stable fibrin clot. High shear stress, as seen in arteries, increases platelet adherence to the subendothelium where unactivated platelets attach to the subendothelium through interactions of platelet glycoproteins with immobilized vWF, a large, multimeric protein with binding sites for several other molecules, including subendothelial collagen. Flowing platelets attach transiently to vWF, resulting in continuous movement of the cells along the surface. Under the lower shear stresses found in veins, unactivated platelets interact with integrins to attach to and immediately arrest on immobilized fibrinogen.[48]

Once platelets adhere to either vWF or fibrinogen, they are activated by secreted products such as adenosine diphosphate or epinephrine, or by surface molecules such as collagen that crosslink the integrins and other platelet receptors. The activated platelets spread and adhere more avidly to the subendothelial surface, which recruits additional platelets into aggregates. Shear-resistant adhesion may be further enhanced by interactions of other integrins or receptors with laminin, fibronectin, and thrombospondin. As thrombin is generated, converting bound fibrinogen to fibrin, the aggregated platelets contract to strengthen the clot.[48]

Endothelial Permeability

Transport across the endothelium can occur via two different pathways: through the endothelial cell (transcellular) or between adjacent cells, through interendothelial junctions (paracellular) (Figure 101-5). The endothelial cell is able to dynamically regulate its paracellular and transcellular pathways for transport of plasma proteins, solutes, and liquid. The semipermeable characteristic of the endothelium (which distinguishes it from the epithelium) is crucial for establishing the transendothelial protein gradient (the colloid osmotic gradient) required for tissue fluid homeostasis. The transcellular pathway, also known as transcytosis, is defined as vesicle-mediated transport of macromolecules, such as plasma proteins, across the endothelial barrier in a caveolae-dependent manner. The paracellular pathway is formed by the minute intercellular space between contacting cells. Its primary function is to restrict free passage of macromolecules in the range of 3 nm and above through interendothelial junctions (IEJs), while allowing the convective and diffusive transport of molecules of less than 3 nm in diameter. Permeability of the IEJs is determined by the adhesive properties of the proteins that comprise the tight junctions and adherens junctions. However, the junctional barrier is a dynamic structure. It responds to permeability-increasing agonists and migrating leukocytes with disassembly of IEJs and to barrier-stabilizing mediators by increasing the surface expression and adhesiveness of junctional proteins in order to strengthen IEJs. There are extensive reviews available on this topic.[49-51]

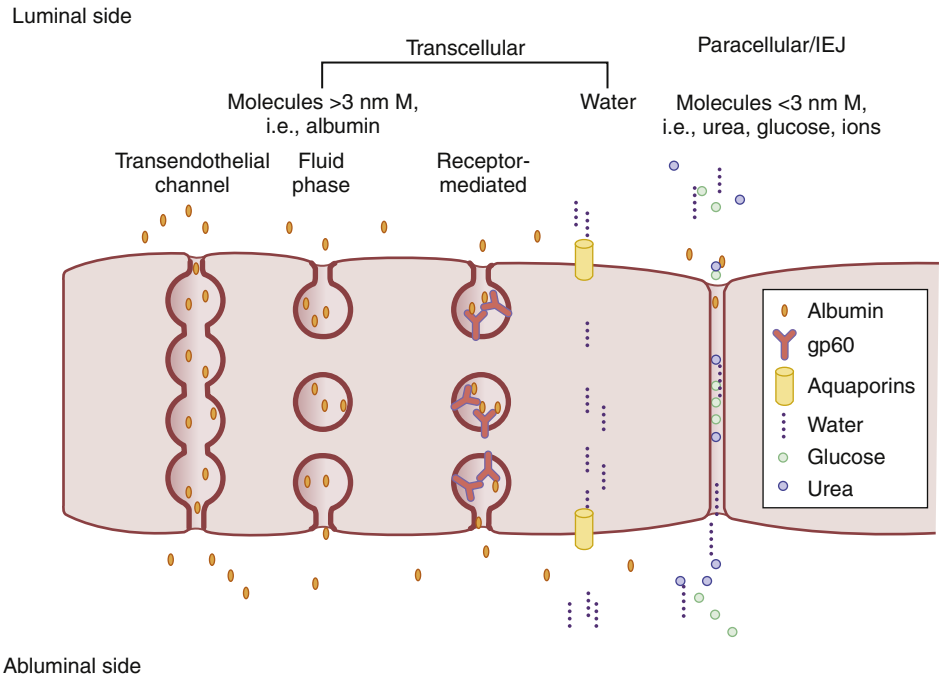

Figure 101–5. Schematic of transport pathways in continuous endothelium. Under basal conditions, the transcellular pathway can mediate the transport of plasma proteins (>3 nm Mr) such as albumin by caveolae via an absorptive (receptor-mediated) or fluid-phase pathway. Transcellular channels can also form transiently in endothelial cells by fusion of multiple caveolae and allow albumin transport. Aquaporins form channels across the lipid bilayer that are highly selective for water molecules and allow their movement across the luminal or abluminal endothelial membrane, thus creating a transendothelial pathway for water. Small molecules including urea and glucose (<3 nm Mr) are transported around individual endothelial cells via the paracellular, i.e., interendothelial junction (IEJ) pathway. *Mr*, Molecular radius. *(Modified from Mehta D, Malik AB: Signaling mechanisms regulating endothelial permeability,* Physiol Rev *86:279–367, 2006.)*

Endothelial Cell Dysfunction

Ischemia-Reperfusion Injury

Recently, it has become apparent that reperfusion of previously ischemic tissues can place the organs at risk for further cellular injury, thereby limiting the recovery of function. The microvasculature, particularly the endothelial cells, is very vulnerable to the deleterious consequences of ischemia and reperfusion (I/R). It is now recognized as a potentially serious problem that is encountered during a variety of standard medical and surgical procedures such as thrombolytic therapy, organ transplantation, and cardiopulmonary bypass.[52]

The molecular and biochemical changes in the vascular wall during I/R are characteristic of an acute inflammatory response (Figure 101-6). The intensity of this inflammatory response can be so severe that the injury response to reperfusion is also manifested in susceptible organs such as in the lungs and cardiovascular system. The resulting systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) are both associated with significant increases in mortality and morbidity.[53]

Microvascular dysfunction associated with I/R is manifested as impaired endothelium-dependent dilation in arterioles, enhanced fluid filtration, leukocyte plugging in capillaries, and the trafficking of leukocytes and plasma protein extravasation in postcapillary venules. During the initial period following reperfusion, activated endothelial cells in the microcirculation produce more oxygen radicals and less nitric oxide. The resulting imbalance between superoxide and nitric oxide in endothelial cells leads to the production and release of inflammatory mediators (e.g., platelet-activating factor, TNF-α) and

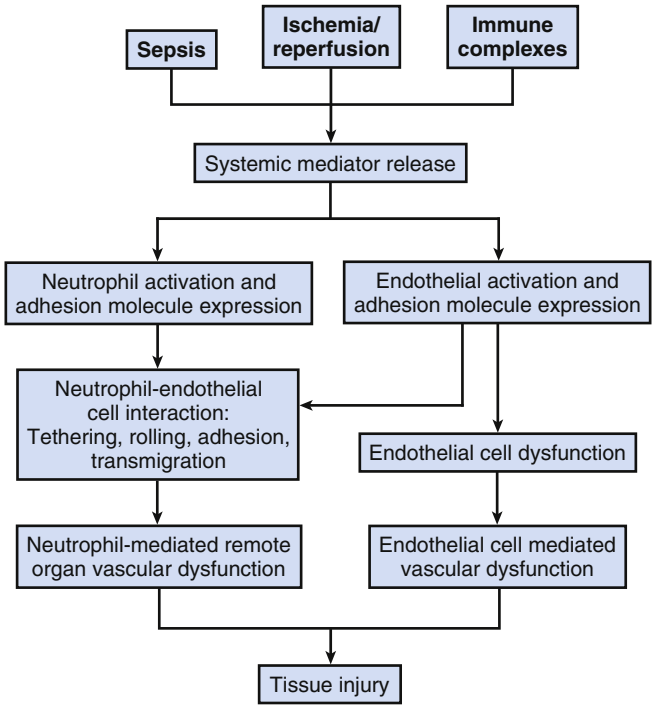

Figure 101–6. Mechanisms that underlie the development of local and remote organ injury following an initial inflammatory event. The activation of endothelial cells and circulating neutrophils lead to the expression and activation of adhesion molecules that facilitate neutrophil invasion of vascular beds, resulting in local and remote organ dysfunction.

enhances the biosynthesis of adhesion molecules that mediate leukocyte-endothelial cell adhesion.[53]

The inflammatory mediators released as a consequence of reperfusion also appear to activate endothelial cells in remote organs that are not exposed to the initial ischemic insult. Oxidants and activated leukocytes have been implicated as mediators of remote organ injury in I/R. This distant response to I/R can result in leukocyte-dependent microvascular injury that is characteristic of SIRS and MODS. The pulmonary damage associated with MODS can range from mild dysfunction as seen in acute lung injury (ALI), to severe failure as in acute respiratory distress syndrome (ARDS). The pulmonary injuries associated with ALI and ARDS include increased pulmonary microvascular permeability and the accumulation of neutrophil-rich alveolar fluid. Respiratory failure is often associated with cardiovascular, hepatic, gastrointestinal, and renal dysfunction as well as central nervous system involvement. MODS is associated with dysfunction of the coagulation cascade and the immune system, resulting in thrombosis, disseminated intravascular coagulation, and immunocompromise. The initiation of MODS may also lead to further tissue ischemia, resulting in further insult.[54]

Sepsis

Sepsis is a generalized systemic response to an infectious insult and manifests itself as SIRS (see Chapters 103 and 104). The clinical syndrome is characterized by a series of circulatory disturbances, including decreased vascular resistance and maldistribution of blood flow in association with impaired oxygen utilization. As a consequence, focal tissue hypoxia and cell injury soon follow the onset of sepsis. Despite aggressive volume resuscitation, systemic administration of antibiotics, vasopressors, and other sophisticated intensive-care measures, sepsis is frequently associated with multiple organ dysfunction and the death of the patient (see Chapter 104).

Although the pathophysiologic process of multiple organ dysfunction is multifactorial, one common feature is the dysfunction of the microcirculation, including the resistance arteries, capillaries, and postcapillary venules. The microcirculation cannot be considered a simple passive conduit. Rather it is a functionally active system of interactions between the vascular wall, circulating, and tissue-associated cells such as leukocytes, platelets, and mast cells, and extracellular mediators that contribute to the regulation of local, downstream, and upstream vascular tone. Sepsis is particularly associated with microvascular endothelial cell dysfunction leading to (1) the breakdown of endothelial barrier function, leading to tissue edema and uncontrolled inflammatory cell infiltration; (2) vasomotor dysfunction, leading to the formation of arteriovenous shunts in association with loss of peripheral resistance; and (3) disturbance of oxygen transport and utilization by tissue cells.[55]

Another major mechanism during sepsis is the change from anticoagulant to procoagulant and the contribution of microthrombi to the disturbance of the microcirculation. Lipopolysaccharide (LPS), an important pathogen product, is recognized by pathogen recognition receptors like toll-like receptors on cells of the innate immune system. This will lead to intracellular signaling and to the production of cytokines and other potent chemokines (see Chapter 90). Cytokines can upregulate tissue factor leading to (over)production of thrombin, downregulation of the protein C pathway, and an increase in PAI-1. The net result is increase in the production of fibrin, depression of the fibrinolysis, and, ultimately, increased microthrombi.

Septic shock is often associated with the loss of fluid from the intravascular into the extravascular space with the potential progressive loss of circulating blood, eventually leading to a depression of cardiac output. Similarly, loss of fluid into the extravascular space can lead to life-threatening edema in the lungs, kidney, and brain of septic patients. The loss of fluid is not believed to be associated with changes in hydrostatic and/or osmotic pressures within the vascular compartment, but rather to the breakdown of endothelial barrier function. The permeability of the vascular barrier can be modified in response to specific stimuli acting on endothelial cells. Many inflammatory agonists mediate endothelial hyperpermeability via a calcium-dependent mechanism. Multiple cascades of intracellular signaling reactions are initiated when an inflammatory agonist binds to its respective receptor expressed on the endothelial surface (e.g., thrombin binds the protease-activated receptor-1, histamine binds its receptor H1, and vascular endothelial growth factor binds its receptor VEGFR-2). This breakdown allows migration of water and macromolecules, including proteins, into the extravascular space. The pathophysiological mechanisms proposed include the separation of tight junctions between endothelial cells, as well as cytoskeleton contraction, rather than destructive changes of endothelial cells leading to defects in the endothelium.[49,56] In animal models of sepsis, a loss of vasoconstrictor response of resistance arterioles to catecholamines is observed and the vasorelaxing response to the microcirculatory segment is blunted. Although in vitro experiments demonstrate decreased biosynthesis of NO by endotoxin-exposed cultured endothelial cells, the overriding reaction with respect to NO synthesis is the upregulation of smooth muscle NO synthase. The ensuing overproduction of NO is the essential factor in the massive peripheral vasodilatation characteristic of the septic state. However, it has also been suggested that endotoxin-induced NO synthesis and consequently increased levels of NO in the septic organism decrease the sensitivity to the relaxing effect of acetylcholine. In septic rats, the vasoconstrictor response to a variety of vasopressor agents (vasopressin, endothelin, angiotensin) was attenuated. The microvascular response could be partially or completely restored by administration of inhibitors of NO, suggesting that NO plays a key role in mediating the vasomotor dysfunction in sepsis.[57]

Recent studies on the microcirculation of the gut have shown the development of a gap between microvascular and venous oxygen tension, suggesting enhanced shunting of the microcirculation. Defects in distributing blood to regional vascular beds or the microcirculation could be responsible for tissue hypoxia and limited oxygen extraction. Recent clinical evidence of decreased microvessel density in the sublingual microcirculation of fluid-resuscitated septic patients is consistent with findings of decreased functional capillary flow in the gut, liver, and skeletal muscle microcirculation in animal models of sepsis. This clinical finding raises the possibility that abnormal microvascular O_2 transport develops in multiple organs despite fluid resuscitation, leading to heterogeneous microvascular dysfunction and local tissue hypoxia in severe cases of sepsis.

Hemolytic-Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and the hemolytic-uremic syndrome (HUS) are related disorders characterized clinically by microangiopathic hemolytic anemia and thrombocytopenia. Pathologically, both conditions include the development of platelet microthrombi that occlude small arterioles and capillaries. Endothelial dysfunction plays a prominent role in the pathogenesis of both disorders. HUS commonly occurs in early childhood (approximately 90% of cases). It often follows an episode of bloody diarrhea caused by enteropathic strains of *Escherichia coli* that release an exotoxin, verotoxin-1 (VT-1) (see also Chapter 71). VT-1 binds with high affinity to receptors expressed in high density on renal glomerular endothelial cells. VT-1 is directly cytotoxic to endothelial cells where it promotes neutrophil-mediated endothelial cell injury. VT-1 induces the production of TNF-α by monocytes and cells within the kidney. In turn, TNF-α, in synergy with interleukin-1, increases VT-1 receptor expression and exacerbates the sensitivity of the endothelium to toxin-mediated and antibody-mediated cytotoxicity. It also promotes vWF release and impairs fibrinolytic activity.[58]

There is considerable evidence to suggest that endothelial cell injury plays a role in the pathogenesis of TTP. Platelet microthrombi in TTP contain abundant vWF but little fibrinogen, in contrast to those seen in disseminated intravascular coagulopathy. A subgroup of patients has been identified who suffer from chronic, relapsing TTP and whose plasma continues to contain elevated levels of unusually large vWF multimers (ULvWF) between relapses. ULvWFs may exacerbate microvascular thrombosis through their ability to aggregate platelets at high levels of shear stress. The secretion of ULvWF by cultured endothelial cells is stimulated by many agonists, including Shiga toxin. However, elevated levels of vWF occur in other thrombotic microangiopathies, and their exact role in TTP/HUS requires further study. Endothelial damage plays a pivotal role in the pathogenesis of the disease. The events that initiate TTP remain unknown. More recently, plasma from patients with TTP and HUS has been reported to induce apoptosis in microvascular endothelial cells. Interestingly, cells from dermal, renal, and cerebral origin were most susceptible, whereas pulmonary and coronary arterial cells were less susceptible.[59]

Vasculitic Disorders

Vasculitis is a disease that targets all levels of the arterial tree from aorta to capillaries, and also affects venules, with leukocyte infiltration and necrosis. Different forms of vasculitis attack different vessels and are classified accordingly. The inflammatory process may target vessels of any type throughout the vascular system, although distinct clinicopathological entities preferentially involve vessels of particular sizes and locations. Small vessels anywhere in the body may be affected by focal necrotizing lesions where extravasation of leukocytes drives the inflammatory responses, resulting in vasculitis. Leukocyte adhesion molecules participating in the interactions with endothelial cells belong to three major families: selectins, sialomucins, and integrins. Interestingly, it is recognized that these interactions participate in tissue specificity in various vasculitic conditions. For instance, specific selectin interactions mediate cutaneous tropism in several inflammatory disorders including graft-versus-host disease and dermatomyositis.[60]

Conclusions

The endothelium can no longer be viewed as a static physical barrier that simply separates the blood for tissue. Rather, the endothelium coordinates key functions of different tissues in normal and pathophysiological conditions. This is accomplished by the interaction of endothelial cells with circulating factors and cells and its ability to transmit biochemical and biophysical signals to surrounding tissues. Increasing understanding of endothelial physiology will lead to novel therapeutic approaches in complex clinical conditions.

References are available online at http://www.expertconsult.com.

Neuroendocrine–Immune Mediator Coordination and Disarray in Critical Illness

Kate Felmet and Joseph A. Carcillo

PEARLS

- Activation of the hypothalamic-pituitary-adrenal axis is normal during stress. Lack of activation in the acute setting causes many of the signs and symptoms of critical illness.
- Relative adrenal insufficiency should be suspected in any patient with catecholamine-resistant shock and in patients with prolonged critical illness.
- Lymphopenia and monocyte dysfunction occurs commonly in the intensive care unit and may result from unopposed immunosuppressive stress hormones.
- Dopamine use suppresses prolactin and growth hormone release and may suppress the immune system and anabolic pathways.
- Opioids used for analgesia may have immunosuppressive effects.
- The neuroendocrine state in prolonged critical illness differs from acute stress and may be dysfunctional.

Clinically relevant cross-talk occurs among the central nervous system, the endocrine system, and the immune system. For example, psychological stress leads to release of cortisol, a potent inhibitor of immune function, whereas immune activation initiates central nervous system pathways generating fever, pain sensation, and behaviors associated with recovery. These neuroendocrine-immune (NEI) interactions are relevant in critical illness. A normally functioning hypothalamic-pituitary-adrenal (HPA) axis, the primary efferent limb of the NEI system, is essential to surviving critical illness. Certain disease states such as septic shock are strongly associated with dysfunction of the NEI system. Drugs used to resuscitate shock, including catecholamines, vasopressin, and glucocorticoids, are mediators for the efferent limb of this system. Dopamine infusion profoundly affects release of the neuroendocrine products growth hormone and prolactin. Molecules of the afferent limb of the NEI system, primarily cytokines, have been targets for adjuvant therapies for severe sepsis.

This chapter distills a broad range of data from the fields of immunology, endocrinology, and neuroscience into clinically useful concepts. We provide a conceptual framework, building on the concept of the stress response and focusing on the best-understood aspects of neuroendocrine mediators and their relevance to critical care. The authors describe situations in which breakdown of the NEI system plays a role in the development of critical illness, and discuss situations in which physicians, using common intensive care unit (ICU) therapies, may inadvertently interfere with NEI function.

Organization of the Stress Response

The stress response has been considered an extension of the fight-or-flight response, which halts growth, digestion, and other daily activities in order to ready the body for immediate action. These signals, namely, activation of the sympathetic nervous system, the HPA axis, and endogenous opioids, are primarily antiinflammatory. If this were the whole of the stress response, then humans, after fleeing their aggressor or delivering their babies, would be left with disrupted epithelial barriers and a suppressed immune system. Modern science has shown that the stress response is a complex dynamic process that can be initiated by the immune system or the central nervous system.

Stress can be understood as any threat to an organism's homeostatic internal milieu. An organism must defend itself against two types of threats. Macroscopic threats, such as an encounter with a predator, an episode of hypotension, or a traumatic hemorrhage, threaten the whole organism at once. The central nervous system response to macroscopic threats has been recognized for decades. Microscopic threats attack epithelial and endothelial barriers that are essential to organ function. To maintain integrity against microscopic threats, the organism must be vigilant against microbial invasion in the face of the wear and tear of daily activities such as digestion, excretion, and procreation. The central stress response to macroscopic threats puts housekeeping on hold as the vital functions are marshaled against an assault. The response to microscopic threats is a matter of day-to-day housekeeping and is primarily the responsibility of the immune system. They are equally important and must balance each other; they are the yin and the yang of the response to stress.

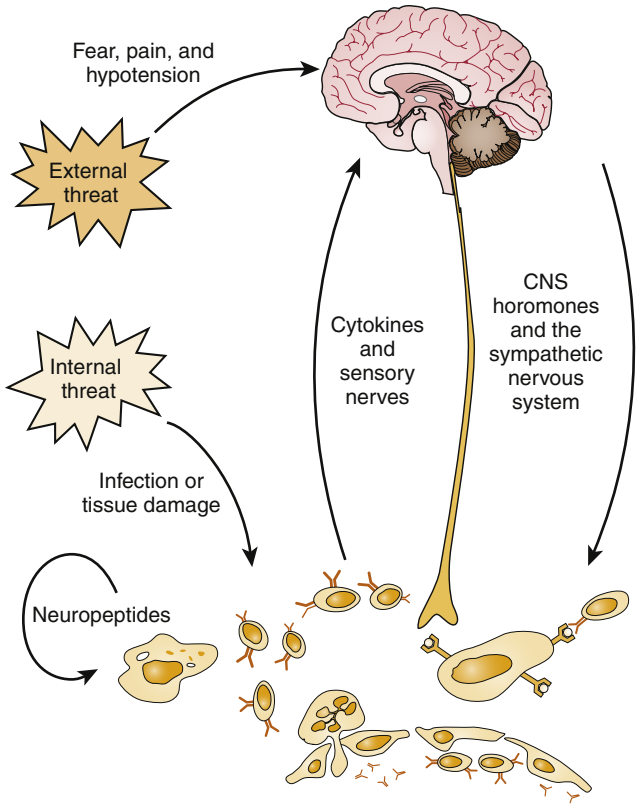

Figure 102–1. Neuroendocrine immune loop. Stimulation of the central stress axis generates immunosuppressive signals (activation of the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, endogenous opioids) and immunosupportive signals (release of proinflammatory peptides, e.g., vasopressin and prolactin). A threat to the homeostatic milieu, in the form of trauma or infection, activates the immune system. Activated immune cells produce cytokines such as tumor necrosis factor-α, interleukin-1, and interleukin-6, which in turn activate the central stress response. Some immune cells produce neuropeptide hormones for autocrine or paracrine action. *CNS,* Central nervous system.

Central Stress Response

All types of stress—physical, emotional, or immune—cause stimulation of the sympathetic nervous system, activation of the HPA axis, and release of hypothalamic hormones, including vasopressin, prolactin, and growth hormone (Figure 102-1). The HPA system is the major humoral coordinator of the central stress response (see Chapter 77). Hypothalamic release of corticotropin-releasing hormone occurs in response to cortical signals generated by fear, pain, or hypotension, as well as in response to immune-derived signal molecules, especially interleukin (IL-1β), tumor necrosis factor (TNF-α), and IL-6.[1] Corticotropin-releasing hormone in the brain stimulates sympathetic outflow and causes release of adrenocorticotropic hormone (ACTH) by the pituitary. Vasopressin, that is also released in response to immune signals and stress, is powerfully synergistic with corticotropin-releasing hormone in promoting ACTH secretion.[2] Circulating ACTH reaches the adrenal cortex, where it stimulates conversion of cholesterol to the steroid hormone cortisol. Cortisol release suppresses further ACTH secretion within minutes and more slowly feeds back to suppress secretion of corticotropin-releasing hormone.[3] Cortisol and its synthetic analogues, the glucocorticoids, act in tandem with the sympathetic nervous system to prepare a body for action by putting growth and housekeeping functions on hold, making fuel substrates available, and supporting blood pressure and intravascular volume. Failure of this normal stress response leads to cardiovascular collapse.

Cortisol inhibits growth in all tissues, decreases deoxyribonucleic acid and ribonucleic acid synthesis, and increases protein catabolism, except in the liver, where protein synthesis is enhanced. Cortisol increases the availability of glucose, amino acids, and free fatty acids for immediate use. Cortisol increases vascular tone and increases expression of adrenergic receptors, potentiating the vasoconstrictive action of catecholamines. Cortisol also regulates the distribution of total body water. It activates the renin-angiotensin system, causing hypertension, and is necessary for secretion of a water load.[3] In suppressing the body's maintenance functions, cortisol suppresses immune responses. Cortisol reduces circulating numbers of lymphocytes, monocytes, and eosinophils by stimulating apoptosis. It stabilizes lysosomal membranes, decreases capillary permeability, impairs demargination of white blood cells and phagocytosis, and decreases release of IL-1, preventing fever. Cortisol supports a T_H2 (humoral immunity) over a T_H1 (cellular immunity) phenotype.[3]

Activation of the sympathetic nervous system complements the actions of cortisol. The impact of sympathetic nervous system stimulation on the immune system is complex and imperfectly understood and is discussed later in this chapter. The parasympathetic limb of the autonomic nervous system plays an important role in regulating the immune response. Fibers from the vagus nerve innervate liver macrophages, called *Kupffer cells,* as well as other abdominal lymphoid organs. Efferent signaling from the vagus nerve decreases the production of inflammatory cytokines by Kupffer cells, macrophages, and other cytokine producing cells, an effect that has been termed the *cholinergic antiinflammatory pathway.*[4] This pathway may be a protective mechanism that blunts the response to sterile endotoxin translocation from the gut. Alternatively, parasympathetic activation may complement the stress response in restraining the magnitude of an inflammatory response to real infection.

In the short term, the immunosuppressive effects of the central stress response may be allowed to predominate, but once the acute danger has passed, the ability to fight infection must be restored and even potentiated. Release of prolactin, growth hormone, vasopressin, and substance P into the bloodstream occurs in tandem with HPA and sympathetic nervous system activation. By binding to specific receptors on immune cells, these peptide hormones function as counter-regulatory mechanisms to the immunosuppressive limb of the stress response.

Prolactin and growth hormone share structural homology with each other and with the immune-derived cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, and IL-7.[5,6] Together these hormones support immune response by stimulating cytokine expression, antibody production, and clonal expansion of lymphocytes. Prolactin and growth hormone directly oppose the lymphocyte apoptosis promoted by cortisol. Growth hormone also affects metabolism, which may be important in critical illness. The overall impact of vasopressin on the immune system is less well understood, but its function in direct interaction with lymphocytes appears to be supportive.

Immune Response to Microscopic Threats

The immune system is a sensory organ that allows early recognition of, and response to, microscopic threats. Day-to-day activities result in wear and tear on epithelial barriers, leading to microbial and other nonself invasion. These peripheral stressors initiate a cascade of molecules and activated cells that amplify the initial signal and stimulate the central stress response. The central stress response, in turn, downregulates and eventually terminates the immune response.

Inflammation and phagocytic cells comprise the first line of defense and recognition. Tissue damage caused by microbial invasion or trauma initiates the nonspecific cascade called the inflammatory response (see Chapters 90 and 91). It leads to vasodilatation, increased capillary permeability, and an influx of phagocytes. Histamine and kinins are important mediators of the inflammatory response. Phagocytic cells may be blood monocytes, neutrophils, or tissue macrophages. Macrophages engulf foreign matter and bacteria, break them down into large molecules, and present these as antigens to T lymphocytes, thus activating the specific adaptive immune response.

Phagocytic cells also produce proinflammatory cytokines, primarily IL-1, IL-6, and TNF-α, which amplify the immune response locally. Cytokines help determine whether the specific immune response takes on a T_H1 or T_H2 phenotype. Cytokines carry messages between different cell types within the immune system and between the immune system and other organ systems. In the latter role, they are thought to comprise the most important afferent limb of the NEI system. Cytokines circulating in the bloodstream reach the central nervous system, where receptors for IL-1α and IL-1β, IL-2, IL-4, IL-6, TNF-α, and interferon (IFN-γ) are found. Afferent nerves also carry inflammatory signals to the brain. When stimulated by cytokines and endotoxin, signals from the vagus lead to HPA axis activation.[7]

Binding of cytokines to their specific receptors in the brain can activate the full spectrum of the central stress response, including release of corticotropin-releasing hormone and other hypothalamic hormones, activation of the sympathetic nervous system, and release of endogenous opioids from the hindbrain and spinal cord. Hypothalamic hormones lead to release of effector molecules such as cortisol and insulin-like growth factor. In general, hypothalamic hormones such as prolactin and growth hormone support the immune response, whereas corticotropin-releasing hormone, ACTH, and cortisol suppress the immune response. NEI mediators also may play a role in determining the predominance of a T_H1 or T_H2 phenotype.

Interestingly, neuroendocrine mediators that trigger the antiinflammatory cascade in the central nervous system, such as vasopressin and corticotropin-releasing hormone, may have the opposite effect when they are released in tissues. Both corticotropin-releasing hormone and vasopressin are clearly immunosupportive in peripheral tissues. Corticotropin-releasing hormone is found in high concentrations at inflammatory sites, although plasma levels may be undetectable.[8,9] Corticotropin-releasing hormone augments T-lymphocyte proliferation and IL-2 expression in vitro, augments cytokine expression by macrophages, and triggers mast cell degranulation.[8,10] Immunoneutralization of corticotropin-releasing hormone decreases inflammation as effectively as neutralizing antibodies to TNF-α.

The normal pathways that lead to increased local concentrations of hypothalamic hormones and their clinical relevance in peripheral tissues are not completely understood. Corticotropin-releasing hormone is a neurotransmitter of postganglionic sympathetic nerves, some of which innervate lymphoid organs and may be a mediator of autonomic control of inflammation. In some cases, immune cells actually secrete neuropeptides for autocrine or paracrine action. Immune cell secretion of neurotransmitters may affect peripheral nerve activity and may represent a second method by which the immune system alerts the central nervous system to the presence of microbial invasion.

Acute Versus Chronic Stress

The body's response to stress has been studied mostly as an acute event occurring in normal healthy people. Through the use of advanced therapies and machines, we have created in the modern ICU a state of prolonged critical illness that does not exist in nature and to which the neuroendocrine system must adapt. The state of prolonged stress is not well understood, but the hormonal milieu that exists and which we intentionally create in the acute phase of resuscitation—that of catecholamine and cortisol excess—likely will not be appropriate later. In chronic critical illness, the excess of ACTH, prolactin, growth hormone, and thyroid hormone observed initially is reversed, and the normal pulsatile pattern of pituitary hormones is diminished or lost.[11] It is unclear whether this represents a beneficial adaptation to critical illness or an unrecognized organ failure.

The neuroendocrine system in critically ill patients cannot be judged by reference to established norms. It may not be possible to know what levels of these hormones are "natural." In studying the NEI system in critical illness, the appropriate hormone level is that associated with the best outcome. In the future, dysfunction of the NEI system that occurs in prolonged critical illness may be recognizable as an organ failure and part of the multiple organ dysfunction complex.

Neuroendocrine–Immune Dysfunction Causing Critical Illness

Some categories of critical illness are caused by dysfunction of the NEI system. Breakdown of the central stress response leads to a shock state. The most obvious example is the autonomic instability associated with spinal shock. Complete adrenal failure with breakdown of the HPA axis causes shock, but this phenomenon is relatively rare. More important to critical care is the syndrome of critical illness–related corticosteroid insufficiency. An acquired, reversible adrenal insufficiency can occur in any critically ill patient but is particularly associated with sepsis and septic shock. A syndrome of inadequate circulating vasopressin also has been implicated in the pathogenesis of shock, particularly vasodilatory or warm shock.

Hypothalamic-Pituitary-Adrenal Axis

In general, critically ill patients have elevated cortisol levels that correspond to the severity of illness. In the acute phase of critical illness, adequate cortisol is necessary for maintenance

of vascular tone and normal catecholamine responsiveness.[12] In some critically ill patients, cortisol levels may be inadequate for their degree of illness or inadequate relative to the ACTH levels measured in their blood. The incidence of relative adrenal insufficiency varies according to author and definition criteria. The reported incidence ranges from 0% to 75% and is higher in patients with septic shock than other ICU patients. Relative adrenal insufficiency is associated with poor outcomes in adults and children.[13,14]

During the prolonged phase of critical illness, the normal association between ACTH and cortisol often is strikingly reversed. In the face of ongoing stress, cortisol levels in critically ill patients tend to remain elevated despite a decline in ACTH levels.[15] Sustained cortisol production may result from direct autonomic innervation of steroidogenic cells, paracrine action of the products of the adrenal medulla, or the action of cytokines, which can directly stimulate cortisol production.[16-18] Decreased cortisol clearance by the liver may contribute to elevated cortisol levels in prolonged critical illness.[15]

Adrenal insufficiency should be suspected in any patient with catecholamine-resistant shock and in patients with prolonged critical illness. Pathologic scenarios that may produce relative or absolute adrenal insufficiency include suppression of corticotropin-releasing hormone or ACTH secretion, adrenal unresponsiveness, increased cortisol clearance, or end-organ unresponsiveness to cortisol (Table 102-1). For a thorough discussion of the causes of relative adrenal insufficiency, the reader is referred to the excellent review by Beishuizen and Thijs.[19]

Defining what constitutes a normal cortisol response to critical illness is difficult because the range of cortisol levels observed in critically ill patients is so broad, varying from the healthy normal level to 20 times normal. Additionally, measured cortisol levels may overestimate biologically active free cortisol in the acute phase of critical illness because levels of cortisol-binding globulin are low.[20,21] Most authors agree that a "normal" level of cortisol in the face of shock probably is inadequate.[19]

The ACTH stimulation test can be used to identify absolute adrenal failure but may fail to identify a clinically significant adrenal insufficiency. The ACTH dose used in the standard test (250 mg for adults and children older than 2 years, 125 mg for children younger than 2 years) produces plasma ACTH levels 100 to 200 times the physiologic maximum stress levels of ACTH. A 1-mg test has been suggested but has not been standardized for adults or children. Beishuizen et al.[22] demonstrated that patients with a normal response to the standard test but an inadequate response to the 1-mg test improved clinically with decreased pressor requirement in response to hydrocortisone treatment. In adult patients with septic shock, a random cortisol level less than 25 μg/dL was a better predictor of a hemodynamic response to hydrocortisone than either the 1-mg or the 250-mg ACTH stimulation test.[23] Most recently, in a study of 30 children with septic shock, a change in cortisol of greater than 9 μg/dL in response to a 1 mg ACTH stimulation test identified patients at increased risk of catecholamine refractory shock but not increased risk of mortality.[24]

Standard reference ranges for normal healthy subjects accept minimum peak values after ACTH stimulation of 18 to 22 mg/dL (500-600 nmol/L) or a minimum change in cortisol level of 7 to 9 mg/dL (200-250 nmol/L). Failure according to these requirements is associated with a high 28-day mortality in adults.[13] ACTH stimulation tests should be interpreted in light of the basal cortisol level, because the change in serum cortisol after ACTH stimulation is a measure of adrenal reserve.

It may be impossible to rely on results of an ACTH stimulation test in the acute setting of severe catecholamine-unresponsive shock, when time is of the essence. Because the criteria for diagnosis of relative adrenal insufficiency in the critical care setting are imprecise, some authors believe a negative or inconclusive result should not prohibit use of glucocorticoids. Instead, a rapid hemodynamic response to glucocorticoids may be the best clue to the diagnosis of relative adrenal insufficiency. One author suggests that, at present, we have no choice but to rely on clinical assessment of the severity of stress and make "an educated guess of the adequacy of the measured serum cortisol concentration."[21]

Table 102–1 Causes of Adrenal Insufficiency

Nervous System	Condition	Comments
Central	Hypothalamic or pituitary disease	
	Brain injury	
	Recent steroid use	Follows the "rule of ones": 1 day of steroid use may suppress adrenal function for 1 week; 1 week for 1 month; 1 month for 1 year
Peripheral	Preexisting adrenal failure	Associated with increased pigmentation, hypoglycemia, mild hyponatremia, and hyperkalemia
	Acute adrenal failure	Adrenal hemorrhage or autoimmune adrenalitis
	Inadequate substrate	Low cholesterol[48]
	P450 impairment	From ketoconazole, etomidate, sepsis, prematurity, or age <6 months[77-79]
	Increased clearance	Occurs with rifampin, phenytoin, and phenobarbital[80]
	End-organ unresponsiveness	Cytokines can change glucocorticoid receptor sensitivity[19,80]
Other	Sepsis/inflammation	Circulating inflammatory mediators can cause hypothalamic-pituitary-adrenal axis suppression, particularly in patients with fungal infection or human immunodeficiency virus[18]

Although several studies on administration of pure glucocorticoids to septic shock patients have failed to demonstrate a survival advantage, the use of steroids with both glucocorticoid and mineralocorticoid activity has shown some benefit.[26,27] Annane et al.[25] reported a large, prospective, placebo-controlled, randomized clinical trial in adults with septic shock, demonstrating that treatment with hydrocortisone (50 mg every 6 hours) and fludrocortisone (50 mg/day) decreased 28-day mortality in all patients. Most of the survival benefit was seen in patients in whom relative adrenal insufficiency was identified by standard-dose corticotropin stimulation test with change in stimulated minus baseline cortisol response of less than 9 μg/dL.[25] A large, international, multicenter trial (CORTICUS trial) investigating this effect found that hydrocortisone given without fludrocortisone hastened resolution of shock but had no impact on mortality.[28] A high percentage of patients in the Annane study were treated with etomidate, an inhibitor of the cytochrome P-450 enzymes responsible for the final step in cortisol synthesis. An *a priori* subgroup analysis of the patients in the CORTICUS trial who received etomidate for intubation found an increased risk of adrenal insufficiency and mortality in these patients. Treatment with hydrocortisone did not change the mortality of patients who received etomidate.[29]

A recent meta-analysis of clinical trials of steroids in septic shock concluded that low-dose long-duration corticosteroids may have an advantage over high doses and shorter duration.[30] Current recommendations for adult sepsis recommend use of low-dose steroids (<300 mg/day of hydrocortisone) for shock that is resistant to fluid resuscitation and catecholamines, without use of the ACTH stimulation test.[31,32] An excellent historical review of the use of steroids for septic shock reminds us that there is still need for clinical equipoise on the use of steroids for septic shock in children.[33] At present, the American College of Critical Care Medicine clinical practice parameters for the hemodynamic support of pediatric and neonatal septic shock recommend the use of hydrocortisone in patients with catecholamine resistance and suspected adrenal insufficiency. Risk factors that should alert the clinician to high risk for adrenal insufficiency include physical examination findings suggestive of absolute adrenal insufficiency, disseminated intravascular coagulation or purpura fulminans, and history of steroid use. The authors would add to this list a history of prolonged stress (i.e., decompensation in a patient during a long ICU stay), severe septic shock, and risk of P-450 impairment as a result of drugs and extreme youth.

The physiologic replacement dose of hydrocortisone is 12.5 mg/m^2/day. In critical illness, dosing ranges from 50 mg/m^2/day in stress states to 50 mg/kg/day in severe shock have been reported, although dosing greater than 300 mg/day of hydrocortisone equivalent is associated with worse outcomes.[31,32] Hydrocortisone has a short half-life and should be given as a bolus, followed by continuous infusion or dosing every 6 hours as per most recent interventional trials. Although critically ill patients may receive steroids for a variety of indications, steroids that lack mineralocorticoid activity may not be sufficient for adrenal replacement in shock. Table 102-2 gives a comparison of the relative glucocorticoid and mineralocorticoid potency of steroids commonly used in the ICU. Glucocorticoids given over a prolonged period are associated with an increased risk for superinfection, gastrointestinal bleeding, hyperglycemia, polyneuropathy of critical illness, and prolonged adrenal insufficiency. Exogenous hydrocortisone should be tapered or discontinued as soon as hemodynamics allow.

Table 102–2 Comparison of Common Corticosteroid Dosing

Dosage	Glucocorticoid Potency (as Hydrocortisone Equivalent Dose)	Mineralocorticoid Potency
Stress dose hydrocortisone: 50 mg/m^2/day	Approximately 2 mg/kg/day	++
Shock dose hydrocortisone: 50 mg/kg/day	50 mg/kg/day	++
Annane study[3]: hydrocortisone 50 mg q6h and fludrocortisone 50 mg/day	Approximately. 3 mg/kg/day	++++
Dexamethasone for postextubation stridor: 0.5 mg/kg q8h	35 mg/kg/day	0
Methylprednisolone in severe asthma: 1 mg/kg q6h	20 mg/kg/day	0
Methylprednisolone in spinal cord injury: 30 mg/kg load followed by 5.4 mg/kg/h over 23 hours	770 mg/kg/day	0

Vasopressin

Vasopressin is a hormone of the posterior pituitary that is secreted in response to high serum osmolarity. Excitation of atrial stretch receptors inhibits vasopressin secretion. Vasopressin is also released in response to stress, inflammatory signals, and some medications. Hypotension, morphine, nicotine, angiotensin II, glucocorticoids, and IL-6 all stimulate release of vasopressin.[2] Circulating vasopressin levels are usually high in the early phase of septic shock, but vasopressin deficiency as been described in vasodilatory shock states in both adults and children.[34,35] The level of vasopressin that is normal in the late phase of sepsis is unclear.[36]

In general, vasopressin decreases water excretion by the kidneys by increasing water reabsorption in the collecting ducts, hence its other name of antidiuretic hormone. Vasopressin also has a potent constricting effect on arterioles throughout the body.[6] Vasopressin potentiates ACTH release leading to cortisol release, which may contribute to its salutary effects in cardiac arrest and vasodilatory shock.[2] Vasopressin has been proposed as a replacement or adjunct to epinephrine in the resuscitation of cardiac arrest and of catecholamine-unresponsive shock. The interest in vasopressin for resuscitation is based on the fact that vasopressin may increase coronary perfusion without increasing myocardial oxygen demand and without the arrhythmogenic effects of epinephrine. Also, repeated doses of vasopressin tend to support blood pressure after the epinephrine response wanes.[37] When given as the first drug in cardiac arrest, vasopressin has been shown to confer a survival advantage in out-of-hospital arrest but not in arrests occurring in stressed, hospitalized patients.[38,39] Vasopressin's

effects on NEI mediators may explain this discrepancy. In a person with normal adrenal reserves of cortisol, exogenous vasopressin may cause a surge of endogenous cortisol, which should improve catecholamine responsiveness. Hospitalized patients with decreased adrenal reserves may not experience this benefit of vasopressin.

Vasopressin is a powerful vasoconstrictor, even in patients with catecholamine unresponsiveness. Because vasopressin dilates the pulmonary, cerebral, and myocardial circulations, it may help to preserve vital organ blood flow. Vasopressin and its synthetic analogue, terlipressin, have also been used as a rescue therapy for severe shock. Case series of the use of vasopressin in patients with catecholamine refractory shock have described the use of doses in the range of 0.00001 to 0.08 units/kg/min.[40-43] Vasopressin has also been used as a catecholamine-sparing hormone replacement, with a goal of restoring high-normal levels rather than titrating to clinical effect. A recent, large, randomized controlled trial of low-dose vasopressin infusion in adult patients found a good safety profile but no impact on mortality when compared with norepinephrine alone.[44] The only pediatric randomized controlled trial so far showed used a dose of 0.0005 units/kg/min, similar to adult trials, and found an increase in mean arterial pressure but no differences in time to hemodynamic stability or other clinical outcomes.[45]

High doses of vasopressin are associated with unacceptable side effects, such as gut and digital ischemia and decreased urine output. However, several small clinical studies have suggested that these problems do not occur at physiologic doses.

Vasopressin has effects on the immune system independent of its effect in stimulating the HPA axis. When given intraventricularly to rats, vasopressin decreases the T-cell response to mitogen independently of the HPA axis, probably via the sympathetic nervous system.[46] Like CRH, vasopressin stimulates immune responses in peripheral tissues. Circulating or local vasopressin enhances lymphocyte reactions and potentiates primary antibody responses.[47] Elevated vasopressin levels are found in a mouse model of autoimmune disease, and antibody neutralization ameliorates the inflammatory response in these mice.[2] Vasopressin can potentiate the release of prolactin, a proinflammatory peptide hormone.[48]

Because vasopressin has immunosuppressive effects when present in the central nervous system and immunosupportive effects when present in peripheral tissues, predicting which effect would predominate during vasopressin infusion in the ICU is difficult.

Intensive Care Unit Therapies That Interfere with the Neuroendocrine–Immune System

The NEI system is so crucial in the maintenance of blood pressure that the most powerful therapies available to resuscitate shock are analogues of naturally occurring NEI mediators. Catecholamines, glucocorticoids, vasopressin, and somatostatin are all hormonal therapies. These molecules are often used without a full understanding of the role they play in the balance between promoting and suppressing immune responses. The incidental effect of most of these therapies is immune suppression (Figure 102-2 and Table 102-3). Prolactin and growth hormone, the NEI mediators that counterbalance the immunosuppressive effect, are particularly subject to suppression by catecholamines, especially dopamine. A prolonged imbalance between the immunosuppressive and immunosupportive elements of the NEI system can lead to development of lymphopenia, which in turn is associated with considerable morbidity and mortality.[49]

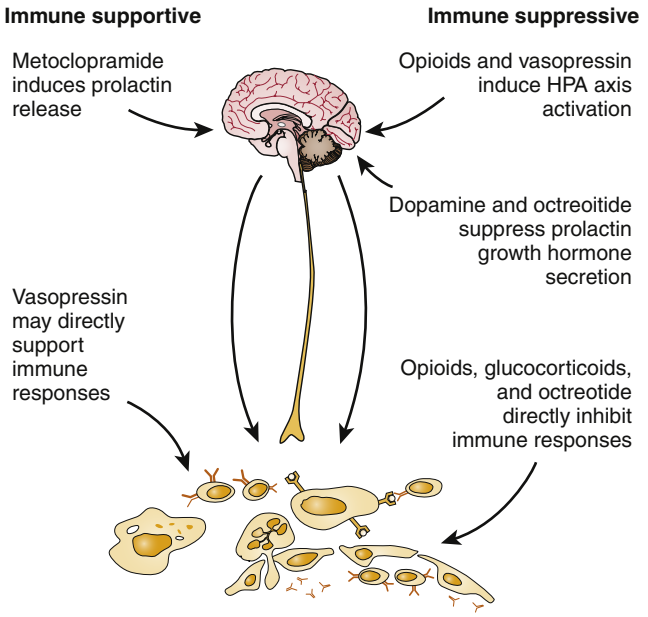

Figure 102–2. Neuroendocrine-immune impact of commonly used intensive care unit (ICU) therapies. Common drug infusions in the ICU influence immune function by altering neuroendocrine secretory activity and by binding to immune cells directly. Opioids and vasopressin activate the hypothalamic-pituitary-adrenal *(HPA)* axis, leading to cortisol release. Dopamine and octreotide block the release of the immunosupportive hormones prolactin and growth hormone. Opioids and octreotide have direct effects on immune cells, decreasing lymphocyte proliferation, primary antibody responses, and monocyte and macrophage function. All of these effects are immunosuppressive. Only vasopressin in the periphery, which supports lymphocyte function, and metoclopramide, which induces prolactin release, are immunosupportive.

Catecholamines and Autonomic Control of Inflammation

Catecholamines are the most important immediate effector molecules of the fight-or-flight response. These drugs impact the NEI system by directly influencing immune responses and by altering the release of other NEI mediators. Norepinephrine is the primary effector molecule for the sympathetic nervous system. Epinephrine is secreted into the bloodstream by the adrenal gland in response to sympathetic nervous system activation. Together they regulate cardiovascular and respiratory function, smooth muscle contraction, and secretions. Like cortisol, they put the housekeeping functions of the body, including digestion, growth, and reproduction, on hold in favor of blood pressure support and mobilization of fuel substrates.[6]

The sympathetic nervous system innervates the immune system. Bone marrow, thymus, spleen, lymph nodes, and gut-associated lymphoid tissue receive adrenergic, dopaminergic,

Table 102–3 Summary of the Effects of Neuroendocrine–Immune Mediators on Immune Cell Types

	T-Cell Proliferation and Cytokine Release	B-Cell Antibody Production	Monocyte Activation	Natural Killer Cell Function	Macrophage Function and Cytokine Release	Neutrophil Chemotaxis
Circulating catecholamines	–	–	±			
Dopamine	–	–	–	–	–	
Prolactin	+	+	+	+	+	?
Opioids	–	–	–		–	
Somatostatin	–	?	?			
Hypothalamic-pituitary-adrenal axis/cortisol	–	–	–		–	–
Vasopressin peripheral	+	+				
CRH peripheral	+				+	

and peptidergic input.[49] T cells and other immune cells have β-adrenergic receptors, as well as specific receptors for dopamine and a variety of neuropeptides (acetylcholine, substance P, neuropeptide Y, somatostatin, prolactin).[34] Sympathetic nerve terminals are in direct apposition to T cells, B cells, and dendritic cells. During development, immune-derived neurotrophic factors may direct the growth of innervating fibers.[50]

The effects of catecholamines on the immune system are complex. Catecholamines increase the production of some proinflammatory cytokines and increase the number of circulating lymphocytes and natural killer (NK) cells.[51] Adrenergic receptor activation inhibits neutrophil function, decreases mitogen-induced T-cell proliferation and decreases both IL-2 production and IL-2R expression on T cells.

The overall impact of sympathetic nervous system activation on immune responses may depend partly on its inhibitory effect on the cholinergic antiinflammatory pathway. Although this pathway is incompletely understood, it is clear that both vagal nerve stimulation and systemically administered agonists to the nicotinic cholinergic receptor attenuate inflammatory cytokine release and organ damage and improve survival in animal models of sepsis.[4] In humans, there is a significant correlation between depressed vagus nerve activity and increased morbidity and mortality in inflammatory states.[52] For a review of the current understanding of the choinergic antiinflammatory pathway, the reader is referred to the recent review by Rosas and colleagues.[4]

The degree to which circulating catecholamines given in the ICU can mimic the effects of sympathetic outflow is unclear. Of more certainty is that catecholamines in pharmacologic dose impact the release of other NEI mediators in vivo. Dopamine has a powerful inhibitory effect on release of the proinflammatory mediator prolactin and has been shown to decrease lymphocyte proliferation.[53,54] Dopamine inhibits pulsatile release of growth hormone, thus contributing to the catabolic state observed in critical illness.[54] Other catecholamines have similar effects, albeit to a much lesser degree.

Growth and Lactogenic Hormone Family

Prolactin

Prolactin is a hormone produced by anterior pituitary cells and lymphocytes that has been shown to have immunoregulatory function. It is best known for its role in promoting milk secretion. Although it is produced in both sexes, prolactin levels are highest in lactating mothers and newborns. Prolactin release is stimulated by suckling, IL-1β, IL-2, IL-6, oxytocin, serotonin, and thyrotropin-releasing hormone. A prolactin secretory response to psychological and physical stress is reported.[5,55,56] In the normal state, prolactin secretion is tonically inhibited by hypothalamic dopamine.

Prolactin may be the most important counterbalance to the immunosuppressive effects of the central stress response. Prolactin supports circulating lymphocyte numbers as a necessary cofactor for IL-2 and mitogen-stimulated proliferation[5] and by opposing glucocorticoid-induced apoptosis.[57] Prolactin increases IL-2 production by T cells and is necessary for expression of the IL-2 receptor. Prolactin increases antibody production by B cells and increases cytokine release capacity of macrophages and NK cells.[5]

Disturbances of prolactin have clinically significant effects on immune function. Prolactin levels are increased in some autoimmune diseases and in association with episodes of organ rejection.[58] The immunosuppressive drug cyclosporine exerts its effect through the prolactin receptor on lymphocytes.[59] Bromocriptine, an oral agent that prevents prolactin release, has shown promise in the treatment of autoimmune disease and in animal models of organ transplantation.[60] Prolactin levels are suppressed in critically ill patients in response to hemorrhage.[61,62] Hemorrhage has been associated with lymphopenia, decreased T-cell proliferative response, and increased risk of sepsis and multiple organ failure.[61] Prolactin administration has been shown to improve cytokine release and survival in posthemorrhage mice subjected to the cecal ligation and puncture experimental model of sepsis.

Pituitary prolactin production is strongly inhibited by exogenous dopamine at doses as low as 1 μg/kg/min.

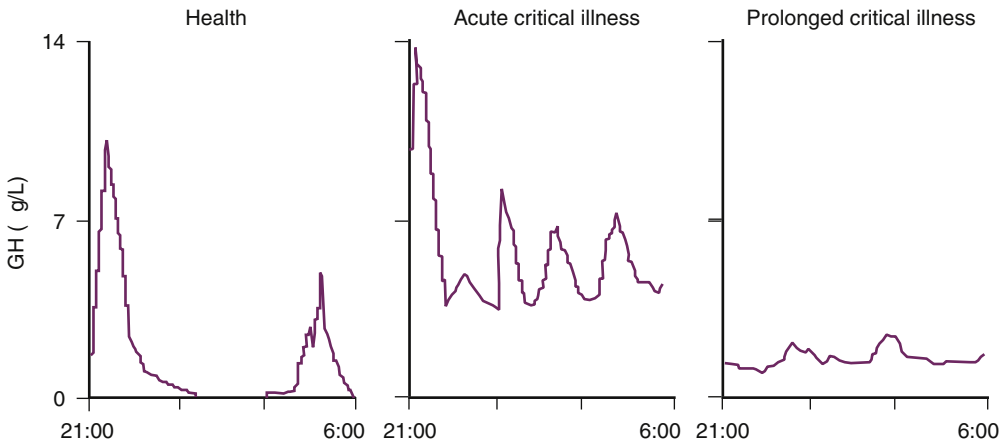

Figure 102–3. Secretion profile of growth hormone in health and illness. A healthy person has robust, predictable nocturnal growth hormone release. In the acute phase of critical illness, both peak levels and interpulse levels are significantly elevated. In prolonged critical illness, growth hormone secretion becomes chaotic, and the mean growth hormone levels are decreased. *(Modified from Van den Berghe G: The neuroendocrine response to stress is a dynamic process,* Best Pract Res Clin Endocrinol Metab *15:407, 2001.)*

Dopamine-associated hypoprolactinemia has been associated with decreased T-cell response to mitogen *ex vivo*, decreased circulating lymphocyte numbers, and increased risk of secondary infection in the ICU.[53,63] Adrenergic agents other than dopamine have a similar, albeit much less potent, effect on prolactin release. Prolactin release may be inadvertently inhibited by somatostatin, serotonin, corticosteroids, and histamine (H_1) blockers. Metoclopramide and vasopressin increase pituitary prolactin release.[55]

Given that prolactin is one of the few antagonists to the overwhelmingly immunosuppressive effects of the stress response, use of therapies that inhibit its release, particularly dopamine, should be carefully considered. Recombinant human prolactin may have therapeutic potential to reverse lymphopenia observed in the ICU and to speed hematopoietic reconstitution after bone marrow transplant.[64]

Growth Hormone and Insulin-like Growth Factor

Growth hormone is a large peptide hormone produced by the anterior pituitary. It is structurally similar to prolactin. Like prolactin, growth hormone has immune stimulatory effects and is suppressed by catecholamines.[65] In states of health, growth hormone increases protein synthesis, gene transcription, and the size and mitosis of somatic cells. It decreases glucose uptake and utilization and promotes differentiation. Growth hormone induces liver production of insulin-like growth factor-1, which mediates many of the effects of growth hormone.[6]

Growth hormone supports the immune response. Animal models suggest an important role for growth hormone in the development of the immune system. In growth hormone–deficient humans, growth hormone increases the differentiation of B-cell and NK-cell activity. Growth hormone increases IL-2 production by lymphocytes and increases IL-1, TNF-α, and superoxide production by monocytes in animal models and in growth hormone-deficient subjects.[58,65] Growth hormone also improves phagocytic cell function. Like prolactin, growth hormone is produced by cells throughout the immune system.[65]

The hypercatabolic state seen in critically ill patients has been attributed in part to growth hormone dysfunction. Trauma, sepsis, and surgery are thought to induce a state of growth hormone resistance.[64,66] Dopamine infusion and prolonged critical illness are associated with lower mean levels of growth hormone and a pronounced flattening in the normal pattern of pulsatile growth hormone release[54,66] (Figure 102-3). The hyperglycemic catabolic state induced by growth hormone depletion and resistance is compounded by the normal stress response, the effects of immune-derived cytokines, and inadequate calorie delivery in the ICU.[67] Use of exogenous growth hormone to preserve muscle and improve healing has received some interest. Administering growth hormone perioperatively improves nitrogen balance, increases liver protein synthesis, increases muscle strength and lean body mass, and decreases postoperative fatigue over controls. Growth hormone also increases the rate of healing in burn patients and increases the rate of protein synthesis in sepsis and trauma patients.[68]

Unfortunately, an elevated growth hormone level in critically ill patients is associated with increased mortality. In two large European studies of growth hormone use in critically ill adults, patients treated with growth hormone had a 1.9- to 2.4-fold relative risk of mortality, mostly due to multiple organ dysfunction syndrome, shock, or uncontrolled infection. Growth hormone-treated patients also had increased morbidity as measured by prolonged mechanical ventilation and longer ICU stay.[69] Increased endogenous growth hormone is associated with increased mortality in children with meningococcemia.[70] A consensus statement from the Growth Hormone Research Society recommends against use of growth hormone in the acute phase of critical illness.[71]

The reasons behind this association between elevated growth hormone and increased morbidity and mortality are not clearly understood. Growth hormone treatment is associated with an increase in blood glucose concentration, which may support bacterial growth.[67] This hypothesis is supported by evidence that tight glycemic control is associated with a decreased risk of death from sepsis in adult surgical patients.[66] Growth hormone's effects on the immune system may play a role. At very high levels, growth hormone binds in significant quantities to the prolactin receptor. Both of these hormones, at 10 to 20 times physiologic levels, may mediate immunosuppressive effects in vitro.[5,6] At more moderate doses, excessive growth hormone may cause

overshoot of the immune/inflammatory response, which could be detrimental.

For more information on growth hormone and insulin-like growth factor in the ICU, the reader is referred to the excellent reviews by Carroll[67] and G. Van den Berghe.[20]

Morphine and Other Opioids

Almost every pediatric ICU patient is given morphine or one of its relatives. The hypotensive effects of exogenous opioids are well known. Endogenous opioids or endorphins are released in response to stress and play a role in the development of shock. The opiate antagonist naloxone attenuates the hypotensive response to endotoxin in animal models. Endorphins decrease sympathetic outflow, whereas exogenous opiates injected intraventricularly result in sympathetic nervous system activation.[72,73]

Opioids have immunosuppressive effects. Opioid abusers and their animal model counterparts have increased susceptibility to infection and sepsis-related mortality. In animal models, this effect is blocked by naloxone.[74] Opioid use increases metastases and decreases survival in tumor-bearing animals.[75,76] Acutely, centrally acting morphine activates the sympathetic nervous system, which in turn innervates immune tissue. Good evidence indicates that most of the observed immunosuppressive effects of morphine occur via this pathway.[77,78] Morphine also activates the HPA axis, which may lead to cortisol-mediated immune suppression, particularly during chronic administration. Opioids induce immune suppression at analgesic doses by binding to classic, naloxone-sensitive opioid receptors in the brain. In addition, both classic and nonclassic opioid receptors are present on immune cells, but the extent to which morphine interacts directly with these cells to cause immune suppression in vivo is unclear.[79-81]

Morphine reduces the T-cell proliferative response to mitogen, increases T-cell apoptosis, and decreases IL-6 levels in vitro. Morphine decreases B-cell antibody production. In vitro, morphine acts directly to decrease T-cell responsiveness by suppressing IL-2 gene expression, but the extent to which this mechanism is important in vivo is unclear.[79-81] Acute and chronic exposure to morphine decreases splenic and peripheral NK cell activity.[80] NK cells have significant tumoricidal activity, and decreased NK cell function may be associated with an increase in tumor cell dissemination and growth of micrometastases.[76]

Treatment with morphine for as little as 36 to 72 hours impairs macrophage response to macrophage colony-stimulating factor in mice and may affect phagocytosis and superoxide production ex vivo. Macrophages from morphine-treated animals are still sensitive to GM-CSF, a recombinant form of which is available for clinical use. This may represent one of the few methods by which clinicians might antagonize the immunosuppressive effects of morphine.[80]

Opioid use is ubiquitous in critical care and may contribute to lymphocyte depletion observed in the ICU. Because many of the effects of opioids on the immune system occur via the μ receptor, morphine derivatives such as fentanyl likely have the same effect. There are no clinical trials examining the impact of opioid treatment on outcomes from infection. Unfortunately, there is no known analgesic with efficacy comparable to the opioids. When the desired effect is anxiolytic, nonopioid alternatives should be considered. More research on this topic is necessary before therapy can be changed. Patients who are dependent on morphine for pain control may someday be candidates for immune stimulants.

Somatostatin

Somatostatin was first discovered as a potent inhibitor of growth hormone release, but it now is known to also inhibit insulin release, decrease secretion and absorption in the gastrointestinal tract, and decrease splanchnic blood flow.[6] Somatostatin analogues (octreotide) are used for treatment of gastrointestinal hemorrhage.

Somatostatin has direct immunosuppressive effects in vitro. Somatostatin receptors are expressed on peripheral T and B lymphocytes, on activated monocytes, and in hematopoietic precursors.[82] The function of these receptors is under investigation. In the bone marrow, somatostatin inhibits proliferation, particularly in response to granulocyte colony-stimulating factor (G-CSF).[83] Somatostatin also decreases prolactin release by the pituitary, and some of its immunosuppressive effects may occur via this mechanism.[55] The effect of octreotide infusions on immune function in critically ill patients has not been studied.

Other Neuroendocrine–Immune Mediators

Researchers are still discovering new neurotransmitters, hormones, and cytokines, and they continue to recognize new NEI roles for well-known molecules. The molecules described here are examples of this interface. At the time of this writing, there are no known therapies targeting these molecules, but they may someday have clinical relevance. If nothing else, they serve as a reminder of the layers of complexity to the NEI system that we do not yet understand.

Macrophage Migration Inhibitory Factor

Macrophage migration inhibitory factor (MIF) was discovered in the 1950s on the basis of its ability to inhibit the migration of macrophages in capillary tubes. More recently, MIF has been recognized as the unique protein hormone released by the anterior pituitary and the adrenal gland in tandem with HPA axis activation. It also is produced by activated macrophages in response to levels of bacterial lipopolysaccharide that are lower than the levels that stimulate TNF-α production, making it a very early mediator of inflammation.[85]

Like prolactin and substance P, MIF antagonizes some of the peripheral effects of glucocorticoids. It appears to play a major role in the amplification of the immune response. MIF promotes cytokine expression by macrophages and T cells. MIF upregulates the expression of toll-like receptors, which are cell surface receptors involved in recognition of bacterial endotoxin by the innate immune system. MIF levels are elevated in septic shock patients compared with nonseptic critically ill patients and correlate with decreased adrenal responsiveness, and MIF levels increase with the development of ARDS.[86,87]

No therapies for modulating the expression or actions of MIF are available. Drugs that oppose MIF may someday play a role in inflammatory conditions such as ARDS and asthma.

Substance P, Neuropeptide Y, and Calcitonin Gene-Related Peptide

Substance P, a neuropeptide present in afferent nerves in the dorsal horn of the spinal column, was originally discovered to be a mediator of pain sensation. Substance P plays a role in inducing inflammation in response to a variety of irritants and may be part of the CNS pathways involved in psychological stress.[67] Immune cells contain receptors for substance P in addition to other neuropeptides. The actions of substance P in the immune system appear to be proinflammatory and immunosupportive. It induces mast cell degranulation, stimulates lymphocyte proliferation and cytokine release, and may play a role in chronic inflammation.[88,89] In vitro and in vivo, substance P counteracts glucocorticoid-mediated apoptosis.[88]

Substance P is one of a growing group of neuropeptides that have been shown to have immune regulatory function. Others include calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal peptide, ghrelin, pro-opiomelanocortin-related peptides, and β endorphins.[65] Whether the actions of neuropeptides on immune cells is stimulatory or inhibitory may depend on the activation state of the cells and the T-cell phenotypes.[90] At the time of this writing, little is known about their function in the normal state or the stress response. Currently, there are no known therapeutic agents directed at them. Further research may prove the importance of these molecules.

Clinical Relevance

The acute phase of critical illness is characterized by supranormal release of neuroendocrine mediators from the hypothalamus and pituitary. As a consequence of this secretory activity, short-term goals of blood pressure support and mobilization of fuel substrates are met at the expense of neglecting homeostatic mechanisms, immune function, growth, and repair. When a patient's own fight-or-flight response is insufficient to maintain perfusion, shock ensues. For intensivists, the NEI system represents a set of tools for influencing the hemodynamic, metabolic, and immune/inflammatory state of the patient. In the first hours to days of critical illness, replacement of an inadequate neuroendocrine response with catecholamines, vasopressin, and/or steroids may be lifesaving.

During the acute phase of critical illness, the antiinflammatory effect of steroids and catecholamines may be beneficial in many patients. Although clinical trials of antiinflammatory therapies in sepsis have generally been disappointing, most authors agree there is a subset of patients whose robust inflammatory response puts them at increased risk for early death from septic shock. During the prolonged phase of critical illness, the effects of fight-or-flight mediators, whether endogenous or exogenous, may be harmful.

Decreased levels of anterior pituitary hormones and loss of the normal pattern of pulsatile release of these hormones characterize the prolonged phase of critical illness (see Figure 102-3). ACTH, growth hormone, thyroid-stimulating hormone, prolactin, and luteinizing hormone are all similarly affected. Cortisol levels remain elevated in chronic critical illness despite a decrease in ACTH release. The metabolic consequence of this neuroendocrine milieu is an impaired ability to use fatty acids as fuel substrates and a tendency to store fat and to waste protein from muscle and organs. The immune consequences are impaired lymphocyte and monocyte function and increased lymphocyte apoptosis. In patients who fail to recover but go on to develop multiple organ dysfunction, the state of catabolism and immune suppression persists even in the absence of dopamine, glucocorticoids, or other well-known suppressors of the somatotropic axis.

Because dysfunction of normal homeostatic mechanisms may occur independently of ICU therapies, it may be tempting to label the neuroendocrine profile of chronically critically ill patients "normal." In fact, prolonged critical illness does not occur without medical intervention, and in the natural state these patients would not survive. In some chronically critically ill patients, the neuroendocrine system may fail as other organ systems fail. Investigators must ask what neuroendocrine milieu is associated with the best outcomes, including recovery of organ function, effective wound healing, and freedom from nosocomial infection.

Prolonged use of steroids, opioids, or hemodynamic support likely plays a role in the immune suppression and the suppression of anabolic pathways seen in chronic critical illness. Duration of immune suppression correlates strongly with the incidence of related infection, so even a low-grade immune suppression may become clinically significant over time. Lymphopenia and monocyte deactivation are associated with increased risk for poor outcomes, including nosocomial infection, prolonged hospital stay and mechanical ventilation, multiple organ dysfunction, and death.[91] In a review of autopsies of children who died of multiple organ failure, among those who were admitted with a diagnosis of sepsis, 75% had persistent infection at autopsy, suggesting that some patients with multiple organ failure have clinically significant immune depression.[10]

After the first week of ICU care, as patients move into the chronic phase of critical illness, it is important to begin to think about restoring the capacity to grow, heal wounds, build muscle, and fight infection. Steroids should be tapered as soon as hemodynamics or underlying conditions allow. Morphine and other opioids should be used no more than necessary to control the patient's pain. In situations where catecholamines have no proven benefit, as in the case of "renal dose" dopamine, it may be appropriate to consider whether the negative effects on the immune system and on metabolism outweigh the potential benefits of the drug.

Clinicians should be vigilant for the acquired immune deficiency that occurs in prolonged critical illness. When lymphopenia is persistent, indicators of T- and B-cell function should be measured. Patients with low CD4 counts may benefit from early prophylaxis against fungus or *Pneumocystis carinii* pneumonia. Patients with low immunoglobulin levels may benefit from intravenous immunoglobulin. In the prolonged phase of critical illness, patients may be candidates for immune stimulants, including G-CSF or GM-CSF. Investigational therapies targeting lymphopenia may be available in the near future.

References are available online at http://www.expertconsult.com.

Sepsis

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PEARLS

- The typical patient with septic shock has simultaneous derangements of cardiovascular function, intravascular volume status, respiratory function, immune/inflammatory regulation, renal function, coagulation, hepatic function, and/or metabolic function.
- The complexity and heterogeneity of septic shock warrants a systematic and multifaceted approach on the part of the pediatric intensivist.
- Although some overlap exists among the terms spanning the sepsis spectrum (systemic inflammatory response syndrome, sepsis, sever sepsis, and septic shock), each term is intended to define a particular patient population.
- Sepsis is now viewed as a dysregulation of the immunologic and inflammatory pathways normally directed toward pathogen eradication and restoration of homeostasis.
- From a clinical standpoint, the treatment of sepsis entails four important goals: initial resuscitation, elimination of pathogen, maintenance of oxygen delivery, and (in the future) carefully directed modulation of the inflammatory response.
- Genomic medicine and systems biology represent novel approaches for studying complex processes such as septic shock.
- The development of robust stratification and phenotyping strategies has the potential to more effectively manage the intrinsic heterogeneity of septic shock, and thus improve the effectiveness of both clinical research and individual patient care.

Management of the patient with septic shock embodies the discipline of pediatric critical care medicine. The typical patient with septic shock has simultaneous derangements of cardiovascular function, intravascular volume status, respiratory function, immune/inflammatory regulation, renal function, coagulation, hepatic function, and/or metabolic function. The degree to which any one of these derangements manifests in a given patient is highly variable and influenced by multiple host and nonhost factors, including developmental stage, presence or absence of comorbidities, causative agent of septic shock, immune/inflammatory status, genetic background, and variations in therapy. These factors combine to profoundly influence the course and ultimate outcome of septic shock.

The complexity of septic shock warrants a systematic and multifaceted approach on the part of the pediatric intensivist. Optimal management requires a strong working knowledge not just of cardiovascular physiology and infectious diseases, but also of multiple organ function/dysfunction, inflammation-related biology, immunity, coagulation, pharmacology, and molecular biology. The pediatric intensivist also needs a working knowledge of genomic medicine for the future management of patients with septic shock. This chapter provides a comprehensive description of the many aspects that influence the development and outcome of septic shock, pathophysiology at the physiologic and molecular levels, contemporary management of septic shock, and what we believe to be the next important future directions in the field. Ultimately, this information must be integrated with bedside experience and clinical acumen, which cannot be supplanted by a book chapter.

Epidemiology

A true picture of the epidemiology of septic shock is clouded by the lack of a reliable case definition. This is true for both the adult and pediatric populations. A few pediatric-specific studies, however, illustrate the importance of septic shock in today's modern intensive care unit (ICU). Proulx et al. analyzed the incidence and outcome of the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock (see next section for definitions) in a single institution.[1] A total of 1058 admissions were analyzed over a 1-year period. SIRS was present in 82% of patients, 23% had sepsis, 4% had severe sepsis, and 2% had septic shock. The overall mortality rate for this patient population was 6%, with the majority of deaths occurring in patients with multiple organ dysfunction syndrome (MODS). Among the patients with MODS, distinct mortality rates were associated with SIRS (40%), sepsis (22%), severe sepsis (25%), and septic shock (52%). Later studies by Watson et al. provide the most comprehensive epidemiologic surveys of pediatric septic shock to date.[2] By linking 1995 hospital records from seven large states (representing 24% of the United States population) with census data, they estimated an incidence of 42,371 cases of severe sepsis in individuals younger than 20 years of age (0.6 cases/1000 population). The

highest incidence was in neonates (5.2 cases/1000 population), compared with children ages 5 to 14 years who had an incidence of 0.2 cases/1000 population. The overall mortality rate in this population was 10.3% (4364 deaths per year nationally). In addition, patients younger than 1 year of age and patients with comorbidities had higher mortality rates than patients between 5 and 14 years old and patients without comorbidities, respectively. Their study also estimated an annual national health care cost of $1.7 billion associated with severe sepsis.

In a follow-up study, Watson et al.[3] compared the epidemiology of severe sepsis between 1995 and 1999. Using a similar strategy as described for their earlier study, they found a 13% increase in the absolute number of cases of severe sepsis during this time period. The majority of the increase was accounted for by severe sepsis in children younger than 1 year of age. In contrast, the overall mortality rate for severe sepsis decreased from 10.3% to 9.0% during this time period.

In the most recent report on the epidemiology of pediatric sepsis, Czaja and colleagues used the discharge diagnosis of severe sepsis for Washington State to investigate the readmission rates and late mortality for children (1 month to 18 years old) following severe sepsis.[4] From 1990 through 2004, 7183 children were diagnosed with severe sepsis and 6.8% of these patients died during the sentinel admission or within 28 days of discharge. Importantly, death certificates confirmed that an additional 434 (6.5%) of the initial survivors died during the follow-up period with the highest late death rate occurring within 2 years of the initial hospitalization. Although most of the early, as well as the late deaths occurred in children with comorbidities (8% early death, 10.4% late death), 8% of children with no comorbidities died during their initial hospitalization with 2% of the 28-day survivors being classified as late deaths.

Collectively, these data illustrate that septic shock continues to present a major public health problem in terms of incidence, mortality, and health care costs. Nevertheless, there is an ongoing need for quality epidemiologic studies of septic shock in children. Quality epidemiologic studies are necessary for our understanding not only of incidence, but also of the impact of new knowledge and therapies. One major issue that must be addressed is the development of more meaningful and consistent case definitions. Consistent case definitions will also facilitate and improve the design of more effective interventional trials specific to the pediatric population. Equally important is objectively measuring long-term outcomes in these patients (i.e., quality of life) beyond the dichotomy of "alive" or "dead." Progress in this important area is steadily coming to fruition.[5-8]

Definitions

Intuitively, the experienced pediatric intensivist knows when he or she encounters a patient with septic shock. Thus strict definitions of sepsis and septic shock could be viewed as having relatively limited value in daily practice. Despite this common perception, there is a clear need for standard definitions of sepsis and septic shock for three primary reasons. First, with the development of standard definitions, we will be able to more accurately characterize the epidemiologic features of septic shock in the pediatric population. Second, as novel, expensive, and potentially higher risk therapies are developed, it will be important to accurately identify and stratify patients early in the course of septic shock if we are to apply those therapies to the most appropriate groups and realize a more favorable risk/benefit ratio in a given patient population. Finally, standard definitions are crucial to the design of much needed, pediatric-specific interventional trials.

Box 103–1 Criteria for SIRS

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

1. Core temperature (rectal, bladder, oral, or central catheter) over 38.5° C or under 36° C.
2. Tachycardia, defined as a mean heart rate more than two standard deviations above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5-hour to 4-hour time period; OR for children less than 1 year old: bradycardia, defined as a mean heart rate under tenth percentile for age in the absence of external vagal stimulus, β-blockers, or congenital heart disease; or otherwise unexplained persistent heart rate depression over a 0.5-hour time period.
3. Tachypnea, defined as mean respiratory rate over ninetieth percentile for age; or the need for mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia); or more than 10% immature neutrophils.

The International Consensus Conference on Pediatric Sepsis and Organ Dysfunction was convened in 2002 to develop pediatric-specific definitions for SIRS, sepsis, severe sepsis, septic shock, and organ failure, and the results of this conference were subsequently published.[9] The standard terms to describe the sepsis spectrum are systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock. Each term is intended to describe a clinical syndrome having increasing illness severity and relatively increasing specificity, which in turn drives important clinical decision and therapeutic processes.

SIRS is not a diagnosis. The term is intended to represent a state of relative inflammatory/immune activation in a given patient, and is said to be present when a patient meets at least two of the four criteria listed in Box 103-1, one of which must be abnormal temperature or abnormal leukocyte count. Thus, patients with diverse clinical conditions, such as sepsis, pancreatitis, burns, or hypermetabolism following major trauma or surgery, can meet criteria for SIRS. *Sepsis* is defined as SIRS secondary to an infection, either documented by microbiology cultures or in the presence of other clinical evidence of infection. *Severe sepsis* is defined by sepsis criteria plus either cardiovascular dysfunction or acute respiratory distress syndrome, or at least two other dysfunctional organ systems. *Septic shock* is defined by sepsis criteria, plus cardiovascular dysfunction. Importantly, each criterion takes into account the influence of developmental age on physiological variables. The reader is referred to the original publication by Goldstein et al.[9] for further details and definitions of organ dysfunction.

Clinical Presentation

As a syndrome that potentially affects the entire body, the clinical presentation of sepsis is highly heterogeneous. The most common clinical manifestations of sepsis include fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, thrombocytopenia, and change in mental status. It should be noted however that, in the absence of meningitis, changes in mental status are relatively late manifestations of septic shock and should not be relied upon for early recognition of shock. One of the earliest signs that alerts caregivers to the possibility of infection is fever. A number of the cytokines elicited in response to infection are pyrogens, particularly interleukin (IL)-1β and tumor necrosis factor (TNF)-α. Patients can also have hypothermia, which is more common in infants than older children. Finally, petechiae and/or purpura can be present and are potentially ominous signs of purpura fulminans.[10]

Shock states can be grouped into four broad categories: hypovolemic, cardiogenic, obstructive, and distributive shock. Septic shock is unique in that all four forms of shock may be involved simultaneously. The patient may have hypovolemic shock resulting from capillary leak, increased insensible water losses, poor intake, and/or decreased effective blood volume secondary to venodilation and arterial dilation (i.e., increased vascular capacitance). Cardiogenic shock manifests as depressed myocardial contractility and low cardiac output secondary to myocardial-depressant effects of bacterial toxins and inflammatory cytokines. Obstructive shock can result indirectly from diffuse microvascular thrombosis, or directly from abdominal compartment syndrome. Distributive shock can result directly from abnormally low systemic vascular resistance, leading to maldistribution of blood flow; or can result indirectly from the inability of tissues to adequately use oxygen at the mitochondrial level (i.e., cytopathic hypoxia).

The degree to which an individual patient manifests these physiologic perturbations is highly variable. In some cases, patients display increased cardiac output with diminished systemic vascular resistance. The presenting symptoms in this type of patient are tachycardia, a hyperdynamic precordium, bounding pulses, and warm, flushed skin characteristic of the distributive mode of shock or the so-called "warm" shock state. Despite this clinical appearance, the perfusion of major organs during warm shock may remain highly compromised secondary to maldistribution of blood flow. Alternatively, a patient with depressed cardiac output and elevated systemic vascular resistance has cool, mottled skin with diminished pulses and poor capillary refill characteristic of the "cold" shock state. Limited data and our collective anecdotal experience suggest that this latter presentation, cold shock, is more common in younger children compared to teenagers and adults.[11] Recently, it has been suggested that patients who develop community-acquired septic shock more commonly present to the ICU with signs of "cold" shock; whereas patients that develop septic shock secondary to catheter-related infections more commonly present to the ICU with signs of "warm" shock.[12] It is important to recognize that a given patient may transition from one shock state to another, and that recognition and reassessment of these classes of shock are absolutely central to the choice of cardiovascular medications.

Patients with sepsis often have presenting symptoms of respiratory abnormalities, including tachypnea and hypoxia. Tachypnea alone can reflect a compensatory, respiratory alkalosis aimed at counteracting a metabolic acidosis secondary to shock. Chest radiograph in this setting often reveals a relatively small cardiac silhouette (potentially reflective of relative hypovolemia) with few vascular markings. However, in the face of capillary leak and decreased myocardial function, patients with septic shock often develop pulmonary edema and acute respiratory failure as fluid resuscitation proceeds. Alternatively, respiratory abnormalities can reflect pneumonia as the primary source of infection, and/or the development of acute respiratory distress syndrome (ARDS). In these situations, chest roentgenography will display patterns of pulmonary infiltrates characteristic of the respective scenarios.

All organ systems can be adversely affected by poor perfusion and decreased oxygen delivery. In addition, all organ systems can be directly or indirectly injured by bacterial toxins, circulating cytokines, and the products of activated white blood cells. The end result of these complex and interrelated pathologic mechanisms is multiple organ dysfunction syndrome, which describes the serial and progressive failure of various organ systems, and is associated with increased morbidity and mortality.[13-15]

Pathogenesis

A large number of clinical and basic science studies have focused on the mechanisms underlying the development of sepsis. At least three major hypotheses have been proposed to explain the development of sepsis and its sequelae. The first hypothesis attributes the development of sepsis to an excessive or uncontrolled host inflammatory response. This "proinflammatory" hypothesis is broadly consistent with the concept of SIRS, and is generally well supported by experimental and clinical data. However, a large number of clinical trials aimed directly at inhibition of various components of this putative excessive inflammatory response have failed, thus leading to the development of alternative hypotheses. One such alternative hypothesis states that sepsis is not directly the result of excessive inflammation, but rather a more direct manifestation of failed antiinflammatory responses. Thus in this alternative hypothesis there is direct failure of the compensatory antiinflammatory response syndrome (CARS), which subsequently permits unchecked proinflammatory responses. Related to the CARS concept is the concept of immunoparalysis, which embodies the third overall hypothesis to account for the clinical manifestations of sepsis. The hypothesis of immunoparalysis postulates that sepsis is not a manifestation of too much or too little inflammation, but rather a form of acquired immunodeficiency (both innate and adaptive immunity), leading to an inability to effectively clear pathogens and their products, which thereby cause direct tissue and organ injury.[16,17]

A conceptual framework for integrating these three hypotheses/paradigms is provided in Figure 103-1. All three paradigms are biologically plausible and supported by the existing literature.[18] While seemingly vastly different in concept, they are not mutually exclusive in the context of a highly heterogeneous syndrome such as human sepsis. That is, it is plausible that all three paradigms are valid across a given cohort of heterogeneous patients with sepsis. In addition, each paradigm has the potential to influence all of the other paradigms, as indicated in Figure 103-1. The following sections review the

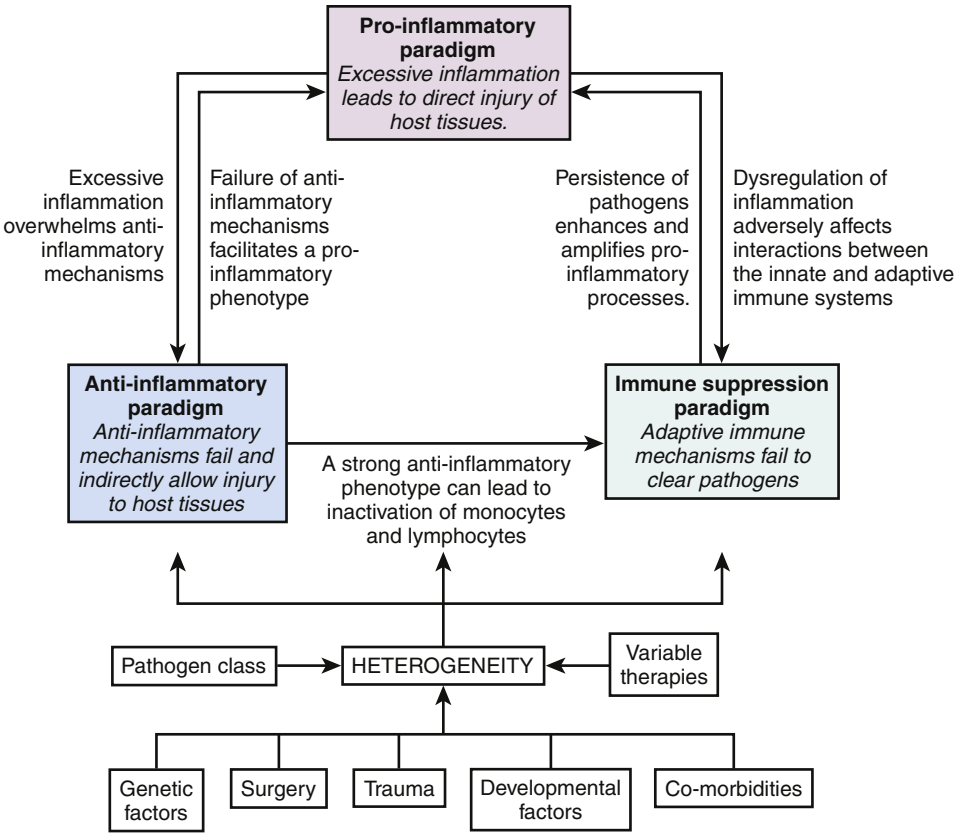


Figure 103–1. The three major paradigms for understanding the pathophysiology of sepsis and septic shock. Although the three paradigms are mechanistically distinct, they are not mutually exclusive. Each paradigm has the potential to influence the other paradigms, and all are potentially operative in a heterogenous patient cohort. Heterogeneity is a major component of septic shock and results from multiple host and environmental factors.

existing literature supporting these three paradigms and will serve to frame the important concept of heterogeneity in sepsis. A major challenge in the field of sepsis is to more effectively understand how a given patient fits into one of these three paradigms (i.e., stratify or phenotype).

Pathogen Recognition and Signal Transduction

The fundamental role of the immune system is to detect, contain, and eradicate invading pathogens. The first step in this process involves pathogen recognition, which is achieved by the activation of pattern recognition receptors (PRRs) on immune cells by pathogen-associated molecular patterns (PAMPs).[19] Examples of PAMPs include lipopolysaccharide from the cell walls of gram-negative bacteria; lipoteichoic acid from the cell walls of gram-positive bacteria; mannans from the cell walls of yeast; double-stranded RNA of viruses; and unmethylated, CpG-rich DNA unique to bacterial genomes. The most well studied PRRs include the family of toll-like receptors (TLRs), which can have relatively specific recognition of PAMPS.[19] For example, TLR-4 recognizes lipopolysaccharide, wherease TLR-2 recognizes lipoteichoic acid. Other examples of PRRs or PRR components include CD-14, scavenger receptors, NOD receptors, pentraxins, and collectins.[20]

Engagement of PRRs on the cell surface of immune cells, by PAMPS, leads to activation of the immune system in the form of phagocytosis, proliferation, and production/secretion of cytokines. The latter process, cytokine expression, serves to orchestrate, direct, and amplify the innate and adaptive immune response toward pathogen eradication. However, if this process becomes dysregulated, this same production of cytokines, though required for pathogen eradication, can inadvertently lead to auto-injury of the host.

Much of the activation of the immune system upon PRR activation relies upon signal transduction mechanisms, which serve to transfer the signal of pathogen recognition at the cell surface to the intracellular compartment in order to induce new gene expression or a change in cellular function. One of the major signal transduction mechanisms of the immune system is the NF-κB pathway, which serves as a master "switch" for the expression of a wide variety of genes involved in inflammation and immunity. Indeed, activation of the NF-κB pathway is a major signaling pathway in the pathophsiology of sepsis, and may represent a potential therapeutic target.[21,22] Another major signaling pathway for the regulation of genes involved in inflammation and immunity is the mitogen-activated protein kinase (MAPK) signaling pathway. The MAPKs consist of three major families: p38 MAPK, extracellular-regulated protein kinase (ERPK), and c-Jun N-terminal kinases (JNK). These major kinase families are also referred to as a stress-activated protein kinases (SAPKs). Similar to the NF-κB pathway, the MAPKs are also regarded as potential therapeutic targets in the context of sepsis.[21,23,24] Finally, there is now increased attention on the phosphatase family of intracellular signaling molecules in the

Box 103–2 Common Features of Cytokines

- Cytokine secretion is relatively brief and self-limited.
- Secretion of many cytokines requires new mRNA transcription and new protein translation.
- Expression and secretion is regulated by specific cellular signals.
- A given cytokine can have multiple cellular sources.
- A given cytokine can have multiple cellular targets.
- A given cytokine can have multiple functions regarding cellular function or activation.
- Cytokines can have redundant activities/functions with other cytokines.
- Many cytokines regulate the activity and expression of other cytokines.

context of sepsis. Whereas kinases direct cellular signaling by adding phosphate groups to intracellular signaling proteins, phosphatases serve to remove phosphate groups from these same intracellular signaling proteins and can thus serve to modulate proinflammatory cell signaling.[25,26]

Cytokines as Principal Mediators of the Sepsis Response

Cytokines represent a broad family of proteins that have paracrine, autocrine, and endocrine properties, and the ability to regulate and modulate virtually all aspects of immunity and inflammation. Common features of cytokines are provided in Box 103-2. Herein we will review a selected group of cytokines thought to play an important role in the pathophysiology of sepsis.

Tumor Necrosis Factor-α

Tumor necrosis factor alpha (TNF-α) is perhaps the most well-studied cytokine that is causally linked to sepsis. Evidence for TNF-α mediation of sepsis includes the observations that TNF is produced by hematopoietic cells; its expression is temporally related to the development of shock; it can by itself induce experimental septic shock in animals; and passive immunization against TNF blunts the endotoxin-induced sepsis response.[27] The proinflammatory effects of TNF include leukocyte-endothelial cell adhesion, transformation to a procoagulant phenotype, induction of inducible nitric oxide synthase, and functioning as a principal "early" cytokine that induces the subsequent cascade of mediators and cytokines promulgating the septic response. Despite a plethora of preclinical studies demonstrating the important proximal role of TNF-α in the pathophysiology of sepsis, multiple clinical trials targeted at neutralization of TNF-α activity have thus far failed to demonstrate efficacy.[28]

Interleukin-1β

Interleukin (IL)-1β has many redundant biological properties to those of TNF-α, and is also considered to be a major early cytokine in the sepsis response.[29] IL-1β leads to inflammatory and immune cell activation via the NF-κB and MAPK pathways. Also, similar to TNF-α, clinical trials targeted at neutralization of IL-1β activity have thus far failed to demonstrate efficacy despite promising preclinical data.

Interleukin-6

Interleukin-6 expression is highly dependent on TNF-α and IL-1β, and is consistently found to be elevated during the course of sepsis.[30] IL-6 is a pleiotropic cytokine possessing a number of functions including driving the acute-phase response in hepatocytes, differentiating myeloid cells, stimulating immunoglobulin production, and activating T-cell proliferation.[31] Because increased IL-6 admission levels have been correlated with death in the context of sepsis, there has been interest in using IL-6 as a stratification biomarker for interventional clinical trials in sepsis. While this stratification approach has been highly effective in animal models of sepsis,[32] it has thus far failed when applied in the clinical setting.[33]

Interleukin-8

Interleukin-8 is a canonical member of the chemokine subclass of cytokines.[34] The term "chemokine" refers to the ability of certain cytokines to serve as chemoattractants, which direct leukocyte movement to sites of infection and inflammation (chemotaxis). Both TNF-α and IL-1β can induce IL-8 production from a variety of cells, including endothelial cells, macrophages, neutrophils, and epithelial cells. IL-8 is the principal human chemoattractant for neutrophils, and appears to play a major role in the recruitment of neutrophils to the lungs in patients with sepsis-induced acute respiratory distress syndrome.[35] Recently, it was demonstrated that serum IL-8 measurements within 24 hours of presentation to the ICU can robustly predict good outcome in children with septic shock receiving standard care.[36] Other chemokines relevant to the pathophysiology of septic shock include monocyte chemoattractant protein 1 (MCP-1) and macrophage inflammatory protein-1 (MIP-1).[34]

Macrophage Migration Inhibitory Factor

Macrophage migration inhibitory factor (MIF) has recently emerged as an important cytokine in the pathophysiology of sepsis, and high levels of MIF in patients with septic shock and ARDS correlate with poor outcome.[37,38] MIF possesses a number of biological activities generally directed toward a proinflammatory phenotype, including skewing of naive T cells toward a Th1 phenotype. An unusual feature of MIF is that its secretion is enhanced by glucocorticoids, whereas the expression and activity of many cytokines are suppressed by glucocorticoids. In turn, MIF has the ability to antagonize the antiinflammatory effects of glucocorticoids.

Interleukin-18

Interleukin-18 has also recently emerged as an important cytokine in the pathophysiology of sepsis.[39] Depending on the local cytokine milieu, IL-18 has the ability to skew naive T cells toward either a Th1 or Th2 phenotype. In addition, it appears that IL-18 may serve as an early biomarker to distinguish between gram-positive and gram-negative sepsis.

Interleukin-10

Interleukin-10 is the best studied and most well known antiinflammatory cytokine.[40,41] As an antiinflammatory cytokine, IL-10 serves to antagonize the proinflammatory effects of other cytokines and can thereby keep inflammation "in check." IL-10 inhibits expression of cytokines such as TNF-α, IL-1β, and IL-8, and can inhibit expression of adhesion molecules. In

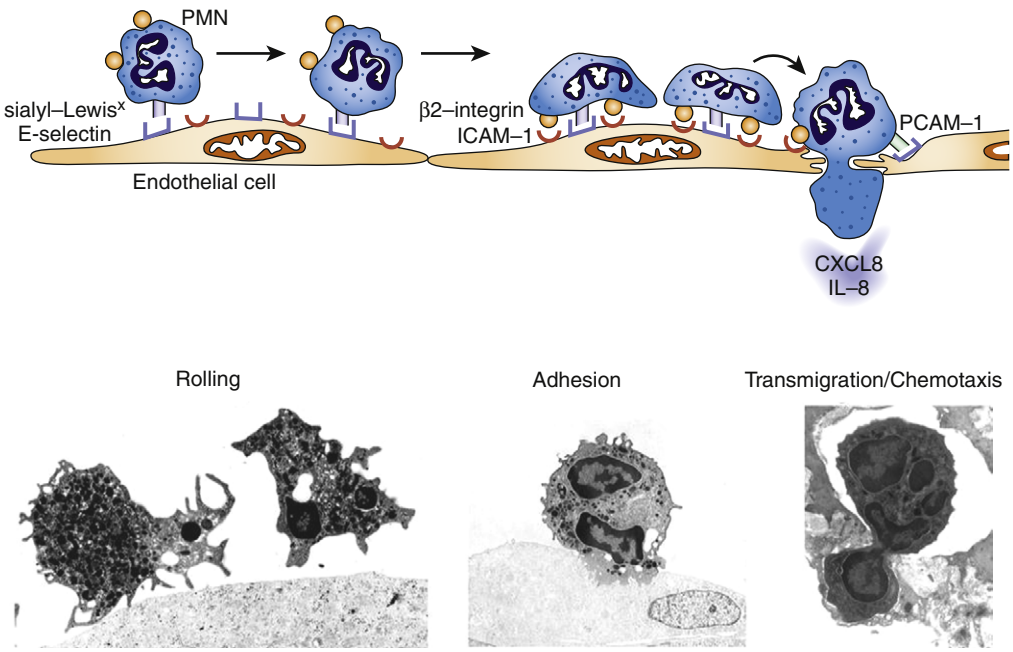


Figure 103–2. Schematic and corresponding electron micrographs highlighting the process of leukocyte-endothelial cell adhesion and leukocyte transmigration from the intravascular compartment to the extravascular compartment. Cytokine-mediated activation of the selectin family of endothelial cell adhesion molecules mediate neutrophil "rolling," followed by ICAM-1-mediated adhesion. After adhesion, neutrophils transmigrate across "openings" between enothelial cell junctions to enter the extravascular space. The transmigration process is directed by chemokines that serve as homing signals for neutrophils and other leukocytes. *(Courtesy Thomas P. Shanley, MD, University of Michigan.)*

addition, IL-10 can "deactivate" monocytes by downregulating the expression of MHC surface molecules. Thus IL-10 has a number of interesting properties that could potentially be leveraged therapeutically to limit excessive inflammation during sepsis. This theoretical consideration must be tempered by the ability of IL-10 to deactivate monocytes and thereby potentially impair the ability to adequately clear infection (i.e., the immune suppression paradigm depicted in Figure 103-1). Indeed, it has been reported that in children with multiple organ dysfunction syndrome, higher plasma IL-10 levels correlate with higher mortality, and higher monocyte mRNA levels of IL-10 correlate with increased length of stay in the ICU.[42] Similar observations have been reported in adult patients with septic shock.[43]

High-Mobility Group Box 1

High-mobility group box 1 (HMGB-1) has long been known as a nonhistone DNA-binding protein. More recently, it has been recognized that HMGB-1 also exists in the extracellular compartment, appears to have proinflammatory properties that may play a role in the pathophysiology of sepsis, and may represent a potential therapeutic target for sepsis.[44] The attraction of HMGB-1 as a therapeutic target in sepsis stems from the observation that it may be a "late mediator" of sepsis in as much as it appears in the extracellular compartment within a time frame that is considerably later than that seen with the canonical sepsis cytokines such as TNF-α and IL-1β. Thus the kinetics of HMGB-1 expression provide a potential therapeutic window that is clinically feasible to exploit. This temporal observation is evident in both experimental models of sepsis and in humans with established septic shock.[45] The biologic properties of HMGB-1 appear to involve activation of toll-like receptors and the receptor for advanced glycation end products (RAGE). More recently, it has been suggested that HMGB-1 intrinsically possesses very little proinflammatory biological activity, but forms highly proinflammatory complexes with cytokines (e.g., IL-1β) and PAMPS (e.g., bacterial DNA and lipopolysaccharide).[46]

HMGB-1 is also a prime example of a class of molecules known as "alarmins" or danger/damage-associated molecular patterns (DAMPs).[47] Broadly speaking, DAMPs represent a class of molecules that normally exist in the intracellular compartment at baseline, but are released from damaged cells into the extracellular compartment during conditions such as trauma or sepsis. DAMPs appear to signal through many of the same PRRs that recognize pathogens, and therefore have the ability to activate the immune/inflammatory system. Because DAMPs are released from damaged cells, they can serve to "alert" the inflammatory system of systemic "damage" or "danger" and can therefore induce appropriate and adaptive activation of defense mechanisms. Alternatively, excessive DAMP-mediated activation of PRRs can lead to unnecessary and maladaptive amplification of inflammation that is damaging to host tissues. Other examples of PAMPs include calgranulins, hepatoma-derived growth factor, heat shock proteins, and uric acid. In this regard, heat shock proteins have been reported to be substantially elevated in the serum of children with septic shock.[48,49]

Adhesion Molecules

An important breakthrough in the molecular understanding of sepsis-induced organ dysfunction came with the identification of the processes responsible for the infiltration of leukocytes into tissues.[50] The "leukocyte-endothelial cell adhesion cascade" (Figure 103-2) is characterized by early cytokine-mediated activation of the selectin family of endothelial cell adhesion molecules that can mediate a process of neutrophil

"rolling," whereby sialyated moieties constitutively present on neutrophils interact with selectins on the endothelial cell membrane (e.g., E-selectin). In the second phase, activation of the "rolling" neutrophil causes increased expression and activation of the integrin family of adhesion molecules that interact with the similarly upregulated intercellular adhesion molecule (ICAM)-1 on the endothelial cell surface. This ligand interaction facilitates firm adhesion of the neutrophil to the endothelium. Subsequently, in response to a variety of chemotactic molecules, neutrophils transmigrate through the endothelial junctions to the site of inflammation. Release of a variety of radical species, both oxygen- and nitrogen-based, and proteases by the activated neutrophils can contribute to pathogen eradication, but paradoxically can also cause endothelial and tissue injury.

Nitric Oxide

Nitric oxide (NO) was discovered in the 1980s to be the molecule responsible for endothelial-derived relaxation of blood vessels.[51,52] Since that time, NO has received tremendous attention as a potential mediator of septic shock.[53] NO is produced by the enzyme nitric oxide synthase (NOS), which converts arginine and oxygen to NO and citrulline. Human NOS exists as three different isoforms (NOS 1, 2, and 3) and each isoform has relatively unique tissue localizations, requirements for NO production, and kinetics of NO production. Several features of NO-related biology support an important role in the pathophysiology of sepsis. First, NOS2 (also referred to as *inducible NOS*) is expressed in response to proinflammatory signals (e.g., lipopolysaccharide, TNF-α, and IL-1β) and produces large amounts of NO for prolonged periods of time. Second, NO can induce pathologic vasodilation and can function as a myocardial depressant. Third, NO can function as an oxidant either alone or by contributing to formation of other highly oxidizing, reactive molecules such as peroxynitrite. Fourth, NO has the potential to negatively affect mitochondrial function. Finally, elevated levels of NO metabolites have been well documented in children with septic shock and the levels correlate with the degree of cardiovascular dysfunction.[54,55] Despite these intriguing biological properties, and a wealth of preclinical data testing the efficacy of NOS inhibition, clinical trials targeted at NOS inhibition have failed to demonstrate efficacy.[56] Because NO has a myriad of biological properties important for maintenance of homeostasis (particularly when NO is produced by the NOS1 and NOS3 isoforms), this lack of efficacy may represent the timing and specificity of NOS isoform inhibition.

The Coagulation Cascade

It is now well established that the inflammatory cascade is directly linked to the coagulation cascade, and that the coagulation cascade can be pathologically activated in the context of sepsis.[57,58] This pathological activation leads to disseminated intravascular coagulation, which subsequently leads to endothelial cell dysfunction and microvascular thrombosis. If the endothelial dysfunction and microvascular thrombosis progress to a critical threshold, end-organ failure ensues.

A complex network of multiple mediators takes part in this pathologic process, including proinflammatory cytokines, tissue factor, antithrombin III, protein C, protein S, tissue factor pathway inhibitor, and plaminogen activator inhibitor type 1 (PAI-1). Increased PAI-1 levels are a particularly strong feature of severe cases of meningococcemia and may be causally linked to a polymorphism in the promoter region of the PAI-1 gene.[59,60] Depressed levels of the endogenous anticoagulants, antithrombin III, protein C, and protein S are consistently documented in the context of septic shock. These observations have led to multiple clinical trials in which recombinant forms of these endogenous anticoagulants have been administered to patients with septic shock. Thus far the only strategy that has been shown to reduce mortality is activated protein C (APC), which now has Food and Drug Administration (FDA) labeling specifically for adult patients with septic shock.[61] The beneficial affects of APC in septic shock are thought to be secondary to both prevention of microvascular thrombosis and an antiinflammatory effect.[62] Unfortunately, a Phase III trial of APC therapy in children with septic shock (the RESOLVE trial) failed to demonstrate efficacy.[63] The RESOLVE trial was terminated after the second interim analysis due to little chance of reaching the primary efficacy endpoint. In addition, there was an increased risk of serious bleeding events in patients younger than 2 months of age. Nonetheless, the RESOLVE trial represents the largest and best-organized pediatric septic shock trial to date and provides an important context and reference point for all future interventional trials in the field of pediatric critical care medicine.

Related to the paradigm of altered coagulation playing an important role in the pathophysiology of sepsis is the concept of thrombocytopenia-associated multiple organ failure (TAMOF).[64] New-onset thrombocytopenia in critically ill patients, including patients with sepsis, correlates with the evolution of persistent organ failure and poor outcome. The mechanistic link between thrombocytopenia and organ failure is thought to involve a form of microangiopathy analagous to thrombotic thrombocytopenic purpura, involving substantial decreases of ADAMTS-13 (A Disintegrin and Metalloprotease with ThromboSpondin motifs). ADAMTS-13 regulates microvascular thrombosis by cleaving the large thrombogenic von Willebrand factor multimers into smaller, less thrombogenic forms. Prelminary experience indicates that plasma exchange restores ADAMTS-13 levels and restores organ function in children with TAMOF.[65] The future conduct of large, multicenter, randomized trials will be imperative to objectively establish the potentially exciting role of plasma exchange in this patient population.

The Peroxisome Proliferator-Activated Receptor-γ Pathway

The peroxisome proliferator-activated receptor-γ (PPARγ) is a member of the PPAR nuclear receptor superfamily and a ligand-activated transcription factor having well-known effects on lipid metabolism and cell proliferation.[66] The thiazolidinedione class of insulin-sensitizing drugs are well known PPARγ ligands (activators) and are currently widely used in the management of type II diabetes. Recently, it has become evident that pharmacologic activation of PPARγ has important antiinflammatory effects that are of significant benefit in experimental models of critical illness, including sepsis.[67-71] The recent demonstration that PPARγ expression and activation is indeed altered in children with septic shock, coupled with the availability of FDA-approved PPARγ ligands,

opens up the realistic possibility of conducting clinical sepsis intervention trials focused on PPARγ activation in the near future.[72]

The Paradigm of Sepsis as an Adaptive Immune Problem

Our conceptual framework of the pathophysiology of septic shock has evolved over the last decade to include the concept of immune paralysis. Whereas septic shock has been traditionally viewed as being a reflection of uncontrolled hyperinflammation (i.e., an innate immunity problem), it is now thought that septic shock also has a strong, perhaps predominant, "antiinflammatory" component that can be manifest as immune suppression and the relative inability to effectively clear an infectious challenge (an adaptive immunity problem).[16,17,73,74] For example, monocyte deactivation related to decreased major histocompatibility complex (MHC) gene mRNA expression and decreased surface expression of MHC molecules have been previously demonstrated in patients with septic shock, including children.[42,43,75,76] With regard to lymphocyte dysfunction, Heidecke and colleagues demonstrated that adult patients with intraabdominal infections and septic shock have defective T cell proliferation and defective T cell–dependent cytokine secretion, all of which is consistent with anergy/immune suppression.[77] Felmet and colleagues identified prolonged lymphopenia and apoptosis-associated depletion of lymphoid organs as independent risk factors for the development of nosocomial infections and multiple organ failure in critically ill children.[78] Animal studies have well documented the requirement of an intact T-cell system to adequately combat a septic challenge.[74,79] More recently, animal-based experiments have demonstrated that experimental septic shock is characterized by widespread apoptosis of T cells, and that preventing T-cell apoptosis positively impacts the outcome of experimental sepsis.[80-87] Importantly, the concept of T-cell apoptosis in human sepsis has been indirectly corroborated by autopsy studies, including children,[78,88] and lymphocyte-based immunophenotyping was recently demonstrated to effectively stratify septic shock outcome in adults.[89] Finally, it has been recently demonstrated in experimental models that alterations of the adaptive immune system in sepsis can persist well beyond the acute period (up to at least 6 weeks) via epigenetic mechanisms affecting dendritic cells.[90,91] Despite these data, formal studies of T-cell function and adaptive immunity in pediatric septic shock have never been conducted in a systematic and comprehensive manner. Such studies hold the promise of radically changing our conceptual approach to the long sought, but not yet realized, goal of rational immune modulation in septic shock.

Genomic Medicine and Sepsis

The initial completion and publication of the human genome, the development of molecular biology tools for efficient high-throughput data generation, and the evolution of the field of biomedical informatics, have combined to generate a new field termed "genomic medicine" and the related field of "systems biology." All aspects of medicine are potentially amenable to the concepts of genomic medicine and systems biology, including pediatric sepsis. One skeptical perspective of this concept is that clinical pediatric sepsis is overly heterogeneous and multifactorial to be credibly interrogated by the current genomic and systems biology approaches. An alternative, and more optimistic, perspective is that the concepts of genomic medicine and systems biology are ideally suited to more effectively address the complex syndromes that we encounter in pediatric critical care medicine, such as septic shock. Herein we will address the two areas of genomic medicine that have been most well developed in the field of pediatric septic shock: candidate-gene association studies and genome-wide expression profiling.

Genetic Influence and Septic Shock

Susceptibility to sepsis and the clinical course of patients with sepsis are both highly heterogeneous, thus raising the strong possibility that the host response to infection is, at least in part, influenced by heritable factors (i.e., genetics).[92] A landmark study by Sorensen et al., published more than 20 years ago, provides strong evidence linking genetics and susceptibility to infection.[93] This study involved a longitudinal cohort of more than 900 adopted children born between 1924 and 1926. The adopted children and both their biologic and adoptive parents were followed through 1982. If a biologic parent died of infection before the age of 50 years, the relative risk of death from infectious causes in the child was 5.8 (95% confidence interval, 2.5 to 13.7), which was higher than for all other causes studied, including cancer and cardiovascular/cerebrovascular disease. In contrast, the death of an adoptive parent from infectious causes did not confer a greater relative risk of death in the adopted child.

More recently, investigations attempting to link genetics with sepsis have largely focused on candidate-gene association studies and gene polymorphisms. A gene polymorphism is defined as the regular occurrence (>1%) in a population of two or more alleles at a particular chromosome location. The most frequent type of polymorphism is called a single nucleotide polymorphism (SNP): a substitution, deletion, or insertion of a single nucleotide that occurs in approximately 1 per every 1000 base pairs of human DNA. SNPs can result in an absolute deficiency in protein, an altered protein, a change in the level of normal protein expression, or no discernible change in protein function or expression. There is a growing body of literature linking SNPs within several genes that regulate inflammation, coagulation, and the immune response with critical illness, and several excellent reviews exist on the topic.[94-97]

The signaling mechanisms involved in pathogen recognition, the immune response, and inflammation were described in previous sections. Herein, we will provide an overview of relevant SNPs that have been described in many of the genes involved in these signaling mechanisms. TLR-4 (the primary receptor for recognition of lipopolysaccharide) mutations have been described in humans, all of which increase susceptibility to infections secondary to gram-negative organisms.[98] While several SNPs in the TLR-4 receptor gene have been described, few have been found to be associated with an increased risk of septic shock or septic shock-related mortality in children. For example, an adenine for guanine substitution 896 base pairs downstream of the transcription start site for TLR-4 (+896) results in replacement of aspartic acid with glycine at amino acid 299 (Asp299Gly). The Asp299Gly polymorphism has been associated with reduced expression

and function of the TLR-4 receptor in vitro.[98,99] Furthermore, adults who carry the Asp299Gly polymorphism appear to be at increased risk for septic shock and poor outcome in several cohort studies.[100-102] While children who carry the Asp299Gly polymorphism appear to be at increased risk of urinary tract infection, this SNP does not appear to influence either the susceptibility or severity of meningococcal septic shock in children.[103,104] These results were further corroborated in a cohort study involving over 500 Gambian children.[105]

SNPs related to other members of the LPS-receptor complex (e.g., CD14, MD-2, and MyD88) have been studied in adult populations, but no such studies have yet to be performed in children.[101,106-109] SNPs in other classes of toll-like receptors have also been studied. For example, gene polymorphisms of TLR-2, the primary pattern recognition receptor for gram-positive bacteria, have been associated with increased risk of infection in children and adults.[110-112]

Several SNPs affecting cytokine expression have been described, but the corresponding gene association studies in critically ill adults with septic shock have been conflicting.[96,97,113] For example, two allelic variants of the TNF-α gene have been described: the wild-type allele TNF1 (guanine at –308A), and TNF2 (adenosine at –308A). The TNF2 allele has been associated with higher expression of TNF-α and increased susceptibility to septic shock and mortality in at least one study involving critically ill adults.[114] Nadel and colleagues found an increased risk of death in critically ill children with meningococcal septic shock who carried the TNF2 allelic variant.[115] Several additional SNPs in TNF-β, IL-1, IL-6, IL-8, and IL-10 have also been shown to influence susceptibility to and severity of septic shock in children.[116-122]

Because dysregulation of the coagulation cascade plays an important role in the pathophysiology of septic shock, several studies have examined polymorphisms of key genes involved in coagulation. For example, the 4G allele of a deletion/insertion (4G/5G) SNP in the promoter region of the plasminogen-activator inhibitor type-1 (PAI-1) gene has been associated with higher plasma concentrations of PAI-1. The 4G allele increases susceptibility to and severity of septic shock, as well as increasing the risk of mortality in children with meningococcal septic shock.[59,123-125] In addition, an SNP in the protein C promoter region has been associated with susceptibility to meningococcemia and illness severity in children.[126]

SNPs in genes involved in phagocytosis and the complement cascade have also been studied in the context of septic shock. For example, SNPs that affect function have been described in virtually all family members of the Fcγ receptor (important for phagocytosis), and several of these SNPs have been associated with susceptibility to meningococcal sepsis, severity of meningococcemia, and poor outcome from meningococcal septic shock.[127-133] In addition, an association between the FcγRIIa polymorphism and infection with other encapsulated bacteria has also been reported.[134,135] Several SNPs in the mannose-binding lectin (MBL) gene have been associated with increased susceptibility to infection, as well as increased illness severity.[136-141] Finally, an SNP of the bactericidal/permeability-increasing protein (BPI) gene has also been associated with increased mortality from septic shock in children.[142] This polymorphism is particularly interesting given that a well-conducted Phase III trial of recombinant BPI in children with septic shock failed to demonstrate efficacy.[143]

It is likely that many more studies are forthcoming in the future that will attempt to link SNPs with the susceptibility and/or outcome of pediatric septic shock, and all need to be carefully considered and evaluated. With respect to validity and wide clinical acceptance, the ideal candidate-gene association study requires several important qualities including biological plausibility, large sample sizes, a priori hypothesis statements and power calculations, accounting for confounding factors, and independent validation.[144]

Genome-Wide Expression Profiling in Children with Septic Shock

The development of microarray technology has provided an unprecedented opportunity to efficiently measure genome-wide mRNA expression patterns in clinical samples. Recently, this approach has been leveraged to understand more comprehensively the pathophysiology of pediatric septic shock, and as a means of discovery and hypothesis generation.

The first publication involving genome-wide expression patterns in pediatric septic shock consisted of 42 children with septic shock that were compared to 15 normal controls.[145] RNA samples were derived from whole blood samples obtained within 24 hours of admission to the pediatric intensive care unit with septic shock. As would be predicted, this comparison between two biological extremes (i.e., normal vs. septic shock), demonstrated a large number of genes (>2000) that were differentially expressed/repressed in patients with septic shock, relative to normal controls. Also as would be expected, the upregulated genes in the patients with septic shock corresponded significantly with functional annotations (i.e., attaching biological information to genomic elements) related to immunity and inflammation.

The most novel finding of this initial genome-wide expression profiling study surrounded the genes that were significantly repressed in the patients with septic shock, relative to controls (more than 1000 genes). Surprisingly, a large number of these repressed genes significantly corresponded to functional annotations and ontologies (i.e., gene attributes across all species) related to zinc biology. Thus, this initial approximation of the genomic response of pediatric septic shock suggested that pediatric septic shock is characterized by repression of a large number of genes that either directly participate in zinc homeostasis, or directly depend on zinc homeostasis for normal functioning. Consistent with this observation, the patients with septic shock that did not survive had significantly lower serum zinc levels compared to the patients with septic shock that survived. These data have generated the testable hypothesis that altered zinc homeostasis may play a role in the pathophysiology of septic shock, and is consistent with the known links between zinc and immune function.[146] Recently, Knoell and colleagues[147] independently corroborated the potential validity of this hypothesis by demonstrating that zinc depletion leads to increased death in a murine model of sepsis, and that zinc supplementation partially reverses this phenotype.

The second microarray-based study in pediatric septic shock focused on longitudinal expression profiles, which consists of comparing gene expression patterns in the same patient cohort over time.[148] RNA samples were obtained within 24 hours of admission to the PICU ("day 1"), and 48 hours later ("day 3"). Thirty children having complete microarray data

on day 1 and day 3 were compared to 15 normal controls. The upregulated genes in the patients with septic shock again corresponded to multiple signaling pathways and gene networks associated with inflammation and immunity. One of the most notable signaling pathways represented by the upregulated gene lists was the IL-10 signaling pathway. As described above, IL-10 is a canonical antiinflammatory signaling molecule for the adaptive immune system in that it represses Th1 cytokine production (lymphocyte inactivation), MHC class II-mediated antigen presentation, and costimulatory molecules for macrophages.[149] A large number of genes corresponding to the IL-10 signaling pathway were persistently upregulated in children with septic shock on both days 1 and 3.

The downregulated gene expression patterns in this longitudinal study again demonstrated large-scale repression of genes corresponding to zinc-related biology. This pattern of repression persisted, to a similar degree, from day 1 to day 3. Another notable gene repression pattern involved T cell receptor signaling and the antigen presentation pathway. Again, this pattern of gene repression was evident as early as day 1, and persisted well into day 3.

In summary, this follow-up study focused on longitudinal genome-wide expression profiles demonstrated persistent repression of genes corresponding to the adaptive immune system. This observation suggests that the pathophysiology of pediatric septic shock may represent a failure of the adaptive immune system and is well in line with the paradigm of "sepsis as an adaptive immune problem," as described above.[16,17,78,79,85,86,88,150-152]

The third microarray-based study in pediatric septic shock focused on validation of previous observations by way of formal class prediction modeling and by the application of alternative filtering and statistical approaches.[153] This study made use of the original data as the "training data set" and a new cohort of patients with septic shock as the "test" or "validation" data set. Using two distinct class prediction algorithms, the gene list derived from the training data set was able to identify the separate cohort of patients with septic shock in the validation data set with 100% accuracy. In addition, the application of alternative gene filtering and statistical approaches to the validation cohort of patients yielded similar observations to that derived from the original data. Namely, the validation data cohort of children with septic shock was also characterized by large-scale repression of genes corresponding to zinc-related biology and adaptive immunity.

The most recent microarray-based studies in pediatric septic shock have addressed two distinct questions: (1) Are the reported gene expression profiles discussed above specific to patients with septic shock, or are they more generic manifestations of critical illness? and (2) Can gene expression profiling be leveraged to identify subsets or subclassifications of children with septic shock?

The first question of specificity was addressed by comparing the gene expression profiles between children with SIRS, children with sepsis, and children with septic shock.[154] These comparisons identified some patterns of conserved gene expression across the pediatric SIRS, sepsis, and septic shock spectrum, particularly with regard to upregulation of genes corresponding to innate immunity and inflammation. There were, however, several notable gene expression patterns that were unique and persistent in the patients with septic shock, relative to the patients with SIRS or sepsis. Specifically, the patients with septic shock had the most prominent and persistent upregulation of genes corresponding to the IL-10 signaling pathway. In addition, repression of zinc biology-related and adaptive immunity-related genes was most prominent and persistent in the patients with septic shock. These data indicate that the previous observations surrounding zinc biology and adaptive immunity are relatively specific to pediatric septic shock, rather than being generic manifestations of critical illness, or even of the sepsis spectrum as a whole.

The second question of subclassification was addressed by using microarray data from 98 children with septic shock.[155] Through a discovery-oriented gene filtering approach and unsupervised hierarchical gene clustering, three putative subclasses of children with septic shock were identified solely based on the gene expression profiles. One of these three expression-based subclasses was characterized by significantly greater repression of genes corresponding to zinc biology and adaptive immunity, compared to the other two putative subgroups. Notably, this subclass of patients had a significantly higher severity of illness and a significantly higher mortality rate compared to the other two subclasses. These data suggest that molecular subclassification, with clinical significance, may be possible through gene expression profiling.

Treatment Strategies

As the biologic response to sepsis becomes better understood and as we refine our ability to phenotype/stratify patients, the approach to treatment of sepsis will become more specific and more sophisticated. At present, however, clinical treatment of sepsis entails four important goals, which for the most part rely on purely supportive measures founded upon the fundamental principles of critical care medicine: initial resuscitation, pathogen elimination, maintenance of oxygen delivery, and carefully directed regulation of the inflammatory response. An update of pediatric and neonatal specific guidelines for sepsis management was recently published.[156]

Initial Resuscitation

As in any disease process, the first step in the treatment of sepsis is the initial stabilization of the patient. In this regard, children present many of the same challenges as adult patients, including respiratory and cardiovascular stabilization. The primary goals of therapy in the first hours are to maintain oxygenation and ventilation, achieve normal perfusion and blood pressure, and reestablish appropriate urine output and mental status.[156]

Children with signs of sepsis may have significantly decreased mental status, raising concern about the ability to protect their airway. Also, in septic shock the work of breathing can represent a significant portion of oxygen consumption (as much as 15% to 30%). Because children with septic shock also receive large amounts of fluid to restore intravascular volume in the context of capillary leak, they are at increased risk for developing pulmonary edema. Consequently, lung compliance decreases and the work of breathing can increase substantially. Together, these respiratory abnormalities often necessitate tracheal intubation and mechanical ventilation. Arterial blood gas analysis often reveals, in early sepsis, respiratory alkalosis from centrally mediated hyperventilation. As sepsis progresses, patients may have hypoxemia and

respiratory acidosis, secondary to parenchymal lung disease and/or hypoventilation due to altered mental status.[156] However, the decision to initiate mechanical ventilation support should not necessarily be contingent on laboratory findings; rather, the decision should be primarily based on clinical findings of increased work of breathing, hypoventilation, and/or impaired mental status. Mechanical ventilation provides the added benefit of reducing work of breathing, therefore decreasing overall oxygen consumption, especially when combined with sedation and paralysis. If early tracheal intubation is chosen, consideration of volume loading and inotropic/vasoactive support is recommended. Sedative agents for induction should be selected to maintain hemodynamic stability. The 2007 pediatric guidelines for septic shock specifically recommend against the use of etomidate due to its adrenal-suppressive effects, and suggest the use of ketamine as a suitable agent to maintain hemodynamic stability.[156] Subsequent studies, however, suggest no effect on mortality or length of stay in adults with septic shock that were intubated with etomidate.[157,158]

For a variety of reasons, patients with sepsis almost universally have decreased effective intravascular volume. Many had poor oral intake of fluid for a period of time prior to developing sepsis. With the development of increased vascular permeability, intravascular volume has been lost because of third spacing. Finally, vasodilation partially related to excessive NO production (see earlier section) results in abnormally increased vascular capacitance, thereby decreasing the effective intravascular volume. When sepsis is suspected, vascular access should be obtained and 20 mL/kg of isotonic fluid administered as quickly as possible. A second peripheral vascular access is recommended, and difficulties in attaining venous access can be overcome with the use of an intraosseous catheter. Intraosseous access can temporarily be the primary route for volume infusion, medications, and blood products when an intravascular access is not readily obtained. While following clinical examination for signs of overly aggressive volume resuscitation (e.g., new onset of rales, increased work of breathing, development of a gallop, abdominal distension, or hepatomegaly), fluid should be administered quickly with the goal of improving blood pressure and tissue perfusion. Administration of more than 60 mL/kg of isotonic fluid in the first hour of resuscitation is associated with improved survival.[159-161] However, volumes up to 200 mL/kg may be required during the first few hours. The importance of vigorous, early, goal-directed therapy (volume repletion, attainment of a target blood pressure, central venous oxygen saturation ≥70%, urine output >1 mL/kg/h) in significantly reducing sepsis mortality has been demonstrated in both adult and pediatric patients.[162,163] A pediatric algorithm for early goal-directed therapy, based on central venous oxygen saturation measurements, is provided in Figure 103-3.

Cardiovascular agents are indicated for fluid-refractory septic shock, and specific agent selection should ideally be predicated on the cardiovascular state of the patient. Patients with septic shock can present with low cardiac output and elevated systemic vascular resistance, high cardiac output and low systemic vascular resistance, or low cardiac output and low systemic vascular resistance. The incidence of sepsis-induced cardiac dysfunction in children is thought to be considerably higher than in adults, potentially representing up to 80% of fluid-refractory patients.[11]

Cardiovascular agents used to support circulation can be classified as inotropes, vasopressors, vasodilators, and inodilators. Inotropes improve cardiac contractility and can increase heart rate. Vasopressors increase systemic and pulmonary vascular resistance. Vasodilators reduce systemic and pulmonary vascular resistance and, although not directly affecting myocardial contractility, improve cardiac output by decreasing afterload. Inodilators simultaneously improve cardiac contractility and reduce afterload. Purely by tradition, the most common initial agent selected for vasoactive support is dopamine, which provides both inotropic support at lower doses (5 to 10 μg/kg/min) and increased vasomotor tone at higher doses (>10 μg/kg/min). Often it is necessary to escalate the dopamine dosage to high levels (up to 20 μg/kg/min), at which point additional agents should be strongly considered. The decision of which second agent to start should be based on the following determinations: whether the cardiovascular compromise is related to inadequate cardiac output from direct cardiodepressant effects, which requires increased inotropy; decreased vascular tone, which requires vasopressors; or increased afterload from vasoconstriction, which requires peripheral vasodilators. Afterload reduction in the context of septic shock is unlikely to be of benefit in a patient who is not adequately fluid-resuscitated. There is not a single strategy meeting the needs of all patients. Consequently, the therapeutic options must be individualized and adjusted according to patient's response.[12,164] In this regard, the clinician often can be assisted by garnering additional data on the basis of invasive monitoring.

Invasive Monitoring

The final step in the initial resuscitation of a child with sepsis is placement of appropriate and necessary vascular access and monitors. However, attention to the clinical examination as part of the ongoing assessment is imperative. In sepsis, the primary clinical endpoints to assess are changes in level of consciousness, decreased urine output, and poor peripheral perfusion characterized by delayed capillary refill and diminished distal pulses. Unfortunately, children with sepsis can be difficult to examine because they often are tracheally intubated and sedated, and may not have produced any initial urine because of severe hypovolemia. Also, they frequently are receiving vasopressors (sometimes excessively), which can make examination of the skin for assessment of perfusion less reliable. For these reasons, invasive monitoring often is necessary and helpful.

Central venous access is a necessity for the child in septic shock. The decision to place a central venous catheter in the internal jugular, subclavian, or femoral position is dictated by a number of factors, such as the experience level of the operator, the presence of coagulopathy, and the possibility of monitoring central venous pressure and central venous oxygen saturation. Central venous catheters provide access for reliable delivery of vasoactive medicines and large volumes of fluid. However, they also can be used to obtain a measurement of central venous pressure (CVP) and, depending on location, may provide an approximate measurement of the mixed venous oxygen saturation.[164-166] Femoral catheters, in the absence of abdominal pathology, can be used to estimate CVP with good correlation.[166] Although use of CVP is very common in clinical practice, the measurement of CVP in isolation

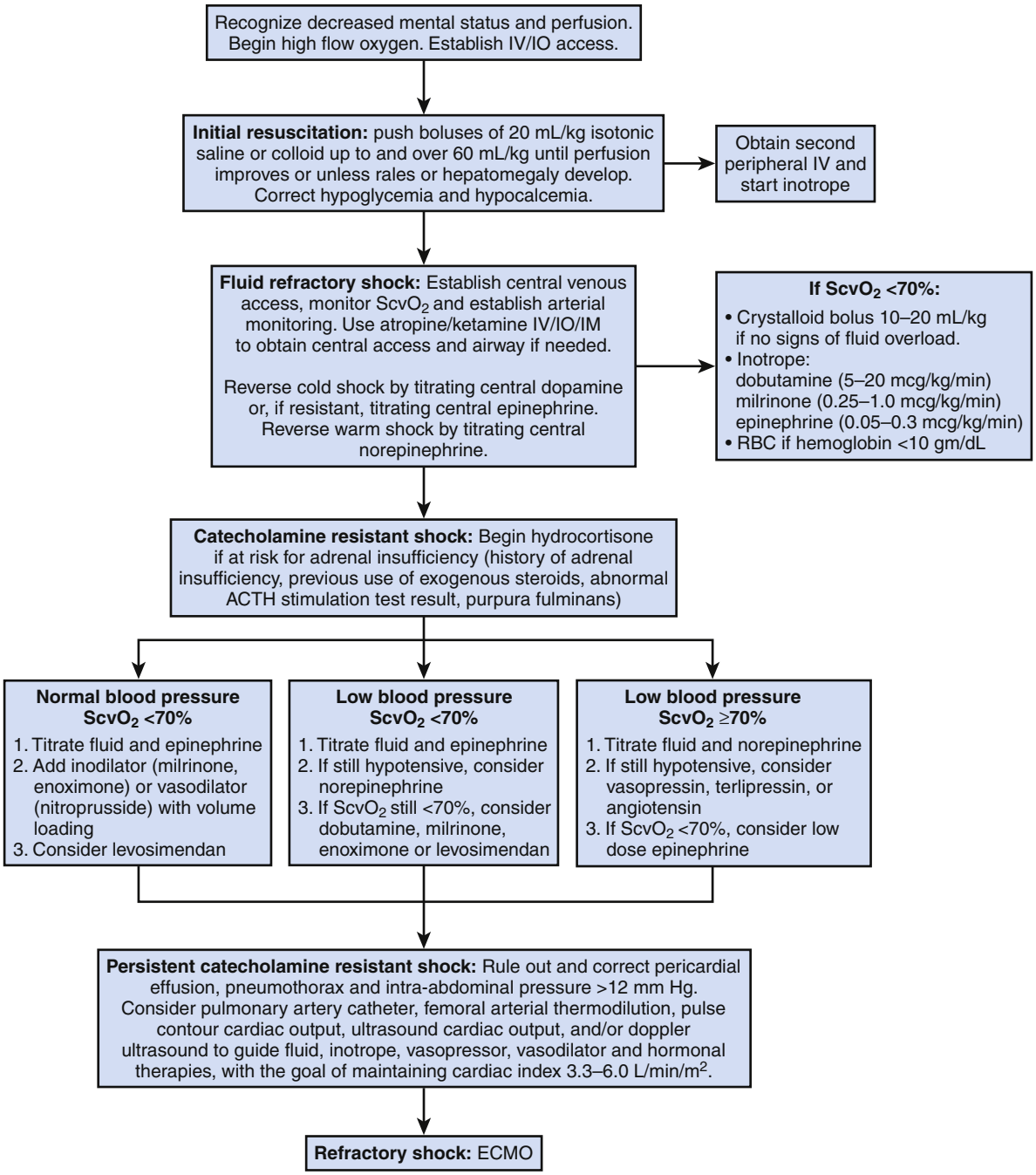


Figure 103–3. Algorithm for early goal directed therapy, guided by central venous saturation, in pediatric septic shock.

cannot reliably estimate volume status or preload of the heart, as it depends on the interactions of cardiac function, cardiac compliance, and intravascular volume.[167,168] For example, a low CVP may be present with hypovolemia and normal cardiac function, but may also be present in a patient with normovolemia and a hyperdynamic status. On the other hand, a high CVP can be observed in hypervolemic patients, but also in normovolemic, or even hypovolemic, patients with cardiac dysfunction. Factors that can elevate CVP even in the presence of hypovolemia include pulmonary hypertension, right ventricular dysfunction, tricuspid regurgitation, high positive end-expiratory pressure, high abdominal pressure, cardiac tamponade, and intracardiac left-to-right shunts. Thus, CVP measurements need to be interpreted in the context of the specific clinical situation and patient.

The measurement of CVP without corresponding direct or indirect measurement of cardiac output also may not discriminate fluid responsiveness.[167] The hemodynamic response to fluid load can be estimated with the application of a fluid challenge, which is the rapid infusion of a fluid bolus of sufficient magnitude to increase CVP by approximately 2 mm Hg. A change of CVP of this magnitude will typically produce, in fluid-responsive patients, a significant change in cardiac output. When a direct measure of cardiac output is not available, other surrogates, such as central venous oxygen saturation, should be followed. A practical maneuver that simulates a fluid

challenge procedure is passive leg-raising. Passive leg-raising to 30° increases venous return and transiently increases cardiac output and blood pressure in a fluid-responsive patient.[169,170] It is important to emphasize, however, that the identification of a fluid-responsive patient does not necessarily mean that the patient needs additional large volumes of fluid.[169]

Accurate determination of the true mixed venous saturation in the pulmonary artery requires a pulmonary arterial catheter (PAC), but approximations of the saturation can be provided by a catheter tip at or near the right atrium. Values of oxygen saturation measured at the right atrium or superior vena cava are slightly different from true mixed venous saturation, but there is a good trend correlation between the two measurements.[164,171,172] Therefore, the use of central venous (right atrium or superior vena cava) oxygen saturation is more practical and feasible as it avoids the requirement for pulmonary artery catheterization. Because of significant differences in oxygen extraction between the upper extremities, abdomen, and lower extremities, venous saturations from a femoral venous line do not accurately correlate with those measured in the pulmonary artery.[166] Measurements of central venous saturation can be achieved through the analysis of blood samples collected from correctly positioned catheters (intermittent), or continuously with the utilization of an indwelling fiberoptic catheter. A superior vena cava oxygen saturation greater than 70%, and therapeutic maneuvers targeted at achieving this goal, are associated with improved outcome in children and adults with septic shock.[162,163]

In the face of severe sepsis and septic shock, an intraarterial catheter becomes necessary. An arterial catheter becomes both a source of continuous clinical information regarding blood pressure, pulse pressure, hemodynamic variation with respiration (i.e., pulsus paradoxus), and an access for frequent blood draws. Whereas blood pressure alone does not always equate to tissue perfusion because of differences in regional perfusion and vasoconstriction, a fluid-resuscitated child with normal or high systolic blood pressure will be more tolerant of manipulations to increase perfusion (i.e., afterload reduction) than children with lower blood pressures. This condition occurs in children who have poor ventricular ejection and high systemic vascular resistance. Therapeutic maneuvers to actively decrease afterload can be more rationally conducted with continuous blood pressure monitoring via an intraarterial catheter.

The arterial blood also provides the most accurate information regarding arterial oxygen content that can be used to both assess the function of the lungs and to maximize oxygen delivery. Additionally, the analysis of the arterial pulse wave can provide a continuous monitoring of the cardiac output. Recent studies reveal that this cardiac output estimation technique can be safely applied in children, and has reasonable correlation with thermodilution or echocardiography-based techniques.[173,174]

Use of PACs to optimize left ventricular preload, monitor changes in cardiac index, and provide accurate measurements of oxygen delivery and consumption is now controversial. Interpretation of PAC data requires the absence of intracardiac shunting and the presence of normal mitral valve function, as either shunting or mitral regurgitation alters cardiac index determination and pulmonary capillary wedge pressure measurements. Because data from critically ill adults showed no benefit of routine PAC use,[175] the use of PACs has substantially declined in critical care medicine, but is thought to be of potential benefit in selected patients.[176] In light of studies showing that the information obtained from PAC can be important in identifying clinically meaningful cardiovascular conditions that are different from what is suspected by clinical impression,[11,176] PAC placement may be considered for pediatric patients who remain in shock after resuscitation and initiation of the usual cardiovascular agents, and in patients having unclear fluid status and cardiac function. Other methods of measuring cardiac output, such as arterial pulse wave analysis, femoral artery thermodilution, Doppler ultrasound, or ultrasound cardiac output monitoring, may be effective substitutes to the use of PAC.

Elimination of Pathogens

Identification of the source of a possible offending organism in septic shock dictates the choice of antimicrobial coverage and is important to long-term outcome, as early administration of appropriate antibiotics is associated with improved survival.[177] While the imperative nature of prompt antibiotic treatment may seem intuitively obvious, it has been well documented that delays in appropriate antibiotic administration have a greater adverse impact on septic shock outcome than do cytokine polymorphisms.[178] Therefore, antibiotic therapy should be started within the first hour of recognition of sepsis, ideally after appropriate cultures have been readily obtained. However, antibiotic administration should not be delayed if obtaining appropriate cultures is technically problematic.

The offending organism and the site of infection also affect prognosis. Fungal infections are associated with the lowest survival rates, followed by bacterial infections, especially meningococcal and pneumococcal infections.[2] It is important to note, however, that the epidemiology of pediatric sepsis is changing, particularly in populations where vaccination policies incorporate immunization against *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* serotype C. While infections caused by these agents have decreased, there are now more cases of nosocomial infections, especially caused by staphylococci and fungi. The majority of infections causing severe sepsis are respiratory or primary bacteremia, with respiratory cases being more common among older children and in community-acquired infections, and primary bacteremia more frequently affecting neonates, children with neoplastic disorders, or those with other comorbidities. Lower survival rates are associated with endocarditis and infections of the central nervous system.[2]

Initial empirical antimicrobial therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that penetrate into the presumed source of the sepsis. The choice of drugs should be guided by the susceptibility patterns of microorganisms in the community and in the hospital.[177] Because of the importance of appropriate antimicrobial therapy, the decision regarding which agents to empirically start must balance potential side effects against maximizing coverage. Initially, broad antibiotic coverage should be started. Neonates should be given ampicillin and either gentamicin or a third-generation cephalosporin such as cefotaxime. In infants and children older than 4 to 6 weeks, the decision to begin vancomycin therapy empirically, in addition to the standard third-generation cephalosporin, should be considered in light of the increasing antibiotic resistance of *Streptococcus pneumoniae*, as well as methicillin-resistant

Staphylococcus aureus. Nosocomial infections and infections in immunocompromised patients require additional coverage for the possibility of *Pseudomonas* species and other resistant organisms. Acyclovir should be given if there is a clinical presentation or suspicion of an overwhelming viral (herpetic) infection, particularly in neonates and infants. Starting antifungal medicines initially in an immunocompetent child usually is not necessary. However, this decision should be reconsidered if the child does not improve over the first 2 days or in case of higher risk for fungal infection (presence of indwelling devices, immunosuppression, or other significant comorbidities). The antimicrobial regimen should be reassessed after 48 to 72 hours on the basis of microbiological and clinical data with the goal of narrowing the antibiotic spectrum to prevent the development of resistance and to reduce toxicity. Once a causative pathogen is identified, there is no evidence that combination therapy is more effective than monotherapy for most bacterial infections. The duration of therapy should typically be 7 to 10 days and guided by clinical response.[177]

Maintenance of Oxygen Delivery

After initial resuscitation and attention to pathogen elimination, ongoing management of sepsis remains primarily supportive, with particular attention to maintenance of adequate oxygen delivery. While this is a fundamental tenet of critical care medicine, the approach may be relatively ineffective in a subset of patients having impaired utilization of oxygen despite adequate oxygen delivery (i.e., cytopathic hypoxia). The assessment of adequate oxygen delivery should be viewed as a dynamic and ongoing process as measured by a combination of parameters including clinical assessment of perfusion, blood pressure, serial lactate measurements, urine output, central/mixed venous oxygen saturation, and, in selected cases, PAC-derived measurements.[162]

Adequate preload is necessary for adequate cardiac output, and consequently for adequate oxygen delivery. Children with sepsis can remain at risk for hypovolemia after an appropriate initial resuscitation because of persistent increased insensible fluid loss, increased vascular capacitance, and capillary leak with third spacing. Anecdotally, some well-resuscitated children have such vigorous urine output after the initial resuscitation that reassessment of fluid balance after the first 24 hours of presentation to the ICU reveals that the fluid balance may actually be close to "even." Thus, providing adequate preload to the patient in septic shock may require increased fluid administration for several days after the initial resuscitation. The choice of fluid to be used in this process is controversial, although there is general agreement that the fluid choice should be isotonic. The three broad choices of fluids are crystalloid, non-blood colloid, and blood products. As evident when calculating the arterial content of oxygen, maintaining an adequate hemoglobin level is an important factor in providing adequate oxygen delivery. Although there is no clear recommended hemoglobin level for children with sepsis, one recent study showed that in patients with central venous oxygen saturation less than 70%, transfusion of packed red blood cells, in combination with other measures to increase oxygen delivery, is associated with improved outcomes.[162]

After initial resuscitation, ongoing myocardial dysfunction and altered vascular tone are likely to persist and will therefore require ongoing titration of cardiovascular drugs to maintain adequate oxygen delivery. Many patients will require titration of inotropes and vasopressors simultaneously, and it must be emphasized that this will likely be a dynamic process requiring constant reassessment of the aforementioned indicators of adequate oxygen delivery. It is important to recognize that blood pressure alone as a goal may not correlate with optimal tissue perfusion and oxygen delivery. This concept is best illustrated by the subset of patients with septic shock who benefit from afterload reduction (i.e., vasodilation). Patients with high systemic vascular resistance (SVR) and low cardiac output, who have adequate preload, can benefit tremendously from inodilators such as milrinone.[179,180] Alternatively, this subset of patients can also benefit from pure vasodilators such as the NO donor, nitroprusside (in combination with a pure inotrope). After institution of afterload reduction, these types of patients may actually have lower blood pressures than one would typically target, but will have enhanced tissue perfusion and oxygen delivery.

A subset of patients will have refractory shock despite optimization of the above management strategies. In this subset, the institution of extracorporeal membrane oxygenation (ECMO) is recommended as a consideration in the context of refractory shock.[156] Our anecdotal and subjective experiences suggest that institution of ECMO support for refractory septic shock can be lifesaving in a subset of patients. The challenges that come with institution of ECMO include the definition of refractory septic shock, timing of ECMO initiation before the onset of irreversible end organ failure, and ensuring that ECMO support is not prematurely or unnecessarily instituted in patients that can be effectively managed with conventional support (i.e., not exposing patients to unnecessary risks).

A summary of approaches to improving the relationship between oxygen delivery and oxygen consumption is provided in Box 103-3.

Box 103–3 Means of Altering the Relationship Between Oxygen Delivery and Oxygen Consumption

Means of Improving Oxygen Delivery:

- Increase cardiac output
  - Increase stroke volume
  - Increase preload (volume resuscitation)
  - Increase contractility (administration of inotropes)
  - Decrease afterload (administration of vasodilators)
  - Increase heart rate (rarely a therapeutic goal in sepsis management)
- Increase arterial oxygen content
  - Increase arterial oxygen tension (administer oxygen, apply positive-pressure ventilation, etc.)
  - Increase arterial oxygen carrying capacity (transfusion of packed red blood cells)
- In select cases, cardiac output and arterial oxygen content can both be increased through the institution of venoarterial extracorporeal membrane oxygenation.

Means of Decreasing Oxygen Consumption:

- Avoid/manage hyperthermia
- Remove work of breathing
- Administer sedation
- Administer paralytics

Additional Management Considerations

Patients with sepsis may have poor nutrition prior to presentation and often are not fed during the first few days of illness. Because of an increased metabolic rate and poor nutrition, patients with sepsis are frequently catabolic and at risk for development of protein-calorie malnutrition.[181] Intestinal ischemia in association with loss of the mucosal barrier from malnutrition is associated with translocation of bacteria and endotoxin from the intestine into the bloodstream. Use of enteral feeding in critically ill patients has been shown to improve survival and decrease hospital stay.[182] The benefit of enteral feeding should be balanced with the risk of stressing intestinal function in the face of poor splanchnic perfusion, especially in the presence of vasopressors such as epinephrine and norepinephrine.[183] Regardless of the feeding mode, adequate nutrition and nitrogen balance are important for maintaining adequate host immune function and achieving homeostasis, as malnutrition adversely affects immune function. Finally, in the absence of enteral feedings, pharmacologic prophylaxis against stress-related gastrointestinal bleeding is recommended by the most recent guidelines.

Fluid overload, as a consequence of aggressive fluid resuscitation and capillary leak, is an important issue that eventually needs to be addressed in virtually all patients with septic shock. General signs of clinically significant fluid overload include hepatomegaly; rales/pulmonary edema; a substantially positive fluid balance; ascites and, potentially, intraabdominal hypertension; and/or 10% increase in body weight. For many patients, institution of diuretic therapy is a simple and effective approach to dealing with fluid overload, in the context of hemodynamic stability and adequate renal function. However, acute kidney injury/renal failure commonly occurs in septic shock and may require institution of some form of renal replacement therapy such as peritoneal dialysis, hemodialysis, or continuous renal replacement therapy (CRRT).

Variations of CRRT are commonly viewed as the most ideal choice for these patients, given the potential ability to meticulously titrate fluid removal in patients with hemodynamic instability. In addition, CRRT has the potential to achieve more than simple fluid removal; inasmuch as high ultrafiltration rates can also provide clearance of standard waste products of metabolism, as well as "mediators" of sepsis (i.e., immune modulation). However, CRRT is also well documented to be associated with clinically significant complications (e.g., hemodynamic instability and electrolyte imbalances) in critically ill children.[184] Thus "timing" and "dose" are important considerations for institution of CRRT in patients with septic shock, and both considerations are predicated on the concept that CRRT represents more than just simply fluid removal and management of uremia.[185] "Timing" refers to the concept of instituting CRRT before the onset of overt renal failure and clinically significant fluid overload. "Dose" refers to the concept of ultrafiltration rates and the potential ability of high filtration rates to achieve more effective immune-modulation. These important concepts represent major challenges in the field that need to be addressed by well-designed, pediatric-specific multicenter trials. Importantly, a recent trial compared high ultrafiltration rates (high-intensity CRRT) to standard ultrafiltration rates (low-intensity CRRT) in over 1500 critically ill adults.[186] There was no difference in the primary outcome variable (90 day mortality) between the two treatment groups. However, there was an intriguing trend toward improved survival in the subset of patients with sepsis that underwent high-intensity CRRT.

Hyperglycemia is well recognized to be associated with increased morbidity and mortality in critically ill patients, including children with sepsis.[187,188] In 2001, van den Berghe and colleagues[189] published a landmark study demonstrating that aggressive insulin therapy to normalize glucose levels to within a very narrow range significantly increased survival in a large cohort of critically ill adult surgical patients. This study strongly suggested that hyperglycemia is not merely a stress-related epiphenomenon of critical illness, but rather a pathologic process that can be addressed by an intensive insulin-based protocol targeting normalization of glucose levels. However, the inability to consistently replicate these findings has led to a great deal of controversy in the field. A recent meta-analysis concluded that tight glucose control does not significantly reduce mortality in critically ill adult patients, but is associated with an increased risk of hypoglycemia.[190] An even more recent, randomized, multicenter trial compared intensive glucose control (81 to 108 mg/dL) to conventional glucose control (<180 mg/dL) in over 6000 critically ill adults.[191] This study concluded that intensive glucose control increased mortality in critically ill adults, relative to conventional glucose control. Finally, another recent trial focused on intensive insulin therapy in adults with sepsis demonstrated no survival benefit, but an increased risk of clinically significant hypoglycemia.[192]

The most current pediatric-specific sepsis guidelines recommend insulin therapy to maintain glucose levels less than or equal to 150 mg/dL, and avoiding hypoglycemia by keeping glucose levels greater than or equal to 80 mg/dL.[156] This is a level 3 recommendation (adequate scientific evidence is lacking but widely supported by available data and expert opinion), but was generated prior to the publication of a recent trial investigating intensive insulin therapy specifically in critically ill children.[193] The majority of patients in this trial (approximately 75%) were surgical patients undergoing correction of congenital heart malformations. Intensive insulin treatment resulted in improved short-term outcomes (decreased ICU length of stay and decreased parameters of inflammation), but also resulted in a 25% rate of hypoglycemia. There are no large pediatric-specific trials addressing insulin-based glucose control specifically in the context of septic shock. Therefore, in light of the current data, and taking into consideration the risks of hypoglycemia in children, a glucose level of no greater than 180 mg/dL seems to be a reasonable target, pending a formal study.

Immune Modulation

Since immune/inflammatory dysregulation is a well-accepted pathophysiological concept in septic shock, there has been a great deal of effort in developing treatment strategies directly targeted at immune/inflammatory modulation. Steroids have long been proposed as a general antiinflammatory strategy. In many clinical settings, patients with septic shock demonstrate worsening of their shock temporally associated with antibiotic administration. It is thought that this phenomenon results from a massive release of bacterial toxins after antibiotic-mediated bacterial killing, and a subsequent inappropriately

exuberant immune/inflammatory response. However, the use of high-dose steroids to blunt this response is now universally accepted to be of no benefit and potentially harmful.[194,195]

A more recent approach to using steroids in septic shock involves the concept of relative adrenal insufficiency, and an association between adrenal insufficiency and catecholamine-refractory shock.[196,197] A landmark study by Annane and colleagues demonstrated a substantial benefit in adults with septic shock having "relative adrenal insufficiency" (based on cortisol levels and ACTH stimulation testing) and treated with replacement hydrocortisone.[198] However, a subsequent trial did not demonstrate the efficacy of hydrocortisone replacement, thus leading to an ongoing, unresolved controversy in the field.[199,200] Conflicting data and controversy also exist in the pediatric septic shock population.[201,202] The role of hydrocortisone replacement in pediatric septic shock represents another major challenge in the field that must be directly addressed by a large, multicenter, randomized trial. Current barriers to conducting this important trial include lack of equipoise in the pediatric critical care community and lack of consensus regarding the definition of relative adrenal insufficiency. Thus, at present, the treatment guidelines suggest hydrocortisone replacement therapy be considered for patients who appear refractory to resuscitative measures, have a known history of adrenal insufficiency, have already received exogenous steroids, or have an abnormal ACTH stimulation test result.[156]

Because the pathophysiology of septic shock is directly linked to circulating pathogen-derived toxins and circulating inflammatory mediators, removal of these molecules via hemofiltration or exchange transfusion (i.e., plasmapheresis) has been hypothesized to improve outcome. Both hemofiltration and plasmapheresis were discussed in previous sections. The fact remains that these approaches, while theoretically well-founded, remain to be proven and cannot be recommended routinely in the absence of more objective data. Both strategies carry significant risks that must be weighed against the potential theoretical benefits. These include difficult vascular access in smaller children, fluid and electrolyte imbalance, hypothermia, anticoagulation requirements because of extracorporeal circuits, and acutely altered hemodynamics when instituting therapy. In addition, beneficial proteins such as albumin, immunoglobulins, clotting factors, and counter-regulatory cytokines may be removed to the detriment of the patient.

Part of the inflammatory response involves cytokines that cause widespread activation of the coagulation cascade with suppression of fibrinolysis, as described in previous sections. Disseminated intravascular coagulation has been implicated in the etiology of multiple organ injury leading to MODS, and is directly linked to alterations of endogenous anticoagulants such as antithrombin III and protein C. While recombinant forms of these anticoagulants are available, they have not been demonstrated to be efficacious in the pediatric population and carry significant risks of serious adverse events due to bleeding.

As previously described, multiple antiinflammatory strategies have been attempted and some are now being reconsidered. These include anti-TNF, anti-IL1, anti-endotoxin, and anti-PAF strategies. Thus far none of these strategies have proven to be of sufficient clinical benefit in septic shock to warrant formal approval as standard of care. It is hoped that better designed studies that carefully stratify patients, consider the presence or absence of an offending pathogen, and possibly identify genetic factors influencing outcome will provide insight into the appropriate immunomodulating agents that will be clinically beneficial to pediatric patients with septic shock. Of note, there are currently two ongoing phase III trials based on a TLR-4 antagonist strategy in adults with septic shock.[203]

An alternative approach to immune modulation in septic shock focuses on immune "enhancement" rather than inhibition of inflammation. As emphasized in previous sections, the paradigm of sepsis as an adaptive immune problem is increasingly gaining credence in the field. Thus there is now growing attention to the use of potentially immune-enhancing agents such as interferon-γ, granulocyte-macrophage colony stimulating factor, zinc, selenium, prolactin, agonist antibody to CD40, and interleukin 7.[17,204-206] Thus, the next major advance in the clinical septic shock may involve one or more of these immune-enhancing approaches, rather than an anti-inflammatory approach.

The Case for More Effective Stratification in Pediatric Septic Shock

The vast majority of interventional clinical trials in septic shock have failed to demonstrate efficacy of the particular test agent. We propose that the reason for failure in these trials is not because the biological/physiological principle being tested was fundamentally flawed. Rather, the primary reason for failure lies in the inability to effectively address the substantial heterogeneity that characterizes the syndrome of septic shock. As indicated throughout this chapter, septic shock is a heterogeneous syndrome with the potential to negatively and directly affect all organ systems, and this heterogeneity has consistently challenged multiple investigators attempting to evaluate the efficacy of various experimental interventions. As astutely stated by Marshall, a key challenge in the field is to reduce and manage this heterogeneity by more effectively stratifying patients for the purposes of more rational and effective clinical research and clinical management.[207] The concept of preintervention stratification in sepsis, and its positive impact on the efficacy of an experimental therapy, was very recently corroborated by the Remick laboratory in a murine model of polymicrobial sepsis.[32]

One potential strategy for stratifying children with septic shock involves early identification of septic shock subclasses based on genome-wide expression patterns. As described above, putative subclasses of children with septic shock have been identified based exclusively on gene expression profiling conducted within 24 hours of admission, and these expression-based subclasses have highly relevant differences in illness severity and mortality.[155] A similar strategy was recently demonstrated in adult patients suffering from trauma.[208] As high-throughput technologies evolve and validation studies are rigorously performed, the ability to conduct expression-based subclassification of pediatric septic shock could very well become a clinical reality.

Another potential strategy for stratifying children with septic shock (and perhaps more readily feasible at present) is biomarker-based stratification. Many biomarkers can be readily measured in the blood compartment, thus providing

a clinically feasible strategy for early stratification of patients. For example, interleukin-8 (IL-8) can be readily and rapidly measured in small volume blood samples. Recently, IL-8 was found to be a very robust outcome biomarker in children with septic shock.[36] Specifically, an IL-8 level, measured within 24 hours of admission to the pediatric intensive care unit, was found to have a 95% negative predictive value for mortality in a derivation cohort of patients. In other words, this particular IL-8 level was able to predict survival in pediatric septic shock with standard care with 95% probability and very narrow confidence intervals. The reliability of this assertion is supported by prospective, formal validation in an independent validation cohort of patients (the RESOLVE database), which demonstrated an identically robust negative predictive value.[36] More recently, a similar observation (98% negative predictive value for mortality) was found by measuring chemokine (C-C motif) ligand 4 (CCL4) serum protein levels within 24 hours of admission to the PICU with septic shock.[209]

It has been proposed that these types of sepsis-outcome biomarkers (i.e., biomarkers having high negative predictive values for mortality) could be used to stratify patients eligible for interventional septic shock trials.[36,209] Patients having a high likelihood of survival with standard care, but otherwise meeting entry criteria for a given interventional trial, could be potentially excluded from the trial based on these biomarkers. Such a stratification strategy would serve to derive a study population with a more optimal risk-to-benefit ratio, thus improving the ability to demonstrate efficacy for a given test agent. This type of strategy would be particularly useful for a test agent carrying more than minimal risk.

While single biomarker-based patient stratification is clinically appealing, it may not be sufficiently robust to meet all clinical and research needs from the combined standpoints of specificity, sensitivity, and positive predictive values. Indeed, the aforementioned studies involving IL-8 and CCL4 had clinically unacceptable specificities, sensitivities, and positive predictive values, relative to the very high negative predictive values. The ideal biomarker-based stratification tool, which would meet a wide range of clinical and research needs, would simultaneously have high specificity, high sensitivity, high positive predictive value, and high negative predictive value.

Given the biological complexity of pediatric septic shock, a stratification strategy based on a panel of multiple biomarkers has more potential to meet the needs of the aforementioned ideal biomarker-based stratification tool. To this end, we have recently derived a panel of 15 biomarkers using a genome-wide expression database of nearly 100 children with septic shock. The database focuses on the gene expression patterns representing the first 24 hours of admission to the pediatric intensive care unit, which is an ideal time-frame for clinically useful stratification. An initial working list of candidate biomarkers was systematically and objectively derived using two complementary statistical tools: analysis of variance (ANOVA) to determine genes differentially regulated between survivors and nonsurvivors, and support vector machines-based class prediction modeling targeted at identification of "survivor" and "nonsurvivor" classes. The final panel of 15 biomarkers was refined from the initial working list based on biological plausibility in the context of sepsis, and the ability to readily measure the biomarkers (proteins) in blood samples. The resulting 15 biomarker list will be used to derive the pediatric sepsis biomarker risk model (PERSEVERE: PEdiatRic SEpsis biomarkEr Risk modEl). PERSEVERE is intended to predict outcome and illness severity for individual patients with septic shock. PERSEVERE will be derived in a formal derivation cohort of patients using statistical modeling approaches, and subsequently validated prospectively in a separate validation cohort. If PERSEVERE comes to fruition, we expect that it will provide an unprecedented decision and stratification tool for the care of individual children with septic shock and for the conduct of interventional clinical trials.

Concluding Perspectives

Sepsis is and will continue to be an important challenge to the pediatric intensivist. Indeed, sepsis is one of the few disease processes for which the pediatric intensivist can claim "ownership." Although much is known about the biological and molecular mechanisms involved in sepsis, much of this knowledge has not directly translated to improved bedside care. At present, most of the therapeutic modalities for sepsis are fundamentally supportive and founded on the basic principles that define the discipline of critical care medicine. Although this approach has directly improved the outcome of sepsis in children, the fact that more than 4000 children per year in the United States alone continue to die in association with severe sepsis warrants further advances. Realization of this goal is feasible but requires further mechanistic insights at the physiological, molecular, and genetic levels, as well as the design of large-scale, pediatric-specific interventional trials complemented by evolving stratification strategies. As "owners" of pediatric septic shock, pediatric intensivists are well positioned to lead this effort on all fronts.

References are available online at http://www.expertconsult.com.

VI Chapter 104

Inflammation and Immunity: Systemic Inflammatory Response Syndrome, Sepsis, Acute Lung Injury, and Multiple Organ Failure

Joseph A. Carcillo, Yong Y. Han, Lesley Doughty, Mark Hall, Trung Nguyen, and Raj K. Aneja

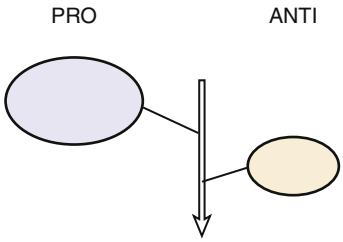
PEARLS

- Systemic inflammatory response syndrome, sepsis, severe sepsis, acute lung injury, acute respiratory distress syndrome, and multiple organ failure are defined by specific clinical criteria. Known outcomes and mechanisms have been evaluated using these clinical syndrome definitions.
- Multiple organ failure (MOF)/multiple organ dysfunction syndrome (MODS) has been classified as primary (occurring in the first 7 days) and secondary (occurring after 7 days). Ninety percent of these patients have MOF at presentation, whereas 10% develop sequential MOF over time with liver and renal involvement following initial lung dysfunction.
- MOF phenotypes include thrombocytopenia-associated MOF, immune paralysis/lymphoid depletion syndrome (predominant TH2 phenotype), viral/lymphoproliferative disorder associated sequential MOF (natural killer cell/cytotoxic T cell/B cell/T-regulatory cell dysfunction), iron overload cardiac/hepatic/pancreatic MOF (secondary hemochromatosis), and hyperleukocytosis MOF (pertussis leukocyte proliferating factor).
- Nonspecific and specific therapies can be successfully directed to patients with MOF/MODS according to these phenotypes, including intensive plasma exchange therapy for thrombocytopenia-associated MOF, rapid tapering of immunosuppressants and administration of low-dose granulocyte-macrophage colony-stimulating factor for immune paralysis, rituximab and intravenous immunoglobulin for posttransplantation proliferative disease, protocols for primary hemophagocytic lymphohistiocytosis, pulse steroids for rheumatologic disease–associated macrophage activation syndrome, interferon-α and intravenous immunoglobulin for secondary hemophagocytic lymphohistiocytosis, iron chelation for iron overload MOF, and leukapheresis for hyperleukocytosis-associated MOF.
- Early goal-directed therapy (time-sensitive achievement of normal blood pressure, capillary refill less than 2 seconds, and central venous oxygen saturation >70%) has been demonstrated as being successful in improving outcomes and reducing the incidence of MOF/MODS. Biomarker goal directed therapy holds similar promise in children with inflammation/immunologic dysfunction-based MOF.

Systemic inflammation can lead to systemic inflammatory response syndrome (SIRS) or sepsis syndrome (when infection is suspected), recognized and defined by the presence of two of the following: tachycardia, tachypnea, fever, and abnormal white blood cell count. Increased systemic inflammation with the compensatory antiinflammatory response syndrome can further mediate severe sepsis (sepsis + single organ failure) and with *immunologic dissonance*, the development of multiple organ failure (MOF) with acute lung injury (bilateral infiltrates with hypoxemia and a partial pressure of oxygen [Pao_2]/fraction of inspired oxygen [Fio_2] ratio <300) or acute respiratory distress syndrome (ARDS) (bilateral infiltrates with hypoxemia and a Pao_2/Fio_2 ratio <200).

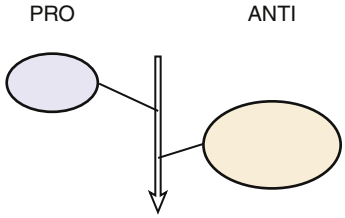
The Inflammation/Coagulation/Immune Dysfunction/Dysregulated Metabolism Hypothesis

Roger Bone popularized the notion that systemic inflammation led to the development of sepsis syndrome and MOF in the 1990s. According to this theory, an initial proinflammatory cytokine response to foreign or self-antigen caused SIRS, a systemic inflammatory response characterized by two of four criteria: tachycardia, tachypnea, fever, and leukocytosis. This syndrome was thought to be mediated



• Temperature changes, tachypnea, tachycardia, acidosis, signs of specific end organ dysfunction.

Figure 104–1. SIRS shows proinflammation self-limited by antiinflammation and eradication of the source of inflammation.



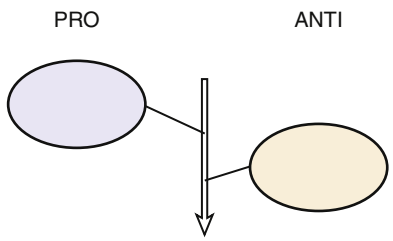
CARS: Compensatory anti-inflammatory response syndrome

• Retaliatory surge of anti-inflammatory mediators released in response to SIRS.

Figure 104–2. The compensatory antiinflammatory response syndrome occurs when the antiinflammatory response is prolonged, leading to increased susceptibility to nosocomial infection.

by increased interleukin (IL)-1 and tumor necrosis factor (TNF)-α levels (Figure 104-1). It could be blunted by nonsteroidal antiinflammatory drugs and hence was prostaglandin mediated. A systemic inflammatory response was called *sepsis* if related to infection and *SIRS* if related to surgery, pancreatitis, or other noninfectious processes. This syndrome was self-limited when antibiotics were used to kill the infection or time allowed recovery from surgery, pancreatitis, and other noninfectious causes. This proinflammatory response was turned off by an antiinflammatory response led by the antiinflammatory cytokine IL-10. When IL-10 resulted in reduction of IL-1 and TNF-α to normal control values, sepsis or SIRS stopped and organ failure did not occur (Figure 104-2). In patients who developed severe sepsis and MOF, the compensatory anti-inflammatory response was unsuccessful in turning off inflammation. Instead, these patients had persistent elevation of the cytokine IL-6 along with IL-10. Bone coined the term *immunologic dissonance* to describe this process. He viewed MOF as an inflammatory condition in which the normal antiinflammatory response was unable to turn off the proinflammatory process (Figure 104-3).

Proulx and colleagues[1] defined pediatric MOF syndromes as primary and secondary. Primary MOF occurred in 90% of children and was present at the time of admission, and secondary MOF occurred in 10% of children and was not present until 7 days after admission.[1] To evaluate the role of inflammation in pediatric sepsis-induced MOF, this group defined children as having no MOF (NMOF) if they had two-organ



Immunologic dissonance

• Massive amounts of both types of mediators are released, but balance cannot be restored.

Figure 104–3. *Immunologic dissonance* refers to patients at greatest risk of MODS/MOF-related death. These patients have uncontrolled proinflammatory and antiinflammatory features with an uneradicated source of inflammation and infection.

failure at presentation but never reached three-organ failure, resolved MOF (RMOF) if they had three-organ failure at admission that resolved to two-organ or less at 48 hours, persistent MOF (PMOF) if they had three or more organ failures at presentation that did not resolve by 48 hours, and sequential MOF (SMOF) if they had acute lung injury/adult respiratory distress syndrome at admission and then progressed to hepatorenal failure/dysfunction.[2] Similar to Proulx's classification, children in the latter investigation with SMOF represented 10% of the population. The mortality rates with NMOF, RMOF, PMOF, and SMOF were 2%, 8%, 35%, and 50%, respectively. The authors then investigated Bone's hypothesis in this categories and reported that patients with NMOF had an increase in IL-10 with subsequent turning off of inflammation; however, those with PMOF or SMOF had persistently high IL-6 and IL-10 levels—the hallmark of Bone's "immunologic dissonance."[2]

Bone's untimely death prevented him from further pursuing the mechanisms by which immunologic dissonance could mediate organ injury. However, Proulx et al. first reviewed the autopsy bank at their hospital and noted that children who died from sepsis-induced MOF exhibited two unsuspected findings compared with children who died of other causes: persistent or unrecognized infection and thrombotic and bleeding complications with organ infarctions. Accordingly, they pursued the notion that immunologic dissonance might lead to an inability to mediate coagulation homeostasis as well as an inability to clear infection. Proinflammatory cytokines including TNF-α and IL-1 induce endothelial activation in vitro with an increased prothrombotic and antifibrinolytic state and expression of adhesion molecules (Figures 104-4 to 104-6). Patients with PMOF had increased tissue factor and plasminogen activator-1 activity as well as circulating adhesion molecules, intercellular adhesion molecule, and vascular adhesion molecule consistent with the hypothesis that immunologic dissonance was associated with an activated prothrombotic/antifibrinolytic endothelium.[3,4] IL-6 also inhibits ADAMTS-13, the von Willebrand factor (vWF) multimer-cleaving protease, in vitro. PMOF patients also had deficient ADAMTS-13 activity compared with NMOF patients, consistent with increased risk of vWF multimer–mediated thrombosis.[5] Increased IL-10 is the hallmark of the TH2 antiinflammatory cytokine response. When the TH2 response is dominant, the TH1 response can be turned

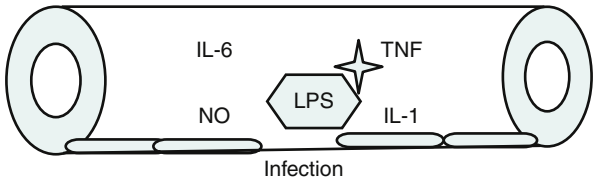


Figure 104–4. Infection evokes a proinflammatory cytokine response that brings blood flow to the site of infection. *LPS,* Lipopolysaccharide.

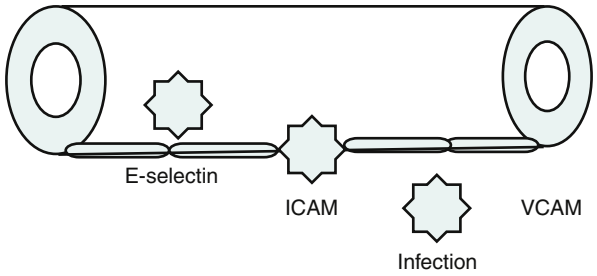


Figure 104–5. The proinflammatory cytokines stimulate expression of adhesion molecules that allow immune cells to roll, stick, and transmigrate to kill the infection. *E-selectin,* Endothelial selectin; *ICAM,* intercellular adhesion molecule; *VCAM,* vascular cell adhesion molecule.

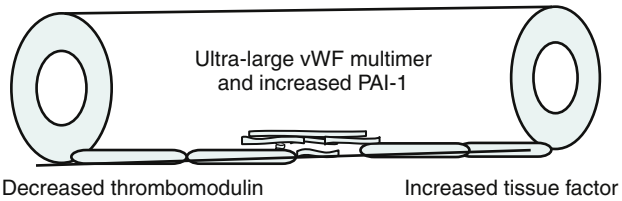


Figure 104–6. The proinflammatory cytokines increase expression of prothrombotic molecules and decrease expression of antithrombotic molecules to seal off endothelium at the site of infection. After the infection is killed and there is no longer a proinflammatory cytokine response, the endothelium returns to its usual antithrombotic, profibrinolytic state. *PAI-1,* Plasminogen activator inhibitor type 1.

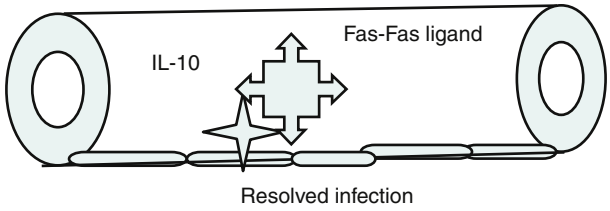


Figure 104–7. After the infection is killed, the antiinflammatory cytokines turn off expression of the proinflammatory cytokines. This results in reduction in monocyte/macrophage TNF production and apoptosis of activated immune cells.

off, a state known as *immune paralysis* (Figure 104-7). These patients have a diminished ex vivo ability to secrete TNF-α from endotoxin-stimulated monocytes or macrophages. Without this ability, infections cannot be terminated. PMOF patients exhibited immune paralysis more frequently than did NMOF patients.[6]

Cytokines and nitric oxide also inhibit cytochrome P450 activity and mitochondrial respiration in vitro. One study group found that patients with PMOF had reduced cytochrome P450 (10-fold) activity compared with patients with NMOF (twofold).[7] *Immunologic dissonance* in PMOF was associated with endotheliopathy, immune paralysis, and poor metabolism, but how was PMOF different from SMOF? The authors determined that patients with SMOF were more likely to have viral or lymphoproliferative disease with very high soluble Fas ligand (sFasL) levels. In vitro, sFasL levels greater than 500 pg/mL cause hepatocyte necrosis. Children with MOF with sFasL levels greater than 500 pg/mL demonstrated liver injury at autopsy.[8] The mechanism of injury in SMOF was different than in patients who presented with MOF (Figure 104-8).

In this decade, investigators from the United Kingdom have investigated the inflammation/immune dysregulation hypothesis in SIRS/sepsis, hypothesizing that reduced complement activity increases the risk of SIRS/sepsis.[9] Mannose-binding lectin (MBL) is the first complement component released and is required for the first 12 hours of complement activity. Approximately 30% of children are MBL deficient. Complement factor H inhibits complement activity. The complement H factor H Y402H polymorphism reduces this complement inhibition activity. Using genotype analyses, these investigators have demonstrated that children at risk for SIRS/sepsis more commonly have deficiencies in MBL production and a reduction in this H factor polymorphism. These two polymorphisms together lead to an even greater risk of SIRS/sepsis than either alone. The interpretation is that diminished complement function prevents rapid clearance of antigen, leading

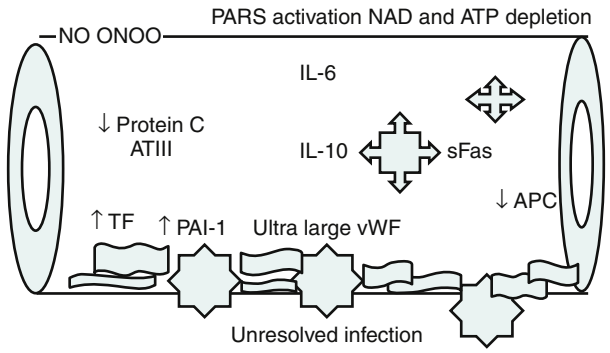


Figure 104–8. In immunologic dissonance, MOF patients are unable to resolve infection and inflammation. They remain in a prothrombotic/antifibrinolytic state with microvascular thrombosis and thrombocytopenia-associated MOF. They also have immunoparalysis with ineffective antigen-presenting cell activity mediated in part by increased IL-10. SMOF can occur when increased sFasL levels higher than 500 pg/mL induce liver injury. Metabolism is also adversely affected as nitric oxide plus superoxide anion lead to the formation of peroxynitrite radicals that inhibit cytochrome P450 activity and mitochondrial respiration. *TF,* Tissue factor; *PAI-1,* plasminogen activator inhibitor type 1; *AT III,* antithrombin III; *NO,* nitric oxide; *ONOO,* peroxynitrite; *PARS,* polyadenosylribose synthase; *APC,* antigen presenting cell.

to the SIRS/sepsis syndrome. The inflammation hypothesis is alive and well in SIRS, sepsis, severe sepsis, and MOF.

Definitions and Scoring

As previously noted, SIRS is defined by two of the following four criteria: tachypnea, tachycardia, fever, and leukocytosis. *Sepsis* is defined as SIRS plus suspected or documented infection. Severe sepsis is defined as sepsis plus organ failure. Acute lung injury is defined by bilateral pulmonary infiltrates and a Pao_2/Fio_2 ratio less than 300. MOF or multiple organ dysfunction

syndrome is defined by failure of more than one organ. Many definitions exist for defining organ failure. Wilkinson and Pollack[10] published the first definitions in pediatrics, which were subsequently modified by Proulx and then again by Doughty.[2] Goldstein and colleagues[11] subsequently developed two more sets of definitions. Doughty et al.[2] developed the organ failure index to score organ failure. This index is a simple integer score that assigns 1 point for each organ failure. Leteurtre and colleagues[12] reported two more MOF scores, the Pediatric Multiple Organ Dysfuction (PEMOD) and the Pediatric Logistic Organ Dysfunction (PELOD) scores.[12] The PEMOD score assigns 1 to 4 points per organ failure depending on severity. The PELOD score logistically weights these scores in the hope of allowing for prognostication. It remains unclear whether the PELOD score can be used in this manner.

Outcomes

In the United States, survival in the setting of SIRS/sepsis is almost universal. Odetola and colleagues[13] reported that survival in severe sepsis is 96%, 98% overall in previously healthy children and 92% in children with chronic diseases. Typpo and colleagues[14] reported that survival from MOF is 90%. Survival rates decrease as the number of organ failures increase.

Multiple Organ Failure/ Dysfunction Phenotypes, Respective Biomarkers, and Therapies

Thrombocytopenia-Associated Multiple Organ Failure

New-onset thrombocytopenia is a harbinger of thrombotic microangiopathy in MOF, especially when accompanied by increased lactate dehydrogenase and reduced renal function (Figure 104-9). Until the current decade, thrombotic microangiopathy of critical illness was believed to be mediated by fibrin, but more recent work suggests that vWF multimer–associated platelet thrombi are an unrecognized cause. If ADAMTS-13 activities (vWF-cleaving protease) are

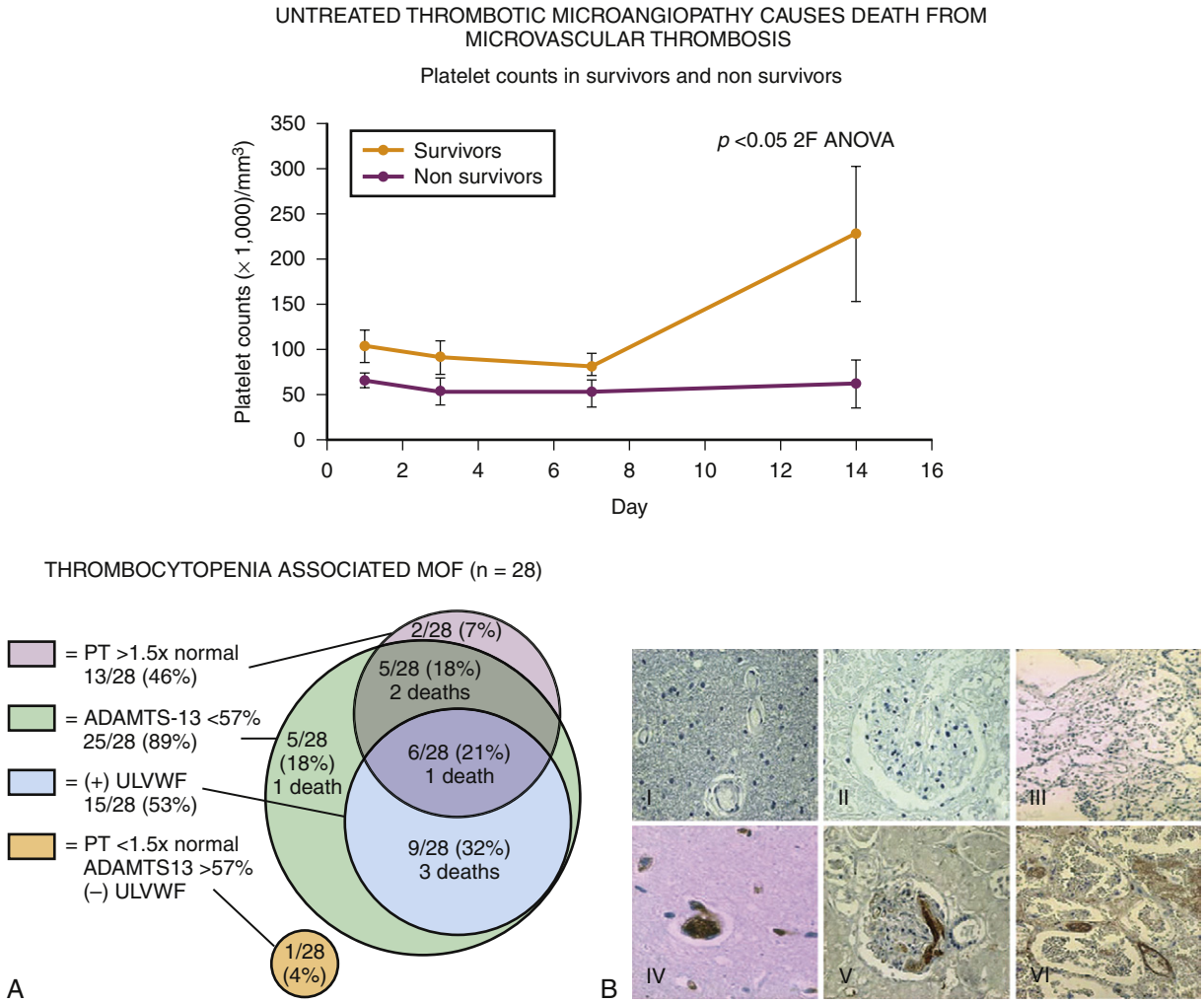


Figure 104–9. Thrombocytopenia-associated MOF is heralded by new-onset thrombocytopenia and MOF. Survivors recover platelet count and nonsurvivors do not. In this study, 89% of these patients had reduced ADAMTS 13 (**A**). At autopsy, patients had vWF multimer thrombi (**B**) in brain (*panel IV*), kidney (*panel V*), and lung (*panel VI*). These microthrombi can resolve with intensive plasma exchange therapy that removes thrombogenic ultralarge vWF multimers and replenishes ADAMTS-13.

less than 57% of control and vWF multimer antigen levels are increased, this form of thrombosis should be highly suspected. Intensive plasma exchange can be required to reverse this process because it removes the thrombogenic ultralarge vWF multimers and replenishes ADAMTS-13 (vWF-cleaving protease) activity.[5,15]

Immune Paralysis and Lymphoid Depletion Syndrome

Adult and neonatal investigators noted the associations among lymphocyte apoptosis, lymphoid depletion, and death from nosocomial sepsis. When dendritic cells, monocytes, or macrophages ingest these apoptotic bodies, a profound TH2 response ensues, with immune paralysis and death associated with uneradicated infection (Figure 104-10). Pediatric studies corroborate these findings with immunoparalysis and prolonged lymphopenia associated with nosocomial infection and death.[6] In transplant recipients, rapid tapering of immune suppressants can restore monocyte function and reverse immune paralysis. In non-immune-suppressed patients, low-dose subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF) can reverse immune paralysis. If patients have hypogammaglobulinemia, intravenous immunoglobulin (IVIG) can be given. If the patient is severely lymphopenic, antimicrobial prophylaxis can be considered.

Viral/Lymphoproliferative Disease–Associated Sequential or Liver-Associated Multiple Organ Failure Syndrome

Viral/lymphoproliferative disease associated with SMOF or liver-associated MOF represents only 10% of MOF, but this diagnosis carries the worst prognosis (Figure 104-11). Liver injury is associated with high sFasL levels (>500 pg/mL).[8] In transplant recipients, the most common cause is post-transplant lymphoproliferative disease. Epstein-Barr virus intercalates the viral IL-10 genome into B cells, preventing activated immune cell death and promoting lymphoproliferation. This is treated by stopping immune suppression, administering the B-cell monoclonal antibody rituximab, and administering interferon-α if necessary. In nontransplant patients with a family history of a similar disease, primary hemophagocytic lymphohistiocytosis (HLH) must be considered. These patients have absent natural killer (NK)/cytotoxic T-lymphocyte (CTL) cell activity secondary to mutations in perforin signaling, rendering them unable to kill viruses and cancer cells. Furthermore, these patients cannot direct programmed cell death in activated immune cells. These patients are treated with chemotherapy and bone marrow transplantation to kill activated immune cells and replenish functioning NK/CTL cells. In patients with rheumatologic disease, this syndrome may be caused

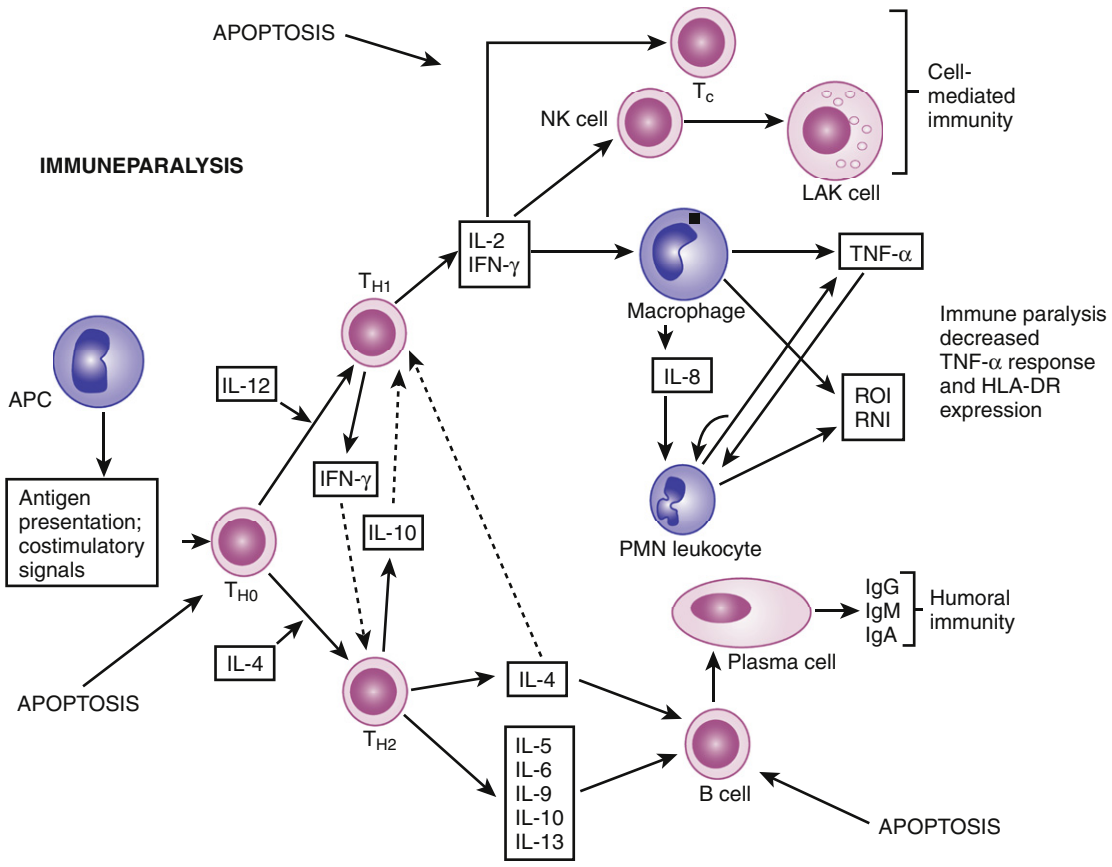


Figure 104–10. MOF patients who develop secondary infections commonly have immuneparalysis with an ex vivo TNF-α response to lipopolysaccharide <200 pg/mL and/or reduced monocyte human leukocyte antigen DR expression <30% or <8000 molecules/cell. Immune function can be restored by holding immunosuppressant therapy and low-dose GM-CSF therapy.

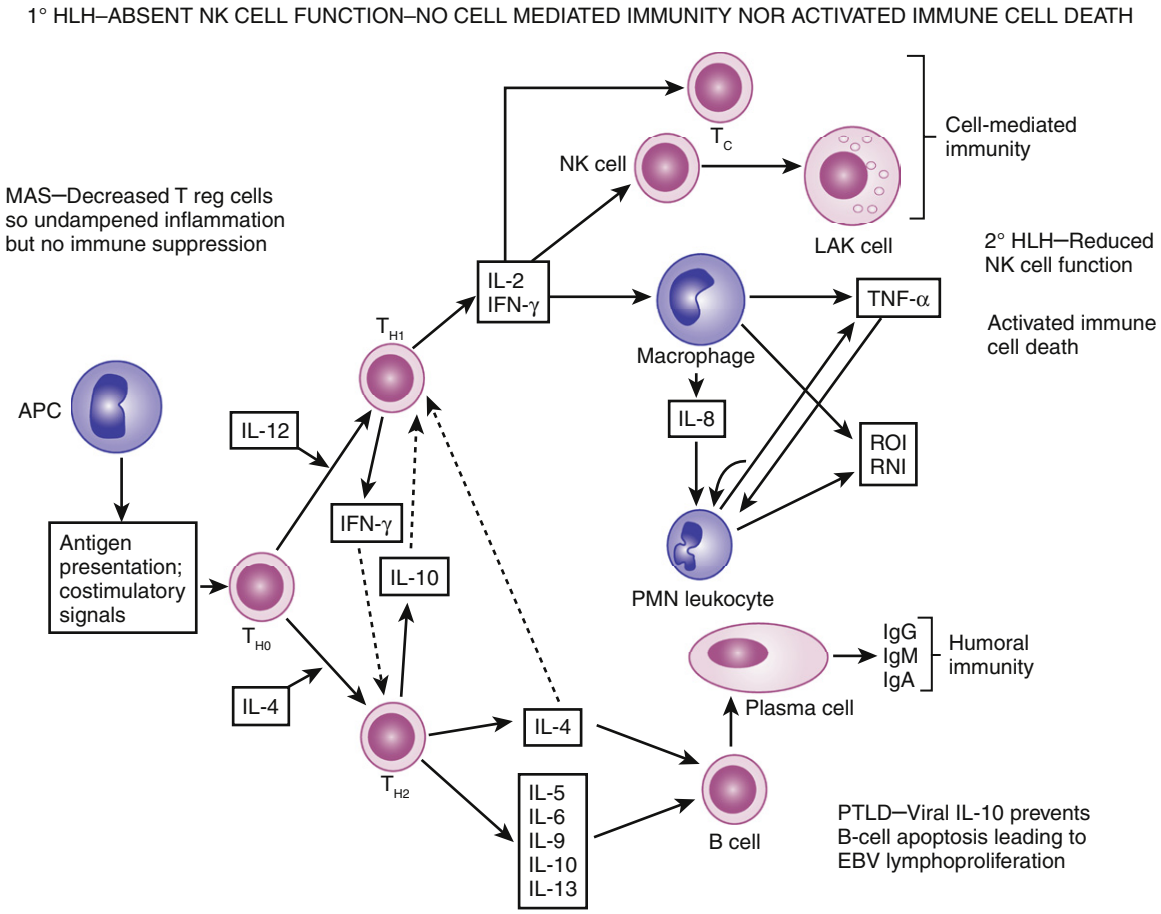


Figure 104–11. SMOF patients have a number of different immune system defects that can be present and require sorting because therapies differ according to cause. *PTLD,* Posttransplant lymphoproliferative disease.

by macrophage activation syndrome (MAS) as a result of decreased T-regulatory cell activity (see Chapter 98). These patients respond well to pulse steroids. Patients with infection-associated or secondary HLH will not have the rash, arthralgias, or serositis of MAS or the family history of primary HLH. These patients have decreased but not absent NK/CTL cell function. Therefore they can kill viruses and cancer cells and induce activated immune cell death, but at a slower rate. These patients respond well to eradication of infection with supportive therapy. In addition, IVIG, plasma exchange, and interferon-α have been reported as successful therapies.[16]

Secondary Hemochromatosis-Associated Cardiac Hepatopancreatic Multiple Organ Failure

Patients who have received multiple blood transfusions (including those with aplastic anemia, liver failure, or hemolytic anemia) develop iron overload with high ferritin level (>1000 μg/L) and iron-binding capacity <50%. Iron deposition can be diagnosed by liver magnetic resonance imaging. Infections thrive with this excess iron, and sepsis-induced MOF is common in this population. Chelation can be considered.

Hyperleukocytosis-Associated Multiple Organ Failure

Leukostasis syndrome is caused by pertussis-associated leukocyte proliferating factor and is predominantly found in infant pertussis. The time-sensitive treatment appears to be leukophoresis or whole blood exchange. These therapies remove toxin and reduce pulmonary leukosequestration.

Therapeutic Approaches to Systemic Inflammatory Response Syndrome, Sepsis, Acute Lung Injury, and Multiple Organ Failue

A patient with SIRS can be distinguished from a patient with sepsis by history. An antecedent history of surgery, pancreatitis, or trauma is supportive of SIRS. The prototype for SIRS can be found in the patient with a spinal fusion or the postoperative cardiac surgery patient. Tissue injury induces the inflammatory complement/cytokine-driven response of tachycardia, tachypnea, fever, and leukocytosis. If the systemic inflammatory response worsens or occurs de novo several days after the antecedent insult, sepsis should be considered and infection

Box 104–1 Nonspecific Therapies to Prevent and Resolve MOF

- Reverse shock in a time-sensitive fashion (ACCM/PALS guidelines)
- Provide effective antibiotics in time-sensitive fashion
- Remove nidus of infection
- Use antitoxins for toxin-mediated disease
- Fluid removal before fluid overload >10% body weight
- Use lung protection strategy of an effective tidal volume <8 mL/kg
- Control hyperglycemia
- Prevent drug toxicity by titrating drugs to liver/kidney function
- Remove toxic drugs as indicated
- Provide nutrition
- Prevent or stop systemic hemolysis

ACCM, American College of Critical Care Medicine; *PALS,* Pediatric Advanced Life Support.

suspected. SIRS is treated by watchful waiting, fluid resuscitation if hypovolemia is suspected, and temperature control as required. Acute lung injury should be treated with supplemental oxygen as needed. SIRS is thought to be a self-limited response that can be prolonged in the presence of decreased complement production found in one third of the population who have MBL and complement H polymorphisms. Of note, the rate of tachycardia and tachypnea decreases with time. If sepsis is suspected, antibiotics should be given.

If SIRS/sepsis progresses to organ failure or MOF, it is no longer a self-limited disease. Further support and interventions are needed (Box 104-1). If acute lung injury progresses, intubation and mechanical ventilation will be needed. Intubation with ketamine as an induction agent in this setting is antiinflammatory and will not interfere with the adrenal stress response. Pulmonary capillary and epithelium leak will result in indirect ARDS, and the patient will need positive end-expiratory pressure to facilitate adequate oxygenation. Protective lung ventilation is recommended. Use of high lung volumes results in increased systemic inflammation and immune paralysis. For this reason, an effective tidal volume of no more than 8 mL/kg/breath is recommended. Cardiovascular management should be goal directed in a time-sensitive manner. Fluid and inotrope administration targeting capillary refill of less than 2 seconds and normal blood pressure in the emergency department is associated with a 40% reduction in mortality rate.[17] Fluid, inotrope, and blood resuscitation directed to attaining superior vena cava oxygen saturation greater than 70% reduced the incidence of MOF (renal and neurologic failure in particular) and mortality rate fourfold in a randomized controlled trial.[18] The use of antibiotics and antitoxins in a time-sensitive and appropriate manner is paramount. In a retrospective cohort study involving 14 North American adult intensive care units, septic patients received effective antibiotics on average 6 hours after the onset of hypotension. Administration of an effective antimicrobial within the first hour of documented hypotension was associated with a survival rate of 79.9%. However, for each subsequent hour delay in administering an effective antimicrobial, average survival decreased by 7.6%.[19]

Careful attention should also be given to fluid balance. When patients have fluid overload greater than 10% total body weight (e.g., up 1 L in a 10-kg child), the risk of death from MOF increases. Diuretic and or extracorporeal therapies, including intermittent renal dialysis and continuous hemofiltration, should be used to remove fluid as needed after initial resuscitation specifically to prevent this level of fluid overload. Nutrition is also important and should be given enterally if possible; if this is not possible, administration should be parenteral. The delivery of a intravenous 10% dextrose solution at maintenance will ensure glucose delivery requirements. This provides all calorie needs on the first day. Feedings or total parenteral nutrition can be started subsequently. Although controversy exists regarding what glucose level should be targeted, there is consensus that glycemic control with insulin is required at some degree of hyperglycemia. Hyperglycemia causes monocyte deactivation, increases C-reactive protein levels and inflammation, reduces immune function globally, and increases risk of thrombosis and MOF. Insulin improves monocyte/macrophage function and reduces systemic inflammation and thrombosis.

Because cytochrome P450 activity is decreased during sepsis induced MOF (approximately 50% in sepsis, 25% with two-organ failure, and 10% with persistent three-organ failure), adjustment of cytochrome P450 metabolized medications is suggested when possible. Medications metabolized by the kidney should be adjusted as well according to creatinine clearance. One way to address reduced drug metabolism is to use drugs that can be followed pharmacokinetically by measured concentrations and pharmacodynamically by physiologic responses to titrated dosing. A nice rule of thumb when giving drugs that do not have pharmacokinetic or pharmacodynamic targets is to double the interval between doses for every doubling of creatinine or bilirubin depending on whether the drug is primarily metabolized through renal or hepatic pathways. Hormone synthesis can also be affected. Patients with adrenal insufficiency or thyroid insufficiency will require replacement.

Unresolving MOF should evoke suspicion that the source of infection is not being eradicated. Persistent inflammation with thrombosis and infection is the cause of PMOF. Careful review of the minimum inhibitory concentration profile of the infection should be performed and antibiotics with the lowest possible minimum inhibitory concentration should be used. If the infection is toxin producing, clindamycin should be given to stop production and IVIG administered to neutralize the toxic effects. The nidus of infection may need to be removed surgically. Barie and colleagues[20] found that surgical sepsis mortality rate was 96% with failed nidus removal compared with only 4% with successful removal. Primary or acquired immune deficiency syndromes can also be the cause of uneradicated infection. Primary immunodeficiencies are usually suspected in children younger than 5 years but can present at any time in life. Initial screening for these syndromes includes white blood cell count, lymphocyte subset, complement level, gammaglobulin level, and tests for chronic granulomatous disease. Secondary immune deficiencies include severe neutropenia (absolute neutrophil count <500) and severe graft-versus-host disease (grade III and above). Neutropenia is most commonly related to bone marrow suppression induced by chemotherapy. Infection eradication and subsequent resolution of MOF occur only after restoration of the neutrophil counts. The pathobiology of graft-versus-host disease is one of donor T cells being directed against host epithelial cells. This results in denudation of the epithelial cell barrier with secondary bacterial and fungal infections. Treatment is difficult but

is directed at stopping T cell–mediated epithelial destruction without concomitantly stopping the host's ability to kill infection. This is the most difficult MOF syndrome to treat.

Hemolysis is another cause of unresolving MOF. Free hemoglobin becomes hemoglobin peroxidase when exposed to superoxide and hydrogen peroxide generated by activated white blood cells. Hemoglobin peroxidase can lead to endothelial cell injury, microvascular constriction secondary to NO scavenging, and when bound to haptoglobin reduction in viable macrophages.[21] The prototype of this form of MOF is found in children with sepsis who are on poorly functioning extracorporeal membrane oxygenation (ECMO) support. If the ECMO circuit induces excessive hemolysis (free hemoglobin >10 μg/L), MOF can ensue. The approach should be to attempt to stop ongoing hemolysis by changing oxygenator circuits, adding a second venous cannula, and reducing ECMO flow. In hemolytic disease such as sickle cell anemia, plasma exchange can help reduce hemolysis and resolve MOF.

Rare medication toxicities can also contribute to unresolving MOF. Patients with intrathecal baclofen pump infusions can develop baclofen withdrawal infusion syndrome when infusions are stopped. This can be remedied by restarting intrathecal baclofen. Linezolid toxicity can also progress to overwhelming lactic acidosis and MOF. Linezolid's antimicrobial activity is mediated through bacterial ribosome poisoning. Unfortunately, human mitochondria can similarly be poisoned by linezolid. Baseline lactate levels should be obtained, and if lactate levels increase while on linezolid, the drug should be stopped before lactic acidosis ensues. Nitroprusside can induce cyanide poisoning. Cyanide levels should be followed when giving this medication. Propofol can cause fatty acid oxidation/mitochondria dysfunction–driven propofol infusion syndrome with overwhelming lactic acidosis. Propofol should not be used for long-term sedation in children younger than 3 years. Systemic drug reactions such as Stevens-Johnson syndrome and delayed hypersensitivity syndromes must also be considered. These scenarios call for discontinuation of the offending agent and watchful supportive care, which can sometimes be tricky. For example, the delayed hypersensitivity skin rash may be difficult to discern in children with more pigmentation. For patients with sulfa drug–related Stevens-Johnson syndrome, it is important to realize that furosemide is also a sulfonylurea.

Even in clinical settings without sophisticated research tests, patients with PMOF can be phenotyped (Table 104-1). New-onset thrombocytopenia with MOF, increase lactate dehydrogenase with or without schistocytes, and renal dysfunction likely reflect a thrombotic microangiopathy that resides within the disseminated intravascular coagulation/thrombotic thrombocytopenic purpura (DIC/TTP) continuum. This complex coagulopathy can be treated with plasma infusion or exchange, protein C, antithrombin III, pentoxifylline, prostacyclin, and/or heparin. New or persistent bacterial or fungal infections in a patient with MOF who does not have evidence of primary or secondary immune deficiency or an uneradicated nidus of infection is highly suggestive of immune paralysis/lymphoid depletion syndrome. Immune suppressant therapies should be rapidly tapered in these patients. Dexamethasone in particular should be stopped and transitioned to hydrocortisone. GM-CSF can be given subcutaneously at 125 μg/m^2 daily subcutaneously to reverse immunoparalysis. If immunoglobulin G levels are less than 500 mg/dL, IVIG should be considered. If the CD4 count is low, antifungal, antiviral, and antiprotozoal prophylaxis can be considered. Patients with SMOF that begins with ARDS and progresses to hepatorenal syndrome should be recognized and treated accordingly. If the child has EBV-related posttransplant lymphoproliferative disease (high EBV titers), rapid immune suppression tapering is recommended along with rituximab and IVIG therapy. If the ferritin level is higher than 500 μg/L, then MAS (rheumatologic signs), secondary hemochromatosis, or the HLH syndrome should be considered. History and physical exam findings of rash, serositis, and arthralgias support MAS and should be treated with pulse steroids. A long-term history of transfusions, a ferritin level greater than 1000 μg/L, and an iron-binding capacity less than 50% suggests secondary hemochromatosis. These patients should be treated with iron chelation therapy. These patients are prone to iron-loving *Aspergillus* infection during chelation therapy. Appropriate antifungal coverage is recommended in these children. In the absence of rheumatologic or secondary hemochromatosis disease, HLH should be considered. A positive family history should invoke evaluation for primary HLH. These patients should have no NK cell cytotoxicity activity and specific

Table 104–1 MOF Phenotypes

Phenotype	Diagnosis	Therapy
Thrombocytopenia-associated MOF	New-onset thrombocytopenia and MOF with increased LDH and renal involvement; ADAMTS 13 <57%	Intensive plasma exchange until resolution
Immunoparalysis MOF	Whole-blood TNF-α response to LPS <200 pg/mL or monocyte HLA DR expression <30% or <8000 molecules/cell for >3 days	Rapidly taper immunosuppressants; give low-dose GM-CSF at 5 μg/kg/day subcutaneously
SMOF	Respiratory then hepatorenal	
	PTLD: EBV disease posttransplantation	Stop immunosuppressants; give rituximab + IVIG
	MAS: rheumatologic disease + ferritin >500 μg/L	Pulse steroids
	Primary HLH: positive family history or consangunity + ferritin >500 μg/L	HLH protocols
	Secondary HLH: infection + ferritin >500 μg/L	Supportive therapies, plasma exchange, interferon-α + IVIG
Iron overload MOF	History of multiple transfusions, ferritin >1000 μg/L, Fe binding >505%	Iron chelation, coverage for *Aspergillus* during chelation
Hyperleukocytosis MOF	Pertussis + high white blood cell count + ARDS and pulmonary hypertension	Leukophoresis or whole-blood exchange

LDH, Lactate dehydrogenase; *HLA,* human leukocyte antigen; *PTLD,* posttransplantation lymphoproliferative disorder.

perforin mutations. Treatment includes chemotherapy followed by bone marrow transplantation. In patients without a family history who have bacterial/fungal infection, secondary HLH is a possibility. These patients have reduced NK cell activity but no perforin mutations. Successful treatment for this group of patients has included interferon-α plus IVIG, steroids plus plasma exchange, and supportive care with eradication of infection. Cancer patients with absent NK cell function and HLH have responded to the IL-2 receptor antibody daclizumab.

Time Course of Systemic Inflammatory Response Syndrome, Sepsis, and Multiple Organ Dysfunction

In general terms, SIRS and sepsis should resolve within 5 days. MOF resolves over 1 week to 3 months. MODS and MOF are related to epithelial cell and endothelial cell dysfunction, damage, and apoptosis. If significant hypoxia/ischemia is the causal event, MOF will not resolve until (1) reepithelialization of lung, liver, and kidney occurs; (2) reendothelialization of the organs occurs; and (3) canalization of microvessels occurs. These processes take 6 weeks to 3 months. Accordingly, health care providers should be patient and not give up on MOF-afflicted children too early.

Summary

Inflammation and immunity are the basis of SIRS, sepsis, acute lung injury, ARDS, and MOF. SIRS and sepsis occur more commonly in patients with reduced complement function. MOF and MODS occur in patients who have epithelial/endothelial cell injury and or microvascular thrombosis caused by unresuscitated shock, ischemia/reperfusion, unresolved inflammation, unresolved infection, and/or drug- or toxin-induced mitochondrial injury. SIRS and sepsis are managed with fluids, temperature control, and antibiotics if infection is present, which usually resolves within 5 days. This approach prevents the development MOF or MODS. If treatment is delayed, then MODS or MOF can occur. Treatment is then used to reverse shock, remove infection, resolve inflammation, and reverse microvascular thrombosis. Phenotype-specific therapies are directed to recovery of endothelial, epithelial, mitochondrial, and immune function. Survival can be 90% with a patient approach.

References are available online at http://www.expertconsult.com.

Principles of Toxin Assessment and Screening

Alan D. Woolf

PEARLS

- The diagnosis of unknown poisoning is based on obtaining a good history and performing a thorough physical examination. Rarely does a laboratory finding reveal a totally unexpected diagnosis.
- Some toxins (e.g., acetaminophen, *Amanita* mushroom poisoning, valproic acid, sulfonylurea medications) are notable for the delay between the time of ingestion to the onset of symptoms. Others, such as methadone or naltrexene, can have symptom recurrence hours after an apparent improvement in consciousness.
- The clinician can often predict the severity of medical outcomes from poisonings simply by noting the timing of progression of the poisoned patient's signs and symptoms of toxicity.

Despite significant progress in preventive measures, poisonings in children and adolescents continue to be common occurrences. More than 51% of almost 2.5 million poison center calls in the United States in 2007 involved children younger than 6 years of age.[1] Although many of these exposures are medically trivial, poisonings account for an important number of all pediatric hospital visits and hospitalizations. Not all children are equally at risk for serious poisoning. The incidence of poisoning is highest among children 1 to 3 years of age. Boys slightly outnumber girls as victims of unintentional exposures. Children with developmental delays and/or pica, as occurs with autistic spectrum disorders, have an increased risk for self-poisoning. A second peak of serious poisonings occurs in adolescence, when a suicide attempt by poisoning (with females disproportionately overrepresented) or a misadventure involving substance abuse becomes the common circumstance underlying a poisoning episode. Adolescents with anorexia nervosa or psychiatric conditions such as clinical depression are especially vulnerable to self-poisoning.

Childhood poisoning typically occurs around mealtime, when parents are preoccupied with food preparation or are otherwise distracted. Many poisonings involve medications or household products that are open and being used at the time of the poisoning. The second most common site of a poisoning other than the child's own home is that of the grandparents. Children in power struggles with parents, and those in socially isolated, stressed families, sometimes experience repeated poisoning events.

Common Agents Involved

The most common agents involved in preschooler poisonings are medications, such as analgesics, cough and cold preparations, and dermatological preparations; household products, such as cleaning agents, soaps, and detergents; and plants. Table 105-1 lists those agents responsible for the majority of calls to poison control centers. The agents most frequently involved in serious pediatric poisonings (those requiring intensive care) are prescription medications (tricyclic antidepressants, anticonvulsants, digitalis, and opiates), alcohol, and hydrocarbon-based household products. Lead poisoning and carbon monoxide poisoning related to house fires are less recognized, but frequent causes of poisoning hospitalization in childhood. International adoptees and children immigrating to the United States may have been exposed to lead, arsenic, or other toxins in a polluted environment in their home countries or by their family's use of poorly regulated remedies. Clinicians should ask caretakers about the types and doses of any medications, herbs, vitamins, diet supplements, or ethnic remedies being used to treat the child's other health problems. Such therapies may be interacting with the toxins responsible for the poisoning or otherwise contributing to the child's toxicity.

Resources for the Clinician

In making the diagnosis of an unknown poisoning, the physician must rely on observation, history-taking abilities, and clinical skills. Laboratory analyses and radiographic findings are sometimes helpful. References such as Drug Information (available annually from the American Hospital Formulary Service [AHFS], American Society of Hospital Pharmacists Bethesda, Md.) and the Poisindex computer database (Micromedex Cooperation, Greenwood Village, Colo.) can be helpful in identifying drugs and their actions and precautions. The regional poison control center (telephone: 800-222-1222) can

Table 105–1 Agents Most Frequently Involved in Childhood (<6 Years) Poisoning-Related Poison Center Calls in the United States (2007)

Toxic Agent	Number of Poison Center Calls	Percent (%) Total
Cosmetics and personal care	168,875	13.7
Cleaning substances	118,068	9.6
Analgesics	104,267	8.4
Foreign bodies	93,830	7.6
Topicals	85,475	6.9
Cough and cold preparations	57,572	4.7
Vitamins	45,498	3.7
Pesticides	43,469	3.5
Plants	40,011	3.2
Antihistamines	34,550	2.8
Gastrointestinal preparations	34,223	2.8
Antimicrobials	32,576	2.6
Arts/crafts/office supplies	28,909	2.3
Alcohols	23,128	1.9
Electrolytes/minerals	22,169	1.8
Hormones and hormone antagonists	19,878	1.6
Deodorizers	19,707	1.6
Food poisoning	18,513	1.5
Herbs/dietary supplements	15,783	1.3
Hydrocarbons	15,390	1.2
Total nonpharmaceuticals	682,925	55.3
Total pharmaceuticals	551,212	44.7
Total	**1,234,137**	**100%**

Percentages are based on the total number of exposures in children <6 years (1,169,478) rather than the number of substances.
Modified from Bronstein AC, Spyker DA, Cantilena LR Jr, et al: 2007 annual report of the American Association of Poison Control Centers' national poison data system (NPDS): 25th annual report, *Clin Toxicol (Phila)* 46(10):927, 2008.

provide helpful consultative services by toxicologists. Such services may include:

1. Assistance with the differential diagnosis by citing toxins known to cause a particular constellation of symptoms and signs
2. Information about drug-drug, drug-chemical, and drug-herb interactions
3. Expected clinical course of the patient, given the known kinetics of the agents involved
4. Help with locating laboratories that can assay tissue samples for exotic drugs and chemicals
5. Advice about current management techniques for specific poisonings
6. Help in locating supplies of particular antidotes, antivenins, or other exotic poisoning medicines
7. Assistance with triage of patients to specialized regionalized therapeutic services for acute poisonings such as hemodialysis or hyperbaric oxygen chambers
8. Surveillance for clusters of poisoning in a community representing a public health hazard
9. Assistance in reporting adverse drug or dietary supplement reactions or medical errors to appropriate public health authorities
10. Assistance to first responders and other public health officials in a community-level hazardous materials emergency
11. Assistance with community-level public education programs and public service announcements aimed at poisoning prevention

Table 105–2 History Taking and Unknown Poisoning in the Pediatric Patient

Environment	Patient	Toxin
Witnesses Time of ingestion Site of ingestion Illness of family Medications of family members Open containers	Intentionality Past medical problems Current medications Known drug allergies Time of symptom onset Prior medical management	Agent(s) involved Exact ingredients Dose (maximum estimated) Concentration members Route of exposure

General Assessment of the Poisoned Patient

History

An accurate history is vitally important in the diagnosis of unknown poisoning. Surprisingly, the physician in the intensive care unit (ICU) may be the first health professional who can sit with parents and carefully review the possible circumstances of the exposure. Poisonings may occur by various routes including ingestion, inhalation, ocular exposure, dermal exposure, mucous membrane involvement, or parenteral exposure. Once the child's condition has been stabilized, the pediatrician should query the family about the incident, with particular attention to the environmental, patient, and toxic agent factors as outlined in Table 105-2. In acute, unintentional exposures in young children, the time of exposure and toxin involved frequently are accurately known. The importance of obtaining the precise ingredients in the suspected toxic agents cannot be overemphasized. Parents should bring the product containers or medication labels. For estimations of liquid toxins, the average swallow of a young child is approximately 5 to 10 mL while that of the older child and adolescent is 10 to 15 mL. The clinician must appreciate the fact that parents frequently minimize the child's exposure to a toxin in an attempt to deny the threat of injury or to assuage their guilt that such an episode occurred. Therefore it is prudent to assume the worst possible scenario in calculating the maximum dose of a drug or household product a child could have swallowed in a poisoning and to treat the patient accordingly. Calculation of the dose the child might have received is sometimes helpful, using the maximum number of missing tablets or amount of liquid, the concentration of the drug or chemical, and the child's weight.

The latency between the time of ingestion and the onset of symptoms is important. The tempo of progression of symptoms and signs also may help the clinician gauge the severity of the intoxication and the urgency with which intervention is necessary. However there are some exceptions to this rule. Patients poisoned by some toxins, such as paraquat and the *Amanita* mushroom toxin, classically have a relatively asymptomatic period of 12 hours or more but then manifest life-threatening pulmonary or hepatic toxicity, respectively.[2,3] Some drugs, such as sulfonylurea hypoglycemics and valproic acid, can also have similar latency periods prior to the onset of severe toxicity.[4,5] Adolescent poisonings are confounded by

the intentionality of the episode and the frequent unreliability of the adolescent's history. Adolescents in distress may be evasive, misleading, or otherwise uncommunicative. Their ability to remember or provide a coherent account of what happened may be distorted by the effects of the drugs taken. The clinician cannot assume that the time of exposure, the dose, or even the toxic agents themselves are accurately recounted.

Physical Examination

The physical examination is crucial for assessment of the patient's medical stability and for identification of the unknown poison. Specific changes in vital signs and symptoms are associated with likely toxins or groups of toxins. Such characteristic clinical patterns of illness are sometimes termed toxidromes. Table 105-3 lists some of the more common toxidromes important in pediatric poisoning. Families are using herbs and diet supplements with increasing frequency to treat their children's illnesses or simply to promote their general well-being. However, serious poisonings in which herbs and dietary supplements are implicated are appearing in the medical literature.[6] Table 105-4 lists some examples of toxicities associated with particular herbal remedies.

Frequently, the gastrointestinal tract is involved early in a poisoning. Nonspecific findings after a drug or chemical overdose include nausea, vomiting, abdominal pain, and loose stools. A variety of drugs can cause fever. Overdoses with cocaine, phenothiazines, atropine, or salicylates often are associated with an elevated temperature. For specific discussions of the effects of toxins on other selected organ systems, the reader is referred to the general reviews listed in the additional readings at the end of this chapter and to other chapters in this textbook on toxicology and poisonings.

Table 105-5 lists examples of drugs and toxic agents associated with specific effects on the cardiovascular system. Drugs with cardiotoxic effects, especially those with membrane stabilizing activity, are among those most commonly associated with life-threatening toxicity. In one 10-year retrospective study, 15 out of 17 poisoned patients requiring extracorporeal life support measures for refractory shock or prolonged cardiac arrest had overdosed on cardiotoxic agents.[7] Toxins may cause hypertension or hypotension by direct effects on vascular smooth muscle, neurogenic effects on autonomic nervous centers governing vascular innervation, direct effects on the heart, or renal effects. Specific agents associated with hypertension include adrenergic stimulants, such as amphetamines, cocaine, phencyclidine, phenylpropanolamine, ephedrine, and phenylephrine. Although the hypertension caused by sympathomimetics frequently lasts only a few hours, it may be associated with acute encephalopathy and/or intracranial hemorrhage.

Acute hypotension frequently is associated with aconite, antiarrhythmic agents, antihypertensive agents, β-adrenergic antagonists, calcium channel antagonists, clonidine, tricyclic antidepressants, opiates, and phenothiazine overdose. Anaphylactic, anaphylactoid, or allergic responses may also result in hypotension.

Tachycardia frequently is associated with ingestion of any of the sympathetic nervous system stimulants listed in Table 105-5. A notable exception is phenylpropanolamine, which, as a pure α-adrenergic receptor agonist, causes peripheral vasoconstriction associated with reflex bradycardia or a normal pulse. Tachycardia also is associated with the ingestion of exogenous thyroid preparations, the early phase of poisoning with tricyclic antidepressants, theophylline overdoses, and caffeine or nicotine intoxications. Bradycardia may accompany exaggerated vagal responses to some compounds or direct negative chronotropic effects on the heart. Interference with the cardiac conduction system may cause a slowed pulse. Cardiac drugs associated with bradyarrhythmias include the calcium channel antagonists, digitalis, and β-adrenergic antagonists. Antiarrhythmic agents such as quinidine and procainamide can slow the pulse. Aconite, an herbal remedy, binds to site 2 of the open-state of voltage-sensitive sodium channels, which then becomes refractory to excitation.[8] Aconite is also arrhythmogenic due, in part, to both its anticholinergic effects and its activation of the ventromedial nucleus of the hypothalamus.

Many drugs and chemicals depress a patient's consciousness either directly or by hypoxia resulting from decreased respiratory drive or simple asphyxia. Table 105-6 provides a suitable scoring system for determining the level of consciousness in the intoxicated patient. The dynamic nature of a

Table 105–3 Common Toxidromes in Pediatric Poisoning

Signs and Symptoms	Agent
Dilated pupils, tachycardia, tachypnea, warm moist skin, flushing, increased sweating, agitation	Sympathomimetic syndrome
Miosis, salivation, diarrhea, bronchorrhea, lacrimation, seizures, respiratory failure, bradycardia	Organophosphate insecticides
Fever, tachypnea, hyperpnea, lethargy, metabolic acidosis	Salicylates
Seizures, metabolic acidosis, history of tuberculosis, hyperglycemia	Isoniazid
Dry mouth and skin, flushed appearance, dilated pupils, fever, ileus, urinary retention, disorientation	Anticholinergic syndrome
Oculogyric crises, dystonia, opisthotonus	Phenothiazines
Severe metabolic acidosis, sluggish pupils, hyperemic retina, blurred vision	Methanol
Hypoglycemia, lethargy, ataxia, seizures, characteristic breath odor	Ethanol
Lethargy or coma, metabolic acidosis, active urinary sediment, crystalluria	Ethylene glycol
Headache, flulike symptoms, lethargy, dizziness, coma	Carbon monoxide
Pinpoint pupils, coma, respiratory depression	Opiate
Hyperthermia, neuromuscular rigidity, autonomic dysfunction, agitation, delirium	Serotonin syndrome
Metabolic acidosis, prolonged QRS interval, coma, seizures, dilated pupils, dysrhythmias	Tricyclic antide pressants
Protracted vomiting, tremors, tachycardia, anxiety, seizures, hypotension	Theophylline
Feeling of impending doom, sudden coma, metabolic acidosis, hypotension, bitter almond odor	Cyanide
Rotatory nystagmus, delirium; "4 C's": combative, catatonia, convulsions, coma	Phencyclidine

Table 105–4 Herbs Associated with Toxicity

Herbal Product	Toxic Chemicals	Toxic Effects
Aconite (*Aconitum* spp.)	Aconitine alkaloids	Nausea, vomiting, paresthesias, weakness, hypotension, asystole, arrhythmias, bradycardia
Chamomile *(Matricaria chamomilla, Anthemis nobilis)*	Allergens	Anaphylaxis, contact dermatitis
Chapparal *(Larrea divaricata, Larrea tridentata)*	Nordihydroguaiaretic acid	Nausea, vomiting, lethargy, hepatitis
Cinnamon oil (*Cinnamomum* spp.)	Cinnamaldehyde	Dermatitis, abuse syndrome
Coltsfoot *(Tussilago farfara)*	Pyrrolizidines	HVOD
Comfrey *(Symphytum officinale)*	Pyrrolizidines	HVOD
Crotalaria spp.	Pyrrolizidines	HVOD
Echinacea (*Echinacea angustifolia, Compositae* spp.)	Polysaccharides	Asthma, atopy, angioedema, anaphylaxis, urticaria
Eucalyptus *(Eucalyptus globulus)*	1,8-cineole	Drowsiness, ataxia, nausea, vomiting, seizures, coma, respiratory failure
Garlic *(Allium sativum)*	Allicin	Dermatitis, chemical burns, oxidizing agent
Germander *(Teucrium chamaedrys)*		Hepatotoxicity
Ginseng *(Panax ginseng)*	Ginsenoside	Ginseng abuse, diarrhea, anxiety, insomnia, hypertension
Glycerated asafetida	Oxidants	Methemoglobinemia
Grousel *(Senecio longilobus)*	Pyrrolizidines	HVOD
Heliotrope, turnsole *(Crotalaria fulva, Heliotropium, Cynoglossum officinale)*	Pyrrolizidines	HVOD
Jin bu huan (*Stephania* spp., *Corydalis* spp.)	L-Tetrahydropalmitine	Hepatitis, lethargy, coma
Kava-kava *(Piper methysticum)*	Kawain, methysticin	Hepatic failure, "kavaism" neurotoxicity
Kelp	Iodine	Thyroid dysfunction
Laetrile	Cyanide	Coma, seizures, death
Licorice *(Glycyrrhiza glabra)*	Glycyrrhetic acid	Hypertension, cardiac arrhythmias, hypokalemia
Ma huang *(Ephedra sinica)*	Ephedrine	Cardiac arrhythmias, seizures, stroke, hypertension
Monkshood *(Aconitum napellus, A. columbianum)*	Aconite	Cardiac arrhythmias, weakness, coma, shock, paresthesias, vomiting, seizures
Nutmeg *(Myristica fragrans)*	Myristicin, eugenol	Hallucinations, emesis, headache
Nux vomica	Strychnine	Seizures, abdominal pain, respiratory arrest
Pennyroyal (*Mentha pulegium* or *Hedeoma* spp.)	Pulegone	Centrilobular liver necrosis, fetotoxicity, seizures, shock
Ragwort (golden) *(Senecio aureus, Echium)*	Pyrrolizidines	HVOD
Wormwood (*Artemisia* spp.)	Thujone	Seizures, dementia, tremors, headache

HVOD, Hepatic veno-occlusive disease.
Modified from Committee on Injuries & Poison Prevention: *Children's environmental health,* ed 2, Elk Grove Village, IL, 2003, American Academy of Pediatrics.

poisoning mandates serial assessments of consciousness using this objective scoring system to gauge accurately whether the patient's overall condition is deteriorating or improving. The effects of therapies such as naloxone or oxygen also can be assessed. In many serious intoxications, such as carbon monoxide or cyanide poisoning, the state of consciousness may be the single best guide to the patient's overall prognosis. Box 105-1 lists some of the agents that may cause coma in the pediatric patient. Box 105-2 lists some common causes of seizures.

Pupil size depends on the balance between dilating and constricting fibers and is under complex autonomic nervous system control. Both sympathetic and parasympathetic nerves regulate the iris and can be affected by a variety of toxins. Anticholinergic drugs such as tricyclic antidepressants, antihistamines, and belladonna paralyze the parasympathetic fibers leading to pupillary dilation. Conversely, agents that inactivate cholinesterase leading to accumulations of acetylcholine (e.g., organophosphate pesticides, physostigmine) constrict the pupil. Ethanol, phenothiazines, and barbiturates also constrict the pupils. Opiates act centrally to cause extreme pupillary constriction (miosis). Sympathomimetics, such as amphetamines and cocaine, cause extreme pupillary dilation (mydriasis). Pilocarpine directly stimulates the sphincter muscle of the iris, causing constriction. Toxins can also be responsible for unequal pupil size. Local instillation of atropine to the eye causes ipsilateral pupillary dilation. It is important to recognize that polydrug overdoses may include agents with opposite pupillary actions. Overreliance on pupillary size alone in deciding which poison is responsible for the patient's

Table 105–5 Toxins Associated with Cardiovascular Findings

Sign	Agents
Tachycardia	Amphetamines Antihistamines Anticholinergics Aconite Cocaine β-Adrenergic agonists (albuterol, terbutaline) Theophylline
Bradycardia	Aconite Antiarrhythmics β-Adrenergic blockers Calcium channel blockers Cardiac glycosides Clonidine Ergotamine Opiates Organophosphates Phenylpropanolamine Quinidine Sedative-hypnotics
Torsades des pointes	Amantadine Antiarrhythmics Amiodarone Arsenic Astemizole Chloral hydrate Chloroquine Cisapride Cyclic antidepressants Disopyramide Encainide Fluoride Lidocaine Mexiletine Organophosphates Terfenadine Quinidine Procainamide Pentamidine Phenothiazines Prenylamine Suxamethonium
Ventricular tachycardia	Aconite Amphetamines Antiarrhythmics (e.g., quinidine, flecainide) Carbamazepine Chloral hydrate Chlorinated hydrocarbons Cocaine Cyclic antidepressants Digitalis Theophylline Thioridazine

condition may lead to a misdiagnosis. Closed head trauma or central nervous system (CNS) hemorrhage, sometimes seen in the context of a poisoning with hypertension-inducing drugs such phenylpropanolamine or ephedrine,[9] can themselves cause pupillary effects.

When treating a disoriented, delirious pediatric patient, the clinician must consider which intoxications may be responsible. Because of their central anticholinergic effects and common availability, antihistamines (e.g., chlorpheniramine, diphenhydramine) must be considered.

Table 105–6 Reed Scale for Clinical Assessment of Consciousness

Grade	Description
0	Asleep, can be aroused, answers questions
1	Comatose, withdraws from painful stimuli, intact reflexes
2	Comatose, does not withdraw from painful stimuli, no respiratory or circulatory depression, intact reflexes
3	Comatose, reflexes absent, no respiratory or circulatory depression
4	Comatose, reflexes absent, respiratory or circulatory problems

From Ellenhorn MJ, Barceloux DG: *Medical toxicology,* New York, 1988, Elsevier.

Box 105–1 Agents Associated with Coma in the Pediatric Patient

Anticonvulsants
Aromatic hydrocarbons
Asphyxiant gases
Barbiturates
Benzodiazepines
Carbon monoxide
Clonidine
Cyanide
Cyclic antidepressants
Ethanol
Ethylene glycol
γ-Butyrolactone
γ-Hydroxybutyrate
Hypoglycemic agents
Ketamine
Lead (encephalopathy)
Lithium
Methanol
Nonbarbiturate sedative-hypnotics
Opiates
Organochlorine pesticides
Phenothiazines
Salicylates

Box 105–2 Agents Associated with Seizures at Presentation

Amphetamines
Camphor
Cocaine
Cyanide
Ephedrine
Gyromitra (mushroom species)
Insecticides
Isoniazid
Methylene dioxymethamphetamine (MDMA)
Monoamine oxidase inhibitors
Nicotine
Phenylpropanolamine
Propoxyphene
Salicylates
Strychnine
Theophylline
Tricyclic antidepressants
Water hemlock (plant)

Alcohol-containing household products or liquor may be responsible. In the adolescent, substances of abuse may cause delirium or hallucinations. Jimsonweed (*Datura stramonium*) plant seeds, containing atropine and other anticholinergic chemicals, can be intentionally chewed by adolescents for their euphoric (and delirium-producing) effects caused by a central anticholinergic syndrome. Hallucinogens include lysergic acid diethylamide (LSD), psilocybin, mescaline, "magic mushrooms," and some amphetamine congeners ("designer drugs," e.g., 3-methoxy 4,5-methylenedioxyamphetamine [MMDA], 3,4-methylenedioxy-*N*-methamphetamine [MDMA, "ecstasy"], or 3,4-methylenedioxy-*N*-ethylamphetamine [MDEA]). Both cocaine and amphetamines can cause an acute psychosis. Newer, smokable forms of methamphetamine (known as "crystal" or "ice") and phencyclidine (PCP) cause symptoms of agitation, aggression, and combativeness. Additionally, intensive care physicians should be alert for abstinence syndromes in adolescents suffering from chronic substance abuse. Drug withdrawal from opiates, benzodiazepines, or alcohol (delirium tremens) often causes agitation, irritability, or even delusional thinking in affected patients. Withdrawal from chronic γ-hydroxybutyrate use (GHB, a popular "designer drug") is characterized by anxiety, insomnia, tremor, confusion, delirium, hallucinations, cardiovascular changes, nausea, vomiting, and diaphoresis.[10] Other neurologic findings may be found depending on the drug or toxin ingested. Phenytoin and phencyclidine frequently cause nystagmus. Opsoclonus (saccadic eye movements) can be caused by drugs such as lithium. Tinnitus is associated with ingestions of ergot, quinine, salicylates, and streptomycin. Changes in color vision may be seen in chronic digitalis overdose or cinchonism (quinidine).

Many poisonings cause skin or cutaneous manifestations. Abusers of intravenous narcotics or other drugs may have needle tracks, characteristic tattoos, or scarring from "skin popping." Those suffering from inhalant abuse frequently have rashes around the nose and mouth as a result of defatting and irritative effects of inhaled solvents. Methemoglobinemia as a result of a variety of oxidizing agents causes acute cyanosis despite relatively normal blood gas values (Box 105-3). A variety of rashes can be seen with adverse drug reactions and allergic responses to drugs, plants, or chemicals. Typical chemical burns may result from dermal exposure to caustics. Alopecia is associated with exposures to antimetabolite medications and other antineoplastic agents and to overdoses of chemicals such as arsenic, thallium, and selenium. Jaundice may result from exposure to carbon tetrachloride, aniline dyes, quinacrine, or phenothiazines.

The physician must be alert to characteristic odors in containers found at the scene of the exposure, of substances spilled on the patient's skin or clothing, or on the patient's breath. Organophosphate insecticides or thallium impart the strong odor of garlic. Cyanide exposures have the characteristic aroma of bitter almond (although 50% of the population is of the genotype that cannot detect the odor of bitter almonds). Ethanol, kerosene, camphor, and gasoline impart their strong odors to the breath. Adolescents abusing glues or volatile organic compounds by inhalation may have a solvent smell on their breath and on their clothes. Table 105-7 lists some of the typical intoxications that can be diagnosed by the patient's breath odors.

Laboratory Tests and Toxin Screens

Although laboratory testing of the blood or urine occasionally reveals an unanticipated toxin involved in an overdose, more frequently it confirms the physician's clinical diagnosis on the basis of a careful history and physical examination. The pediatric intensive care physician is well advised to know which compounds are included in the toxicology screen performed by the institution because the menu of substances detectable by a commercial laboratory is variable and frequently based on cost, ease of detection, available technical equipment, relative frequency of the overdose in the community, and other considerations. Most hospitals include the following compounds on a toxicology screen: acetaminophen, ethanol, barbiturates, opiates, anticonvulsants, some benzodiazepines, phenothiazines, and salicylates. Some toxicology screens may or may not include drugs of abuse (e.g., amphetamines, cocaine, tetrahydrocannabinol), older tricyclic antidepressants (e.g., amitriptyline, imipramine), and methanol. Many common toxic agents, including carbon monoxide, cyanide, methemoglobin, iron, lithium, heavy metals such as lead or arsenic, and ethylene glycol, are never included on a toxicology screen and must be ordered specifically.

A "negative" toxicology screen result does not rule out the diagnosis of a toxic exposure. For example, some enzyme multiplied immunoassay technique (EMIT) assays routinely used to screen for opiates do not necessarily detect dextromethorphan, a chemically related compound commonly used in cough preparations and also abused by adolescents. An adolescent whose urine test is negative for opiates could, in fact, be suffering from the adverse effects of dextromethorphan intoxication. The more specific a clinician is in communicating with laboratory personnel about which toxins are suspected clinically, the more directed laboratory personnel can be in seeking specific answers through laboratory methods. Because some toxins (for example cocaine, other drugs of abuse, some heavy metals) are detected more easily in urine than in the blood, both specimens should be submitted when the toxicology screen is ordered. Gastric contents can be assessed when the patient is seen shortly after an ingestion, before absorption of the drug or chemical is likely.

Some toxicology screens include, as a first step, qualitative spot chromatography tests or thin-layer chromatography (TLC) in the analysis of an unknown sample of blood or urine. These tests are accurate for qualitative analysis of the presence of a toxin, but are imprecise for quantitative analysis. For many compounds, TLC or spot test analyses may have unacceptable false-positive rates or cross-reactions within a class of chemicals. For a more quantitative confirmation of the presence of a drug or chemical, EMIT can be performed as a screening test. An immunoassay positive for a drug must be confirmed by a second technique before the drug is considered present in the blood or urine. For more precise assays, as "second" techniques to confirm the results of screening assays, and for detection of more exotic drugs or chemicals, high-pressure liquid chromatography (HPLC) or gas-liquid phase chromatography/mass spectrometry (GLC-MS) are used. For detecting heavy metals and many salts, flame ionization spectroscopy or atomic absorption spectroscopy is the quantitative assay of choice. Reliability in the screening for drugs or toxins requires not only a sound analytic technique but also adequate sample collection, chain of custody (in cases involving judicial

Box 105–3 Drugs, Chemicals, and Foods Causing Methemoglobinemia

Drugs

Acetanilid
Amyl nitrite
Benzocaine
Cetacaine
Chloroquine
Chloroquinone
Clofazimine
Dapsone (sulfones)
Diaminodiphenylsulfone
Hydroxylamine
Lidocaine
Menadione
Methylene blue
Metoclopramide
Nitroglycerin
Nitrosobenzene
Para-aminobenzoic acid
Para-aminopropiophenone
Para-hydroxylaminopropiophenone
Phenacetin
Phenazopyridine hydrochloride (Pyridium)
Phenylhydroxylamine
Phenytoin
Potassium permanganate
Prilocaine
Primaquine
Procaine
Resorcinol
Silver nitrate
Sodium nitrate
Sodium nitrite
Sodium nitroprusside
Sulfamethoxazole
Sulfanilamide
Sulfapyridine
Sulfathiazide

Chemicals

Acetanilid
Alloxan
Ammonium nitrate
Aniline dyes
Antipyrine
Arsine
Benzene derivatives
Butyl nitrite
Chlorates
Chlorobenzene
Cobalt preparations
Dimethylaniline
Dinitrobenzene
Dinitrophenol
Dinitrotoluene
Hydroquinone
Inks/shoe polish
Isobutyl nitrite
Menthol
Naphthalene
Naphthylamines
Nitrates/nitrites
Nitric oxide
Nitroalkanes
Nitrobenzene
Nitrofuran
Nitrogen oxide
Nitrogen trifluoride
Nitroglycerin
Nitrophenol
Nitrous gases/nitric oxide
Ozone
Para-bromoaniline
Paraquat (or Monolinuron)
Para-toluidine
Phenazopyridine
Phenetidin
Phenols
Phenylhydrazine
Phenylhydroxylamine
Pyridine
Smoke (products of combustion)
Sulfones
Toluidine
Trinitrotoluene
Xylidine

Foods

Beets
Cabbage
Nitrite/nitrate preservatives
Nitrogen-rich foods
Preserved meats
Spinach
Well water (elevated nitrates)

prosecution), and timely reporting of the results. Sources of error include delay in the time between sample collection and assay, problems with sample collection (wrong tube, loss of fluid, poor labeling), natural chemical reactions (volatilization, enzymatic degradation), purposeful sample alteration, technical limits on the detection threshold of the assay used, and misinterpretation of the units in reporting the results. Quantitative assessments of some toxins correlate with the severity of intoxication. Serum concentrations of acetaminophen, aspirin, barbiturates, carbamazepine, carbon monoxide, digoxin, ethanol, ethylene glycol, iron, isopropanol, lead, lithium, methanol, phenytoin, and theophylline are useful in guiding patient management. Co-oximetry can provide blood levels of abnormal hemoglobins caused by toxins, such as carboxyhemoglobin, sulfhemoglobin, and methemoglobinemia. Box 105-3 lists drugs, chemicals, and foods capable of causing methemoglobinemia in susceptible individuals.

Certain toxins (e.g., ethanol, ethylene glycol, isopropanol, methanol) introduce osmotically active particles into the serum. These particles increase serum osmolality, which can be measured by either vapor pressure or freezing point depression. However, vapor pressure techniques give falsely low values in the presence of volatiles (such as any of the alcohols) and should not be used in the monitoring of poisoning cases. The calculated serum osmolality is derived by the following equation: Calculated serum osmolality = [2 × Na (in mEq/L)] + [Blood urea nitrogen (in g/dL)/2.8] + [Glucose (in mg/dL)/18]. Calculated osmolality then is subtracted from the measured osmolality. The measured osmolality – calculated osmolality = Osmolar gap. A normal osmolar gap is between -3

Table 105–7 Toxins Associated with Characteristic Breath Odors

Toxin	Characteristic Odor
Acetone	Ketones
Arsenic	Garlic
Camphor	Mothballs
Chloroform	Sweet
Cyanide	Bitter almond
Ethanol	Alcohol
Hydrogen sulfide	Rotten eggs
Isopropanol	Ketones
Methyl salicylate	Wintergreen
Nicotine	Stale tobacco
Organophosphates	Garlic
N-3-pyridylmethyl-N′-p-nitrophenyl urea	Peanuts (rat poison)
Paraldehyde, chloral hydrate	Pears (urine)
Phenol, cresol	Phenolic
Phosphorus	Garlic
Salicylates	Acetone
Thallium	Garlic
Turpentine	Violets

Table 105–8 Osmolar Gap Conversions to Calculate Serum Concentration: Alcohols and Glycols

Toxin	Conversion Factor
Methanol	2.6
Ethanol	4.3
Ethylene glycol	5.0
Acetone	5.5
Isopropanol	5.9

Serum concentration (mg/dL) of given toxin divided by corresponding conversion factor equals serum osmolality (mOsm/kg H_2O) attributable to that toxin.

and 10 mOsm/kg H_2O. The presence of toxins listed in Table 105-8 is associated with an elevated osmolar gap. An estimate of the serum toxin concentration can be derived using the serum osmolality as measured by the freezing point depression technique, calculating the osmolar gap, and applying the conversion factors listed in Table 105-8. Intensivists are cautioned that elevated osmolar gaps also are seen in patients with lipemic blood or in those receiving therapies such as mannitol, glycerol, sorbitol, propylene glycol, or some types of contrast agents in preparation for diagnostic imaging studies. Conversely, a falsely low osmolar gap can be seen in ethylene glycol or methanol poisoning if the vapor pressure method of serum osmolarity determination is erroneously used.

The principle of electroneutrality requires that positive and negative charged molecules in the serum must balance. The presence of toxins in the blood that cause a metabolic acidosis also frequently increase the gap between the total measured versus theoretical anions by the direct addition of organic acid anions, the indirect generation of such anions, or (rarely) the reduction of cations in the serum. The anion gap calculation is derived as follows: Anion gap = $Na^+ - (Cl^- + HCO_3^-)$, where all components are expressed in milliequivalents per liter. The "normal" anionic gap ranges from 3 to 16 mEq/L in older children and adults. Hypoalbuminemia or diluted blood both can cause misleadingly low anion gaps. The presence of elevated concentrations of unmeasured anions (e.g., as a result of dehydration or treatment with sodium salts of citrate, lactate, or acetate) or conditions associated with a decrease in unmeasured cations (e.g., as a result of hypomagnesemia, hypocalcemia, hypokalemia) can lead to an elevated anion gap. Table 105-9 lists toxins associated with changes in the total serum anions.

Table 105–9 Anion Gap Changes Associated with Specific Toxin Exposures

Elevated Anion Gap	Depressed Anion Gap
Methanol	Bromide
Paraldehyde, phenformin	Lithium
Iron, isoniazid	
Ethylene glycol, ethanol	
Salicylate, strychnine	

Many agents that cause seizures (e.g., isoniazid, organochlorine pesticides, theophylline, tricyclic antidepressants) or excessive muscular activity and hyperthermia (e.g., cocaine, amphetamines, phencyclidine, neuroleptic malignant syndrome, serotonin syndrome) may predispose the patient to rhabdomyolysis and subsequent myoglobin-induced acute renal failure. The overdose patient who is agitated or delirious and is held in physical restraints for long periods of time and the overdose comatose patient who has muscle necrosis from dependency position injury are at high risk for rhabdomyolysis. Laboratory parameters that may be useful in serial monitoring in such circumstances include serum lactic acid, creatine phosphokinase, aldolase, and myoglobin levels and urinary sediment, urine output, and urinary myoglobin levels. Alternatively, a urine dipstick that is positive for blood and negative for red blood cells contains either hemoglobin or myoglobin.

Frequently other baseline laboratory evaluations are included in the initial evaluation of the patient. Depending on the agent involved and the clinical course, the following tests often are clinically useful in the evaluation of the poisoned patient: arterial blood gases (acid-base assessment), blood count, platelet count, leukocyte differential, blood clotting parameters, electrocardiogram, electroencephalogram, liver function tests, renal function tests, serum electrolytes and blood glucose, and urinalysis including urine pH.

Additional Investigations

Radiographic Studies

Radiographs can be helpful in locating swallowed foreign bodies having toxic potential. Patients who have ingested disc batteries should undergo serial chest and abdominal radiography to ensure that the battery has cleared the esophagus and is continuing to move along the gastrointestinal tract.

Drug smugglers who have swallowed quantities of heroin or cocaine-filled balloons, condoms, or other containers can be diagnosed as a "body packer" by radiographic examination.[11] Chest and abdominal x-ray films may be of value in locating pills, tablets, or, in some cases of childhood lead poisoning, lead-containing paint chips or plaster. Sometimes agglutinated masses of pills (bezoars) can be detected in this manner or even highlighted by the use of small amounts of radiopaque contrast material. Box 105-4 lists some drugs and chemicals that may be visualized on x-ray films.

Diagnostic Trials

For a few suspected toxins, administration of an antidote not only initiates therapy but also assists in the diagnosis of the agent involved. Table 105-10 lists some of the diagnostic trials that may be appropriate in the pediatric ICU setting. For example, flumazenil, a specific benzodiazepine antagonist, can be used as a diagnostic agent administered to the comatose patient. At an intravenous dose of 1 to 2 mg, adults show a rapid improvement in consciousness (analogous to naloxone's effectiveness in reversing narcotic-induced CNS depression) after overdose involving a variety of benzodiazepines. Caution must be exercised; if a second, seizure-causing agent such as a tricyclic antidepressant has also been coingested, then the reversal of the benzodiazepine's anticonvulsant effects may inadvertently unmask seizures in the victim. Physostigmine can be of benefit in pediatric patients who have ingested Jimsonweed seeds (*Datura stramonium*) or other pure anticholinergic agents; however, caution is dictated in unknown poisonings where cardiac conduction toxicity is a consideration, since physostigmine itself can cause severe cardiac toxicity, bradycardia, and asystole.[12]

Box 105–4 Drugs and Chemicals that May Be Radiopaque

Bezoars, bags (filled with illegal drugs)
Calcium carbonate
Chloral hydrate
Enteric-coated tablets
Heavy metals
Iodine
Iron
Phenothiazines
Potassium compounds

Summary

More than 2 million poisonings, with about 50% occurring in children younger than 6 years, are reported to poison centers in the United States annually. Intensive care physicians face some of their greatest diagnostic challenges when confronted with patients who are admitted to the hospital with a baffling constellation of symptoms and signs and whose differential diagnosis includes poisoning. A careful medical history explores the intersection of underlying patient factors, likely toxic agents, and conducive environmental circumstances within the context of a time line of evolving symptoms. The history alone will often clarify the clinical picture and suggest to the clinician potential drugs or toxins that might be responsible for the patient's illness. Physical findings attendant to a comprehensive examination of the patient, with a focus on vital signs and those organ systems typically affected by toxic injury, such as the skin, gastrointestinal, cardiovascular, pulmonary, and neurological systems, may confirm the clinician's suspicions. Knowledge of common toxidromes can help the intensive care physician to focus his or her thinking as to which poison or pharmacological category of toxic agents may be responsible. Repeated physical examinations and monitoring over time are essential to determining additional management needs and judging more accurately the patient's prognosis and likely medical outcome. The nearest regional poison control center has 24-hour availability of medical toxicology expertise. Toxicologists can assist the intensivist with timely and state-of-the-art, specialist-level consultation in the diagnosis and management of individual patients. For a few suspected toxins, diagnostic studies can be helpful in the assessment of the severity of toxicity and in the prediction of a patient's expected hospital course and outcome. While broad toxic screens are rarely helpful, qualitative or quantitative blood or urine levels of some specific drugs or chemicals can be invaluable in the assessment of the poisoned patient. The investigation of anion or osmolar gaps, derangements in blood gases or electrolytes, electrocardiographic abnormalities caused by cardiotoxic agents, and/or special imaging studies will often be indicated

Table 105–10 Useful Diagnostic Trials

Agent Detected	Agent Administered	Technique	Positive Results
Anticholinergic agents (pure)	Physostigmine	0.02 mg/kg slow IV (maximum 0.5 mg)	Improved consciousness
Benzodiazepines	Flumazenil	0.2-0.3 mg/kg IV (maximum 3 mg)	Improved consciousness
Iron	Deferoxamine	40 mg/kg IM (maximum 2 g)	"Vin rose" urine color
Opiates	Naloxone hydrochloride	0.03 mg/kg (up to 4 mg)	Improved consciousness
Organophosphate	Atropine	0.1 mg/kg	Mydriasis, less secretions
Phenothiazine (dystonia)	Diphenhydramine	1–2 mg/kg IV (maximum 25 mg)	Resolution
Phenothiazine (NMS)	Dantrolene	1–3 mg/kg IV	Resolution
Insulin reaction	Dextrose	1 g/kg IV	Improved consciousness
Isoniazid	Pyridoxine	5 g IV	Seizures abate; improved consciousness

NMS, Neuroleptic malignant syndrome.

in critically ill patients. The administration of an antidote in selected cases may not only initiate therapy but also assist in the diagnosis of the poison involved, since an improvement in a patient's clinical status soon after receipt of the antidote may confirm the clinician's tentative diagnosis.

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Toxidromes and Their Treatment

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PEARLS

- When given for a benzodiazepine overdose, flumazenil may precipitate acute withdrawal in the patient who habitually uses benzodiazepines or may unmask seizures caused by a coingested substance.
- Although rare, pulmonary edema may be a serious complication of reversal of opioids with naloxone.
- β-Adrenergic antagonists, when used to lower blood pressure in a sympathomimetic overdose, may lead to unopposed α-receptor stimulation and therefore paradoxic worsening of hypertension.
- Physostigmine should be reserved for severe, life-threatening manifestations of anticholinergic toxicity because of the risk of asystole or seizures. It is absolutely contraindicated in the reversal of the anticholinergic toxidrome produced by tricyclic antidepressant ingestion.
- Pulse oximetry is unreliable in methemoglobinemia and may show falsely increased or falsely decreased values depending on the methemoglobin concentration.
- Methylene blue should not be administered to individuals with known glucose-6-phosphate dehydrogenase deficiency because they lack adequate concentrations of reduced nicotinamide adenine dinucleotide phosphate to produce reductase activity and because methylene blue can trigger hemolysis or methemoglobinemia in those individuals.
- The skin is a distinguishing factor between sympathomimetic (pale, cool, and diaphoretic) and anticholinergic (flushed, warm, and dry) toxidromes.
- The toxic differential diagnosis of hyperthermia should include malignant hyperthermia, serotonin syndrome, neuroleptic malignant syndrome, sympathomimetic poisoning, and anticholinergic poisoning.
- An elevated osmolar gap suggests ingestion of a toxic alcohol, whereas a normal result does not exclude it. Levels in the blood are the gold standard for diagnosis and prognosis.
- Succinylcholine is generally contraindicated in cholinesterase inhibitor toxicity, and its duration of effect will be significantly prolonged.
- Nitrites should be used with extreme caution in patients with cyanide poisoning and concomitant carbon monoxide poisoning because of the risk of further decreasing oxygen-carrying capacity.
- Total iron-binding capacity may be falsely elevated in patients with acute iron overdose and is not a reliable marker in iron toxicity.
- In the United States, the local Regional Poison Center may be reached by calling 800-222-1222.

Every year almost 2.5 million human exposures to toxic substances are reported to poison centers in the United States.[1] Of these, approximately 60% involve children younger than 12 years, and this age group accounts for approximately 4% of the reported fatalities. Although 75% of calls are managed without referral to a health care facility, of the 25% of patients who are seen in a health care facility, one in eight is admitted to a critical care unit.

In most cases of poisoning, the agents involved are known, or at least circumstantial evidence points to a specific toxin or toxins. However, even in cases in which the toxic exposure is unknown or the clinical presentation is inconsistent with the history, the intensivise care physician can find physical and analytical clues of the inciting agent and provide targeted therapy. The term *toxidrome,* a contraction of *toxic syndrome,* refers to a constellation of signs associated with certain substances or groups of substances. Several toxidromes have been described; although their expression may not be complete in every case, they can provide valuable information to guide investigation and treatment. A list of toxidromes appears in Chapter 105.

The patient should be examined carefully and thoroughly, paying particular attention to vital signs, mental status, pupil size and reactivity, skin characteristics (color, temperature, moisture), and bowel sounds. Other important aspects of the physical examination include muscle tone, respiratory effort, presence of tremor, and characteristics of the mucous membranes. Laboratory investigations may help narrow the differential diagnosis and determine the need for additional examination while guiding therapy. However, diagnostic laboratory tests should be reviewed with caution. Some assays may further cloud the clinical picture because of false-positive results from cross-reactivity and may lead to an inaccurate diagnosis, inappropriate therapy, or withholding of a specific antidote.[2] Utility of a specific test should be based on its probability of indicating or guiding therapy and prognosis of end-organ toxicity.

This chapter addresses some common presentations of toxic ingestions and their treatment. For more in-depth information, the reader is referred to several comprehensive textbooks of medical toxicology.

Opiates

The classic triad of respiratory depression, coma, and miosis is seen with both naturally occurring opiates and synthetic opioids. Additional features include bradycardia, hypotension,

and decreased gastrointestinal (GI) motility. A similar clinical picture may be encountered with ingestion of clonidine, other imidazoline derivatives found in over-the-counter eye drops or nasal sprays, or tizanidine, all of which are centrally acting α_2-adrenergic agonists that decrease sympathetic tone.[3-5] Not all patients exposed to an opiate present with the classic toxidrome. Respiration becomes shallow with increasing central nervous system (CNS) depression, so hypercarbia may occur before overt respiratory depression.[6-9] In addition, several opiates and opioids, including morphine, meperidine, pentazocine, diphenoxylate/atropine, and propoxyphene, may result in mid-position or mydriatic pupils either from their pharmacologic activity or from brain anoxia.[3,10,11]

Effects on respiration are likely a result of action at the μ-receptors. Analgesic effect is exerted through action at both μ- and κ-receptors.[6] Several opioids have been designed to function as agonist-antagonists. In general, they provide spinal analgesia through agonist effects at the κ-receptors and simultaneously antagonize μ-receptors. This allows them to provide pain relief at higher doses while reaching a ceiling effect on respiratory depression.[7] However, in overdose, receptor selectivity may be lost, and decreased respiratory drive can occur with these medications.

Naloxone is an opiate receptor antagonist that reverses the toxic effects of opioids. A starting dose of 0.1 mg/kg intravenously is recommended to prevent the need for artificial ventilation in life-threatening opiate-induced respiratory depression. If no intravenous access is available, it can be administered subcutaneously, intramuscularly, or via endotracheal tube. However, the intramuscular route exhibits variable pharmacokinetics with an unpredictable duration of action and may therefore allow recurrent sedation after a period during which the patient is thought to be free of further toxicity. Naloxone may precipitate acute withdrawal in opioid-dependent individuals; in such patients a lower starting dose, titrated upward to effect, may be warranted. Because of the different receptor affinities of each opioid, some individuals may not respond to lower doses of naloxone. The titration should proceed upward to 10 mg, at which point if no response has been illicited, naloxone should be discontinued and an etiology other than opioids should be considered for the cause of respiratory depression.[12] In patients with apnea, artificial ventilation should be promptly provided before the administration of naloxone. Because the duration of action of naloxone is shorter than that of most opioids, repeated doses or a continuous intravenous infusion may be necessary. The accepted infusion rate is two thirds of the initial reversal dose per hour.[12]

Reversal of opioid toxicity has been associated with pulmonary edema, although this has also been described in the setting of opiate toxicity itself.[13-16] Naloxone has been reported anecdotally to reverse clonidine overdose, although failure of naloxone to reverse clonidine has also been described.[17] Naloxone administration has occasionally been associated with significant hypertension.[18,19] This is usually short lived and does not require treatment. If hypertension persists, treatment should consist of a short-acting antihypertensive such as nitroprusside so that the drug and its effects can be quickly stopped. This will prevent the development of hypotension as the hypertensive crisis resolves.

Nalmefene is a newer, long-acting opiate receptor antagonist. It is available as a parenteral product with a potency equivalent to naloxone on a milligram-per-milligram basis but with a duration of action nearly five times longer.[20-22] Its half-life can range from 2 to 8 hours. Before it is administered, a test dose of naloxone should be used to exclude the possibility of acute withdrawal. In at least one prospective, controlled trial, it offered no advantage over naloxone.[21] It has a similar side effect profile, including cases of short-lived noncardiogenic pulmonary edema, and may provide false security in a patient who has ingested a long-acting opioid in which symptoms may recur after the antagonist has worn off.

Sympathomimetic Agents

Symptoms and signs of sympathetic excess may be seen with a number of therapeutic and illicit agents that either mimic endogenous excitatory neurotransmitters or act on receptors to increase their release.[23] Drugs that produce the sympathomimetic toxidrome are listed in Box 106-1. Any or all of the manifestations in Box 106-2 may be observed depending on the agent involved. Agents with predominantly β-adrenergic activity are more likely to produce tachycardia and hypotension from peripheral vasodilation compared with agents with predominantly α-adrenergic effects that may produce severe hypertension with reflex bradycardia. Hyperthermia, rhabdomyolysis, and myoglobinuria may result from increased metabolic activity. Additional morbidity, including ischemic or hemorrhagic stroke, have been documented. With cocaine use, for example, cases of myocardial ischemia and infarction have been reported[23,24] Thrombolytics should not be used unless the patient has confirmed myocardial infarction and is at low risk for intracranial bleeding.[25] The methylxanthines, caffeine and theophylline, are not sympathomimetics per se, but they may produce many of the same clinical features as a result of their β-adrenergic activity and effect on adenosine receptors.[26-28] Patients with acute overdose of methylxanthines may initially present with severe GI symptoms and quickly progress to hypotension, tachydysrhythmias, and status epilepticus.[27,29,30] Designer amphetamines, such as methylenedioxyamphetamine (MDMA) and its derivatives, additionally cause a release of serotonin and may precipitate hallucinations in addition to the sympathomimetic effects listed above. These patients are at risk for seizures, dysrhythmias, hyperthermia, rhabdomyolysis, the syndrome of inappropriate secretion of antidiuretic hormone resulting in hyponatramia, and disseminated intravascular coagulation.[28,31]

Benzodiazepines are the first-line agent to reduce CNS catecholamine release, thereby eliminating severe hypertension, tachycardia, agitation, and muscle overactivity. Large doses may be required. Caution should be exercised when adrenergic antagonists are used to treat tachycardia and hypertension; β-adrenergic antagonist use may result in unopposed α-adrenergic receptor stimulation and cause a paradoxic worsening of hypertension. Although labetalol is a β-antagonist with weak α-blocking activity, it has not been shown to be effective in this scenario. Concomitant administration of a vasodilator in refractory hypertension is recommended.[23,24,32] Agents such as cocaine may deplete norepinephrine, leading to cardiovascular collapse. Therefore short-acting agents are the only advisable treatment for hypertension if benzodiazepines administration has failed. Seizures should also be managed with benzodiazepines. In patients refractory to this therapy, a barbituate such as phenobarbital should be considered.

Box 106–1 Agents that Cause Sympathomimetic Syndrome

Albuterol
Amphetamines
Caffeine
Catecholamines
Cocaine
Ephedrine
Ketamine
Phencyclidine (PCP)
Phenylephrine
Phenylpropanolamine
Pseudoephedrine
Terbutaline
Theophylline

Box 106–2 Sympathomimetic Toxidrome Features

Agitation
Seizures
Mydriasis
Tachycardia
Hypertension
Diaphoresis
Pallor
Cool skin
Fever

Box 106–3 Anticholinergic Agents

Antihistamines (e.g., diphenhydramine, hydroxyzine)
Atropine
Benztropine mesylate
Carbamazepine
Cyclic antidepressants
Cyclobenzaprine
Hyoscyamine
Jimsonweed
Oxybutynin
Phenothiazines
Scopolamine
Trihexyphenidyl

Box 106–4 Anticholinergic Toxidrome Features

Agitation
Delirium
Coma
Mydriasis
Dry mouth
Warm, dry, flushed skin
Tachycardia
Hypertension
Fever
Urinary retention
Decreased bowel sounds

Phenytoin does not play a role in seizures resulting from toxicity and, in the case of methylxanthines, may actually worsen patient outcome by lowering the seizure threshold.[28] Confirmation by urinary drug screening is of little use in the emergency setting. While a positive test result for cocaine is likely confirmatory for its use, a positive result for amphetamines is not. Several medications cross-react to produce a false-positive amphetamine presence, including buproprion[2] and pseudoephedrine.[23]

Anticholinergic Agents

The anticholinergic toxidrome, more appropriately referred to as an *antimuscarinic toxidrome,* is produced by a number of agents that possess antimuscarinic properties as their primary effect or as a side effect. Examples of such toxins are provided in Box 106-3. Muscarinic receptors are located in the CNS, in the target organs of the parasympathetic nervous system (PNS), and in the sweat glands (sympathetic nervous system).[33] The syndrome may have features that are similar to those of the sympathomimetic toxidrome (Box 106-4). Examination of the skin usually provides clues to differentiate between the two; the patient will be dry in this scenario versus increased diaphoresis with sympathomimetic toxicity. Hypertension and tachycardia are typically less severe than when seen with sympathomimetics. Also, the dilated pupils in the anticholinergic syndrome are nonreactive because there is associated cycloplegia.[33,34]

Because sweating is inhibited in intoxicated patients, treatment of agitation is important to prevent hyperthermia. Benzodiazepines are the drug of choice. Physostigmine is a cholinesterase inhibitor that may be used to reverse the central and peripheral manifestations of anticholinergic toxicity.[33] Because of case reports of convulsions[35] or asystole[36] associated with administration of physostigmine, it should not be used to treat the anticholinergic manifestations of tricyclic antidepressant overdose. Diphenhydramine overdose can present with anticholinergic toxicity and also manifest electrocardiographic (ECG) changes, including sodium channel blockade. Therefore the use of physostigmine to reverse toxicity in this patient population should be approached with caution. In general, physostigmine has a short duration of action compared with the anticholinergic agent ingested; because of its severe side effects, it has fallen out of favor as an antidote for most previously indicated ingestions.

Cholinergic Agents

Cholinergic agents are best divided into the following three categories: muscarinic agents, nicotinic agents, and cholinesterase inhibitors. The muscarinic agents act in the CNS, at postganglionic parasympathetic nerve endings, and in the sweat glands. Nicotinic agents act in the CNS, in the autonomic ganglia (both sympathetic and parasympathetic), and at the neuromuscular junction. Cholinesterase inhibitors increase the available acetylcholine in the cholinergic synapse and present with a combination of symptoms that result from action at both the nicotinic and muscarinic receptors.[37,38] Agents with cholinergic activity are listed in Box 106-5. Signs and symptoms of cholinergic excess are listed in Box 106-6.

Direct-acting muscarinic agents produce typical features of excessive parasympathetic activity. Nicotine produces salivation, nausea, and vomiting.[37,38] Hypotension, bradycardia,

Box 106–5 Drugs Causing Cholinergic Excess

Inhibitors of Acetylcholinesterase

Organophosphate insecticides (malathion, parathion, diazinon)
Carbamate insecticides (aldicarb, carbaryl, propoxur)
Nerve agents (soman, sarin, tabun, Vx, cyclosarin)
Drugs used for myasthenia gravis or reversal of neuromuscular blockade (e.g., physostigmine, pyridostigmine, neostigmine, edrophonium)

Direct Muscarinic Agonists

Bethanechol
Carbachol
Methacholine
Pilocarpine
Muscarinic mushrooms (e.g., *Clitocybe* spp., *Inocybe* spp.)

Nicotinic agents

Nicotine
Water hemlock

Box 106–6 Cholinergic Toxidrome Features

Muscarinic Effects (DUMBBELS)

Diarrhea
Urinary incontinence
Miosis
Bradycardia
Bronchorrhea
Emesis
Lacrimation
Salivation

Nicotinic Effects

Fasciculations
Weakness
Paralysis
Tachycardia
Hypertension
Agitation

Central Effects

Lethargy
Coma
Agitation
Seizures

and respiratory depression can be preceded by tachycardia, hypertension, and tachypnea. Central features include initial stimulation followed by seizures, lethargy, and coma. Neuromuscular blockade may occur. Management of nicotine poisoning, which can be severe, is entirely supportive.[39-41] Children are at increased risk of nicotine poisoning from ingestion of cigarettes or chewing tobacco as well as from exposure to smoking cessation products, including gums, lozenges, patches, and inhalers.

Cholinesterase inhibitors, such as organophosphate pesticides and nerve agents, produce a mixed picture of toxicity. Parasympathetic manifestations tend to dominate the autonomic component of toxicity. Organophosphates bind to and inactivate acetylcholinesterase, preventing the normal termination of cholinergic stimulation at the postsynaptic receptors. The end result is excessive nicotinic and muscarinic activity in the PNS and CNS. At the neuromuscular junction, the result is depolarizing neuromuscular blockade. Over time the enzyme becomes phosphorylated, a process referred to as *aging*. Not all organophosphorous agents age at the same rate. Some nerve agents may age in as quickly as a few minutes, whereas some pesticides can take as long as 72 hours to permanently inactivate the cholinesteraseses.[42] Cholinesterase activity is only restored by synthesis of a new enzyme.[38] Carbamates bind reversibly to acetylcholinesterase, and the enzyme/chemical complex undergoes spontaneous hydrolysis, generally restoring cholinesterase function within hours. Carbamates do not penetrate the CNS well, so central manifestations are less severe. Because these agents cause bronchorrhea, bronchospasm, decreased respiratory drive, and paralysis of the muscles involved in breathing, death results from respiratory failure. The order of appearance of signs and symptoms depends on the route of administration. With dermal exposure, the first manifestation may be local hyperhidrosis, followed by systemic manifestations once the agent is absorbed through the skin. Inhalational exposure results in initial upper airway manifestations and respiratory distress. Ingestion presents with drooling and vomiting as the earliest expression of toxicity.

Treatment of cholinergic toxicity involves atropine to reverse the muscarinic effects, an oxime to reverse neuromuscular blockade, and benzodiazepines to treat seizures. Extremely large doses of atropine may be necessary, and the end point of therapy is the drying of secretions, not heart rate or pupil size. Organophosphate-poisoned patients may manifest tachycardia as a result of their exposure, and atropine is not contraindicated in these patients. Tachycardia during therapy is limited and not life-threatening.[42,43] Depending on the agent involved, repeated doses or a constant infusion may be necessary. Pralidoxime is the oxime available and indicated for organophosphate poisoning in North America. It works by preventing aging of the cholinesterase and reactivating the enzyme. Pralidoxime is generally not indicated in carbamate overdose because of the reversible binding of toxin to acetylcholinesterase, which limits the duration of toxicity.[38] Pralidoxime does not readily cross the blood-brain barrier, and benzodiazepines should initially be provided for the prevention of seizures.[43] Cholinesterase levels can be obtained in poisoned patients and may confirm exposure and indicate the severity of toxicity. However, they are usually not available in real time and should not be used to guide therapy because this will likely delay treatment of the severely poisoned patient.

Methemoglobinemia

Methemoglobinemia results from the oxidization of iron in hemoglobin from the ferrous (2+) form to the ferric (3+) form. It results in the inability to carry oxygen; by shifting the oxygen saturation curve to the left, it decreases off-loading of any bound oxygen at the tissues.[44] Methemoglobinemia is associated with drugs and toxins that cause oxidative stress (Box 106-7). Clinically, the patient appears cyanotic, and the cyanosis does not respond to the administration of oxygen. The blood may have a chocolate color, and exposure of the blood sample to oxygen does not restore a normal appearance. The diagnosis is confirmed by multiple-wavelength co-oximetry. Standard pulse oximetry, which uses only two wavelengths of

Box 106–7 Toxins that Cause Methemoglobinemia

Benzocaine
Dapsone
Inhaled nitric oxide
Lidocaine
Naphthalene (found in certain mothballs)
Nitrates
Nitrites
Nitroprusside
Phenazopyridine
Prilocaine
Sulfonamides

light, cannot reliably be used to assess the degree of methemoglobinemia. However, newer models of pulse oximeters that use several different wavelengths of light may be used to measure methemoglobin levels. Standard pulse oximetry may overestimate or underestimate true oxygen saturation depending on the methemoglobin level.[45,46] In a patient with cyanosis and a normal partial pressure of oxygen, methemoglobinemia should be suspected.

The body produces a small amount of methemoglobin (typically <1%). Under normal physiologic conditions, this is reduced by a methemoglobin reductase dependent on reduced nicotinamide adenine dinucleotide (NADPH). Additional reduction can occurr through a minor pathway requiring the presence of reduced NADPH. Because a large oxidative stress overwhelms the reducing capacity of these pathways, the result is clinically apparent methemoglobinemia.

Patients may appear blue with methemoglobin concentrations as low as 15 g/L, treatment may not be required. The appearance of cyanosis depends on the total methemoglobin present. Although anemic patients have less hemoglobin to convert to methemoglobin, this is usually a larger percent of their functioning hemoglobin. So, although they may not manifest cyanosis, they are less tolerant of methemoglobin at a lower percentage and are more likely to express symptoms of hypoxia.[44] Therapy should be provided according to the signs of hypoxia and not the methemoglobin level or the presence of cyanosis. If required, treatment begins with the administration of 100% oxygen (to maximize oxygen-carrying capacity with the certainty that unaffected hemoglobin is fully saturated), followed by intravenous methylene blue at a dose of 1 mg/kg. Methylene blue facilitates the reduction of the oxydized heme iron of methemoglobin to its normal state by NADPH-dependent methemoglobin reductase. Response is rapid and occurs within 30 minutes. Depending on the toxin involved, in the case of dapsone, recrudescent methemoglobinemia may be seen and may require repeated doses of methylene blue. The total (cumulative) dose should not exceed 7 mg/kg because methylene blue can itself be an oxidizing agent, cause additional methemoglobinemia, and potentially lead to hemolysis. Methylene blue may be ineffective in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, in whom it may increase the risk of hemolysis or methemoglobinemia. In general, the patient can safely be treated with two doses of methylene blue; if no response is elicited, G6PD deficiency should be suspected. G6PD testing, however, should not be conducted until several months after resolution of the methemoglobinemia. When done concommittantly with the insult, patients will have a false-positive result for the deficiency. In nonresponding patients who are severely ill, exchange transfusion should be considered. Although hyperbaric oxygen increases the percent of oxgen-saturated blood, this is likely not beneficial for treatment of methemoglobinemia because no functioning hemoglobin has been added and patients will return to their previous state when removed from the chamber.[44,47]

Hyperthermia

Several distinct hyperthermia syndromes may result from xenobiotics. In addition to the following syndromes described, the sympathomimetic and anticholinergic syndromes may also cause hyperpyrexia and are detailed separately. Distinction of malignant hyperthermia, serotonin syndrome, and neuroleptic malignant syndrome are provided in Table 106-1. While differences exist, there is also potential for overlap, and diagnosis may be difficult when there is no previous patient history available.

Malignant Hyperthermia

Malignant hyperthermia is a genetically determined condition that is triggered by exposure to depolarizing neuromuscular blocking agents (succinylcholine) or inhalational anesthetic agents. It is a life-threatening condition that results from dysfunction of the ryanodine receptors. This elevates the intracellular calcium in somatic muscle cells, resulting in rigidity and muscle damage. This syndrome requires prompt intervention with aggressive cooling and treatment with dantrolene, which allows muscle relaxation through blockade of calcium release from the sarcoplasmic reticulum.[48] Malignant hyperthermia is discussed in more detail in Chapter 124.

Serotonin Syndrome

Serotonin syndrome is a constellation of features resulting from excessive serotonergic activity in the CNS. It is most commonly associated with therapeutic regimens that include two or more drugs that increase CNS serotonin transmission, often by different mechanisms (Box 106-8). Serotonin syndrome has also been described with single agents in overdose, with the most commonly mentioned being clomipramine, a potent tricyclic antidepressant. Hallmark features include altered mental status, excessive muscle activity, and autonomic instability. Diagnostic criteria have been suggested by Sternbach.[49] This diagnosis requires history of exposure to a serotonergic agent(s) and the presence of three of the following: mental status change, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and/or fever. A distinguishing feature from the other hyperthermic syndromes is the presence of rigidity and hyperreflexia more pronounced in the lower limbs than in the upper limbs and the rigidity described more as "clasp knife" than "lead pipe."[48,50] Symptoms typically start within hours of exposure to the offending agent and resolve within 24 hours, providing a quick-on, quick-off effect. Most cases are mild and self-limiting; however, patients with severe toxicity may develop extreme hyperthermia and rhabdomyolysis with renal failure and cardiovascular collapse. Treatment is supportive: withdrawal of all serotonergic agents, benzodiazepines for muscle overactivity,

Table 106–1 Differences Between Drug-Induced Hyperthermia Syndromes

Syndrome	Causative Agent	Timing of Onset	Treatment
Malignant hyperthermia	Depolarizing neuromuscular blockers or Inhalational anesthetics	Minutes	Dantrolene
Serotonin syndrome	Coadministration of two or more serotonergic agents	Hours	Supportive care, cyproheptadine
NMS	Antipsychotic drugs	Days	Supportive care, bromocriptine

Box 106–8 Drugs Associated with Serotonin Syndrome

Amphetamines
Bupropion
Cocaine
Dextromethorphan
Fenfluramine
Lithium
Lysergic acid diethylamide (LSD)
L-tryptophan
Meperidine
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Trazodone
TCAs
Venlafaxine

and aggressive cooling. Cyproheptadine, a serotonin blocker, has been proposed for the treatment of serotonin syndrome. Doses range from 16 to 32 mg in divided doses up to four times daily. Although it might be considered to prevent further progression of the syndrome early in its course, its utility has not been established.[51-53] In cases of severe hyperthermia, cyproheptadine will do little to prevent further symptoms and should be abandoned for more aggressive therapy with cooling and paralysis with a nondepolarizing paralytic.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a constellation of features triggered by exposure to neuroleptic drugs (phenothiazines, butyrophenones, atypical antipsychotics). It is most commonly associated with initiation of therapy or with a dose escalation; it can also be triggered by the addition of a serotoninergic agent to an established antidopaminergic agent or the withdrawal of dopaminergic agents used to treat Parkinson disease.[54,58] The onset is insidious, occurring over several days. The diagnosis requires exposure to a neuroleptic drug, fever, muscular rigidity, and at least two of the following: mental status change, mutism, tachycardia, labile blood pressure, diaphoresis, dysphagia, tremor, incontinence, leukocytosis, or elevated creatine kinase level.[55] Muscle rigidity in this syndrome is often described as "lead pipe" and greater in the upper extremities than in the lower extremities. Distinguishing NMS from lethal catatonia may be difficult. NMS is thought to represent the extreme end of the spectrum of extrapyramidal (antidopaminergic) side effects of these medications. Unlike its milder counterparts, however, it is unresponsive to centrally acting anticholinergic agents; therefore diphenhydramine or benztropine have no role in the treatment of this syndrome. The recommended treatment is supportive, including sedation, neuromuscular blockade with a nondepolarizing paralytic, and active cooling if required. Hyperthermia does not respond to antipyretics. Myoglobinuria and renal failure may complicate the course. Bromocriptine, a dopamine receptor agonist, and dantrolene have been advocated in the treatment of NMS, but their value is debated.[56] Because it is a syndrome that results from CNS activation, dantrolene's action at the muscle end plate is likely not effective, and its nonselective activity on skeletal muscle could theoretically weaken the diaphragm and increase respiratory dysfunction.[57]

Box 106–9 Agents that Cause Anion Gap Metabolic Acidosis

Carbon monoxide
Cyanide
Ethylene glycol
Iron
Isoniazid
Metformin
Methanol
Paraldehyde
Phenformin
Salicylates

Metabolic Acidosis with Increased Anion Gap

Metabolic acidosis is a laboratory toxidrome that presents a substantial differential diagnosis. Common nontoxicologic causes of this disorder in children include diabetic ketoacidosis, uremia, lactic acidosis, and inborn errors of metabolism. The agents most commonly associated with metabolic acidosis are listed in Box 106-9 (also see Chapter 68). In addition, any agent causing shock will increase lactate and cause metabolic acidosis with an increased anion gap. Note that although metabolic acidosis from toxic agents is generally associated with an increase in the anion gap, nonanion gap acidosis may be seen with the therapeutic use of carbonic anhydrase inhibitors such as acetazolamide or topiramate, or with toxins that cause renal tubulopathy with chronic use such as toluene (an agent seen commonly with inhalant abuse).

Methanol and Ethylene Glycol

Methanol and ethylene glycol are toxic alcohols found in various automotive antifreeze products and as chemical reagents. Ethylene glycol has a sweet taste that may be masked by the

addition of bittering agents to many antifreeze products. Ethylene glycol–containing radiator antifreeze products contain fluorescein, and examination of the urine under a Wood's lamp has been advocated to screen for ingestion.[59] In one study, even in the absence of ingestions, urinary fluorescence was shown in most hospitalized pediatric patients[60]; in addition, several types of hospital tubing and plastic containers may provide their own fluorescence under a Wood's lamp, calling into question the usefulness of this simple test.

Both compounds produce CNS depression, with intoxication seen more substantially with ethylene glycol than with methanol. Beyond that, they have little toxic effect in their parent form. Both substances are metabolized by alcohol dehydrogenase to highly toxic metabolites. The end product of methanol metabolism is formic acid, which causes severe metabolic acidosis and retinal toxicity described as "snowstorm blindness." Ethylene glycol is converted to a number of intermediate toxic products and ultimately to oxalate. This conversion results in severe metabolic acidosis, renal failure, and hypocalcemia through binding of oxylate to calcium to form crystals.[61]

Ingestions greater than 0.5 mL/kg of either agent are potentially toxic, and ingestions of more than 1 mL/kg are potentially fatal. Because both substances are osmotically active, they will increase serum osmolality and therefore raise the osmolar gap, the difference between calculated serum osmolarity and actual osmolality as determined by freezing point depression. Caution should be exercised in interpreting this gap. Because the normal range is −8 to +12, significant levels of toxic alcohols may be present with a "normal" osmolar gap. In short, an elevated gap suggests toxic alcohol poisoning, but a normal result does not exclude it.[62] As the parent compound is metabolized and the anion gap increases from the development of acid metabolites, the osmolar gap will fall and therefore may be normal in patients presenting with symptoms of toxicity. Measured levels of ethylene glycol and methanol are the gold standard for diagnosis and treatment guidance. Hemodialysis is indicated in severely toxic patients, even when the parent compound is no longer detectable, to eliminate toxic metabolites and correct metabolic abnormalities.

Once the diagnosis of toxic alcohol poisoning is made and life-sustaining measures have been undertaken, initial therapy is targeted at blocking alcohol dehydrogenase to limit further generation of toxic metabolites. This may be achieved either with ethanol or with fomepizole. Ethanol infusion is difficult to titrate; requires frequent measurements; and carries the risks of inebriation, CNS depression, hypoglycemia, and hypotension. Fomepizole, a drug with known kinetics and approval by the Food and Drug Administration (FDA) for the treatment of toxic alcohol poisoning, is the agent of choice. A loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours is sufficient. The dose must be increased to 15 mg/kg after 48 hours because of induction of its own metabolism. In addition, the dosing regimen requires adjustment during hemodilayisis to maintain suffucient concentrations to continue to block alcohol dehydrogenase because fomepizole is itself dialyzable.[63] Once alcohol dehydrogenase is blocked, the parent alcohol is excreted through the kidneys with a half-life of 19.7 hours for ethylene glycol[64] and 54 hours for methanol.[63] Hemodialysis is recommended in the presence of high levels of methanol or ethylene glycol, in the presence of significant acidosis or electrolyte disturbance, or if there is renal or visual impairment.

Table 106–2 Half-Life of COHb

Oxygen Concentration	Half-Life
21% (room air)	4–5 hours
100% (mask or endotracheal)	60–90 minutes
100% (hyperbaric molecular oxygen)	20–30 minutes

Carbon Monoxide

Carbon monoxide (CO) is the product of incomplete combustion of carbonaceous fuels. These include natural gas, fuel oil, gasoline, propane, and charcoal. CO causes tissue hypoxia through several mechanisms: it binds with high affinity to oxygen-binding sites of hemoglobin; it binds to myoglobin and disrupts the transfer of oxygen from erythrocytes to mitochondria; it binds to mitochondrial cytochrome oxidase; and it interferes with electron transport and adenosine triphosphate production. CO also displaces nitric oxide from platelets, leading to increased generation of the free radical peroxynitrite. Standard pulse oximetry is unreliable at detecting CO poisoning and overestimates arterial oxygen saturation. The diagnosis is made with multiple-wavelength co-oximetry on a blood sample. Additional CO levels are not required with appropriate oxygen therapy because they will reliably decrease with time. An exception to this rule occurs in the case of inhalation of methylene chloride, found in degreasers and furniture strippers. Its metabolism leads to endogenous production of CO. In this case, serial levels should be obtained, watching for a downward trend during treatment.

Correlation between symptoms and carboxyhemoglobin (COHb) level is poor, but a level should be obtained to confirm the diagnosis. At low levels of CO, symptoms are nonspecific and include fatigue, malaise, nausea, and headache. Higher concentrations lead to impaired cognition and finally coma. CO poisoning may also cause hypotension and syncope, explained in part by the effect of CO on nitric oxide. CO poisoning is also associated with delayed or persistent neurologic sequelae, particularly in patients who lose consciousness or demonstrate syncope.

Treatment consists of accelerating the removal of CO from hemoglobin by providing as much oxygen as possible. The half-life of COHb under various oxygen concentrations is provided in Table 106-2. Hyperbaric oxygen (HBO), the administration of oxygen at supra-atmospheric pressure, has been advocated in the treatment of severe CO poisoning.[65] In addition to increasing the rate of resolution of COHb, it accelerates the removal of CO from cytochrome oxidase. However, because most CO has been eliminated from the blood by the time the patient is placed in the chamber, the benefits are likley seen from the reduction of leukocyte adhesion to endothelium.[66] It is through this last mechanism that HBO is proposed to decrease the incidence of delayed neurologic sequelae, although two randomized trials have led to conflicting results.[65,67] There are no clinical trials of HBO in children. Although its use remains controversial, it is recommended in children who have a history of loss of consciousness or syncope or who have persistent neurologic findings on examination despite treatment with simple oxygen. A thorough neurologic exam should evaluate the patient for persistant ataxia when attempting to walk as well as other cerebellar signs. Adverse reactions to HBO therapy include

claustrophobia, barotrauma (pneumothorax, tympanic membrane rupture), and oxygen toxicity (seizures).[67] It is recommended that if the patient is to undergo HBO treatment, it should be completed within 24 hours of exposure. Patients who have had a cardiac arrest are not considered candidates for HBO.[65] Fetal hemoglobin has a higher affinity for CO than does adult hemoglobin. As a result, neonates may have higher COHb levels than older children with the same exposure. Although the fetus may serve as an additional compartment, or "sink," for CO, exhibiting higher CO levels, no data on pregnancy and HBO therapy are available.

Cyanide

Cyanide is a highly toxic compound that may produce poisoning from a variety of sources. It is widely used as a reagent in industry. A number of plants, including the seeds of several edible fruits (e.g., apples, cherries, peaches, pears), contain cyanogenic glycosides that may be converted to cyanide in the GI tract. The unapproved substance Laetrile, sometimes used to treat cancer, is synthesized from amygdalin, a cyanogenic glycoside. Fires, particularly those in which certain plastics or fabrics are combusted, can generate hydrogen cyanide (HCN). Finally, iatrogenic cyanide poisoning results from administration of nitroprusside, which is metabolized to cyanide and can cause toxicity at high doses, after prolonged therapy without coadministration of sodium thiosulfate, or in the presence of renal failure.[68,69]

Cyanide produces toxicity rapidly, especially through inhalation of HCN. Cyanide salts (sodium cyanide [NaCN], potassium cyanide [KCN]), when ingested, are converted to HCN in the presence of gastric acid and then absorbed. Cyanide binds to heme iron in the cytochrome complex IV of the electron transport chain (cytochrome C oxidase), resulting in inhibition of oxidative phosphorylation. Consequently, the patient is unable to use oxygen to produce adenosine triphosphate, and the result is energy failure. Signs and symptoms are nonspecific and reflect tissue hypoxia. However, a symptomatic patient with a lactate level of 10 mmol/L or more is highly suspect for cyanide toxicity.[70] Death may occur within minutes. Venous oxygen levels are elevated from the impairment of oxygen use at the cellular level. However, because of this, patients do not appear cyanotic.

Treatment of cyanide poisoning involves immediate life support measures followed by administration of an antidote. The traditional three-antidote kit contains inhaled amyl nitrite, intravenous sodium nitrite, and intravenous sodium thiosulfate. Amyl nitrite is only used if intravenous access is unavailable. Nitrites are therapeutic by inducing methemoglobinemia. Although the mechanism of action of nitrites in cyanide poisoning is incompletely understood, it is postulated that methemoglobin has a higher affinity for cyanide than cytochrome oxidase and therefore removes cyanide from the affected cytochromes. Nitrites are potent vasodilators and can cause significant hypotension that may be avoided by slow administration. However, the most significant vasodilation occurs in the most hypoxic tissues, and therefore this effect may provide additional therapuetic benefits. Excessive methemoglobinemia is a potential risk. The initial dose in pediatric patients is 0.2 mL/kg of a 3% solution. The dose should be decreased in the presence of anemia. Nitrites should not immediately be administered to fire victims, who may have significant CO poisoning. The induction of methemoglobin in these individuals may reduce oxygen-carrying capacity below critical levels. The third antidote, sodium thiosulfate, reacts with cyanide in the presence of the mitochondrial enzyme rhodanese to produce the nontoxic thiocyanate that is then excreted in the urine. Although part of a three-antidote kit, sodium thiosulfate may be used without nitrites and can be administred early in patients with significant CO levels because it will not affect hemoglobin. It, too, can cause hypotension if administered rapidly. Additional side effects may include nausea and vomiting; however, it has a minimal adverse effect profile. Hydroxocobalamin (HCO) is an alternative antidote that has been used to treat fire victims in France for several years; it is now available in the United States.[71,72] It is a cobalt-containing molecule that allows cyanide to replace a hydroxyl group to produce cyanocobalamin (vitamin B_{12}), which is then excreted in the urine.This antidote, although effective, may be limited by its adverse affects, interference with laboratory assays, and expense. Patients may experience hypertension after administration. Both their skin and body fluids will exhibit a reddish hue as a result of the red color of cyanocobalamin. This discoloration interferes with several important assays that may be needed for patient monitoring because many of the analyses performed in the lab are colorimetric. Patients have also reported severe acne 1 to 2 weeks after administration.[72] Pediatric administration consists of a 70 mg/kg dose administered over 30 minutes (IV push is acceptable in severe toxicity). A second dose may be administered if necessary over a total administration time of 6 to 8 hours. The onset of action of HCO is more immediate than sodium thiosulfate, which may take up to 20 minutes to exert its effect. However, because HCO must be reconstituted slowly over 20 minutes and still requires intravenous access, its administration time limits its onset of action and therefore likely provides no benefit over thiosulfate in this respect. It is suspected that the two medications will work synergystically but should be administered in separate lines. To date there are no comparative trials to show that hydroxocobalamin alone is superior to the traditional three-antidote kit.

Iron

Iron is available alone and in combination with other vitamins. Several salts have different proportions of elemental iron. Iron toxicity is often divided into several phases. The first phase occurs early, usually within 30 minutes, and consists of GI manifestations of vomiting and diarrhea, which may include both hematemesis and hematochezia. Fluid and electrolyte losses may be severe during this period, and aggressive resuscitation may be necessary. The second phase, the so-called *latent period,* is a quiescent phase in which the initial GI symptoms have ceased but the patient continues to feel unwell. This is not truly a quiescent phase because the patient may remain tachycardic, and an anion gap metabolic acidosis develops. The third phase, which begins after 12 hours, is characterized by cardiovascular collapse and shock; the fourth phase is liver failure. The corrosive effect of iron on the GI tract may also lead to the development of scarring or stricture after recovery from acute toxicity.[73] Doses higher than 20 mg/kg of elemental iron reliably produce GI irritation, although systemic toxicity is generally not seen with doses less than 60 mg/kg. Absence of a prodromal GI phase within 4 hours of ingestion generally precludes the development of serious systemic iron toxicity.[74]

Iron is not effectively adsorbed to activated charcoal, and lavage of the stomach or whole-bowel irrigation can be considered if iron tablets are suspected to have remained in the GI tract. Plain radiographs of the abdomen may help visualize the location of pills and guide decontamination decisions, although not all forms of iron can be visualized. Multivitamins, children's preparations, and liquid preparations will not be visible on radiographs. Serum iron levels should be determined within 6 hours of ingestion; after that time, significant redistribution to tissues may have occurred. Total iron-binding capacity, used in the evaluation of chronic iron overload, may be falsely elevated in acute iron ingestion and should not be used in treatment decisions.

Chelation with deferoxamine is indicated for serum levels higher than 500 μg/dL or for signs of circulatory failure.[75] The initial dose is 15 mg/kg/h intravenously. If the patient remains symptomatic beyond 24 hours, the deferoxamine dose should be decreased or temporarily discontinued because prolonged use beyond this time is associated with the development of acute respiratory distress syndrome.[76] Interestingly, children's multivitamin preparations do not produce toxicity at the same iron content as adult preparations, and very few children have ever experienced toxicity with large ingestions.[73] Prenatal vitamins, on the other hand, except those containing iron carbonyl, have led to extreme toxicity even in minor ingestions.

Isoniazid

Isoniazid (INH), a relative of pyridoxine and nicotinic acid, is a hydrazine used in the treatment of tuberculosis. It has a complex set of metabolic actions on several enzyme systems but produces its acute toxicity primarily by interfering with pyridoxine metabolism. INH both inhibits pyridoxine phosphokinase, which is required to activate pyridoxine by conversion to pyridoxal-5-phosphate, and reacts with pyridoxal-5-phosphate to form an inactive metabolite that interferes with and prevents the conversion of glutamate to γ-aminobutyric acid (GABA). After the acute ingestion of a large quantity of INH, early GI symptoms and drowsiness are followed by seizures, coma, and metabolic acidosis. The seizures result from the depletion of GABA and are difficult to control with usual anticonvulsant therapy. The acidosis results from lactate and is produced by seizure activity and possible interference by INH in the conversion of lactate to pyruvate. Treatment of INH poisoning is with pyridoxine, which should be administered in a dose equal to the ingested dose of INH (by weight). If the dose ingested is unknown, 5 g is a reasonable empiric starting dose. INH is effectively removed by hemodialysis, although the efficacy of pyridoxine should obviate its need in most cases. Benzodiazepines may work synergistically with pyridoxine; phenobarbital may also be considered in refractory cases.

Ingestion of mushrooms from the group of hydrazine-containing mushrooms, including *Gyrometra* spp., produces a toxicity identical to INH through its interefence with pyridoxal-5-phosphate and depletion of GABA. This mushroom toxicity is treated with an empiric starting dose of 5 g of pyridoxine in the same manner as above.

Salicylates

There are several forms of salicylate, the most common of which is acetylsalicylic acid (ASA), or aspirin. The most potent form is wintergreen oil, which is made up of 98% methylsalicylate. Other forms include bismuth subsalicylate, sodium salicylate, and magnesium salicylate. Doses up to 100 mg/kg are likely to produce only minimal toxicity, whereas doses above 300 mg/kg may have serious consequences, including death.

Early signs of salicylate toxicity include an increase in minute ventilation (primary respiratory alkalosis), tinnitus, nausea, and vomiting. Salicylates also produce metabolic acidosis through several mechanisms including uncoupling of oxidative phosphorylation and inhibition of the tricarboxylic acid cycle. Mixed-picture respiratory alkalosis and metabolic acidosis from an ingestion are nearly pathognomonic for salicylate intoxication and warrant obtaining a salicylate level for evaluation. Uncoupling of oxidative phosphorylation may also lead to hyperpyrexia. Cerebral edema and pulmonary edema are rare but potentially fatal complications of salicylate poisoning and are more common with chronic toxicity than with acute poisoning. Levels greater than 35 mg/dL produce minor symptoms; significant toxicity and acidosis start to manifest at approximately 45 mg/dL in acute ingestion. Patients with chronic ingestion or exposure may show more severe symptoms at much lower levels (approximately 30 mg/dL).

Enhancement of the elimination of salicylates may be achieved through alkalinization of the urine. This is accomplished by administration of an infusion of sodium bicarbonate. The urine pH should be frequently monitored (every void in patients without a catheter) and the bicarbonate infusion rate adjusted accordingly to target a urine pH above 7.5. The goal is to maintain a normal urine output and not to perform forced diuresis. Serum pH should be periodically monitored to avoid serious alkalemia. In addition, serial potassium and magnesium levels should be obtained and maintained in the normal range. As the body tries to retain potassium, it will exchange it for protons in the urine, and obtaining an alkaline urine will be nearly impossible. Potassium can be added to the alkalinizing fluid and/or provided as a separate infusion. Patients should also be monitored for glucose. A bolus of dextrose may be warranted[77] even if serum glucose levels are normal in salicylate ingestion with depressed sensorium. In a patient with significant CNS alteration and/or salicylate levels greater than 70 mg/dL, hemodialysis is an effective method for salicylate clearance. As levels approach the therapeutic range, the free fraction of salicylate declines and the efficiency of dialysis is diminished. Its use should be considered for very high serum levels; in the presence of renal impairment, volume overload, or pulmonary edema; and in the case of severe electrolyte or acid-base abnormalities.

Bradycardia, Hypotension, and Cardiac Conduction Abnormality

The most important cardiovascular agents that cause bradycardia and hypotension are calcium channel antagonists, β-adrenergic antagonists, and digoxin. All these agents may result in severe toxicity that requires specific therapy.

Calcium Channel Antagonists

Calcium channel blockers exert their action on L-type calcium channels in the heart and vascular smooth muscle. Blockade of calcium channels in the heart results in negative inotropic,

chronotropic, and dromotropic effects. Blockade of calcium channels in arteriolar smooth muscle causes vasodilation. Dihydropyridine calcium channel antagonists (e.g., nifedipine, amlodipine, felodipine, nicardipine) act primarily on the vascular smooth muscle. Verapamil, in addition to vasodilatory effects, also has potent cardiac calcium channel–blocking activity and may cause bradycardia, heart block, and myocardial depression. Diltiazem has similar effects to verapamil but is a less potent inhibitor of cardiac calcium channels. Calcium channel blockers also impair the release of insulin in overdose and may cause significant hyperglycemia.

Treatment depends on the agent involved and the severity of toxicity. Except in extremely large ingestions, dihydropyridines produce hypotension and reflex tachycardia. These patients may respond to volume expansion alone. Intravenous calcium and vasopressors are indicated if the hypotension remains refractory to intravenous fluids. Verapamil and diltiazem overdose is further complicated by pump failure. These patients may benefit from inotropes such as dobutamine. Glucagon, which acts at a receptor other than the β-receptor, increases cyclic adenosine monophosphate (cAMP) and has been reported to reverse refractory hypotension in calcium channel overdose. The reported dose is 0.15 mg/kg intravenous bolus followed by an infusion of 0.05 to 0.1 mg/kg/hr.[78] Phosphodiesterase inhibitors (amrinone, milrinone) may provide some efficacy by preventing the destruction of cAMP. However, animal data have not shown these to be of benefit over glucagon.[79,80]

High-dose insulin/euglycemia therapy has shown efficacy in several successful animal models as well as in several case reports and case series to reverse cardiogenic shock associated with calcium channel antagonist overdose.[81,82] The recommended dose is from 0.5 to 1 unit/kg of insulin as a bolus, followed by an infusion titrated to efficacy. Given the risks of hypoglycemia and its profound deleterious effects, serum glucose concentration should be monitored hourly. Patients with overdose of calcium channel antagonists are not usually responsive to transcutaneous pacing because of an inability to capture. If capture is achieved, the patient should be paced at a low rate, near 60, to attempt to maximize filling of the ventircules. However, most patients exhibit a decreased contractility that, even with pacing, prevents achievement of significant cardiac output. Patients who are unresponsive to medical management should be considered for a left ventricular assist device or extracorporeal life support (see Chapters 27 and 53, respectively).

β-Adrenergic Antagonists

β-Adrenergic antagonists comprise a fairly extensive list of therapeutic agents that are largely distinguished from each other by their selectivity (or lack thereof) for the β_1 receptor. Atenolol, metoprolol, esmolol, and acebutolol are β_1-selective agents, whereas agents such as propranolol, nadolol, and pindolol act both at β_1 and β_2 receptors. Propranolol is unique in that it is highly lipophilic and has sodium channel–blocking activity. Labetalol, in addition to β-blocking activity, possesses α-receptor–blocking activity. β_1 Receptors are largely found in the heart, and agonism causes positive inotropic and chronotropic effects. β_2 Receptors are found in the airway smooth muscle, where they cause bronchodilation; in the small blood vessels, where they cause vasodilation; and in several other organs, where they have a number of effects that are not important in the context of poisoning.

Acute overdose of β-adrenergic antagonists results in bradycardia, hypotension, and conduction delay. Toxicity is generally much lower than with calcium channel antagonists such as verapamil and diltiazem. Bronchospasm may occur in susceptible individuals. Propranolol, by virtue of its sodium channel–blocking activity, causes QRS widening, exaggerated negative inotropy, chronotropy, and conduction delay. Patients are also risk for coma and seizures because of the drug's ability to cross into the CNS. Labetalol may cause vasodilation in addition to β-receptor blockade. Hypoglycemia may also be seen with drugs in this class and has been reported in children with usual dosing of propranolol.[83,84]

Treatment beyond monitoring is not necessary if the only manifestation is asymptomatic bradycardia. Patients with bradycardia and hypotension may respond to atropine, although they are expected to have decreased vagal tone to start with. β-Agonists have variable effects in the presence of β-adrenertgic blockade. In theory, mixed agonists could worsen hypotension by causing β_2 receptor–mediated vasodilation. The phosphodiesterase inhibitors amrinone and milrinone have a theoretical benefit of improving contractility by blocking the breakdown of cAMP but have not been shown to be more effective than glucagon.[79,80] Glucagon acts by a nonadrenergic receptor to increase intracellular cAMP and improve cardiac contractility. The recommended dose is the same as that previously described for calcium channel blockers. Patients who do not respond to these measures, such as patients with calcium channel blocker overdose, should be considered for extracorporeal life support. Seizures should be treated with benzodiazepines as first-line therapy, and bronchospasm may respond to anticholinergic agents if inhaled β_2-agonists fail to overcome the β-blockade.

Digoxin

Digoxin and related digitalis glycosides are used in the management of cardiac failure and tachydysrhythmias. Digoxin blocks the sodium-potassium adenosine triphosphatase (Na/K-ATPase) and ultimately leads to increased intracellular calcium concentration and improved contractility. It also increases vagal tone and causes sinoatrial (SA) and atrioventricular (AV) nodal depression. In overdose, sympathetic tone is increased and may lead to increased automaticity.

Overdose of digoxin presents with nausea, vomiting, lethargy or confusion, and cardiac dysrhythmias. Although virtually every rhythm has been described in digoxin toxicity, bidirectional ventricular tachycardia and atrial tachycardia with AV block are characteristic. Blockade of Na/K-ATPase causes hyperkalemia, and levels greater than 5.5 mEq/L have been associated with a significant mortality rate.[85] The diagnosis is confirmed with measurement of the serum digoxin level. Because of a long distribution phase, the serum level may not accurately reflect tissue levels until at least 6 hours after ingestion.

Sinus bradycardia or heart block may respond to atropine alone. More serious arrhythmias are an indication for treatment with digoxin-specific Fab fragments (e.g. Digibind, DigiFab). Drugs that further depress the SA or AV node should be avoided. Hyperkalemia resolves with Fab fragment therapy because it restores function of the Na-K pump.

Because digoxin causes intracellular hypercalcemia, calcium is best avoided because it could theoretically increase toxicity.[86] Fab fragment therapy in children is indicated with known digoxin ingestion (strong history of ingestion of at least 0.1 mg/kg or digoxin level greater than 5 ng/mL) and signs and symptoms of digoxin toxicity (rapidly progressing signs and symptoms of digoxin toxicity or potentially life-threatening arrhythmias or serum potassium level greater than 6 mEq/L).[87]

A clinical picture similar to digoxin poisoning may be seen with the ingestion of certain cardiac glycoside-containing plants such as oleander. Oleander poisoning may cause a false-positive result on digoxin immunoassay and may respond to Fab fragment therapy.[88] An antidote dose cannot be calculated from the level obtained because of the differences between digoxin and the cardiac glycoside found in the ingested plant. Therefore an empiric dose of 10 to 20 vials is recommended in both pediatric patients and adults.

Acetaminophen (Paracetamol)

Although it does not cause a toxidrome per se, acetaminophen is the most commonly ingested drug in intentional overdose. It may cause fulminant hepatic failure leading to admission to the pediatric intensive care unit. Major routes of elimination of acetaminophen are through conjugation or sulfation and then excretion in the urine. A minor pathway is via CYP2E1 to produce *N*-acetyl-p-benzoquinone-imine (NAPQI), a toxic metabolite capable of binding to hepatocytes and causing cell death. With therapeutic doses of acetaminophen, NAPQI is rapidly detoxified by glutathione. In overdose, larger amounts are formed and may overwhelm the available glutathione stores, resulting in a centrilobular hepatic necrosis.

Patients may initially present with nausea and vomiting, but often they have no symptoms or signs. Initial metabolic acidosis may occur with extremely large ingestions. Transaminases begin to be elevate at approximately 24 hours after ingestion and peak between 48 and 72 hours. Patients either progress to fulminant hepatic failure or recover completely (see Chapter 88). Treatment with *N*-acetylcysteine (NAC) reduces the incidence of hepatotoxicity when administered in a timely fashion after overdose. NAC acts through several mechanisms, including enhancing the synthesis of glutathione and as a possible free radical scavenger.[88] It is most efficacious when administered within 10 hours of ingestion but has shown benefit when administered to patients presenting after this window of time.[88] In one study, intravenous NAC decreased the risk of death from acetaminophen-induced fulminant hepatic failure even in patients who presented with already established hepatic encephalopathy.[89] Decision to treat an acute ingestion is based on plotting a single acetaminophen blood level at least 4 hours after ingestion on the Rumack-Matthew nomogram (Figure 106-1). After 24 hours, the nomogram is of no benefit. An acetaminophen level should be measured and liver function analysed to assess the patient's risk for development of toxicity or potential prognosis. In addition, the nomogram has not been validated in chronic ingestion or multiple, staggered ingestions. In these cases, the nomogram should not be relied on for an assessment of toxicity. A poison control center should be consulted for specific treatment advice in those scenarios.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are a group of drugs with potentially serious toxicity that are used in the treatment of psychiatric disorders, enuresis, and pain syndromes. Although

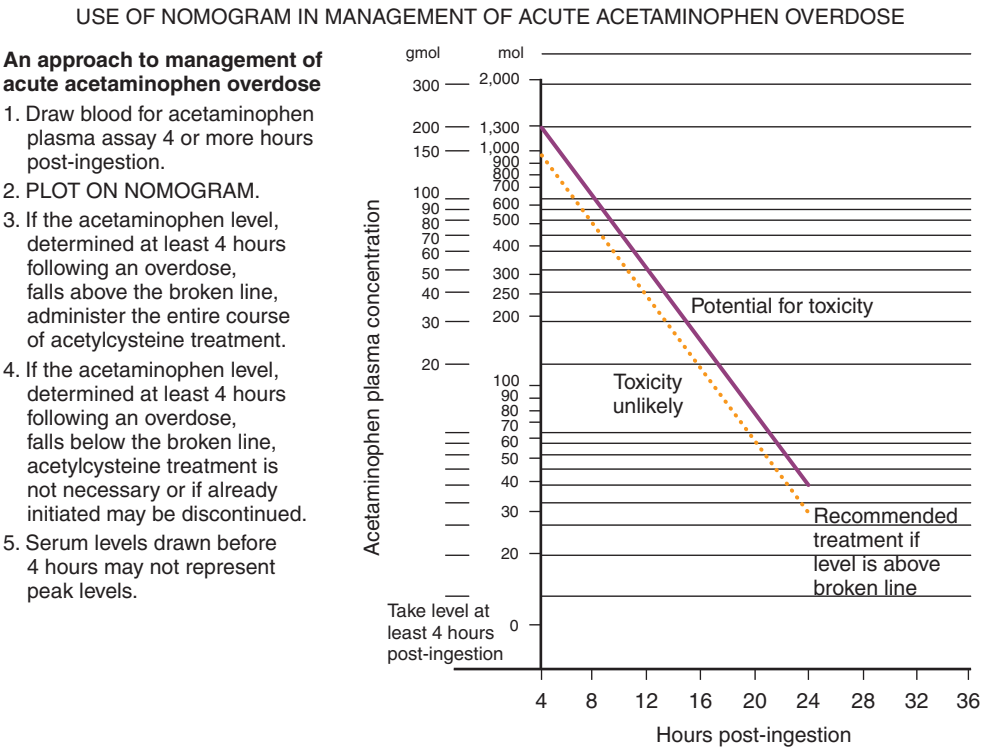

Figure 106–1. Use of a nomogram in the management of acute acetaminophen overdose.

in the treatment of depression they have largely been supplanted as first-line agents by less toxic compounds, they still represent a significant cause of morbidity and death.

TCAs have multiple mechanisms of toxicity and produce a wide spectrum of clinical effects. Their anticholinergic properties may produce the anticholinergic toxidrome (se Box 106-4). α-Adrenergic inhibition may cause sedation and hypotension. Blockade of cardiac sodium channels causes decreased myocardial contractility and is seen on the ECG as widening of the QRS complex. QRS widening correlates with the development of seizures (QRS >100 ms) and arrhythmias (QRS >160 ms).[90] Potassium channel blockade leads to a prolonged QT interval. Seizures, which tend to be single and short lived, occur and may be attributable to a combination of TCA effects on GABA and on reuptake of biogenic amines in the CNS. This constellation of anticholinergic syndrome, seizures, hypotension, and widening of the QRS complex should create a high index of suspicion for TCA overdose. A similar picture may be seen with type Ia antiarrhythmics.

Severe toxicity tends to occur early in the course of TCA poisoning. Patients who do not manifest QRS widening, conduction abnormalities on ECG, altered mental status, seizures, or hypotension within the first 6 hours can be classified as low risk and no longer need PICU monitoring.[91] Anticholinergic manifestations should be treated supportively only. Seizures, if prolonged, should be treated with benzodiazepines. If benzodiazepines have been coingested by the patient, then flumazenil, a benzodiazepine receptor antagonist, should not be administered because it may unmask TCA-induced seizures. Widening of the QRS complex (>100 ms in adults) or ventricular arrhythmias should be treated with sodium bicarbonate to produce alkalinization of the serum. Bicarbonate should be given in boluses of 1 to 2 mEq/kg until ECG improvement is seen (narrowing of the QRS). Recurrence of QRS widening may be treated in the same manner. Alternatively, a bicarbonate infusion can be started after the initial bolus to maintain alkalemia (with monitoring to prevent overalkalinization [i.e., pH >7.55]). If continuous infusion of bicarbonate is performed, it may be stopped and the ECG monitored after approximately 6 hours of normal ECG tracings. Although drug levels are available for monitoring these medications in therapy, they serve no purpose in acute toxicity, and studies have shown that ECG findings are superior predictors of toxicity on this scenario.

References are available online at http://www.expertconsult.com.

Bites and Stings

Sean P. Bush

PEARLS

- Snakebite-related injury and death are reduced most by rapid transport, intensive care, and the administration of antivenin.
- Measures not recommended for snakebite first aid are incision, suction, tourniquets, electric shock, ice directly on wound, alcohol, or folk therapies.
- Antivenins can induce immediate anaphylactic (type I hypersensitivity) or anaphylactoid reactions, which can be rapidly life threatening. Airway swelling, wheezing, shock, and urticaria characterize these reactions. Anaphylactic and anaphylactoid reactions are treated with antihistamines, histamine (H_2) blockers, epinephrine, steroids, and ventilatory/circulatory support as needed.
- All children with snake envenomations should be admitted to the hospital. Serious effects can be delayed and can recur even after treatment with antivenin.
- Typically, a widow spider bite site has a "target" appearance. There may be a central reddened, indurated area around fang puncture site(s) surrounded by an area of blanching and an outer halo of redness. The findings around the bite wound may be subtle.
- Any bee, wasp, or ant can cause toxic, even fatal, complications when they attack en masse. Sting removal after a honeybee sting should be done as quickly as possible, regardless of the method of removal.

The general principles of envenomation medicine are similar around the world, although the availability of resources varies widely. A comprehensive discussion of all available antivenins is beyond the scope of this text.[1] On the basis of my experience and in consideration of space constraints, the scope of this textbook, and its audience, the chapter focuses on United States antivenins. Readers are encouraged to become familiar with the prescribing information for the antivenin(s) available in their area(s) of practice for the envenomations they may encounter.

Snakebites

Snakebite is a particularly challenging clinical problem because of the wide variety of toxic effects. Children with snakebites may have little more than a fang puncture mark, or they may have multisystem failure and death.[2,3] Part of this is due to the extreme variability of snake venom, even within the same species.[4] Snake venom contains multiple enzymes, proteins, and peptides that can damage local tissues and have serious systemic effects. Unfortunately, it is difficult to predict at the time of the bite which patients will have relatively mild symptoms and which will have a rapidly progressive and potentially fatal envenomation syndrome.

Snakebite envenomation syndromes can be loosely associated with snake family. Viperidae includes old-world vipers and pit vipers (collectively referred to as viperids). Most snakebites in the United States are inflicted by pit vipers, which include rattlesnakes, cottonmouths (also known as water moccasins), and copperheads.[5] All pit vipers have a triangular head, elliptical pupils, and a heat-sensing pit between the eye and nostril (Figure 107-1).[6] The pit organ has thermal receptors that can detect temperature differences of 68° C at 1.5 m in predatory interactions and 108° C at 1 m in defensive contexts (A. Krochman, personal communication, January 17, 2005). The family Elapidae ("elapids") includes cobras, coral snakes, kraits, and mambas.[7] Their venom effects can be as diverse as the species that make up this family of snakes. Cobras are showy, hooded, high-profile snakes that inhabit Africa and southern Asia (Figure 107-2). The coral snakes of the Americas and kraits of Asia and India are often small, shy, colorfully banded snakes (Figure 107-3). Mambas in Africa are long, lean, and very fast. Australian elapids can be large and nondescript. Sea snakes possess some of the world's most toxic snake venom, although few bites occur mostly because of the marine distribution and nonaggressive temperament of these snakes. Most snakes from the Colubridae family ("colubrids") are considered harmless, although several species possess venom and some have primitively specialized teeth to facilitate venom delivery. Some, such as the boomslang in Africa, are considered dangerous to humans, and antivenin is produced.

Epidemiology

It is often stated that children are more severely affected by snakebite than adults.[8] Indeed some preliminary data suggest that smaller patients have increased severity. There is not much in terms of evidence, however, to support the assertion that outcomes for children are worse than adults. For example, of the more than 100,000 exposures and two dozen deaths

Figure 107–1. Copperhead (*Agkistrodon contortrix*). *(Photo Courtesy Sean Bush, MD.)*

Figure 107–2. Red spitting cobra (*Naja pallida*). *(Photo Courtesy Mike Cardwell.)*

described by the American Association of Poison Control Centers (AAPCC) since its first report in 1983, only a relatively small percentage of the deaths are described in pediatric patients.[9] In some respects, children are no different than adults when it comes to snakebite. For instance, antivenin dosing is not based on the patient's weight,[10,11] yet there are a few concerns specific to pediatric patients. For example, because young children may not be able to give a good description of the snake or circumstances, it may be unclear whether a venomous snake has bitten them.

Figure 107–3. Eastern coral snake (*Micrurus fulvius*). *(Photo Courtesy Mike Cardwell.)*

Pathophysiology

Although viper and pit viper venom composition varies from snake to snake, components can lead to capillary leak, abnormal clotting, inefficient muscle movement, or neurotoxicity. Capillary leak and abnormal clotting can lead to tachycardia, hypotension, or even hemorrhagic shock. Neurotoxicity or inefficient muscle movement can lead to respiratory difficulty or distress.[12] Meanwhile, proteolytic enzymes, predominant in viper and pit viper venoms, digest tissue. The longer enzymatic components of venom have time to work, the more tissue gets damaged. Thus "time is tissue."[13] The sooner that antivenin can be started, the sooner that irreversible injury can be prevented.[14] After tissue is injured by way of digestion, however, antivenin will not reverse the damage; it will have to heal over time.[15] Myotoxicity and rhabdomyolysis can ensue.

Envenomation by most elapids is notable for severe neurological dysfunction, such as cranial nerve abnormalities, paralysis, and respiratory arrest. Some elapids, however, such as spitting and monocellate cobras, can also cause local necrosis. Most do not induce coagulopathy. Other symptoms and signs may include swelling, lethargy, vomiting, chest pain, and shock. Some cobras and cobralike species can "spit" venom toward the face of an antagonist, which can result in eye pain and visual impairment. Sea snake envenomation can cause profound neurotoxicity and myotoxicity, but generally does not induce coagulopathy or result in serious local injury. Sea snakes are found in waters around Southeast Asia and Australia. Additionally, some individuals may experience anaphylactic or anaphylactoid reactions to venom.[16,17] Finally, some responses can be attributed to anxiety, although this should be a diagnosis of exclusion.[6]

Clinical Presentation

Immediately after a snakebite, the only apparent manifestation may be fang puncture wounds. If a patient is seen soon after a snakebite, an envenomation syndrome might not have developed yet. The onset of symptoms and signs can occur rapidly or it may be insidious. Generally the more severe an envenomation, the more rapidly it progresses; however, even a

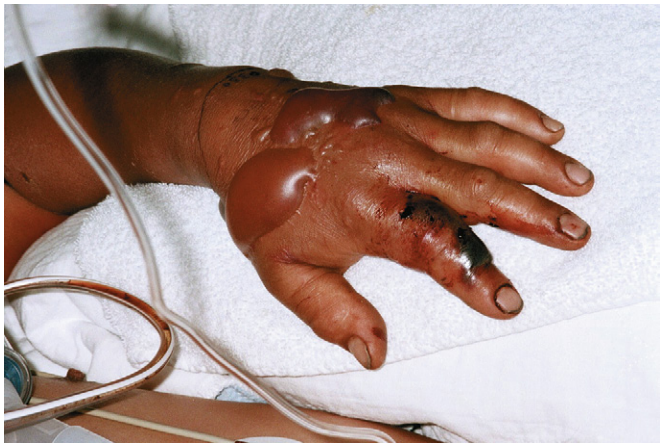

Figure 107–4. Southern Pacific rattlesnake (*Crotalus helleri*) bite wounds. *(Photo Courtesy Sean Bush, MD.)*

Figure 107–5. Ptosis after Mohave rattlesnake (*Crotalus scutulatus*) envenomation. *(Photo Courtesy Sean Bush, MD.)*

slowly progressing envenomation can lead to severe sequelae. If a patient is seen very late, the envenomation could have already run its course, and antivenin will not be as effective.[14]

Snakebites by pit vipers and vipers cause pain around the bite site as tissues distort with swelling. There may or may not be associated taste changes. Difficulty breathing can follow many types of venomous snakebites and can progress to respiratory distress or failure in some cases. Patients may experience nausea, vomiting or diarrhea, and venom-induced coagulopathies (often associated with viper and pit viper envenomation) can lead to hematemesis, hematochezia, or both. Certain snakebites, such as those inflicted by most elapids and some populations of rattlesnakes, can also be associated with neurological symptoms, such as motor weakness or paresthesias. Syncope or lethargy can result from severe or prolonged hypotension.[6] Vital signs may reflect tachycardia, hypotension or hypertension, tachypnea, or hypoventilation. On physical examination, there may be one, two, or more fang puncture wounds, or none may be discernible. There is usually tenderness and swelling surrounding the bite site, which expands as the venom spreads locally. Other local signs can include erythema, ecchymosis, and bullae after viperid envenomation (Figure 107-4). Systemic evidence of viperid envenomation may manifest in many ways. There may be abnormal bleeding, such as prolonged bleeding from fang puncture wounds or intravenous (IV) start sites. Patients may have epistaxis or gingival bleeding. Serious and potentially life-threatening bleeding may manifest via the gastrointestinal tract or within the cranium. In extremely rare instances, snakebite can also cause hypercoagulability, which can lead to infarcts. Additionally, there may be neurological signs, such as ptosis (Figure 107-5), and muscle fasciculations or "myokymia."[6]

Diagnostic Studies

Initial laboratory tests after pit viper or viper envenomation should include a complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen, and a type and screen. Venom-induced coagulopathy is common after many types of viperid envenomations and is most typically characterized by thrombocytopenia and hypofibrinogenemia. Even if coagulation values are normal on presentation, they may need to be rechecked depending on the clinical scenario. Venom-induced coagulopathies can develop late, recur, or persist. If initial laboratory findings are abnormal, more frequent monitoring may be necessary depending on how severely abnormal they are and how they respond to treatment. If the findings are abnormal, repeating the CBC, PT, PTT, INR, and fibrinogen tests 1 hour after completion of an infusion of antivenin may be helpful to monitor treatment efficacy. When laboratory values are rechecked, in addition to the initial laboratory panel, additional blood should be sent for creatine kinase (CK), electrolytes, blood urea nitrogen, and creatinine clearance. All snakebite can result in rhabdomyolysis, which usually responds to aggressive fluid hydration, but can require dialysis if myoglobinuric renal failure develops. In certain regions, such as Australia, venom detection kits (e.g., enzyme-linked immunosorbent assays) may be available to help identify species and guide specific antivenin selection. Other diagnostic studies may be indicated on the basis of a patient's medical history or special circumstances.[6]

Pitfalls

It is possible that a snakebite might be mistaken for a puncture wound from another cause (e.g., from a plant thorn), if the patient is seen very early, if the envenomation is mild, or if there are difficulties obtaining a reliable history. If there is any question about whether a patient has been bitten by a venomous snake, an observation period and diagnostic studies may help clarify the diagnosis. Snakebites usually progress if significant envenomation has occurred. Certain signs (e.g., ecchymosis), symptoms (e.g., local paresthesias), and laboratory data (e.g., thrombocytopenia, hypofibrinogenemia), if affected, are fairly consistent with viperid envenomation. If a bite by an elapid is suspected, envenomation should be assumed until proven otherwise after adequate observation and evaluation.

Prehospital Care

The factors that most reduce snakebite-related injury and death in the United States are rapid transport, intensive care, and the administration of antivenin.[18] All patients with

snakebites should be transported to the hospital as expeditiously and safely as possible, preferably through a 911 call (where available). The following measures are not recommended for first aid: incision, suction, tourniquets, electric shock, ice directly on wound, alcohol, or folk therapies.[19-21] Insufficient evidence exists for splinting or positioning (e.g., above or below the level of the heart). Therefore the extremity should initially be maintained in a neutral position of comfort. The Australian technique of pressure immobilization resulted in significantly longer survival, but higher intracompartmental pressures after artificial, intramuscular (IM) western diamondback rattlesnake envenomation in a pig model.[22] This technique involves immediately wrapping the entire extremity that was bitten starting at the bite site and proceeding proximally with an elastic Ace wrap or crepe bandage as tightly as one would wrap for a sprain, then splinting and immobilizing the extremity. Although pressure immobilization is not recommended widely, certain scenarios may warrant its use. It is generally not recommended for most viper bites or for bites by spitting cobras, but it is recommended for most types of Australian fauna, cape cobras, kraits, coral snakes, mambas, and sea snakes. Once pressure immobilization is placed, it should not be removed until preparations are made to manage acute toxicity and/or immediate hypersensitivity because of a potential bolus effect after its removal. Although it is difficult to predict snakebite severity at the time of the bite, certain factors may reflect increased likelihood of a more severe envenomation: large snake size, dangerous snake species, small patient size, prolonged fang contact, previous snakebites (treated or not) or exposures to snakes, or delays to medical care.

Emergency and Critical Care

All emergency personnel should be able to distinguish a venomous from a nonvenomous snake if it occurs naturally in their region of practice. If there is uncertainty about whether a particular snake is venomous, consider taking photographs of the snake from a safe distance of at least 6 feet away using a digital or Polaroid camera. These images can be seen immediately and may help make clinical decisions. Although it may be helpful to identify the species of snake,[15,23] transporting it (alive or dead) is discouraged because of inherent dangers with capturing it. On scene, snakes should only be moved or contained if absolutely necessary. A snake hook or long shovel may be helpful to move the snake into a large, empty trash canister where it can be recovered by professionals, such as an animal control agent.

Airway support, advanced pediatric life support protocol, or both should be provided as needed. Severe respiratory difficulty may require intubation and mechanical ventilation. Check vitals frequently, provide oxygen, and place monitors (cardiac, blood pressure, and pulse oximetry). Start two IV lines. Central venous or intraosseous access may need to be obtained. It may be appropriate to avoid placing a central line in a noncompressible site (e.g., internal jugular) after viperid envenomation because of the risk of bleeding from venom-induced coagulopathy. A normal saline fluid bolus of 20 mL/kg should be administered. If there is evidence of shock, give a second fluid bolus. Because viperid envenomation can induce coagulopathy and bleeding, transfusion may be required after treatment with two fluid boluses. Give packed red blood cells of 10 mL/kg for acute, life-threatening blood loss or anemia. Persistent hypotension may require the administration of vasopressors and inotropic agents. Urine output may be used as a measure of adequate hydration and to check for the occurrence of rhabdomyolysis. The patient should take nothing by mouth until it has been determined that the patient will not need airway control and mechanical ventilation.

After pit viper or viper envenomation, remove rings, other constricting jewelry, and clothing in anticipation of severe swelling. The expanding area of swelling and tenderness can be used to follow the progression of viperid envenomations. Tenderness is more sensitive than swelling for detecting progression. Also, it is preferable to follow the advancing edge of tenderness or swelling than to follow serial measurements of circumference. Palpate until the edge of advancing tenderness is found. Mark this leading edge with a permanent marker and write the time alongside. Repeat this often enough to gauge progression. This may mean checking every 15 to 20 minutes initially. Once antivenin is started, it should still be followed every 1 to 2 hours.

All hospitals should stock at least enough antivenin to treat one patient. This should be arranged ahead of time if possible, although sometimes there are antivenin shortages and other resource challenges. Presently only one agent is commercially available in the United States for treatment of pit viper envenomation: Crotalidae Polyvalent Immune Fab (Ovine), which goes by the trade name CroFab (Protherics Inc., Nashville, Tenn.).[24] Antivenin Crotalidae Polyvalent is no longer produced. Several manufacturers produce antivenin for bites in Africa (e.g., South African Vaccine Producers), Asia, Europe, and Australia (e.g., Commonwealth Serum Laboratories [CSL]), and the Americas (e.g., Instituto Bioclon in Mexico, Instituto Clodomiro Picado in Costa Rica, and the Butantan Institute in Brazil). A polyvalent sea snake antivenin (CSL) is the drug of choice for sea snake envenomation, but tiger snake antivenin may have adequate efficacy if sea snake antivenin is not available. Information on antivenin should be researched ahead of time, and practitioners should be familiar with sources and administration techniques for the antivenins available for envenomations they may encounter. Each antivenin has varying specificity, efficacy, and safety. Some antivenins developed for one species may have some efficacy against other closely related species. If an exotic envenomation is encountered in the United States, calling the AAPCC or consulting the Antivenom Index may help locate antivenin. Many zoos stock antivenins for the exotic species they keep. If antivenin is unavailable, a patient with an elapid or sea snake envenomation may need his or her airway secured and ventilatory support provided for days or even weeks. Meanwhile, hypotension should be treated with IV fluids and then vasopressors. Edrophonium may temporarily improve weakened muscles of respiration after elapid envenomation while awaiting antivenin.

There are various suggested methods to determine the need for antivenin in your patient. Many grading scales are available, but it is better to treat a patient based on envenomation progression or potential. Grading scales should not be used for elapid or sea snake envenomations. Antivenin should be given promptly for best results, although it may have benefit for days to weeks after an envenomation. Anytime antivenin is given, allergic reactions should be anticipated. It may be helpful to know whether the patient has allergies or previous

exposures to papain, papaya or animal serums, or other agents used to make antivenin. Obtain informed consent when possible. Many of the principles of antivenin administration are similar. The technique for administering CroFab is outlined as an example. A starting dose of CroFab is 4 to 6 vials,[25] which is the same for children as it is in adults. Each vial is reconstituted with 10 ml of sterile water. It can take anywhere from about 10 to 30 minutes to go into solution. It is best to swirl or roll the vials between the hands rather than to shake them. After each vial goes into solution, it should be further diluted into a total volume of 250 mL of normal saline. No skin test is recommended for CroFab, although manufacturers of many other types of antivenin recommend skin testing. With CroFab, the infusion is started slowly, at a rate of 1 mL/min for the first 10 minutes. While the infusion is started, a physician skilled in resuscitation should be at bedside. Difficult airway equipment, epinephrine, diphenhydramine and a histamine (H_2) blocker (e.g., cimetidine) should be immediately available. If the infusion is tolerated for the first 10 minutes without evidence of an adverse reaction, the rate should be increased to complete thee total volume of 250 mL/hour. If there is a problem at any time, stop the infusion, treat the adverse reaction accordingly, and reassess the need to continue antivenin treatment. A physician should be nearby at all times during the remainder of the infusions. Repeat four- to six-vial increments until initial control is achieved. Initial control is defined as the arrest or significant slowing of progression of any and all components of the envenomation syndrome (i.e., minimal to no further advancement of swelling, improvement of systemic effects, and improving coagulopathy). Assess at up to 1 hour after each dose. After initial control is achieved, a maintenance dose of two vials of CroFab every 6 hours for three doses is recommended in the prescribing information, although maintenance dosing has been shown not to reduce recurrence phenomena.[26] Read the package insert for additional details.[25] For pharmacokinetic reasons that are not entirely understood, recurrence phenomena are associated with antivenins.[27-29] Local recurrence is the return of new progressive swelling after initial control. That is, the leading edge of tenderness or swelling begins to advance again. An additional two vials of CroFab should be given as soon as progressive swelling recurs, and more antivenin may be necessary to regain control, although experience has shown that local effects may continue to progress despite additional antivenin. Patients with rattlesnake bites commonly have thrombocytopenia and hypofibrinogenemia, which can resolve with CroFab and then recur (coagulopathy recurrence). Indications for an additional two vials of CroFab are serious abnormal bleeding, fibrinogen less than 50 μg/mL, platelet count less than 25,000 mm^3, INR greater than 3, multicomponent coagulopathy, worsening trend in patient with prior severe coagulopathy, high-risk behavior for trauma, or comorbid conditions that increase bleeding risk. Coagulopathy can recur as late as 2 weeks or more after treatment.

It is necessary to transfuse if antivenin does not correct coagulopathy or if there is an imminent risk of serious bleeding. Transfusion of the appropriate blood product is generally recommended for life-threatening bleeding, platelets less than 20,000 mm^3 and refractory to antivenin, or hemoglobin less than 7 g/dL. Additionally, fresh frozen plasma, platelets, or both may be required to treat venom-induced coagulopathy if antivenin does not promptly resolve. Consider computed tomography of the brain if the patient has a severe headache or an altered level of consciousness with a severe coagulopathy. Ocular exposure to venom necessitates prompt and copious irrigation and an ophthalmologist's evaluation.

Provide pain relief (e.g., fentanyl 1 μg/kg/dose IV/IM, may repeat at 30- to 60-minute intervals or morphine sulfate, in increments of 0.02 mg/kg up to 0.1 to 0.2 mg/kg IV, titrated to relief of pain while maintaining a respiratory rate and blood pressure that is appropriate for age). Nonsteroidal antiinflammatory drugs (NSAIDs) are contraindicated for approximately 2 weeks after viper and pit viper envenomation because they can contribute to venom-induced coagulopathy and bleeding.

Prophylactic antibiotics are unnecessary. Empiric antibiotic therapy should only be started if an infection develops and once aerobic and anaerobic wound cultures have been obtained. If an abscess occurs, it should be drained in standard fashion. An infected snakebite should prompt a further examination of the wounds for potential retained teeth or fangs.[5]

Envenomations by vipers and pit vipers are remarkable for the amount of swelling they can produce. With prompt and adequate antivenin treatment, fasciotomy or digit dermotomy is rarely indicated, even after severe viperid envenomation.[30-33] Fasciotomy, however, may be indicated if measured compartment pressures remain persistently and severely elevated despite adequate antivenin. Antivenin has been shown to limit the decrease in perfusion pressure associated with compartment syndrome.[34] Compartment syndrome may manifest subjectively, with complaints of increasing pain, and objectively, with tenderness on passive muscle stretch, a rock hard feel to the compartment, or a diminished capillary refill. True compartment syndrome, however, is rare after snakebites, even in patients with severe swelling. It may be difficult to distinguish compartment syndrome from the effects of envenomation. Similar to compartment syndrome, viperid envenomation may cause a bluish discoloration of the skin or pallor (because of subcutaneous bruising), severe swelling, paresthesias, and pain. If effects are only caused by envenomation and the patient does not have compartment syndrome, capillary refill should be normal and compartmental pressures should not be elevated. If compartment pressures are elevated, Gold et al.[31] recommend limb elevation, along with IV mannitol (1 to 2 mg/kg) administration and an additional four to six vials of CroFab over 1 hour. Consultation with a surgeon (e.g., general, orthopedic, or hand) should be initiated concurrently. Compartment pressures should be measured before surgical intervention.

Therapeutic Complications

Antivenins can induce immediate anaphylactic (type I hypersensitivity) or anaphylactoid reactions, which can be rapidly life-threatening. Airway swelling, wheezing, shock, and urticaria characterize these reactions. Anaphylactic and anaphylactoid reactions are treated with antihistamines, H_2 blockers, epinephrine, steroids, and ventilatory/circulatory support as needed.

Antivenins can also cause serum sickness, a delayed (type III hypersensitivity) reaction characterized by fever, urticaria, lymphadenopathy, and polyarthralgias days to weeks after treatment. Although serum sickness can be an uncomfortable experience, it is usually benign and self-limited, and the patient is treated on an outpatient basis with antihistamines

and steroids. Also, adverse reactions are much less common after treatment with Fab-based antivenins than they are with whole immunoglobulin formulations.[14] All commercially available antivenins in the United States use mercury, in the form of thimerosal, as a preservative, which in high doses can cause nerve and kidney toxicities in small children.[25]

Resources

The AAPCC can assist in the management of envenomations. Poison control may be contacted at 800-222-1222.

Disposition

It is prudent to admit all children with snake envenomations to the hospital. Serious effects can be delayed and can recur even after treatment with antivenin. Therefore close observation with monitoring, frequent measurements of swelling/tenderness, and neurological checks for at least 24 hours are recommended. This degree of monitoring may require transfer and admission to a pediatric intensive care unit (PICU). On discharge, the patient should return immediately for further swelling or severe pain. Additionally, the patient should return immediately for any abnormal bleeding or bruising, dark tarry stools, petechiae, or severe headache. Also, patients should be given wound care instructions and told to return for signs of wound infection. Signs of serum sickness should be outlined, and the patient should return or follow up if these signs show up anytime in the few weeks after treatment with antivenin. The patient should be told not to take NSAIDs for 2 weeks after a pit viper or viper bite. Instead, acetaminophen with or without a combined opiate analgesic should be prescribed. The patient should not engage in contact sports or schedule any elective surgery or dental work for 2 weeks after viperid bites. Recommend that the patient drink plenty of liquids and advise that the patient return if decreased urination or cola-colored urine is noticed. Some patients may need referral to a physical therapist. Blisters, blebs, and bullae should be left in place but may need debridement along with necrotic tissue after several days, so surgical referral as appropriate is suggested.[30] Skin grafting is sometimes necessary. If the patient was bitten on the foot or leg, crutches and crutch training should be provided. The patient should be encouraged, however, to bear weight and mobilize the extremity as tolerated. In some cases, a next-day wound check may be appropriate. Otherwise, the patient should return or follow up in a few days.[28] At that time, laboratory tests may need to be repeated, depending on the clinical scenario. Retreat with antivenin as needed.

Prognosis

Most patients recover fully after snakebite. Viperid envenomation results, however, in tissue loss, deformity, or loss of function in a clinically significant percentage of patients.[8,35]

Preventative measures should be explained to parents and children. Teach children to leave snakes alone. They should never touch, handle, or try to kill venomous snakes. Many people are bitten when they are intentionally interacting with the snake. Even after a snake is believed to be dead, fangs still can inject venom. Snakes that were presumed dead have bitten many people and delivered serious, even fatal, envenomations. Additionally, a snake can strike faster and farther than one might think—about half its body length. Children should stay at least two giant steps away from snakes. If a child finds a snake, he or she should tell an adult. Additionally, tell children not to reach or step into places that they cannot see. Wearing boots and jeans may prevent some (but not all) snakebites.

Future Directions

Modifications of the antivenin molecule or formulations may reduce recurrence phenomena, and this is being investigated. Several antivenins are being developed by Instituto Bioclon for use in the United States and other parts of the world.

Widow Spider Bites

Widow spiders belong to the genus Latrodectus and are represented in the United States by the black widows (Figure 107-6), the brown widow, and the red-legged widow.[36] The redback spider is endemic to Australia. Other species, such as the kara kurt and black button spider, are found in other parts of the world, including Europe, South America, and South Africa. The adult female black widow spider is approximately 2 cm in length and shiny black with a red-orange hourglass or spot on the ventral abdomen. The male is much smaller, brown, and much less commonly implicated in human envenoming. Juvenile females are also brown with yellow and white markings but have the general body shape of the adult. Males and juveniles have a pale hourglass shape, similar to adult females. Webs are irregular; low lying; and commonly seen in garages, barns, outhouses, and foliage. Other widow spiders around the world are generally black but may have red spots, such as the kara kurt, or a dorsal red stripe, such as the redback spider. The brown widow is brown with red and yellow markings. Similar species include the false black widow or cupboard spider, *Steatoda* spp., which can produce symptoms that are similar in character but milder in intensity than widow spiders.

Figure 107–6. Black widow spider (*Latrodectus hesperus*). *(Photo Courtesy Sean Bush, MD.)*

Epidemiology

No deaths caused by widow spider envenomation have been reported to the AAPCC since its first annual report in 1983. A few recent deaths have been reported, however, after a black widow spider bite in Greece, Mexico, and the United States.[37,38]

Pathophysiology

The envenomation syndrome caused by the various species of widow spiders around the world is similar.[39,40] The predominant clinical effects after widow spider envenomation are neurological and autonomic.

Clinical Presentation

Typically, the bite site has a "target" appearance. There may be a central reddened, indurated area around fang puncture site(s) surrounded by an area of blanching and an outer halo of redness (Figure 107-7). The findings around the bite wound may be subtle, and the wound does not become necrotic. The predominant symptoms frequently involve painful muscle cramping. If a person is bitten on the lower extremity, pain usually progresses from the foot, up the leg, and into the back and abdomen. If a person is bitten on the upper extremity, pain usually progresses from the hand, up the arm, and into the chest and abdomen. Abdominal pain may be so severe as to mimic an acute abdomen, with tenderness and rigidity.[41] Diaphoresis locally around the bite site is distinctive for widow spider envenomation, although diaphoresis may be diffuse and profuse or it may manifest in unusual patterns remote from the bite site. Local piloerection is sometimes seen. Patients may exhibit "Latrodectus facies" (Figure 107-8), which is characterized by spasm of facial muscles; edematous eyelids; and lacrimation, which may be mistaken for an allergic reaction. Other common symptoms and signs include high blood pressure, rapid heart rate, nausea, vomiting, headache, and anxiety. In a typical progression, symptoms onset within an hour, reach maximum intensity by about 12 hours, and can last for days to weeks. Unusual presentations have been described after widow spider envenomation including pulmonary edema, myocarditis, and priapism.[37,42] It has been suggested that there may be increased danger to pediatric patients with widow spider bites and that this population may require more aggressive treatment and hospitalization, although this assertion has been challenged.[43] Little evidence supports either assertion. A recent and well-documented fatality from widow spider envenomation involved a healthy 19-year-old woman. Other recent reports involved adults as well.

Diagnostic Studies

Rhabdomyolysis has been reported after widow spider envenomation,[42] so a total CK test should be performed if severe envenomation develops. If the patient has respiratory difficulty, a chest radiograph should be obtained. Electrocardiography or echocardiography may detect that rare case of venom-induced myocarditis in a critically ill patient. Otherwise, diagnostic tests are not particularly helpful. If the diagnosis is uncertain, evaluation should be aimed at uncovering other causes such as appendicitis.

Pitfalls

Misdiagnosing an acute abdomen in a patient with a widow spider envenomation could lead to unnecessary surgery.

Emergency and Critical Care

There are two basic treatment options. Widow spider envenomation can be managed with antivenin or a combination of pain medications and sedatives. There are risks and benefits associated with each. Management with an opioid analgesic, such as fentanyl 1 μg/kg/dose IV/IM, may repeat at 30- to 60-minute intervals or morphine in increments of 0.02 mg/kg up to 0.1 to 0.2 mg/kg IV/IM, and a benzodiazepine such as lorazepam 0.01 to 0.03 mg/kg IV is generally considered safe. This treatment option, however, is purely palliative, and symptoms may persist for days or even weeks. The pain and discomfort associated with widow spider envenomation can be severe. In contrast, antivenin is remarkably effective. Unfortunately it can be associated with severe side effects and death.[44] Because death is so rare after widow spider envenomation, some would argue that the treatment is more dangerous than the bite itself. Historically, IV calcium was recommended, although it has now been found to be ineffective.[44]

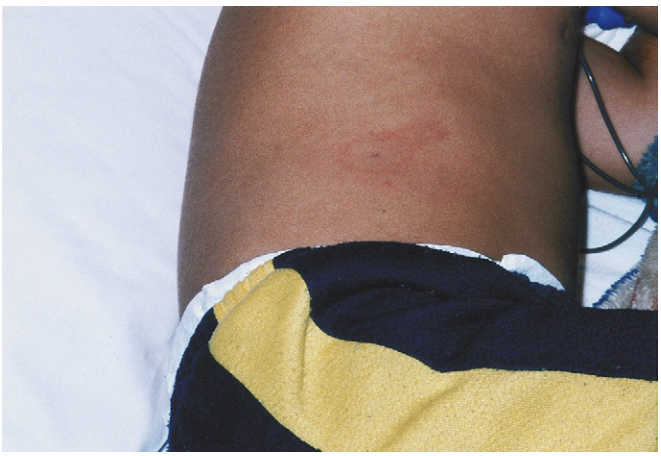

Figure 107–7. Black widow spider bite site. *(Photo Courtesy Sean Bush, MD.)*

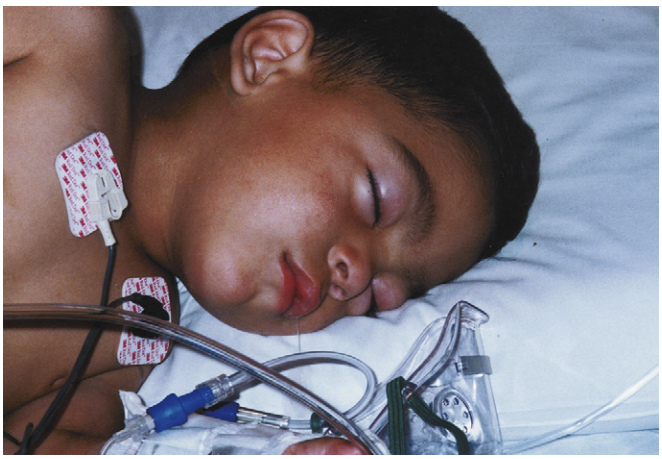

Figure 107–8. Latrodectus facies. *(Photo Courtesy Sean Bush, MD.)*

Several antivenins have been manufactured including Black Widow Spider Antivenin (equine) in the United States, Australia Redback Spider Antivenom, and South Africa spider antivenin (button spider).[1] Indications for antivenin use and routes of administration vary around the world. According to the package insert of Black Widow Spider Antivenin, one vial should be reconstituted in 2.5 mL of the sterile diluent supplied. It is further diluted into a volume of 50 mL saline and administered IV over 15 minutes. Patients usually experience dramatic relief within an hour of treatment with one vial, although sometimes two and rarely three vials are necessary. It may be effective days, weeks, or possibly even longer after the envenomation.[45] The risk of allergy to antivenin must be weighed against the benefit of relieving prolonged discomfort, avoiding hospitalization, and preventing complications. Although most widow spider envenomations can be managed with opioid analgesics and benzodiazepines, antivenin may be indicated for patients who have severe envenomations with pain refractory to these measures. Antivenin should be given if there is an imminent risk of a severe complication of envenomation. Factors that could increase the risk of antivenin include allergy or previous exposure to horse serum or a medical history of reactive airways.[46] Antibiotics are not indicated for widow spider envenomation. Also, update tetanus prophylaxis as appropriate.

Therapeutic Complications

Serious, even fatal, adverse reactions have been documented after treatment with black widow spider antivenin. Anaphylactic and anaphylactoid reactions to antivenin can occur and may even be more life threatening than the envenomation itself. Skin testing, with the intradermal injection of 0.02 mL of the test material supplied and the observation for an urticarial wheal in 10 minutes, variably predicts immediate hypersensitivity to antivenin and may influence the decision regarding its administration. Premedication with antihistamines (H_1 and H_2 blockers) may reduce the likelihood that an acute allergic reaction will occur. Serum sickness, characterized by fever, urticaria, lymphadenopathy, and polyarthralgias, can occur days to weeks after treatment and is treated with antihistamines and steroids.

Resources

The AAPCC may be helpful with management of widow spider envenomations and can be contacted at (800) 222-1222.

Disposition

Because it so effectively resolves symptoms, antivenin has been shown to decrease the need for hospitalization after widow spider envenomation. Admission to the hospital and possibly the PICU is prudent for severely symptomatic children, those with intractable pain and contraindications to antivenin, those with unusual complications of envenomation, and those who have anaphylaxis to antivenin. Patients who experience relief with opioid analgesics, benzodiazepines, or antivenin may be discharged. On discharge, signs of serum sickness should be outlined, and the patient should return or follow up if these signs show up anytime in the few weeks after treatment with antivenin.

Prognosis

The envenomation syndrome usually resolves completely, with or without treatment, and does not leave the patient with long-term sequelae. Death is rare.

Prevention

Spider bites may be prevented by eliminating the spider's food and habitat; by shaking sheets, shoes, and clothing before donning; by keeping the child's bed away from the wall; and by brushing spiders off rather than crushing them.

Future Directions

Safer antivenins are being developed and investigated.

Hymenoptera Stings (Bees, Wasps, and Ants)

Stings by bees, wasps, and ants are less of a toxicological concern than they are an allergic one. Details on treatment of anaphylaxis are covered elsewhere in this text. The focus of this section will be mass envenomation. Any bee, wasp, or ant can cause toxic, even fatal, complications when they attack in large numbers. Bee behavior, however, can vary, even within the same species. European honeybees tend to be docile and will tolerate approach of their hive to some degree, but can become provoked. Africanized honeybees (*Apis mellifera scutellata*) are much more aggressive and will defend their hive much more proactively. Africanized honeybees were imported to South America in the 1950s to boost honey production, and they have steadily extended their range northward into the southwestern United States. The primary difference between Africanized and European honeybees is their behavior in that Africanized honeybees behave much more aggressively. The effect of an individual stinging event is similar. Subtle wing morphological differences and DNA testing can also distinguish the bees.

If a person is swarmed by bees or wasps, the best thing for the person to do is create barriers between himself or herself and the bees. For example, getting behind a door will evade many bees and getting behind another door will evade many more. Older children may be able to outrun bees, which fly at approximately 4 mph and may pursue up to 150 yards. Younger children, however, may be unable to run fast or far enough. Attempting to submerge oneself or another person in water is not recommended because Africanized honeybees will wait until the person surfaces to continue delivering stings. This can result in multiple stings to the airway. A lethal dose of honeybee stings is estimated at 500 to 1200, but serious envenomation can result from as few as 50 stings (or even fewer after certain species of wasp stings). Sting removal should be done as quickly as possible, regardless of the method of removal. Even a delay of a second or two (to find a knife or credit card) results in a higher dose of venom injected. Contrary to conventional advice, it has been shown that grasping the stinger does not increase the venom dose.

Clinical complications can include hemolysis, coagulopathy, rhabdomyolysis, and liver dysfunction. Delayed toxic reactions have been documented, and so 24-hour hospitalization is recommended for pediatric and older patients, as well as patients

with underlying medical problems or abnormal laboratory test results within a 6-hour observation period and those with 50 or more stings.[47] Laboratory analysis should be aimed at uncovering the aforementioned clinical complications. Treatment involves IV fluids, intensive care, and possibly dialysis and transfusion as needed. For sensitive individuals, venom immunotherapy in children leads to a significantly lower risk of systemic reaction to stings even decades later.[48]

If an Africanized honeybee hive is suspected, local vector control authorities should be contacted. Avoiding perfume and brightly colored clothes may prevent some stings. Similar to African honeybees, fire ants (Solenopsis invicta) are extending their range in the southeastern United States and can cause serious (even fatal) complications after massive envenomation, particularly in infants and small children. These ants typically bite and sting.

References are available online at http://www.expertconsult.com.

Heat Injury

Ofer Yanay and Eli Gilad

PEARLS

- According to the Centers for Disease Control and Prevention, from 1979 to 1999, 6864 deaths were attributable to excessive heat exposure in the United States. During this period, more people died of extreme heat than as a result of hurricanes, lightning, tornadoes, floods, and earthquakes combined.
- With an increased occurrence of heat waves, even in temperate areas, the risk of heat-related illness is rapidly increasing.
- After the onset of heat stroke, the inflammatory response may continue despite adequate control of body temperature. Inflammation, coagulopathy, and progression to multiple organ failure may ensue. New approaches for modulation of the inflammatory response may play a role in treatment of heat-related injury in the future.
- Thorough knowledge and understanding of these disorders may prevent the progression from heat stress to heat stroke.
- Maintaining organ perfusion and rapid cooling are the major treatment goals for patients with heat stroke.
- The central nervous system is particularly vulnerable to heat, with the cerebellum being most susceptible. Pyramidal dysfunction, dysphagia, mental changes, quadriparesis, extrapyramidal syndrome, and neuropathy have all been described.
- Neurologic dysfunction is a cardinal feature of heat stroke. Brain dysfunction is usually severe but may be subtle, manifesting only as inappropriate behavior or impaired judgment; more often, however, patients have delirium or coma.

The interest in heat-related illnesses has grown enormously, largely because of global warming and an increased frequency of heat waves.[1,2] According to the Centers for Disease Control and Prevention, from 1999 to 2003, excessive heat exposure caused 3442 deaths in the United States.[3] During this period, more people died of extreme heat than as a result of hurricanes, lightning, tornadoes, floods, and earthquakes. Among the pediatric population, neonates and infants are at highest risk, mainly because of poorly developed thermoregulatory mechanisms and total dependence on caregivers to provide adequate protection from excessive heat. Children with mental illness and chronic diseases are at high risk. Adolescents are also at increased risk mostly due to poor judgment or intoxication.

Over the past decade, the understanding of cellular and molecular responses to heat stress has improved dramatically. This is a multiorgan injury resulting from a complex interplay between the cytotoxic effect of the heat and the inflammatory and coagulation responses of the host.[4] Despite progress in the understanding of the pathophysiology of heat injury, treatment remains supportive, with emphasis on immediate cooling. Prevention and education are still the best tools available in the hands of healthcare providers to minimize heat-related morbidity and death. This chapter covers the epidemiology, pathophysiology, clinical manifestations, and treatment of nonexertional heat-related illness in the pediatric population.

Definitions

There are several heat-related illnesses that may take the form of heat syncope, heat cramps, heat exhaustion, or heat stroke. The following are key terms used in this chapter:

1. *Heat syncope* (fainting) is a mild form of heat illness, which results from physical exertion in a hot environment. In an effort to increase heat loss, the skin blood vessels dilate to such an extent that blood flow to the brain is reduced. This reduction results in symptoms of lightheadedness, dizziness, headache, increased pulse rate, restlessness, nausea, vomiting, and possibly even a brief loss of consciousness. Inadequate fluid replacement, which leads to dehydration, contributes significantly to the problem.
2. *Heat cramps* are painful sustained muscle contractions, most often in the legs or abdominal wall, primarily due to inadequate circulation, dehydration, hyponatremia, and muscle fatigue. Body temperature is usually normal.[5,6]
3. *Heat exhaustion* is a mild-to-moderate illness due to water or salt depletion (excessive sweat) resulting from exposure to high environmental heat or strenuous physical exercise. The patient may have a headache, intense thirst, muscle weakness, dizziness, fainting, nausea, and visual disturbances. Core temperature may be normal or elevated, but is less than 40° C. Postural hypotension may occur.

4. *Heat stroke* is a life-threatening emergency that occurs when core temperature exceeds 40° C and the patient is in hypovolemic shock and has central nervous system abnormalities such as delirium, convulsions, or coma. Exposure to environmental heat (classic heat stroke) or strenuous physical exercise (exertional heat stroke) can cause heat stroke. Alternatively it can be defined as a form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates.[4]
5. *Exertional heat stroke* develops in a previously healthy patient in the setting of a recreational or occupational exercise. It results from heat production by muscular work, which exceeds the body's ability to dissipate it.
6. *Classic heat stroke* develops in the setting of high ambient temperature. The term nonexertional heat stroke has also been used to describe classic high ambient temperature heat stroke.
7. *Heat index* is a measure of the effect of combined elements (e.g., heat and humidity) on the body.
8. *Wet-bulb temperature* is a standard created to reflect the combined influence of temperature and humidity.
9. *Wet-bulb globe temperature* (WBGT) is an index of heat stress that reflects the combined influence of temperature, humidity, and solar radiation.
10. *A heat wave* is three or more consecutive days of air temperatures greater than or equal to 90° F (≥32.2° C).
11. *Heat-related death,* according to the definition by the National Association of Medical Examiners (NAME), includes exposure to high ambient temperature either causing the death or substantially contributing to it; cases in which the body temperature at the time of collapse was greater than or equal to 105.8° F (≥40.6° C); and a history of exposure to high ambient temperature and the reasonable exclusion of other causes of hyperthermia.[7] Because death rates from other causes (e.g., cardiovascular and respiratory disease) increase during heat waves, deaths classified as caused by hyperthermia represent only a portion of heat-related death.

Epidemiology

Excessive heat is the second largest contributor to death by natural events in the United States.[8] In the period from 1999 to 2003, an annual average of 688 deaths in the United States was attributable to "excessive heat exposure." Persons aged 15 years and younger accounted for 7% of deaths within the group of deaths caused by weather conditions.[9] During heat waves, there is a significant increase in the heat-related death rate. For example, in 1980, a year with a record heat wave, the death rate was more than three times higher than that for any other year during the 19-year period of 1979 to 1997.[10] Data on heat-related death are imprecise because this condition is underdiagnosed, its definition varies,[4] and many cases of patients with near-fatal heat stroke who survive the acute hospitalization have a high 1-year death rate.[11] In Saudi Arabia, where the temperature is extremely hot, the incidence of heat stroke varies seasonally, from 22 to 250 cases per 100,000 population.[12] Heat-related illness is reported from subtropical and cold parts of the world as well. In Taiwan, a subtropical country without any history of heat waves, a cluster of heat shock cases was reported during periods of sustained hotter-than-average temperatures.[13] In an observational study in which cold and hot areas in Europe were compared, it was shown that heat-related death started at higher temperatures in hot regions than in cold ones.[14] High ambient temperature and humidity, lack of acclimatization, unavailability of air conditioning, and vigorous physical activity[15] are major predisposing factors for heat-related illness. Within the pediatric population, children younger than 2 years are at higher risk, with specific factors like diarrheal disease, sweat gland dysfunction, child neglect, and underlying chronic or febrile illness contributing. Risk factors for adolescents include poor judgment that may lead to continuation of physical exertion despite warning symptoms. Alcohol and drug abuse and exposure to environmental toxins may put the adolescent at risk. Neuroleptic phenothiazines and tricyclic antidepressants, taken for medical indications; amphetamine and derivatives; marijuana and cocaine; or organophosphates, constituents of many pesticides, may all lead to heat-related illness.[16] Their effect may be due to impaired heat loss or increased heat production.[17] Lithium and fluoxetine (Prozac) may induce heat intolerance.[18]

Pathophysiology and Pathogenesis of Heat-Related Illnesses

Understanding the systemic and cellular pathophysiology of heat-related illnesses involves an appreciation of thermoregulation, physiologic alterations directly related to hyperthermia, acute phase response, and the production of heat shock proteins (HSPs). For normal enzymatic and cellular function, it is essential that body core temperature be maintained within a narrow range of about 37° C ± 0.5 to 0.9° C.[16,19] The thermoregulation system, controlled by the hypothalamus, receives input from thermosensitive receptors in the skin and body core, compares the data with a reference level (the "set point"), and responds to an elevation of 0.3° C[16,20] with activation of heat loss mechanisms.[4,16,21]

Heat dissipation occurs by means of four mechanisms: (1) conduction to the adjacent air and objects, (2) convection through air or liquid, (3) radiation of heat energy, and (4) evaporation. Once activated by the hypothalamus, the efferent heat response is both autonomic and behavioral. Blood delivery to the body surface is increased by sympathetic discharge causing cutaneous vasodilatation. Blood flow may increase eightfold to sixteenfold, up to 8 L/min.[22] Thermal sweating, in response to parasympathetic discharge, can produce approximately 1 L/h/m^2 of body surface of sweat. Evaporation of 1.7 mL of sweat will consume 1 kCal of heat energy; thus at maximal efficiency sweating can dissipate 588 kCal of energy per hour. Secondary to cutaneous vasodilatation and sweating, blood is shunted toward the periphery, and visceral perfusion is reduced, especially to the liver, kidneys, and intestines.[23] Rising core temperature will also lead to tachycardia, a high cardiac output state, and an increase in minute ventilation. When ambient temperature equals or exceeds body temperature, conduction, convection, and radiation cease to be effective. Losses of salt and water through sweating may lead to dehydration and salt depletion, resulting in impaired thermoregulation.[24] A combination of high ambient humidity and temperature creates a particularly dangerous situation. With ambient humidity of 90% to

95%, evaporation of sweat essentially stops, and if ambient temperature reaches body temperature, the body can no longer eliminate heat.

Acclimatization

Prolonged exposure to a hot environment results in adaptation and tolerance to higher temperature levels. Acclimatization to heat may take several weeks and involves multiple organs. Sweat glands develop increased capacity to secrete sweat, plasma volume is increased, and the renin-angiotensin-aldosterone axis is activated and leads to improved salt conservation. The adaptability of the cardiovascular system is probably the most important single determinant of one's ability to tolerate heat stress.[4,25] Even acclimatized people have definite limitations for heat tolerance. Once driven beyond a critical level, progression to a catastrophic condition may result.

Hyperthermia directly induces cellular injury. The severity of injury is cumulative, so exposure to a very high temperature for a brief period of time may cause similar injury to an exposure to a lower temperature for a longer period of time.[26] Once extreme temperatures of 49° to 50° C have been reached, full destruction and cell necrosis occur. At lower temperatures cell death is mainly due to apoptosis.[27]

Acute Phase Response

Heat stress initiates cellular acute phase responses aimed at protecting against injury and promoting tissue repair. A variety of cytokines are produced in response to heat stress. Cytokines mediate a wide range of cellular, systemic, and both proinflammatory and antiinflammatory acute phase protein productions. For example, interleukin-6 (IL-6) has a pivotal role in modulating synthesis of inflammatory cytokines, both locally and systemically.[4,28] IL-6 also stimulates production of antiinflammatory cytokines, which inhibit production of reactive oxygen species (ROS) and proteolytic enzyme release from activated leukocytes.[28,29] Plasma levels of both proinflammatory (tumor necrosis factor alpha [TNF-α], IL-1, and interferon-γ) and antiinflammatory cytokines (IL-6, IL-10, TNF receptors p55 and p75) are elevated in patients with heat stroke.[30-35] Soluble TNF, IL-2, and IL-6 receptors are also elevated in heat stroke.[36,37] It has been shown that the severity of symptoms during heat stroke correlates well with IL-1 and IL-6 levels.[30] Progression from heat stress to heat stroke depends on the time and extent of exposure to severe environmental conditions, but the acute phase response may continue after the patient is cooled. Onset of inflammation may be local with systemic progression,[4,35] involving endothelial cell activation, release of endothelial vasoactive factors,[38] endothelial cell injury, and microvascular thrombosis.[38-41] The gastrointestinal tract may also play a role in the exaggeration of the inflammatory response. Vascular congestion, hemorrhage, thrombosis, and massive loss of surface epithelium in the jejunum was observed in a baboon model of heat stroke.[42] These changes facilitate bacterial and endotoxin translocation which contributes significantly to inflammation and multiple organ dysfunction syndrome (MODS).[23,43-46] Evidence for this phenomenon exists in animal models, but much less in humans.[23,43,45-49] Alterations in the barrier function of the intestines may allow leakage of endotoxins that fuel the inflammatory response.

Part of the effect on endothelial cells involves activation of both the coagulation and the fibrinolytic systems.[40] Heat stress by itself is a procoagulation condition since it causes platelet clumping in small vessels. In addition, heat stress may mediate endotoxemia, elevated levels of proinflammatory cytokines, and macrophage activation (via factor VIIa), all of which are well known inducers of coagulation. Injured endothelium, (e.g., heat stroke) plays an important role in producing and releasing both procoagulant and anticoagulant substances (e.g., von Willebrand factor antigen [vWF-Ag], tissue plasminogen activator, and plasminogen activator inhibitor).[38,39] Circulating vWF-Ag, thrombomodulin, endothelin-1, nitric oxide (NO) metabolites, soluble E-selectin, and ICAM-1 (intercellular adhesion molecule 1) are elevated in heat-related illness, creating a clinical picture of disseminated intravascular coagulation (DIC).[38,50-52] The cooling of patients with heat stroke reverses only part of these coagulation abnormalities.[40] Another aspect of the cellular response to stress involves the heat shock response.

Nearly all cells will respond to heat stress with increased production of HSPs. Expression of HSP is controlled mainly at the gene transcription level. Increased intracellular HSP levels facilitate tolerance to heat stress with better cell survival.[53,54] In animal models, it has been shown that preconditioning with heat or chemical stress conferred significant protection against heat stroke-induced hyperthermia, hypotension, and brain injury.[55-57] These effects were mediated mainly by Hsp70 and Hsp72.[56] Blocking the production of HSP results in increased cellular sensitivity to even mild degrees of heat stress.[58] Conditions associated with low level of expression of HSP such as lack of acclimatization or certain genetic polymorphisms may make certain patients more vulnerable to heat stress or faster progression to heat stroke. There appears to be a preferential expression of different families of HSPs in different cell populations. There are also distinct post-injury time frames of induction for each family of HSP, emphasizing differences in cellular functional requirements for each family of HSP.[59] It was suggested that Hsp72 may be used as a semiquantitative diagnostic probe of heat stress.[60] In one human study, researchers found that levels of autoantibodies against Hsp71 in heat-induced diseases correlated well with the severity of illness.[61] Thus the individual response to heat stress depends on the direct thermal injury (including thermal cytotoxicity, cardiovascular failure, and hypoxia in the face of increased metabolic requirement) and the acute-phase response of the host. Genetic factors likely play a significant role in determining response to heat stress. This complex interplay between leukocytes, endothelial and epithelial cells, and a variety of systemic changes may lead to the most extreme form of heat-related illness, heat stroke. A similar sequence of events has been shown to occur in sepsis.[62] Recent studies, using a baboon model for heat stroke, provide more data on pathways of heat stroke-induced tissue injury and cell death. This model can be used to evaluate clinical changes and may be suitable to test immunomodulation therapies to improve outcome.[42,63]

Systemic Clinical Features

Involvement of multiple organs may be seen, to a certain degree, in heat syncope, heat cramps, and exhaustion. Heat stroke is a true systemic disorder. Per definition, core temperature must exceed 40° C, and the patient exhibits hypovolemic

shock and central nervous system abnormalities such as delirium, convulsions, or coma. The heat stroke-mediated systemic dysfunction was shown to be similar to exertional heat stroke in reported cases with adult patients.[11]

Central Nervous System

Neurologic dysfunction is a cardinal feature of heat stroke. Brain dysfunction is usually severe but may be subtle, manifesting only as inappropriate behavior or impaired judgment; more often, however, patients have delirium or coma.[21] Seizures may occur, especially during cooling. The central nervous system is particularly vulnerable to heat, the cerebellum being most susceptible.[64] Pyramidal dysfunction, dysphagia, mental changes, quadriparesis, extrapyramidal syndrome, and neuropathy have all been described.[21,65] No data regarding long-term neurologic outcome in children have been reported. In one adult series, 33% of the patients had moderate to severe impairment of neurologic function at discharge from the hospital.[11]

Pulmonary

The pulmonary system is not involved in early stages of heat-related illnesses. However, a high incidence (23% to 25%) of acute respiratory distress syndrome (ARDS) has been reported in adult patients with heat stroke.[66,67] Patients with ARDS have a poor prognosis, with up to a 75% mortality rate.[66] Lung involvement is part of the systemic response, as indicated by the fact that all patients who had ARDS also had coagulopathy and DIC.[66]

Cardiovascular

The cardiovascular system is usually compromised in heat-related illness. Hypotension and shock may result from dehydration, translocation of blood from central circulation to the periphery, or increased production of NO.[21] Usually, circulation is hyperdynamic in these patients, with tachycardia and high cardiac output.[68] Vasomotor tone may remain abnormally low, even after normal temperature and intravascular volume have been restored.[25] Electrocardiographic changes are common in patients with heat stroke, including rhythm disturbances, conduction defects, prolonged QT interval, and ST segment changes. These may subside with cooling or may require correction of potassium, magnesium, or calcium abnormalities.[69]

Renal

Elevated blood urea nitrogen and creatinine levels are seen even in mild heat-related disease such as heat cramps.[70] Moderate to severe renal insufficiency is common in classic heat stroke (up to 53% in one series[11]). Direct thermal injury, hypoperfusion (due to dehydration, cardiac failure, or both), rhabdomyolysis with myoglobinuria, release of vasoactive mediators, and DIC may all contribute to renal injury.[4,21,71,72]

Gastroenterologic

Involvement of the gastrointestinal system plays a significant role in the development of MODS in patients with heat stroke.[4,73] The importance of the gastrointestinal system in other forms of heat-related illnesses is not well studied. Jejunal injury may lead to mild to moderate diarrhea. The liver may be severely injured in heat stroke. This is a metabolically active organ and a major site of heat production in the body. During periods of hyperthermia, liver temperature is among the highest of any organ in the body, putting it at high risk for injury.[26] Abnormal liver function tests may be seen during heat-related illnesses. Elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GT), lactate dehydrogenase (LDH), and total bilirubin have been described.[11,21,70] Patients with heat stroke demonstrate a typical rise in AST and ALT levels within 30 minutes from onset, that peaks at 48 to 72 hours following injury, with return to normal values after 10 to 14 days.[26,74] Severe liver damage is more common in exertional heat stroke. Fulminant liver failure is rare and usually carries a grave prognosis even with liver transplantation.[75]

Metabolic

Early in the course of heat injury, the most common acid-base abnormality is a mixed non-anion gap metabolic acidosis and respiratory alkalosis. Hypokalemia resulting from the respiratory alkalosis, sweat losses, and renal wasting may change to hyperkalemia because of leak of cellular potassium. Several hours into the injury the clinical picture changes into a predominantly metabolic acidosis that is caused by sustained tissue injury.[11,21,76]

Hematologic

Thrombocytopenia, an elevated clotting time, and DIC are well documented in patients with heat stroke.[4,11,21,41] The pathophysiology of DIC in patients with heat stroke has been previously discussed. The rapid decline of hematocrit in the first 24 hours following heat stroke is a common feature. This is partially explained by rehydration, but is most probably multifactorial. The red blood cell (RBC) half-life is shortened after heat stroke. In addition, RBCs are more fragile following exposure to high temperatures, leading to early removal from the circulation.[26] Hypersegmented neutrophils may be observed in peripheral blood for the first few hours following the onset of heat stroke. The cause for theis phenomenon is unclear. These cells are thought to be undergoing changes associated with apoptosis.[26]

Infectious

In the early phase of heat stroke, blood culture findings are negative,[77] but within 24 hours from admission, one study demonstrated that up to 27% of patients had positive blood cultures and 25% had positive urine cultures.[11] The existing data come from adult series. The incidence of positive findings in blood or urine cultures in the pediatric population with heat stroke is unknown.

Treatment

The treatment of heat stroke starts at the scene with removing the patient from the circumstances that led to heat stroke in order to prevent any further increase in core temperature.

Rapid cooling and maintenance of organ system perfusion and function are the two major goals. Adherence to the basic resuscitative guidelines is required, with protection of the airway, management of breathing and monitoring for hypovolemia/shock, and appropriate fluid resuscitation. The most severely affected children have altered mental status, rising body temperature, and hypovolemic shock. After the airway is secured, the child with heat stroke should be moved to a cool environment; clothes should be removed; intravenous access should be obtained with one or two large-bore catheters; and a normal saline or lactated Ringer solution bolus of 20 mL/kg should be administered. Fluid resuscitation, besides ensuring organ perfusion, increases heat dissipation and lowers core temperature[24] by improving skin blood flow. Cooling should be started as early as possible with whatever method is available, and the patient should be transported to the nearest hospital appropriate for children. Decreasing body temperature below 38.9° C within 30 minutes of presentation has been shown to improve survival.[21]

A variety of cooling methods have been used to promote heat loss, and controversy continues regarding the best cooling technique. Cold/ice-water immersion was twice as rapid in reducing the core temperature as the evaporative spray method in patients with exertional heat stroke.[78] The mechanism for this rapid cooling relates to the high thermal gradient between skin and ice-water, leading to a faster heat loss by conductance as compared with evaporation.[79] Ice water is readily available, does not require special equipment, and is suitable for both classic and exertional heat stroke. While some authors regard ice water immersion to be the most efficient cooling method,[80] others claim there is no evidence to support the superiority of any cooling technique, especially in classic heat stroke.[81,82] Critics of immersion point out that it may complicate resuscitation efforts of the comatose child who requires endotracheal intubation, mechanical ventilation, and close observation. Also, it is uncomfortable to the conscious child and may cause shivering and cutaneous vasoconstriction, which is counterproductive. Sponging the patient with ice water while massaging the body and using a fan may overcome some of these disadvantages, yet other studies have shown that keeping the skin relatively warm while allowing evaporation and convection to dissipate body heat is the most rapid way to decrease core body temperature.[83,84] This can be done with special cooling units,[83,85] but the concept of keeping the patient "wet and windy" can be easily achieved with the application of tepid water to the skin while a fan is used to keep high air flow and to maintain cool ambient temperature.[86] Thus hospitals located in high-risk areas may consider buying special equipment, but most emergency departments and pediatric intensive care units (PICUs) may use this technique with readily available equipment.

Cooling blankets are widely used in the PICU setting. The effectiveness of this approach was evaluated only in patients with fever[87] and no data are available concerning heatstroke patients. Invasive cooling techniques including iced peritoneal lavage as well as bladder and gastric lavage have been suggested and investigated to some extent. Peritoneal lavage is difficult to perform and requires placement of a peritoneal catheter and trained personnel. Evidence for gastric lavage comes mostly from canine models and was found to have no advantage over evaporative cooling.[82] Recent reports of an intravascular cooling device to control body temperature found the system to be highly effective. However, as this was not evaluated on patients with heatstroke, it cannot be recommended at this point.[88,89] Antipyretics cannot be recommended since their effect has not been systematically studied in this group of patients.[82] In addition, these drugs lower body temperature by normalizing the elevated hypothalamic set point. In heat stroke, the elevated body temperature reflects failure of cooling mechanism rather than abnormal set point. Acetaminophen and salicylates should be avoided due to their potential to aggravate coagulopathy and hepatic injury.[81,82] Dantrolene, which has been used successfully in the treatment of malignant hyperthermia and neuroleptic malignant syndrome, has been administered in the treatment of heat stress. Some studies have claimed that it may be effective in the treatment of heat stroke,[90,91] whereas in others, including a double-blind randomized study,[92] it was shown to be ineffective.

Once a core body temperature of 38.9° C has been achieved, active cooling may be be stopped. This end point appears to be safe in terms of mortality. Unfortunately a safe end point for long-term morbidity (particularly neurologic outcome) has not yet been established.[81] All pediatric patients with heat stroke should be observed in the PICU, even if respiratory support is not required. Basic laboratory workup should include electrolytes (including sodium, potassium, magnesium, phosphate, and calcium), renal and liver function tests, complete blood count, and coagulation studies. Urine output should be followed closely, and a urine sample should be sent for myoglobin analysis. As previously mentioned, patients with heat stroke may continue to deteriorate even after body temperature is normalized because of the inflammatory response. There are no specific guidelines for treating patients with MODS that results from heat stroke.

Prevention is still the best treatment for heat-related illness. Whenever possible, people should acclimatize themselves to hot weather. Physical activity should be undertaken during cooler hours, and water intake should be increased. Children should never be left unattended in a closed car, especially during hot weather. Physicians' awareness and knowledge may promote diagnosis of early forms of heat-related illness, thus preventing progression to heat stroke. On a national level, a good weather forecasting system and air-conditioned shelters for vulnerable populations may decrease heat-related morbidity and death during heat waves.[93,94]

References are available online at http://www.expertconsult.com.

Accidental Hypothermia

Björn Gunnarsson and Christopher M.B. Heard

PEARLS

- Accidental hypothermia is a potentially lethal complication of exposure to cold. It can occur as a result of exposure to cold air, water immersion, or submersion (near-drowning).
- Risk factors include accidents, neglect, toxins, mental disorders, and violence.
- Information about the duration and severity of cold exposure, scene details, and any other associated injuries may help in the selection of the appropriate facility and rewarming methods.
- Many organ systems are affected by hypothermia including a marked depression of cerebral blood flow and oxygen use.
- Rescuers should initiate resuscitation on all patients with hypothermia unless the patient has a frozen chest or any other obvious nonsurvivable injury. The key of rescue in all individuals with hypothermia is prevention of further heat loss, careful transport, and rewarming. Avoiding excessive activity and abrupt movements of patients with hypothermia is important because this may precipitate cardiac dysrhythmias.
- Various techniques have been used for in-hospital resuscitation from deep hypothermia. Active external rewarming has been shown to be effective. However, extracorporeal rewarming of blood is the preferred method to resuscitate patients with severe hypothermia and cardiac arrest or cardiovascular instability.
- Prediction of patient outcome is difficult. The decision to terminate resuscitative efforts must be based on the unique circumstances of each case.

Humans have a high capacity to dissipate heat and a relative poor capacity to increase heat production. As such, humans rely heavily on environmental regulation in the form of clothing and warm shelter to maintain normal body temperature. Thermoregulation is controlled by the hypothalamus. Heat production increases with movement. Shivering increases the rate of heat production three to five times above resting levels, but at the cost of greatly increased oxygen consumption. There are four primary means of heat loss: (1) conduction, (2) convection, (3) radiation, and (4) evaporation. Changes in the environment can radically increase heat loss (e.g., cold-water immersion can increase conductive heat loss by a factor of 32).[1] Susceptibility to heat loss is greater in children than in adults because of a large surface area relative to body mass and less subcutaneous tissue, but severe accidental hypothermia is uncommonly encountered in most pediatric intensive care units. Neonates have a capacity for nonshivering thermogenesis, primarily by metabolism of brown fat; however, this is at the cost of greatly increased oxygen consumption. Neonates are therefore extremely sensitive to relatively minor deviations from neutral thermal environment.

There is no uniformity in the definition of hypothermia. The 2005 European Resuscitation Council Guidelines for Resuscitation classify a core temperature of 35° C to 32° C as mild hypothermia, 32° C to 30° C as moderate hypothermia, and less than 30° C as severe hypothermia.[2] Hypothermia is further classified as accidental or intentional (as in cardiopulmonary bypass) and primary or secondary. Primary accidental hypothermia is due to environmental exposure, with no underlying medical condition causing disruption of temperature regulation.

Pathophysiology

The body can compensate to a great degree for mild hypothermia. The hypothalamus sends signals that produce cutaneous vasoconstriction, increased muscle tone, and metabolic rate. When muscle tone reaches a certain level, shivering thermogenesis begins. The clinical manifestations depend on the severity, acuity, and duration of temperature reduction; the patient's age; premorbid conditions; and superimposed disease states. Each organ system may be affected by hypothermia.[3,4]

Central Nervous System

Central nervous system dysfunction is progressive. Cerebral oxygen consumption decreases in proportion to the reduction in metabolism. Cerebral blood flow decreases 6% to 7% for each 1° C decrease in temperature.[1] Mild hypothermia may be associated with confusion, dysarthria, and impaired judgment.[3-5] Deep tendon reflexes are depressed at core temperature lower than 32° C because of slowed peripheral nerve conduction. As body temperature drops, many patients no longer complain of cold. Shivering thermogenesis ceases at approximately 31° C. Pupillary responses decline and dilated unreactive pupils may be noted at temperatures lower than 30° C. Patients may experience hallucinations and sometimes paradoxically remove their clothes. The electroencephalogram (EEG) shows abnormal activity at temperatures less than 32° C, and at 20° C the EEG may appear consistent with brain death.[1]

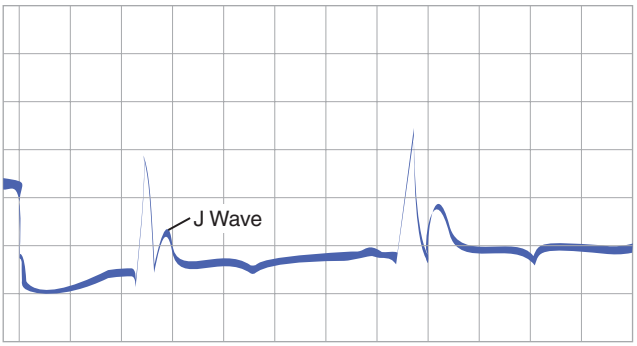

Figure 109–1. Characteristic J or Osborne wave of hypothermia closely follows the QRS. It may be mistaken for T wave with narrow QT interval if the true T wave is not appreciated. Slightly rounded peak distinguishes it from the R′ of bundle branch block. *(Data from Welton D, Mattox K, Miller R, et al: Treatment of profound hypothermia,* JAMA *240:2291, 1978.)*

Cardiovascular System

The initial cardiovascular responses are vasoconstriction, tachycardia, and increased cardiac output.[5] Further hypothermia results in decreased pacemaker and conduction velocity, causing bradycardia, heart block, and prolongation of PR, QRS, and QT intervals. Bradycardia becomes severe by 32° C. The myocardium becomes irritable and arrhythmias are common when core temperature reaches 30° C. The electrocardiogram may show characteristic J or Osborne wave following the QRS complex (Figure 109-1).[1,6-10] The presence of this wave is not pathognomonic for hypothermia and has no prognostic implications.[11] Myocardial contractility, systemic blood pressure, and cardiac output are often decreased dramatically in patients who have severe hypothermia. These changes may be persistent during rewarming.[12] Patients with hypothermia generally are volume contracted because of cold-induced diuresis.[1,5,13]

Respiratory System

Hypothermia affects tissue oxygenation through several complex physiologic mechanisms. Initially, the respiratory rate may be increased. As hypothermia worsens, the respiratory center becomes depressed and hypoventilation causes carbon dioxide retention, although the increase in carbon dioxide is blunted because of decreased production with increasing hypothermia. Respiratory arrest is a late occurrence. Suppression of cough and mucociliary reflexes leads to atelectasis and pneumonia.[5] Oxygen delivery to the tissues is further compromised through the shifting of the oxyhemoglobin dissociation curve to the left.[1] Blood gas analyzers warm blood to 37° C before analysis.[14] In patients with hypothermia, arterial blood gases show higher oxygen and carbon dioxide levels and a lower pH than a patient's actual values. The best approach to interpretation is to compare the uncorrected blood gas values with the normal values at 37° C (alpha-stat strategy).[15-17]

Renal System

Renal injury may occur either because of hypothermia or during the rewarming process.[18] The mechanisms involved in cold diuresis may include peripheral vasoconstriction and blunted response to antidiuretic hormone. Renal vasoconstriction and ischemia to the kidney may lead to oliguria and acute tubular necrosis in those with severe hypothermia.[5] Progressive hypokalemia develops during hypothermia, probably because of the shifting of potassium from extracellular to intracellular compartment, and significant hyperkalemia may develop during rewarming.[19-21] Metabolic and respiratory acidoses are not uncommon findings in patients who have moderate and severe hypothermia.[14] Hemodialysis has been required for renal failure and may also be of use as an active rewarming strategy.[22]

Coagulation

Hypothermia inhibits the intrinsic and extrinsic pathways in the clotting process. The degree of coagulopathy, however, is often underestimated because dynamic coagulation tests are generally performed at 37° C in the laboratory. Thrombocytopenia, from bone marrow suppression and splenic sequestration, and platelet dysfunction are common.[1,15]

Treatment

The key to rescue in all individuals with hypothermia is prevention of further heat loss, careful transport, and rewarming.[1] Wet clothes should be removed, and the individuals should be insulated and shielded from wind and cold. Paying special attention to the head and neck is important because radiant heat loss from those areas can be profound. Detecting signs of life in patients with deep hypothermia may be difficult, and the rescuer should therefore assess breathing and then pulse for 30 to 60 seconds to confirm respiratory arrest, cardiac arrest, or bradycardia. Chest compressions should be started immediately if the patient is pulseless with no detectable signs of circulation. Endotracheal intubation should be performed if the patient with hypothermia is unconscious or if ventilation is inadequate. Anecdotal reports of sudden cardiac death associated with tracheal intubation appear to be exaggerated, particularly if the patient is adequately preoxygenated and the procedure is performed in a gentle manner. If cervical spine injury is suspected, the neutral position must be maintained with manual cervical stabilization. Care should be taken not to overventilate the patient's lungs because this can increase ventricular irritability.[23] Rewarming by the administration of warmed humidified oxygen (42° C to 46° C) and warmed saline (43° C) should begin as soon as possible. Ringer's lactate solution is not recommended because a hypothermic liver cannot metabolize lactate. Defibrillation can be tried up to three times for ventricular tachycardia or fibrillation. If arrhythmia is resistant to three shocks in a patient with deep hypothermia, then further defibrillation attempts should be deferred until core temperature is increased. The hypothermic heart may also have a reduced response to cardioactive drugs and pacemaker stimulation.[1,2] Therefore the efficacy of drugs in severe hypothermia is limited and there is concern that medications can accumulate to toxic levels if they are administered repeatedly.[24-26]

No randomized controlled clinical trials in which rewarming methods are compared exist.[16] The rewarming of patients who are conscious and who have only mild or moderate hypothermia can be achieved with passive techniques (e.g., blankets, warm shelter). Management of severe hypothermia in the field is more controversial. Active external rewarming

with heat devices (e.g., forced air, radiant heat, warm bath, warm packs) requires careful monitoring and should therefore be used with caution. The concerns are core temperature afterdrop and rewarming shock.[1,4,15,16,27-29] The term *core temperature afterdrop* refers to a continued decrease in core temperature and associated clinical deterioration of a patient after rewarming has begun. Some researchers suggest that peripheral vasodilatation due to external rewarming leads to circulation of cold blood into the core of the body.[28] Simple equilibration of temperature between the periphery and the core is probably a far more important mechanism. Heat flows from the core to the periphery during cooling and the opposite is true during external rewarming. However, there is a delay in the reversal of temperature flow in deeper tissues and the core temperature may decrease for some time after rewarming has begun. It follows that the magnitude of core temperature afterdrop is greater if cooling is rapid because the temperature gradient between the surface and core is greater.[30] The hazard of afterdrop may be overrated. It is not uncommon, though, for patients with hypothermia to have "rewarming shock" or "postrescue collapse."[1,29,31,33] However, the underlying pathophysiologic condition behind this remains obscure and several mechanisms may contribute including myocardial dysfunction, decreased vascular tone, derangements of the microcirculation, and hypoxia or sudden changes in pH.[12,29,31] Depleted intravascular volume may also contribute to the development of shock, and most patients will benefit from volume expansion.[1,14] The patient should be kept horizontal to minimize hypotension and sympathetic discharge. Avoiding excessive activity and abrupt movements of patients with hypothermia is important because this may precipitate cardiac dysrhythmias.

Techniques that can be used for in-hospital rewarming of hemodynamically stable patients include continued active external rewarming, and active core rewarming with lavage of body cavities or warming of blood with extracorporal circulation. Active external rewarming can be effective, and there are several reports of successful use of active external rewarming or minimally invasive techniques in children with severe hypothermia and cardiac arrest.[33-41] Cardiopulmonary bypass should be considered in patients, even those without cardiac arrest, who suffer from severe hypothermia. It remains the preferred method to resuscitate patients with severe hypothermia and cardiac arrest or cardiovascular instability.[1,2,42-52] In most reports, partial bypass from femoral artery to femoral vein is described in adult patients. Full bypass with a median sternotomy may be preferable in small children.[44,53] Other methods of core rewarming that can be considered include peritoneal lavage with heated potassium-free dialysate, thoracic lavage, and the use of esophageal rewarming tubes.[54-57]

Outcome

Knowledge about outcome is mostly based on adult studies and isolated pediatric case reports. If rewarmed and resuscitated, patients with accidental hypothermia may recover neurologically intact after prolonged arrest. This was recently confirmed in a 16-year longitudinal review of profound hypothermia. In this series of 46 Swiss patients with deep hypothermia (temperature <28° C) and circulatory arrest, 32 underwent rewarming with cardiopulmonary bypass and 15 of those were long-term survivors, all with excellent functional outcome.[43] Recovery has occurred in an adult patient who sustained prolonged circulatory arrest with initial core temperature of 13.7° C, and there are many reports of successful resuscitation of children with severe hypothermia.[31,37-40,53,58]

If drowning precedes the hypothermia, successful resuscitation is rare. This has been confirmed in a recent series of 26 Norwegian patients, with hypothermia and circulatory failure or cardiac arrest, who were resuscitated with the use of extracorporeal circulation. Of those who probably had asphyxia before and during cooling, only 1 of 15 survived, compared with 7 of 11 patients who did not have asphyxia.[44] Most cases in the asphyxia group were pediatric drowning accidents. Authors from the same institution recently reported a remarkable story of a 48-year-old male who capsized his boat in a Norwegian fjord during the month of December. He was wearing a personal heart rate monitor/pulse watch which recorded his heart rate during the incident. The sea temperature was 3.5° C. He managed to keep his head out of water for some time, but then submersed and went into a cardiac arrest 38 minutes after the boat capsized. He had no signs of life when rescued from the sea 26 minutes later. Cardiopulmonary resuscitation was initiated 31 minutes after the onset of cardiac arrest and was continued for 90 minutes until cardiopulmonary bypass was established, at which time his heart was in asystole and the core body temperature 20.6° C. He made a full recovery.[59] There are also many reports of dramatic recovery after prolonged cold-water submersion of pediatric patients.[31,38,40,41,50,60,61] Cases of good outcome in near-drowning victims are generally associated with water temperatures at, or near, freezing and hypothermia on arrival to hospital. It is therefore reasonable to assume that good outcome in these cases must be associated with cerebral hypothermia.[16,59,60,62] Rapid cooling of the body because large surface area relative to body mass and little subcutaneous tissue may offer protection to pediatric patients. Furthermore, it is thought that rapid cooling of the brain may largely depend on repeated aspiration of cold water into the lungs.[29,50,62,63] Reviews from Finland and Canada, however, did not show a correlation between water temperature and age on outcome, so other factors must play a critical role.[60,64,65]

Severe coagulopathy, acidosis (venous pH ≤6.5), and hyperkalemia (>10 mmol/L) are among factors that have been associated with poor outcome.[46,66] These laboratory values may help identify those who had irreversible asphyxia before hypothermia commenced, but no chemical factor can predict with accuracy who will survive.[16,44,67] A good example of this is a 31-month-old girl who survived extreme hypothermia. Her rectal temperature on arrival to the hospital was 14.2° C, and her serum potassium level was 11.8 mmol/L.[53] Clinical judgment will have to be exercised, and it must be kept in mind that children with accidental hypothermia have tremendous potential for good outcome despite a catastrophic presentation. A reasonable approach, in most cases, is to resuscitate and warm the child aggressively until the core temperature reaches near normal. At that point, if no signs of life are present and the patient is not responding to aggressive life support measures, termination of resuscitation may be indicated.

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VII Chapter 110

Drowning

Mary W. Lieh-Lai, Ajit A. Sarnaik, and Ashok P. Sarnaik

PEARLS

- As defined by the World Congress, drowning is a process of respiratory impairment from submersion or immersion in liquid. The definition implies that a drowning victim develops an air-liquid interface that prevents breathing air. All other terms such as *near-drowning* and *secondary drowning* should not to be used in standardized literature.
- Central nervous system injury is by far the most important cause of death and long-term functional impairment among drowning survivors.
- The outcome of drowning victims depends largely on the success of resuscitative measures at the scene of injury. Patients who are successfully resuscitated and who are conscious on arrival to a hospital have an excellent chance of intact survival. Monitoring of intracranial pressure in the management of drowning victims has not been shown to be useful.
- Pulmonary edema encountered in children after drowning is due to acute respiratory distress syndrome and not from fluid overload. It should be treated with positive end-expiratory pressure and not diuretics. Such children are often hypovolemic and may require isotonic fluid resuscitation.
- In an unexplained drowning episode or with a similar history in familial members, an underlying predisposing disorder such as long QT syndrome should be suspected.

Of all the clinical entities encountered in a pediatric intensive care unit, drowning accidents are among the most tragic. Within minutes, previously healthy children with hopeful futures die or are left severely incapacitated with no chance of meaningful cognition. The parents, once full of dreams for their youngsters, are suddenly beset with tremendous grief and guilt because in many instances the accident could have been prevented by simple measures.

Definitions

The definition of drowning events remains a source of confusion. In addition to *drowning*, various terms such as *near-drowning, suffocation by submersion in water, secondary drowning, immersion syndrome,* and *wet and dry drowning* have been used. The plethora of terms and the lack of a standard definition have made it difficult to analyze and compare studies and outcomes. In June 2002, the World Congress on Drowning was convened to develop a more standardized definition of drowning using the Utstein-style for uniform reporting of data, and to make recommendations regarding preventive measures and care. The Congress was initiated by the *Maatschappij tot Redding van Drenkelingen* (Dutch Organization to Rescue People from Drowning), an organization established in Amsterdam in 1767 to promote drowning awareness in the Netherlands.[1] The final recommendation of the Congress was to define *drowning* as the process of experiencing respiratory impairment from submersion/immersion in liquid. The definition implies that a drowning victim develops an air-liquid interface that prevents the breathing of air. All other terms such as *near-drowning* and *secondary drowning* were abandoned. Outcome is described according to death or survival with survivors further categorized according to neurologic function. Papa et al. performed a systematic review of definitions for drowning accidents in 2005 and identified at least 43 publications where various definitions of drowning were used (Table 110-1).[2] They concluded that there is a need to use a single, uniform definition of drowning and supported the one recommended by the Utstein Focus World Congress on Drowning.

Epidemiology

In 2005, the latest year for which statistics are available, drowning accounted for 30% of all deaths in children from 1 to 4 years of age.[3] Drowning is the second-leading cause of unintentional injury-related deaths in children age 1 to 14 years. Those younger than 5 years and males aged 15 to 19 years are the two groups most at risk. Males are four times more likely to die from unintentional drowning than females. Between 2000 and 2005, the mortality rate from drowning of African Americans of all ages was 1.3 times that of whites, and among children age 5 to 14 years, the rate was 3.2 times higher. Cultural and racial differences in access to swimming pools and emphasis on swimming skills may play a role in the difference in drowning rates. Children younger than 1 year most often drown in bathtubs, buckets, or toilets. Child abuse should be investigated in these situations.[4] As many as 35% of children between the ages of 10 to 18 months are able to climb into a bathtub.[5] Drowning in a bathtub should not therefore be considered as a priori evidence of child abuse. Others at risk for bathtub drowning are those with seizure disorders.[6] The residential swimming pool is the most common site for drowning in children younger than

Table 110–1 Categories and Terms Used to Describe Drowning

Terms	Explanation
SPECIFIC CATEGORIES	
Primary vs. secondary	"Secondary drowning" is delayed death from drowning from complications *or* death occurring in minutes to days after initial recovery.
Wet vs. dry/with aspiration vs. without aspiration	"Dry drowning" or "without aspiration" is laryngeal spasm with no or little aspiration of water *or* from respiratory obstruction and asphyxia from a liquid medium. "Wet drowning" or "with aspiration" indicates that aspiration of fluids has occurred.
Warm vs. cold water	"Cold water drowning" is drowning in an outside body of water during the autumn, winter, and early spring months with a patient core temperature of ≤32° C on arrival to the emergency department. Some use water temperature <20° C.
Salt vs. fresh water	Kind of water in which incident occurred.
Active vs. passive (or silent)	"Active" refers to a witnessed drowning event in which victim makes some motion. In "passive" drowning, the victim is found motionless.
Intentional vs. nonintentional	Describes cause.
Fatal vs. nonfatal	Describes outcome.
Submersion vs. immersion	"Submersion" suggests the head was submerged in water; "immersion" suggests the head was out of water.
With and without hospitalization	Whether victim was admitted to hospital.
SPECIFIC CIRCUMSTANCES	
Iceberg phenomenon	People who have been submerged but have subsequently not died from drowning.
Immersion frigida	Death from cooling in water.
Immersion syndrome/ immediate disappearance syndrome	Occurs when syncope is provoked by sudden contact with water at least less than 5° C, presumably from bradycardia, tachycardia, or arrhythmia.
Save	Rescue of victim from water by someone who perceived individual to be a potential victim of submersion injury.

From Papa L, Hoelle R, Idris A: Systematic review of definitions for drowning incidents, *Resuscitation* 65:255–264, 2005.

5 years, whereas older children and adults more frequently drown in canals, lakes, ponds, and oceans.[7] Drowning is highest during the summer months. Most children who drown were last seen inside the home, in the care of one or both parents, but left unsupervised for less than 5 minutes.[8]

Other important risk factors in drowning deaths include failure to wear a life jacket and alcohol use. In 2006, the U.S. Coast Guard reviewed reports of boating incidents. Of the 500 people who drowned, 9 of 10 were not wearing life jackets.[9] Alcohol use is involved in up to half of adolescent and adult deaths associated with water recreation.[10] Ethanol and other neurotropic agents can diminish manual dexterity, impair judgment, and increase risk-taking behavior. Recent alcohol consumption by supervising adults may also contribute to submersion accidents involving children.[11] Expert swimmers have also been known to drown during underwater swimming. The practice of hyperventilation to prolong the duration of underwater swimming is particularly hazardous in this regard because significant hypoxemia may result in loss of consciousness before hypercarbia stimulates respiration and alerts the swimmer of the urgent need to breathe.[12]

Review of the drowning literature suggests that the key to prevention includes careful supervision of children, and education of the public regarding drowning prevention and the hazards of drowning. Children playing near or in water should always be supervised by a responsible adult who is not distracted by any other activity. Alcohol should be avoided before or during swimming, boating, and while supervising children. A four-sided, self-closing, self-latching fence at least 4 feet high that completely separates the house and play area of the yard should be installed around household pools. Those who are in or around natural bodies of water should wear U.S. Coast Guard approved life jackets irrespective of distance to be travelled, size of boat, or swimming ability.[9]

Pathophysiologic Considerations

The sequence of events after submersion has been described by Karpovich[13] in an animal model. After the initial panic and violent struggle, automatic swimming movements are followed by breath-holding and swallowing of large amounts of water. Subsequently, water is aspirated into the lungs as a result of attempts to breathe. Convulsions and spasmodic efforts resulting from asphyxia precede death. The single most important and prognostically significant consequence of drowning is decreased oxygen delivery to the tissues. A number of clinical variables determine the magnitude of hypoxia and the subject's ability to withstand it. The pathophysiology of drowning is thus closely integrated with the genesis of hypoxemia and its effects on various organ functions. A working knowledge of these pathophysiologic principles and multiorgan involvement is extremely helpful in directing therapeutic strategies for optimum survival.

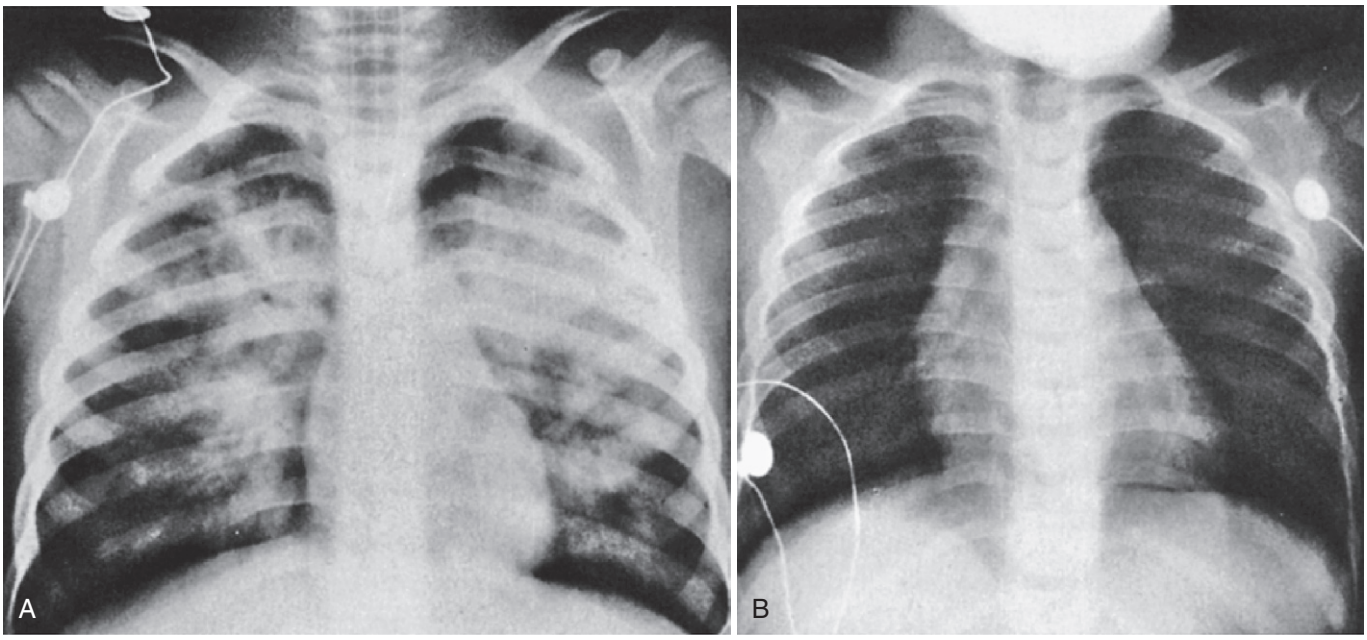

Figure 110–1. Drowning with and without aspiration. Radiographs show a patient with severe pulmonary edema (**A**), and another without significant fluid aspiration (**B**). *(From Ciullo JV, editor:* Clinics in sports medicine, *Philadelphia, 1986, WB Saunders.)*

Type of Aspirated Fluid

Although the differences between changes in electrolytes and blood volume after salt and fresh water aspiration have been emphasized in the past, they are of little clinical significance in patients who survive long enough to be transported to a medical facility.[14] Aspiration of more than 11 mL/kg of fluid is required for blood volume to be altered, and aspiration of more than 22 mL/kg is necessary before significant electrolyte changes occur.[15,16] Most drowning victims aspirate less than 3 to 4 mL/kg of fluid. Hypervolemia resulting from fresh water aspiration is rarely a problem. Most drowning victims are hypovolemic regardless of the type of aspiration because of excessive capillary permeability resulting from asphyxia and the loss of protein-rich fluid into the alveoli.

Pulmonary Effects

Functional residual capacity (FRC) is the only source of gas exchange at the pulmonary capillary level in the submerged state. Increased metabolic demands from struggling, breath-holding, a depletion of FRC from breathing efforts, and aspiration of fluid into the lungs all result in seriously compromised O_2 uptake and CO_2 elimination, with consequent hypoxia and hypercarbia. Between 10% and 15% of drowning victims have severe laryngospasm after submersion resulting in fatal asphyxiation without aspiration of water into their lungs (Figure 110-1). A combined respiratory and metabolic acidosis caused by hypercapnia and anaerobic metabolism is often encountered. Patients without significant fluid aspiration recover from asphyxia rapidly if they are successfully resuscitated before cardiac arrest or irreversible brain damage occurs. Aspiration of fluid, however, results in persistently abnormal gas exchange. Aspiration of a little as 1 to 3 mL/kg of fluid results in profound impairment of gas exchange.[16,17] Soon after the aspiration of fluid, there is an elevation of $Paco_2$ and a fall in Pao_2 as a result of airway obstruction, hypoventilation, and impaired gas exchange between alveoli and pulmonary capillary blood. With adequate resuscitation, normocapnia or even hypocapnia is usually achieved while hypoxemia persists, indicating a significant ventilation/perfusion mismatch and diffusion defect leading to intrapulmonary shunting and venous admixture.[18]

The surfactant system of the lung is affected differently in fresh water and seawater aspiration.[19] Freshwater aspiration results in marked disruption of the surfactant system of the lung resulting in alveolar instability and atelectasis. Seawater, because of its hypertonicity, draws water into the alveoli. Although the surfactant may be diluted by the presence of seawater in alveoli, its surface tension properties are not significantly altered. Zhu et al.[20] examined serum levels of pulmonary surfactant-associated protein and lung weights in 53 victims of fatal drowning. They showed significantly heavier lungs in those who drowned in seawater versus freshwater, suggesting an osmolar effect. Although they found no difference in serum surfactant-associated protein, intra-alveolar aggregates of pulmonary surfactant associated protein were noted more frequently in those who drowned in freshwater. This is likely related to the disruption of surfactant noted in freshwater drowning. Karch demonstrated marked changes in the pulmonary vasculature in rabbits within 30 minutes of aspiration of both freshwater and salt water.[21] Mitochondrial swelling and disruption of pulmonary vascular endothelial cells were consistently observed in these experiments. Clinically, pulmonary abnormalities are encountered in both fresh and sea water aspiration. These are consistent with pronounced injury to alveoli and pulmonary capillaries resulting in increased membrane permeability, exudation of proteinaceous material in alveoli, pulmonary edema, decreased lung compliance, and increased airway resistance. The extent of these abnormalities may not be manifested fully for several hours after the submersion episode and may be progressive in nature.

Acute respiratory distress syndrome (ARDS) is the hallmark of delayed pulmonary insufficiency resulting from aspiration

in drowning. This is characterized by progression of alveolar-capillary block, increased capillary permeability, and pulmonary edema. Reduced FRC and diffusion barrier resulting from accumulation of fluid and inflammatory cells in the alveoli and interstitium further accentuate hypoxemia. Aspiration of stomach contents and other debris such as sand, mud, and algae may also impair gas exchange. Bacterial pneumonia resulting from aspiration of contaminated water may further contribute to pulmonary insufficiency. A number of factors contribute to drowning-associated pneumonia. These include aspiration of vomitus or aspiration of contaminated material from water that may contain sewage. Water temperature plays a role, with warmer temperatures predisposing to a higher number of organisms. The chemical composition of the water such as pH, salt content, and presence of organic and inorganic substances influence bacterial growth as well. Organisms include aerobic gram-negative bacteria such as *Klebsiella* and *Pseudomonas*, and gram-positive bacteria, which include *Streptococcus pneumoniae* and *Staphylococcus aureus*. Fungi such as aspergillus have been reported to cause drowning-associated pneumonia as well. The diagnosis of pneumonia is based on clinical parameters such as fever, leukocytosis, respiratory cultures, and new infiltrates on chest radiographs.

Understanding the alterations in pulmonary mechanics is important in order to provide the necessary support in the least injurious fashion. The predominant respiratory manifestations of drowning are those of ARDS. Although pulmonary involvement is often bilateral and diffuse, there is considerable inhomogeneity, with some areas more affected than others. Overall, lung compliance is reduced, necessitating higher inflation pressures to maintain adequate tidal volume (Vt). Low Vt at low FRC leads to a vicious cycle of atelectasis, decreased compliance and further reduction in Vt. The critical opening pressure necessary to begin alveolar inflation is increased. Appropriate positive end-expiratory pressure (PEEP) needs to be administered to maintain the necessary FRC for adequate oxygenation and ventilation above the critical opening pressure. Airway resistance is relatively less affected or only minimally elevated unless there is airway obstruction from aspirated debris. Time constant, a product of compliance and resistance, reflects the time needed for pressure equilibration between the proximal airway and alveoli to occur. In ARDS, time constant is decreased allowing for quicker approximation of pressures at these sites during the inspiratory and expiratory phases of the mechanical ventilation. Relatively large tidal volume ventilation (10 to 12 mL/kg) is associated with greater ventilator-induced lung injury in ARDS, whereas smaller tidal volume ventilation (6 mL/kg) is associated with less volutrauma. Because of the changes in the time constant, prolongation of inspiratory time to improve oxygenation and increasing the respiratory rate for CO_2 elimination are often effective options during mechanical ventilation.

Cardiovascular Effects

Profound cardiovascular instability is often encountered after a severe submersion event thereby posing an immediate threat to survival after the initial rescue. The hypoxemia that occurs because of ventilation-perfusion mismatch can cause life-threatening dysrhythmias such as ventricular tachycardia, ventricular fibrillation, and asystole. The two determinants of oxygen delivery, namely cardiac output and arterial O_2 content, can be adversely affected by the submersion event. A decrease in Pao_2, if sufficiently severe, decreases oxygen saturation and therefore arterial O_2 content. This decrease in arterial O_2 content can cause a decrease in myocardial oxygen delivery, which contributes to worsening cardiac output and decreased myocardial perfusion pressure. Smooth muscle contraction banding in the media of major coronary arteries and local ventricular myocytes with focal myocardial necrosis have been described after a submersion episode.[22,23] Cytosolic calcium overload and oxygen-derived free radicals have also been implicated in the mechanism of myocardial injury after resuscitation after cardiac arrest.[24] Cardiogenic shock may result from hypoxic damage to the myocardium. Metabolic acidosis may further impair myocardial performance. Additionally, therapeutic application of PEEP causes decreased venous return, right and left ventricular preload, and right ventricular afterload while decreasing left ventricular afterload. Right ventricular afterload is also increased by structural pulmonary microvascular damage and humoral inflammatory mediators involved in ARDS. The right ventricle is anatomically designed to tolerate increased preload, but it is not as tolerant of high pressures and afterload as the left ventricle. If pulmonary hypertension is severe enough, it may lead to decreased left ventricular preload due to right ventricular failure. These factors, as well as the excessive capillary permeability of pulmonary and systemic capillaries, result in hypovolemia and decreased left ventricular filling pressures. These alterations of components of oxygen delivery; namely oxygen content, myocardial contractility, left and right ventricular afterload, and preload, can potentially result in an inadequate supply of oxygen to tissues to meet their metabolic demands.

Central Nervous System Effects

Hypoxia, if sufficiently prolonged, causes profound disturbances of central nervous system (CNS) function. The severity of brain injury depends on the magnitude and duration of hypoxia and cerebral hypoperfusion, as well as on mechanisms of secondary brain injury. Oxygen depletion and impaired neuronal metabolism result in loss of consciousness. However, even severe encephalopathy is reversible if the victim is promptly rescued and successfully resuscitated.

After restoration of adequate cerebral oxygen delivery after the initial hypoxia and/or hypoperfusion after drowning, there are several mechanisms of secondary brain injury at the tissue, synaptic, and cellular level. At the tissue level, increased intracranial pressure (ICP), and alterations in cerebral blood flow can adversely impact local tissue oxygen delivery. At the synaptic level, the excitotoxic neurotransmitter glutamate can cause an imbalance in the neuronal supply and demand. Intracellularly, accumulation of cytosolic calcium, neuronal energy failure associated with DNA damage and repair, the generation of oxygen derived free radicals, and activation of the triggers of apoptosis and necrosis can all contribute to secondary neuronal death.

There are several developmental factors that render the neurologic effects of pediatric cardiac arrest and hypoxia different than that of adults. Similar to other causes of pediatric asphyxia, such as foreign body airway obstruction, apnea, asthma, and suffocation, cardiac arrest encountered after drowning is preceded by a period of hypoxic perfusion. This leads to worse neurologic injury as opposed to a sudden

cardiac arrest, such as that induced by a dysrhythmia, which is the more common precipitating factor for adult cardiac arrest.[25,26] Approximately 13% of all children with cardiopulmonary arrest survive to hospital discharge, and only 9% if the arrest occurred outside the hospital.[27] Studies in humans and animals indicate that there are several developmental differences in excitotoxic pathways. In the neonatal period, there is increased vulnerability to NMDA receptor activation[28] and glutamate toxicity,[29] as well as heightened capability for apoptosis, which, albeit an important process of normal brain development, may render the immature brain vulnerable to neuronal loss after an insult.[30] In addition, a developmental difference exists in cerebral blood flow (CBF) after cardiac arrest. In adult models of cardiac arrest, global hyperemia is present for 15 to 30 minutes after return of spontaneous circulation followed by delayed hypoperfusion that persists for several hours. In an immature animal model of a brief asphyxial cardiac arrest, hyperemia is observed for 10 minutes after return of spontaneous circulation followed by restoration of baseline CBF, whereas prolonged cardiac arrest is followed by hypoperfusion and blood pressure-dependent CBF.[31]

Effects on Other Organ Systems

Multisystem failure resulting from prolonged ischemic-hypoxic state, sepsis, and therapeutic modalities used to manage these children may complicate the clinical course.[32] Renal and hepatic insufficiency, disseminated intravascular coagulation, gastrointestinal injury, and metabolic abnormalities are important management considerations. However, these complications rarely pose a threat to survival in an otherwise salvageable patient.

Submersion Hypothermia

Hypothermia has been shown in numerous animal and human studies to mitigate many of the processes involved in the development of secondary brain injury from both trauma and asphyxia. Positive effects of hypothermia include a decrease in cerebral metabolic rate, ICP, excitotoxic neurotransmission, cytotoxic edema, generation of deleterious oxygen-derived free radicals, and the cerebral hyperemia which can cause ischemia/reperfusion injury and further increase ICP. These effects of hypothermia are particularly germane to drowning injury, as astonishingly good outcomes have been reported in children submerged in ice water (< 5° C) for prolonged periods.[15,39] It appears that for submersion hypothermia to be protective, rapid cooling in ice water is necessary, as a lesser degree of hypothermia in warmer water does not offer cerebral protection.[40] Furthermore, intact survival is more an exception than a rule in patients with prolonged submersion, even in ice water. The young and the elderly are most susceptible to hypothermia. Infants lose heat rapidly when subjected to a hypothermic environment because of their relatively large surface area. Its protective effects notwithstanding, hypothermia by itself poses a direct threat to survival, due to its adverse effects on cardiac rhythm.

Mammalian Diving Reflex

A certain degree of protection against submersion hypoxia has been proposed to occur in the form of a response similar to the diving reflex observed in seals and other air-breathing diving mammals. The ability of these animals to remain submerged for periods up to 20 minutes is due to a remarkable redistribution of blood flow that occurs after diving underwater. While heart, brain, and lungs remain adequately perfused, blood flow to tissues resistant to hypoxia (i.e., gastrointestinal tract, skin, and muscle) is markedly reduced. Significant bradycardia occurs with a reduction in cardiac output. Such a response, albeit quantitatively less, is also observed in humans after total body immersion.[33] The mammalian diving reflex acts as an oxygen-conserving adaptation in response to submersion. It has been proposed that this reflex is most active in infancy and is potentiated by fear and low water temperature.[34] A combination of marked bradycardia and impalpable pulses resulting from vasoconstriction may make the victim appear dead at a time when mouth-to-mouth resuscitation could be life-saving.[33] Clinical studies involving children and adults have failed to demonstrate an efficient diving reflex in response to cold-water submersion.[35,36] Young children had a significantly decreased breath-hold duration and consequently a weaker dive response compared with older children and adults.[36] The role of the mammalian diving reflex in enabling children to withstand prolonged cold-water submersion thus remains controversial.

Preexisting Associated Conditions

An underlying etiologic mechanism should be explored depending upon the clinical scenario involving unexplained drowning. Children with seizure disorders are at greater risk for submersion accidents. Similarly an occurrence of vasovagal syncope or a hypoglycemic episode during swimming may be the underlying factor responsible for drowning. Occult cardiomyopathy or a cardiac arrhythmia should also be considered in an unexplained drowning event. An episode of drowning might be the first manifestation of long QT syndrome (LQTS). Ackerman et al. studied blood samples or archived autopsy tissue samples in 35 cases of autosomal dominant LQTS. Six of these patients had a personal history or extended family history of near-drowning. All of these patients were found to have LQTS mutations at *KVLQT1* whereas such an abnormality was found in only 3 of the remaining 29 patients who did not have a personal or family history of submersion episode.[37] Thus swimming appears to be a gene-specific (*KVLQT1)* arrhythmogenic trigger for LQTS. Diagnosis of inherited LQTS allows for identification of other family members with similar affliction. Yoshinaga et al. showed that face immersion in cold water results in abnormal lengthening of the QT interval in children identified with nonfamilial LQTS, and such children could potentially be at risk of a life-threatening arrhythmia during swimming.[38]

Management

Because the full extent of CNS injury cannot be adequately determined immediately after the rescue, all drowning victims should receive aggressive basic and advanced life support at the site of the accident and in the emergency department. The primary determinant of survival and maximal brain salvage is prompt and effective management of hypoxemia and acidosis. In this context, the management in the immediate postdrowning period is of paramount importance. The success or failure

of cardiopulmonary resuscitation (CPR) at the site of the accident often determines the outcome.[41,42] The issue of the duration of submersion in relation to the success of resuscitation is often raised. Although asphyxia for longer than 5 minutes frequently results in significant brain injury, this should not be a consideration in deciding whether or not to initiate on-site resuscitation. The emotional excitement surrounding the accident makes it impossible to accurately estimate the duration of hypoxia.

Management at the Scene

Ensuring the adequacy of the airway, breathing, and circulation is the goal of basic life support after the initial rescue. In cases of inadequate airway and cardiopulmonary status, CPR must be instituted immediately. The fundamentals of basic life support are the same after drowning as for any other situation requiring CPR; however, some practical aspects are worth considering. In the management of a drowning victim, the aim of resuscitation at the scene is to prevent irreversible tissue injury from prolonged hypoxia and ischemia. The victim should be removed from the water as soon as possible. Mouth-to-mouth breathing should be performed even while in the water if it can be accomplished. The stability of the cervical spine must be ensured, especially in drowning suspected to be related to diving. To this end, the preferred airway opening maneuver is anterior displacement of the jaw, rather than extension of the neck. Chest compressions should not be attempted in the water because it is ineffective and wastes valuable time.[43] Prolonged attempts to remove water from the lungs are futile and may hinder ongoing ventilatory support. Heimlich and Patrick[44] have recommended the use of subdiaphragmatic pressure in drowning victims to remove water from the airway. In addition to the fact that most drowning victims aspirate relatively small amounts of water, there is no evidence to suggest that the Heimlich maneuver can remove aspirated fresh water or pulmonary edema fluid.[42] On the other hand, such patients frequently swallow large amounts of water. Consequently, increased abdominal pressure may result in regurgitation of gastric contents into the oropharynx and aspiration into the tracheobronchial tree.[45] Any debris observed in the oropharynx should be removed before initiation of mouth-to-mouth breathing. Presence of airway obstruction caused by a foreign body should be suspected if effective chest expansion cannot be accomplished with appropriate ventilatory technique. A subdiaphragmatic thrust in such a situation would be indicated. As soon as the equipment becomes available, ventilation with 100% oxygen via bag-valve mask device should be initiated for patients who are not breathing adequately. Pressure used during resuscitation to inflate the lungs of submersion victims may have to be higher than anticipated because of reduced compliance of the edematous lungs. A PEEP valve should be used, if available. Overinflation should be avoided, however, because this can lead to pulmonary barotrauma, and overdistention of the stomach with regurgitation and aspiration of gastric contents. In patients who are too obtunded to maintain airway protection, exhibit hypoxia, or otherwise unable to maintain oxygenation despite bag-valve mask ventilation, endotracheal intubation should be performed. Noninvasive assessment of oxygenation and ventilation with the use of pulse oximetry, end-tidal CO_2, and transcutaneous O_2/CO_2 monitor provides valuable information especially during transport of such patients. Last, a common precipitating cause of drowning is cardiac dysrhythmia. In children, the most likely causes include myocarditis or familial long QT syndrome. Therefore, an automatic external defibrillator device, if available, should be applied to any patient who has not achieved adequate return of spontaneous circulation.

Emergency Department Evaluation and Stabilization

As with any form of accidental injury, other forms of associated trauma must be considered. Children who slip and fall into the pool may sustain external head injury such as abrasions, lacerations, and contusions. Occasionally, profuse bleeding from scalp lacerations may be sufficient to aggravate hypovolemic shock. Even in the absence of external signs of trauma, the possibility of intracranial lesions or bleeding should be entertained. In bathtub drowning, or in instances where child abuse is suspected, fractures and other evidence of previous injury should be looked for. In adolescent victims, drowning is frequently associated with illicit drug or alcohol use. When appropriate, urine and blood toxicology tests should be performed. Spinal injuries associated with drowning are not uncommon, especially with diving accidents involving young adults.[42]

The need for hospitalization should be determined by the severity of the drowning episode and clinical evaluation. All patients with a history of drowning should be observed in the emergency department for at least 4 to 6 hours. Those with insignificant history and normal physical examination may be safely treated as outpatients.[46] Patients with respiratory symptoms, decreased O_2 saturation indicated by pulse oximetry or blood gas determination, and altered sensorium should be hospitalized.

The extent of cerebral hypoxia can be quantified by Conn's criteria as category A (awake), category B (blunted consciousness), and category C (comatose). Category C is subclassified into C_1 (decorticate), C_2 (decerebrate), and C_3 (flaccid).[47] The Glasgow Coma Scale has also been proposed to estimate severity of neurologic dysfunction.[48] Both the Glasgow Coma Scale and Conn's classification are helpful in determining management and judging response to therapy and for prognostication.

Maintaining adequate airway, respirations, and peripheral perfusion with continued attention to oxygenation, ventilation, and cardiac performance should take priority. Electrocardiographic monitoring and arterial blood gas determination should be performed as soon as possible. Ventricular dysrhythmias, asystole, and hypotension may result from the asphyxial episode and are commonly encountered during the early resuscitation phase. The standard CPR techniques also apply to the drowned child. Patients with respiratory acidosis and hypoxemia, and those who are unconscious with significant respiratory distress or poor respiratory efforts, require endotracheal intubation and mechanical ventilation. Early use of PEEP is effective in reversing hypoxemia. Because pulmonary edema is not caused by hypervolemia in drowning, diuretics are not helpful and, in addition, may exacerbate the prevalent hypovolemia. Therefore pulmonary edema after near-drowning is best treated by mechanical ventilation with positive pressure breathing and PEEP rather than diuretics. Hypovolemia is commonly encountered in the early resuscitation phase. Isotonic crystalloids (20 mL/kg) or colloids

(10 mL/kg) infused over 15 to 20 minutes should be used for intravascular volume expansion. Additional volume expansion can be carried out based on clinical and hemodynamic status. Administration of large amounts of hypotonic fluid is contraindicated because such solutions are ineffective for intravascular volume expansion. Furthermore, the resultant decrease in serum osmolality may exacerbate cerebral edema. In the face of continued hypotension and/or impaired peripheral perfusion after appropriate intravascular volume expansion, inotropic support using dopamine or dobutamine may be necessary. Central venous pressure monitoring is extremely helpful for ongoing assessment and management of intravascular volume. Mild-to-moderate metabolic acidosis may resolve along with improvement of oxygenation and tissue perfusion. In more severe cases, sodium bicarbonate administration may be necessary based on blood gas values. Radiologic studies should include a chest radiograph to determine the presence or absence of pneumothorax or pneumomediastinum. Unless head injury is suspected, computed tomography scan of the head is usually not necessary because early findings are often normal even in the face of severe hypoxic damage.[49]

Severe bradycardia and intense vasoconstriction associated with marked hypothermia (<32° C) may make drowning victims appear dead. However, resuscitative efforts should be continued while normalizing body temperature. Treatment of hypothermia is discussed elsewhere in the textbook.

Management in the Intensive Care Unit

Continued attention to oxygenation and ventilation status and cardiac performance is essential. Pulse oximetry is readily available and provides a good indication of oxygen saturation and may especially be useful in continuous monitoring of patients who may develop ARDS. However, because of the nature of the oxygen-hemoglobin dissociation curve, pulse oximetry does not accurately reflect changes in Pao_2 greater than 70 mm Hg. Arterial and central venous pressure monitoring are necessary in most patients who require intensive care. A useful parameter to monitor is mixed venous oxygen saturation. Provided arterial oxygen content and oxygen consumption remain constant, venous oxygen saturation is a useful indicator of changes in cardiac output.

The need for endotracheal intubation and different ventilatory strategies should be determined on an individual basis and by clinical judgment. Respiratory acidosis, Pao_2 less than 60 mm Hg with an FIo_2 greater than 0.5, clinical signs of impending respiratory fatigue, and depressed level of consciousness are the most common indications for mechanical ventilation. Early use of PEEP and supplemental oxygen are extremely effective in reversing hypoxemia. The goal of mechanical ventilation is to provide adequate gas exchange to ensure tissue viability while minimizing the inevitable ventilator-associated injury from oxygen, barotrauma, volutrauma, and ineffective tracheobronchial toilet. Ventilatory strategy should take into account the major alterations in pulmonary mechanics. As noted earlier, most children who drown have decreased FRC, compliance, and time constant along with increased critical opening pressure. Salutary effects of PEEP are from maintaining alveolar stability, alveolar recruitment and increasing FRC. It stabilizes the relatively softer chest wall of a child thus minimizing chest wall recoil and further decrease in FRC. PEEP also displaces intra-alveolar water into interstitial and perilymphatic spaces resulting in decreased venous admixture and improved compliance. On the other hand excessive amounts of PEEP can result in decreased venous return and cardiac output, pulmonary overdistension and decreased compliance, and barotrauma. Maintenance of normovolemia is an important consideration in patients receiving PEEP.

It is now recognized that in patients with acute lung injury and ARDS, ventilation with lower tidal volumes (6 mL/kg) results in improved survival compared to those ventilated with a larger tidal volume (12 mL/kg).[50] There are various ventilatory strategies that may be used to minimize barotrauma in a patient with ARDS while maintaining adequate gas exchange. The underlying principle is to recruit lung volume by application of optimum PEEP to maintain FRC above the critical opening pressure and ventilate with a tidal volume approximating 6 to 7 mL/kg. Both pressure controlled and volume controlled strategies can be used using this principle. The authors recommend pressure controlled ventilation with a relatively low peak airway pressure and prolonged inspiratory time while still allowing adequate time for complete exhalation. Alternatively, the pressure-regulated, volume-control mode can also be used to deliver a preset tidal volume with the minimum possible inflating pressure. The level of PEEP can be optimized by gradual increments depending on its effects on the Pao_2/FIo_2 ratio and cardiovascular function. The ability of modern ventilators to display exhaled tidal volume and graphic displays of flow, pressure and volume waveforms has enabled the clinician to adjust mechanical ventilatory support according to individual alterations in pulmonary mechanics. Optimal PEEP as evidenced by improvement in dynamic compliance can be determined by measuring exhaled tidal volume at varying levels of PEEP. When PEEP exceeds critical opening pressure or the lower inflection point on the pressure/volume curve, dynamic compliance improves. Ventilatory rate, inspiratory/expiratory times, and peak airway pressures can also be adjusted according to their effects on dynamic compliance, and by ascertaining the return of expiratory flow to baseline. In patients without CNS injury and intracranial hypertension, the technique of permissive hypercapnia can be used to minimize barotrauma in a patient with ARDS. This involves using lower inflation pressures or tidal volume and accepting higher levels of PCO_2 as long as pH remains near normal.

High-frequency ventilation is another strategy that can be used in the management of hypoxic respiratory failure. This mode of ventilation uses a relatively high mean airway pressure while minimizing excessive fluctuations in pressures during the respiratory cycle. High-frequency ventilation is a safe and effective modality in the treatment of severe acute respiratory failure that is unresponsive to conventional mechanical ventilation.[51,52] Although extracorporeal life support (ECLS) has been used for rewarming in patients with severe hypothermia following drowning in cold water, the routine use of ECLS for the treatment of ARDS associated with drowning is less clear. The presumed benefit of ECLS is the avoidance of barotrauma and oxygen toxicity in patients who do not improve despite maximum ventilatory support. However, the risks of carotid artery ligation for the purposes of ECLS cannulation in patients who may have suffered hypoxic-ischemic CNS injury are unknown.

Recent studies have shown the benefits of the administration of exogenous surfactant in children with ARDS.[53]

Evidence indicates disruption of surfactant, particularly in those children who drown in freshwater. Exogenous surfactant administration may be a reasonable therapeutic modality in children who develop ARDS after drowning, and who have persistent pulmonary insufficiency in spite of aggressive respiratory support including high-frequency ventilation. While there are no randomized controlled trials examining the benefits of surfactant administration in patients with ARDS following drowning, there are case reports that describe improvement in oxygenation following instillation of exogenous surfactant.[54,55]

Secondary bacterial infection resulting from aspiration or as a complication of endotracheal intubation and mechanical ventilation is sometimes observed. There is no evidence to suggest that "prophylactic" antibiotics help prevent drowning-associated pneumonia.[56] However, fulminant *Staphylococcus pneumoniae* bacterial sepsis and pneumonia have been described shortly after a severe submersion injury. It is therefore reasonable to institute empiric antibiotic therapy in patients with severe cardiopulmonary deterioration especially when this occurs after a period of stability.[57] The use of corticosteroids for aspiration pneumonia is probably of no benefit.[58]

After the patient is successfully resuscitated, the severity of encephalopathy is the main determinant of mortality and morbidity from drowning. With improved techniques of cardiopulmonary support, delayed deaths resulting from pulmonary insufficiency are becoming less frequent. CNS injury is by far the most important cause of death and long-term functional impairment among the immediate survivors of drowning accidents. Measures for cerebral protection after drowning have been used by several investigators.[34,47] The emphasis of such modalities is on managing cerebral edema, controlling intracranial hypertension, and decreasing cerebral metabolic requirements with the use of fluid restriction, diuretics, hypothermia, corticosteroids, and barbiturates. However, studies have failed to demonstrate beneficial effects of such therapy in improving the outcome of hypoxic encephalopathy associated with drowning.[59] Furthermore, a significant increase in infections and pulmonary insufficiency was observed in association with therapeutic hypothermia in this setting. Pentobarbital has the theoretical advantage of decreasing cerebral oxygen demand. However, induction of pentobarbital coma, although effective in controlling intracranial hypertension, has not improved the neurologic outcome of comatose children following hypoxic-ischemic brain injury.[59-61] The role of cerebral edema and intracranial hypertension in potentiating CNS injury in otherwise salvageable children is questionable in this setting. The authors' experience suggests that significant intracranial hypertension is not commonly encountered in the early post-immersion period, whereas late, uncontrollable intracranial hypertension carries an unfavorable prognosis.[62] Additionally, satisfactory control of intracranial hypertension has not been shown to result in improved outcome.[59,60,62] It appears that the occurrence of cerebral edema and intracranial hypertension 2 to 3 days after a submersion accident is a reflection of the early hypoxic injury rather than a manifestation of a reversible process. Late, persistent intracranial hypertension associated with a comatose state is of ominous significance and is almost always associated with an unfavorable outcome.[62]

Currently, the routine use of ICP monitoring in children with hypoxic-ischemic encephalopathy after drowning is not recommended. The emphasis of management of a comatose child in the immediate post-drowning period should be on maintaining adequate oxygenation/ventilation, oxygen delivery with avoidance of hypotonic fluid and fluid overload. Pathophysiologic changes from asphyxia, as well as various therapies aimed at cerebral salvage such as barbiturates and osmotic diuresis may adversely affect myocardial performance.[63] Cardiovascular support with maintenance of intravascular volume and the use of inotropic agents is often necessary to maintain optimum organ perfusion in patients who have suffered a significant hypoxic-ischemic insult.

The neuroprotective properties of therapeutic hypothermia that have been extensively demonstrated in laboratory studies suggest potential merits as a therapy in some children, including victims of drowning. A randomized controlled trial of therapeutic hypothermia has shown benefits in neonatal hypoxic-ischemic encephalopathy,[64] and such therapy is currently being studied in older children. Much of the interest in the clinical application of therapeutic hypothermia originated in the treatment of submersion injury. In the late 1970s, Conn showed improvement in neurologic outcome in children who were victims of submersion injury, using "HYPER" therapy that included hypothermia, hyperventilation, neuromuscular blockade, barbiturates, and dehydration.[34] However, subsequent studies in pediatric drowning injury showed that not only did hypothermia not improve outcome, it increased infectious complications.[59,65] It is possible that studies designed with a different depth and/or duration of hypothermia, or rewarming procedure may yield different results. Although hypothermia has been shown to decrease ICP in trauma, rebound intracranial hypertension can occur during rewarming.[66,67] Thus, in cases of cold water drowning, although the patient should be actively warmed to prevent arrhythmias and secondary infections, once a core body temperature of 30° C is achieved, warming should be slower and more passive to prevent increases in cerebral blood flow and ICP, ischemia/reperfusion injury, and fever from overaggressive rewarming. However, given the lack of positive randomized controlled trials in pediatric asphyxial arrest or in submersion injury, hypothermia cannot be strongly recommended as a therapy at this time.

Prognosis

The outcome of drowning victims depends largely on the success of resuscitative measures at the scene of injury. Patients who are successfully resuscitated and who are conscious on arrival at the hospital have an excellent chance of intact survival.[41,68,69] With improved ventilatory techniques and aggressive management, pulmonary injury can be successfully managed in most patients. However, some groups have suggested that the neurologic prognosis is very poor if the patient arrives comatose in the emergency department, whether or not they receive aggressive "brain resuscitation" (i.e., goal-directed therapy for optimization of cerebral perfusion pressure).[70] Variables such as age, length of submersion, serum pH, and body temperature, although previously thought to influence outcome,[71] have not been shown to be reliable prognostic indicators.[61] In addition, our experience suggests that the absence of cognitive function 72 hours after the hypoxic episode is strongly associated with either death or survival in a persistent vegetative state.[62] The need for continued CPR at the hospital, CPR greater than 25 minutes,

fixed and dilated pupils, seizures, flaccidity, Glasgow Coma Scale of 5 or less, and decreased cerebral blood flow are of poor prognostic significance in the absence of hypothermia. Severe hypothermia has been shown to influence the outcome favorably even after prolonged submersion; however, not all hypothermic submersion victims are fortunate to escape serious neurologic damage. A database review of 267 cases of serious pediatric submersion events in Massachusetts from 1994 to 2000 showed better outcome in younger age groups, females, and Hispanic children, and worse outcomes in African-American children.[72] These data likely reflect differences in time to first responder arrival, and suggest that prevention strategies should take into account differences in age, gender, and ethnicity.

References are available online at http://www.expertconsult.com.

Burn and Inhalation Injuries

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PEARLS

- The accurate estimation of the extent and depth of burn injury is crucial for appropriate resuscitation and maintenance of adequate urine output and hemodynamics.
- Early endotracheal intubation of pediatric burn patients with suspected inhalation injury is essential to reduce morbidity and mortality.
- Enteral nutrition via oral intake or post–pyloric feeding tube early postburn is recommended.

Burns account for approximately 2 million injuries annually in the United States alone,[1] of which 500,000 seek medical treatment and 100,000 require hospitalization.[2] Approximately 50% of burns occur in the pediatric population,[3] with children younger than 5 years representing 17% of reported burn cases.[2] Infants and children are a unique patient population that demonstrate increased susceptibility to death.[4] Not only do young children have limited physiologic reserves, but their patterns of injury are very different from adults. Although thermal burns secondary to scald or flame are by far the most common etiologies in children and adults, injuries from chemical and electrical burns may be devastating and require early recognition and treatment. Pediatric burn diagnosis and management is complex and requires the expertise of a multidisciplinary team.

With appropriate resuscitation and nutritional support, prompt recognition and management of inhalational injury, and early surgical treatment, mortality rates can be minimized.[5] This has been noted in tertiary care institutions, such as the Shriners Hospitals for Children, which focus on the treatment of pediatric burns. It is no coincidence that more than 60% of burns in the United States are admitted to one of 125 hospitals with specialized burn centers.[2] These centers are staffed by experienced burn and plastic surgeons working with a cadre of anesthesiologists, burn nurses, pharmacists, respiratory therapists, occupational and physical therapists, and social workers to produce optimal outcomes for pediatric patients. Although care in this specialized setting is not required for most pediatric burns, an understanding of burn pathophysiology and the principles of burn management will aid in the care of these patients by all clinicians.

Types of Burn Injuries

Scald Burns

Infants and toddlers younger than 5 years have a higher incidence of scald burns compared with older children.[6,7] In recent series, scald injuries accounted for the majority of pediatric burn admissions both globally and in the United States.[8-10] Accidental hot liquid spills account for many of these injuries and a thorough history should include the type and consistency of the causative liquid. Compared with water and thin liquids, oil and thick soups have a higher heat capacity and are more viscous. This may translate into longer contact and higher temperatures causing greater skin and soft-tissue damage.[11] In general, water heated to a temperature of 140° C will cause a deep burn after 3 seconds of contact; water heated to 160° C will cause the same burn after 1 second of contact.[12] Current preventive strategies to minimize accidental scald burn injuries include educational campaigns and legislation to mandate maximum water heater settings of 140° C, both with mixed results.[13,14] Scald burns are more likely to be associated with child abuse than other types of burn injuries.[15] Classic scald patterns consistent with child abuse include glovelike or stockinglike burns to the hands or feet, and/or symmetric burns to the buttocks, legs, or perineum. Concomitant injuries including fractures and retinal hemorrhages, as well as delays in seeking treatment or inconsistencies in the patient history, should trigger concern. These scenarios must prompt a full evaluation by social services with referral to appropriate state or government agencies regardless of the depth or extent of burn.

Thermal Burns

Thermal injury secondary to flame or contact with hot objects remains prevalent in pediatric burn injuries.[16] They account for approximately 50% of all burn admissions. Injuries from contact or flame are the most common cause of burn injury in children older than 5 years.[17] Up to 90% of injuries are minor and can be managed on an outpatient basis with good outcomes.[18] In larger burns, however, mortality is greatly influenced by the size of the burn, the age of the patient, and the presence or absence of concomitant inhalation injury.[5,18] The extent of soft tissue injury is greatly dependent on the duration of exposure and the presence and type of clothing material, all of which should be investigated during the initial evaluation.

Electrical Burns

Electrical burns remain a rare but devastating type of injury, accounting for 2% to 3% of pediatric burns.[19] The majority of injuries involve electrical cords and outlets, with a rare minority from lightening. Most homes in the United States use alternating current (AC), which although more efficient than direct current (DC), is more dangerous.[20] Injuries caused by AC have the potential for increased tissue damage from tetanic contractions caused by cyclic flow of electricity.[19] In addition, the "let go" threshold, the maximum current a person can grasp and "let go," is lower for children than adults.[19] Children are more susceptible to electrical injuries from their propensity to chew on cords or insert objects into outlets. Wet or moist skin, including the mucous membranes around the mouth, has negligible resistance, and these injuries often result in considerable soft tissue trauma. Nerves, blood vessels, and muscles exhibit the least resistance, as compared to bone, fat, and tendons.[19] The clinician should be aware that lack of overt skin damage may mask more significant underlying soft-tissue damage.

Chemical Burns

Chemical burns represent a unique group of injuries, the most common of which are caused by strong bases contained in common household products. Alkali drain cleaners composed of sodium hydroxide cause significant tissue injury from interaction with cutaneous lipids. Initial treatment of chemical burns includes copious irrigation with tepid water for more than 15 minutes. The severity of injury is determined not only by the type and concentration of the chemical, but the duration of exposure.[21] Appropriate treatment of chemical burns never involves neutralization of the acid or base as the resultant exothermic reaction worsens tissue injury. Hydrofluoric acid burns represent a distinct clinical scenario. In addition to being a corrosive agent, fluoride causes a severe, deep liquefaction necrosis.[22] Copious irrigation will attenuate the initial chemical burn, but neutralization with calcium or magnesium is occasionally necessary to halt further necrosis. Current treatment recommendations include topical calcium and close monitoring of serum calcium levels with supplementation as necessary.[22]

Depth and Extent of the Burn Injury

Normal Anatomy

The skin serves a thermoregulatory role, along with providing protection against fluid loss, mechanical damage, and infection. Divided into two distinct layers, the epidermis consists of keratinocytes, melanocytes, and Langerhans cells, all with barrier function. The dermis consists of structural proteins and cells responsible for tensile strength.[23] Additional appendages including blood vessels, hair follicles, and sweat glands are rooted in the dermis and are responsible for the regeneration of epidermal cells after superficial injury.[18] Assessment of burn depth is vital as deeper burns destroy these dermal appendages. Without skin grafting, the wounds heal from the margins of injury resulting in delayed healing, wound infection, and debilitating scars and contractures.

Superficial Burns

Traditionally, burn depth has been categorized as either first, second, third, or fourth degree. Although these terms are commonly used, division of burn depth and severity guided by the need for surgical treatment may be more clinically relevant. First-degree, or superficial, burns are characterized by erythematous changes, lack of blistering, and significant pain. Damage is isolated to part of the epidermis only, sparing the dermis and dermal structures. These burns blanch easily on examination and heal within 2 to 3 days after the damaged epidermis desquamates. This level of injury is exemplified by sun overexposure. Scarring is rare given the superficial depth.[18]

Superficial Partial-Thickness Burns

Superficial partial-thickness burn wounds differ from first-degree burns in that the entire epidermis and superficial dermis are injured in the former. These burns typically form fluid-containing blisters at the dermal-epidermal junction. After debridement, the underlying dermis is erythematous, wet-appearing, painful, and blanches with pressure. As the deeper dermis is left undamaged, wounds heal within 2 weeks without the need for skin grafting, typically without hypertrophic scarring.[18]

Deep Partial-Thickness Burns

Both superficial and deep partial-thickness burns have traditionally been classified as second-degree burns. The two categories merit distinction as deep partial-thickness burns behave clinically similar to third-degree burns. Deep partial-thickness burns blister, but as tissue damage extends deep into the dermis, the blister base may appear to have a mottled pink and white appearance. The blood vessels of the dermis are partially damaged, giving rise to variance in discoloration of the wound base. These wounds do not easily blanch and are less painful than superficial burns due to nerve injury. Treatment of these wounds customarily requires excision and grafting. Some burn surgeons advocate initial monitoring for up to 14 days to allow for demarcation. Arguments in favor of this approach cite the need for fewer operations and less extensive grafting. Rarely, these wounds will heal without surgical intervention, but remain at risk for developing hypertrophic burn scars and/or contractures.[18]

Full-Thickness Burns

Full-thickness burns are synonymous with third-degree injuries. These wounds are defined by complete involvement of all skin layers and require definitive surgical management. On examination, these wounds are white, cherry red, brown, or black in color, and do not blanch with pressure. The burned areas are dry and often leathery compared to normal skin. Wounds are typically insensate because of superficial nerve injury. Fourth-degree burns are full-thickness injuries involving the underlying subcutaneous fat, muscle, and tendons. These injuries are more commonly associated with limb loss and/or need for extensive reconstruction in addition to grafting.[18]

Zones of Injury

Burn wounds continue to evolve for days after the initial injury and the subsequent inflammatory process may last for several months.[24] The wound is divided into zones of injury: the zone of coagulation, the zone of stasis, and the zone of hyperemia. The zone of coagulation is easily identified, as it comprises the necrotic tissues closest to the injury site. The zone of hyperemia consists of normal, uninjured skin with a physiologic increase of blood flow in response to local tissue injury. The zone of stasis is located between the zones of coagulation and hyperemia, representing an area of ongoing injury.[23] Poor perfusion of this zone can result in the progression of initially viable tissue in this area to further necrosis and deeper wounds. Current research is looking at new methods to salvage these zones of intermediate injury.[25]

Estimating the Extent of the Burn

An accurate assessment of both the extent and depth of the burn is necessary to guide initial therapy and minimize morbidity and mortality. Total body surface area (TBSA) involvement of the burned area is an independent risk factor that correlates with length of hospital stay and mortality in pediatric burn injuries[5]; however, the extent of burn injuries may be overestimated up to 75% by the initial care provider.[26] This results in over-resuscitation with resultant devastating complications, inappropriate transfer to burn centers, and poor use of limited resources.[27] Newer methods are being researched to improve the calculation of burn surface area using computerized imaging, two- and three-dimensional graphics, and body contour reproductions.[28]

Current methods of calculating combined second- and and third-degree burn size in adults include burn diagrams, the "rule of nines," and a general estimate that the palm and fingers of one hand account for 1% of the normal body surface area.[29] Palaski and Tennison developed the rule of nines, a rough estimation of adult body surface area divided into multiples of 9%.[30] This calculation rarely underestimates TBSA, but often overestimates it, especially in children.[30] Body surface area is distributed differently in children and infants due to proportionally larger heads and smaller extremities. This supports the need for age-specific surface area charts such as the Lund Browder diagram to better estimate the extent of burn in children (Figure 111-1).

Early Management of Burn Injuries

After removing or extinguishing the source, burns should be washed with tepid water.[31] Chemical burns should be flushed copiously to remove the inciting agent and prevent further tissue damage. Ice or iced water has been shown in animal studies to increase tissue damage and mortality, and should not be used given the added risk of hypothermia in patients with more extensive burns.[32,33] Approximately 10% of all burn patients present with additional traumatic injuries and the primary caregiver should not be distracted by obvious external burn injury when performing a rapid trauma evaluation.[18] Patients with severe burn shock or trauma are at risk for loss of airway due to altered mental status or supraglottic obstruction from edema formation.[34] Signs of potential inhalation injury include facial burns, singed nasal hairs, carbonaceous sputum, hypoxia, and history of entrapment in an enclosed space. Individually, these symptoms carry a high false-positive rate for inhalation injury, but merit temporary treatment with supplemental oxygen until a definitive diagnosis is made. Evaluation of circulation includes intravenous access and resuscitation in pediatric burns greater than 10% TBSA because these injuries are characterized by a systemic inflammatory response that may lead to hemodynamic lability.[24,35] Electrical injuries require specific evaluation given the propensity for compartment syndromes and multiorgan system involvement. Cardiac dysrhythmias and direct muscle necrosis can develop with high voltage electrical burns, requiring intervention or prolonged cardiac monitoring.[19] Seizures and spinal cord transections are possible, as well as respiratory arrest secondary to injury of the brainstem or tetany of the respiratory musculature.[19]

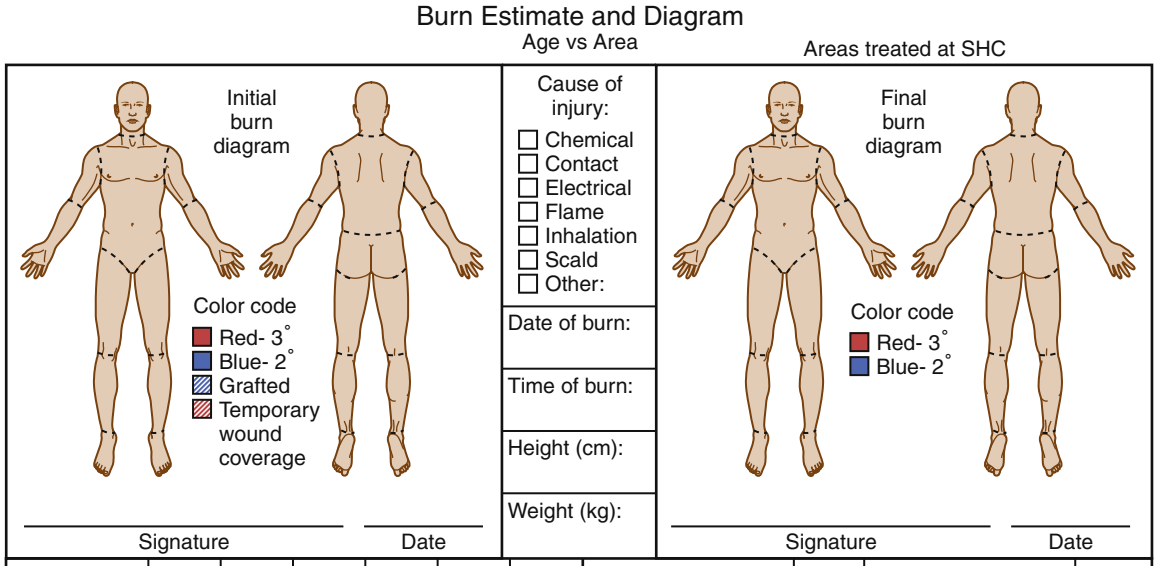
After a complete primary and secondary survey, attention should turn to evaluation and management of the burn injury. Using appropriate tools such as the Lund Browder chart, the depth and extent of burn should be assessed and used to guide further care. Approximately 60% to 70% of burns seen in emergency departments involve less than 10% TBSA.[36] The majority of these burns can safely be treated with minor debridement, oral hydration, topical wound care, and outpatient follow-up. Those patients requiring supplemental nutrition or hydration, or who fail outpatient treatment, may need continued care in an inpatient setting. In adults with more than 20% TBSA involvement, in infants with more than 10% TBSA involvement, or if there is a suspicion for inhalation injury, inpatient treatment with intravenous resuscitation and potential transfer to a burn center should be considered.

Transfer to Burn Centers

The optimal treatment and management of large or complicated burn injuries is in a high volume center by a multidisciplinary team including burn surgeons and nurses, physical and occupational therapists, dieticians, psychiatrists, respiratory therapists and social service support staff.[18,37] Current American Burn Association guidelines recommend the transfer of patients with severe injuries or those meetings specific criteria to dedicated burn centers (Box 111-1). Before transfer, wounds should be covered with clean, dry material or nonadherent gauze.[3] The use of wet dressings should be avoided to prevent development of hypothermia and subsequent complications in patients with large burn wounds.[37] Tetanus prophylaxis should be administered along with appropriate pain control before transport. In patients with extensive burns, a Foley catheter should be inserted to help guide fluid management.

Burn Resuscitation

In children with more than 10% TBSA involvement, adequate intravenous access should be obtained via peripheral or central routes. In burns less than 20% TBSA with no associated comorbidities or injuries, resuscitation via peripheral access can be performed. Delayed initiation of resuscitation has been shown to increase mortality following severe burn injury in children.[5] Infusion of a balanced crystalloid solution should be started as soon as intravenous access is obtained, with the



Area	Birth 1 yr.	1–4 yrs.	5–9 yrs.	10–14 yrs.	15 yrs.	Adult	Initial TBSA 2°	Initial TBSA 3°	Initial TBSA Total	Potential Donor site	Final TBSA 2°	Final TBSA 3°	Final TBSA Total	Graft size
Head	19	17	13	11	9	7								
Neck	2	2	2	2	2	2								
Ant. trunk	13	13	13	13	13	13								
Post. trunk	13	13	13	13	13	13								
R. Buttock	2.5	2.5	2.5	2.5	2.5	2.5								
L. Buttock	2.5	2.5	2.5	2.5	2.5	2.5								
Genitalia	1	1	1	1	1	1								
R. U. arm	4	4	4	4	4	4								
L.U. arm	4	4	4	4	4	4								
R.L. arm	3	3	3	3	3	3								
L.L. arm	3	3	3	3	3	3								
R. hand	2.5	2.5	2.5	2.5	2.5	2.5								
L. hand	2.5	2.5	2.5	2.5	2.5	2.5								
R. thigh	5.5	6.5	8	8.5	9	9.5								
L. thigh	5.5	6.5	8	8.5	9	9.5								
R. leg	5	5	5.5	6	6.5	7								
L. leg	5	5	5.5	6	6.5	7								
R. foot	3.5	3.5	3.5	3.5	3.5	3.5								
L. foot	3.5	3.5	3.5	3.5	3.5	3.5								
						Total:								

Figure 111–1. Shriners Hospitals for Children diagram used for estimation of burn depth and extent in the acute pediatric burn patient.

Box 111–1 American Burn Association Criteria for Burn Center Referral

- Partial and full-thickness burns >10% TBSA in patients <10 years or >50 years
- Partial and full-thickness burns >20% TBSA in patients in other age groups
- Partial and full-thickness burns involving face, hands, feet, genitalia, perineum, or major joints
- Electrical burns
- Chemical burns
- Inhalation injury
- Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or increase mortality rate
- Any burn with concomitant trauma in which the burn injury poses the greatest risk
- Burn injury in children admitted to hospitals without qualified personnel or equipment for pediatric care
- Burn injury in patients requiring special social, emotional, or rehabilitative support, including child abuse cases

infusion rate titrated after full assessment of burn injury. Initial resuscitation guidelines have historically followed one of two formulas, the Parkland or modified Brooke. These formulas serve only as guidelines. Resuscitation must be tailored to each individual patient with the goal of restoring and maintaining perfusion without inducing fluid overload.

The Parkland formula was developed in the 1970s by Baxter and Shires, arising out of 30% to 50% TBSA flame burn experiments in dogs. They found that resuscitating with a higher volume in the first 8 hours improved cardiac output, which could be maintained over the next 16 hours with lower fluid rates. Based on these studies, recommendations for resuscitation of large burns using the Parkland formula were extrapolated.[38] This formula recommends the total administration of 4 mL/kg/%TBSA burn over the first 24 hours postinjury. One half of this volume is administered during the first 8 hours with the remaining volume delivered during the next 16 hours.

While the Parkland formula is the most widely used resuscitation formula, it is closely followed by the modified Brooke formula. Based on work done at the Brooke Army

Burn Center, Pruitt et al. altered the original Brooke formula, which recommended 1.5 mL/kg/%TBSA burn of crystalloid and 0.5 mL/kg/%TBSA burn of colloid. This group demonstrated that a lower volume of fluid could achieve the same endpoints of resuscitation as the Parkland formula.[38] The modified Brooke formula calls for 2 mL/kg/%TBSA burn of balanced salt solution over the first 24 hours after injury and no colloids. Although both formulas call for the titration of fluid rates; in a comparative analysis, the Parkland formula more often resulted in overresuscitation, proving to be an independent risk factor for mortality.[39] A separate comparative study found no clinical differences in outcomes between patients resuscitated using these two formulas.[40]

Consensus fluid resuscitation by standardized formula has not been reached.[38] In children, resuscitation strategies should include the administration of estimated basal fluid requirements in addition to the replacement of extensive fluid losses secondary to burn injury. At our institution the child's basal fluid requirements (1500 mL/m^2 body surface area or 2000 mL/m^2 body surface area for children younger than 2 years) are added to the resuscitation calculated using the Parkland formula (Figure 111-2). All formulas rely on the accurate assessment of extent and depth of burn in order to provide appropriate resuscitation. Fluid requirements should be titrated for clinical endpoints including urine output of 0.5 to 1 mL/kg/hr in children[39] and restoration of appropriate hemodynamic parameters.[38] To avoid the complications of inadequate or excessive resuscitation, current research is being performed to examine the utility and efficacy of closed-loop autonomous resuscitation.[41]

Colloid Resuscitation

The timing and use of colloid in burn resuscitation is controversial. Historically, initial resuscitation formulas called for its use in the first 24 hours after injury as an adjunct to crystalloid.[38] In pediatric patients with extensive burn injury, colloid replacement is sometimes necessary due to rapid serum protein decrease resulting in crystalloid resuscitation failure.[42] Patients who receive colloid as part of their resuscitation require less crystalloid and total fluid compared to those receiving crystalloid only.[43] However, recent evidence has shown that colloid resuscitation provides no long-term benefits, does not affect mortality, and is more expensive compared to crystalloid solutions.[44] The theoretical reduction in complications and mortality with colloid use has not been demonstrated in human trials.

Complications of Resuscitation

Inadequate resuscitation may result in poor perfusion to both vital organs and the evolving zone of stasis. This leads to necrosis of previously viable tissue and progression of superficial burns to deeper injuries requiring grafting.[25] The complications of over-resuscitation are similarly of great concern. Recent review of the literature has shown that a significant proportion of burn injuries are being resuscitated with fluid volumes in excess of that calculated by the Parkland formula due to use of fluid resuscitation algorithms based on bolus therapy (i.e., Pediatric Advanced Life Support).[45] The volume infused should be continuously titrated to avoid both over-resuscitation and underresuscitation[42] with little to no role for fluid bolus therapy during initial burn management.

Risks for the development of compartment syndrome in the extremities, torso, or abdomen have been linked to the presence of deep, full-thickness circumferential burns, as well as the volume of fluid infused during resuscitation. Severe burn injury results in a systemic inflammatory response leading to microcirculatory leak, vasodilatation, and decreased cardiac output and contractility.[46] With tissue edema, reperfusion injury following resuscitation, and external compression from circumferential burns, compartment syndromes may develop, most commonly within the first 24 to 48 hours. Excessive fluid resuscitation increases the incidence of compartment syndrome and leads to

RESUSCITATION CALCULATIONS

I. RESUSCITATION

A. Calculated resuscitation and basal requirement (less than 2 yrs. — 2000 mL/m^2)

1. (4 mL _____ kg _____ % burn) + (1500 mL _____ m^2) = mL/24 hours
   (_____) + (_____) = _____ mL/24 hours

B. Resuscitation fluid per 8 hours

1. 1st 8 hours _____ mL, _____ mL/hr.
2. 2nd 8 hours _____ mL, _____ mL/hr.
3. 3rd 8 hours _____ mL, _____ mL/hr.

II. MAINTENANCE FLUIDS

A. Basal fluid requirement — 1500 mL/m^2 (less than 2 yrs. — 2000 mL/m^2)

1. Total body surface area _____ m^2
2. 24 hours _____ mL
3. Hourly _____ mL/hr.

B. Evaporative water loss

1. Adults — (25 + % burn) m^2 = mL/hr.
   Children — (35 + % burn) m^2 = mL/hr.
2. Calculated evaporative water loss
   a. (_____ + _____ % burn) _____ m^2 = _____ mL/hr;_____ mL/24 hours

C. Total maintenance fluids — Basal requirement and evaporative water loss

1. 24 hours _____ mL
2. Hourly _____ mL

Figure 111–2. Shriners Hospital for Children–Cincinnati resuscitation worksheet, an adaptation of the Parkland formula for resuscitation of the acute pediatric burn patient.

additional complications.[47] Clinical suspicion of compartment syndrome is supported by findings of delayed capillary refill, cyanosis, paresthesias, and diminished pulses. It is imperative to make the diagnosis before the loss of pulses as this indicates long-standing compartment syndrome with a higher likelihood of muscle necrosis and nerve damage. Compartment pressures can be measured using an 18 gauge needle connected to an arterial pressure transducer with placement under the eschar into subcutaneous or subfascial tissue. A pressure greater than 30 mm Hg is considered diagnostic, mandating decompression through escharotomy and/or fasciotomy. Escharotomies are performed at the bedside under sedation with electrocautery utilized to incise the full length of eschar down to subcutaneous fat. Bulging of muscle and surrounding tissues demonstrates adequate decompression. Fasciotomies are generally performed in the operating room under general anesthesia. All extremity compartments must be opened with evaluation of muscle for signs of necrosis. Escharotomies and fasciotomies should only be performed by experienced practitioners due to increased morbidity from incorrectly executed procedures.[48]

Abdominal hypertension with subsequent compartment syndrome significantly decreases perfusion to vital organs including the small and large bowel, liver, and kidneys, thereby contributing to the development of multisystem organ failure.[38] Patients will often present clinically with abdominal distention and decreased urine output. In addition, decreased pulmonary compliance secondary to elevated abdominal pressures can compound respiratory challenges. The incidence of intraabdominal hypertension in patients with extensive burns is approximately 70%, with up to 20% of those identified requiring decompressive laparotomy.[46] Preventive measures to avoid abdominal compartment syndrome include appropriate titration of resuscitation fluid, as well as early recognition of abdominal hypertension through serial bladder pressure evaluations.[49] Timely decompressive laparotomy should be performed at the onset of increased compartment pressures to avoid significantly increased morbidity and mortality related to fluid loss with an open abdomen. In small children, percutaneous drainage using peritoneal dialysis catheters may be an effective alternative to laparotomy provided that the increased intraabdominal pressure is related to fluid accumulation and not organ edema.

The development of pulmonary complications including acute lung injury, pulmonary edema, and acute respiratory distress syndrome (ARDS) has been attributed to excessive fluid resuscitation.[50] In the absence of inhalation injury, the systemic inflammation seen after severe burn injury results in third spacing of fluids and the accumulation of interstitial edema in the lungs. The treatment of this immune response remains challenging. Alternative resuscitation strategies including the use of colloid and hypertonic saline as adjuncts to crystalloids are continually being investigated with mixed results.[51,52] In several series, the presence of inhalation injury results in increased resuscitation fluid requirements and is predictive of the development of respiratory failure and increased mortality.[5,18,44,53]

Inhalational Injury

The diagnosis of inhalation injury in burn patients is important as a clear link exists between inhalation injury and mortality,[54-56] with the presence of inhalation injury being the single most important risk factor for mortality.[5,56-61]

Pathophysiology of Inhalation Injury

Inhalation injury involves exposure of the upper airway to heated dry air or steam. The lower airway, consisting of the tracheobronchial tree and lung parenchyma, is rarely injured by heated dry air because of reflexive vocal cord closure and evaporative cooling capacity.[12,62] Direct thermal injury manifests similar to cutaneous thermal injury with a resultant inflammatory response and edema. Histamine release, signaled by increasing complement at the site of injury, produces reactive oxygen and nitrogen species after formation of xanthine oxidase. These reactive species increase vascular permeability leading to extrusion of fluid and increased tissue edema. Prolonged extrusion of proteinaceous exudate and associated tissue edema may result in the formation of airway casts and obstruction, similar to mucous plugging.[63] Smoke and inhaled toxins pose a particular risk to both upper and lower airways. Toxins such as ammonia, sulfur oxides, pyrolysates and chlorine gas, form strong alkalis and acids upon contact with moist mucosal walls.[64] Fat-soluble agents such as aromatics activate alveolar macrophages and may initiate direct cellular damage[65] resulting in hyperemia of the airway, which can be visible shortly after injury. If inhalants induce an inflammatory response in the pulmonary parenchyma, surfactant synthesis may be disrupted with further worsening of lung compliance.[66] Loss of ciliary action in the respiratory mucosa can lead to increased pulmonary infections, ultimately resulting in irreparable damage to the respiratory tree.[58]

Carbon monoxide (CO) and cyanide are key components of inhalation injury in the acute burn patient. During fires, incomplete oxidation of hydrocarbons leads to formation of CO. CO is an odorless, colorless gas well known for its rapid uptake in the lungs and deleterious effects including tachypnea, hypoxia, altered mental status, coma, and death.[67] Clinical signs stem from an increased affinity of CO to bind hemoglobin, resulting in carboxyhemoglobin formation and as well as left shift of the oxygen-hemoglobin dissociation curve that impairs oxygen delivery at the tissue level. Relative tissue hypoxia ensues with subsequent metabolic acidosis. Hydrogen cyanide, a colorless gas with an odor described as being similar to bitter almonds, is produced by combustion of carbon and nitrogen-containing substances (i.e., wool, cotton). Cyanide inhibits oxidative phosphorylation via reversible inhibition of cytochrome C oxidase.[68] Similar to CO poisoning, cyanide poisoning produces relative tissue anoxia and metabolic acidosis.

Diagnosis of Inhalation Injury

The diagnosis of inhalation injury begins with a focused history and physical examination. The mechanism of injury provides a strong indication of the risk in the pediatric burn patient. Closed-space burns involving steam, combustibles, hot gases, or explosions should alert the treating physician to possible airway injury. Inhalation injury may occur without evidence of cutaneous burns. Acute pulmonary insufficiency may manifest in the first 36 hours, pulmonary edema between 48 to 96 hours, finally culminating in bronchopneumonia 3 to 10 days postburn. The physical exam should include inspection for soot in the oropharynx, carbonaceous sputum, singed nasal or facial hairs, and burns involving the face or neck. Signs of respiratory distress including wheezing, stridor, tachypnea

or hoarseness, along with altered mental status, agitation, anxiety or obtundation are indicative of inhalation injury. Many pediatric patients with inhalation injury will develop progressive respiratory failure, tachypnea, hypoxia, and cyanosis after resuscitation, even when appearing normal upon initial presentation. To compound matters, noninvasive monitoring of pulse oximetry in burn patients can be misleading. For this reason, laboratory and invasive studies are pertinent to diagnosis. Initial laboratory studies should include arterial blood gas (ABG) analysis and measurement of carboxyhemoglobin. A PaO_2/FiO_2 ratio less than 300 on completion of resuscitation is indicative of significant inhalation injury,[69] along with possible early evidence of acute lung injury. Albeit controversial, this ratio has been proposed as an indicator of poor outcome in burn patients.[70-73] ABG values may suggest a diagnosis with demonstration of either respiratory or metabolic acidosis, but are often misleading, especially if values are within normal limits. Carboxyhemoglobin values should be correlated with time from injury and oxygen therapy provided in the interim. The half life of CO is 240 to 320 minutes, decreasing to 40 to 80 minutes with 100% normobaric oxygen.[74] If suspected, blood cyanide levels should be also drawn.[75]

Chest radiographs and computed tomography scans are insensitive for the diagnosis due to a relatively normal lung and airway appearance early in the clinical course.[76,77] Repeat studies over time may demonstrate development of pulmonary edema or ARDS. Xenon-133 scanning may demonstrate trapping or delayed excretion of the isotope within injured lungs.[78] This technique is limited by availability of technology and technical expertise, and is oftentimes used as a confirmatory test where other methods have yielded inconclusive results.[69] Fiberoptic bronchoscopy is the gold standard for the diagnosis of inhalation injury. Direct visualization of the supraglottic and infraglottic airway allows quantification of hyperemia, exudate, mucosal sloughing, edema and presence of carbonaceous material. In a study spanning a 10-year period, 71% of pediatric patients with inhalation injury were diagnosed using bronchoscopy versus 25% by history/clinical exam alone and 4% by carboxyhemoglobin levels.[56] In some cases, fiberoptic bronchoscopy can be therapeutic with removal of excessive exudate, plugs or casts followed by placement of an endotracheal tube.[79]

Management of Inhalation Injury

Inhalation injuries can quickly progress to obstruction, hypoxia and death, so timely endotracheal intubation is required. In pediatric patients, small sized airways, the inability to perform bronchoscopy, and an increased likelihood of adverse events necessitate early endotracheal intubation. When endotracheal intubation is not indicated, nasopharyngeal airways should be considered. Oxygen therapy at an FIo_2 of 1.0 should be initiated immediately to treat increased carboxyhemoglobin levels and provide maximal oxygen delivery to peripheral tissues. Duration of oxygen therapy depends on patient condition and can be quantified by documenting return of carboxyhemoglobin levels to below 10% and normalization of acidosis.[80] Continuous pulse oximetry is used after carboxyhemoglobin levels have normalized.

Following endotracheal intubation, the acute burn patient with inhalation injury may benefit from either a volumetric diffusive respiratory (VDR) mode or an airway pressure release ventilation (APRV) mode of ventilation. The choice of mode is dictated by patient condition, clinician and staff familiarity, and treatments required (i.e., repeat bronchoscopy, inhalation agents). The use of high-frequency oscillatory ventilation may complicate treatment in the patient with inhalation injury due to inability to provide inhaled agents at proper doses or to perform regular bronchoscopy.[81] The VDR (Figure 111-3) provides ventilation and oxygenation with a decreased mean airway pressure, reducing the risk of barotrauma. The mechanism involves high-frequency ventilation with progressive accumulation of subtidal breaths and passive exhalation once a set airway pressure is met,[82] allowing for gas exchange through more recruited alveoli. The amplitude of subtidal breaths correlates with peak inspiratory pressure and the frequency of subtidal breaths is adjusted to maximize oxygenation. By altering the I/E ratio, a diffusive (lower I/E) or percussive (higher I/E) flow wave is created. In a small prospective study of pediatric burn patients, Rodeberg et al. demonstrated increased Pao_2, increased Pao_2/FIo_2 ratio, and decreased mean airway pressure, all without affecting hemodynamic function.[82,83] Long term, this mode has been shown to decrease pneumonia and mortality compared to individuals treated with conventional modes of ventilation.[84-86] APRV (Figure 111-4), in its most simple form, is a reverse I/E method of ventilation with two levels of PEEP support. High PEEP is continuous during a prolonged inspiratory time, providing for adequate oxygenation and recruitment of closed alveoli. Low PEEP is exerted during expiration and facilitates ventilation while maintaining recruitment of alveoli. The benefit to patients is reduced barotrauma, improved oxygenation and ventilation due to improved V/Q matching, and decreased sedation and paralysis requirements because of patient comfort. Unlike the VDR, there is no percussive component involved; however, the external movement of secretions may occur through another mechanism.[87] While data exist supporting the use of APRV over conventional modes of ventilation in surgical intensive care and trauma patients, randomized control trials have not been completed in burn patients.

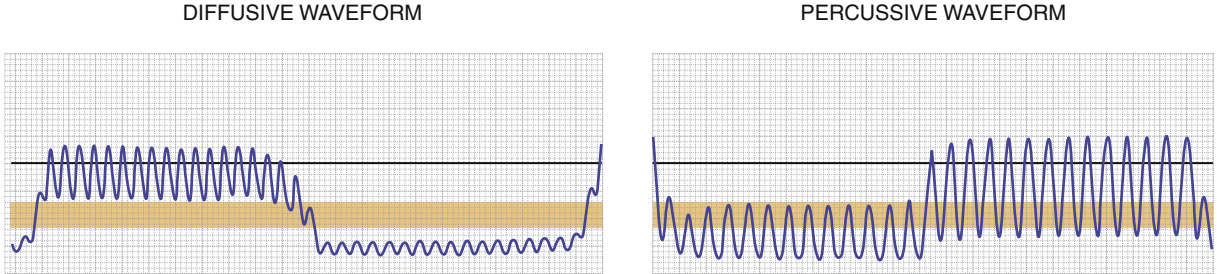


Figure 111–3. Volumetric diffusive respiratory ventilation pressure-time tracings. Percussive and diffusive waveforms from a pediatric burn patient volumetric diffusive respiratory ventilator at Shriners Hospital for Children–Cincinnati.

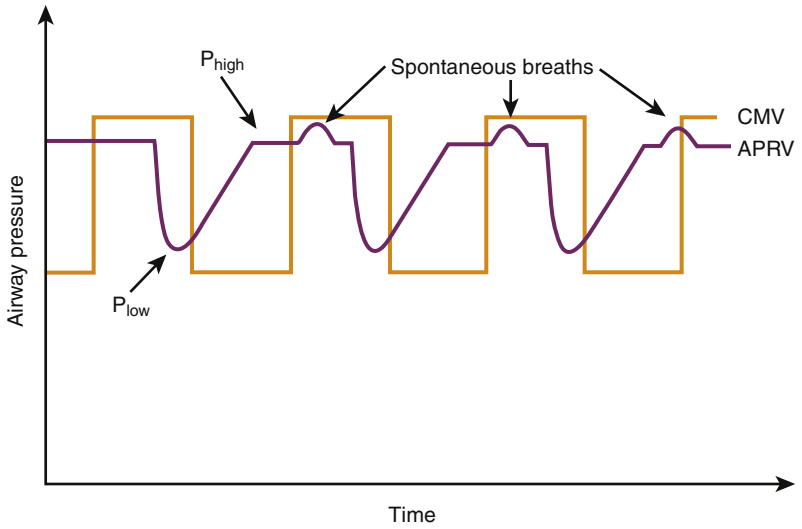


Figure 111–4. Airway pressure release ventilation and controlled mechanical ventilation pressure-time tracing. *(Modified from Fan E, Stewart TE: New modalities of mechanical ventilation: high frequency oscillatory ventilation and airway pressure release ventilation,* Clin Chest Med *27:615-625, 2006.)*

Venovenous extracorporeal oxygenation (ECMO), or extracorporeal life support (ECLS), is more commonly used in the nonburned neonate with respiratory failure. However, its use is documented in burn patients refractory to conventional ventilation strategies. Kane et al. found that nonsurvivors had greater peak and mean airway pressures prior to onset of ECLS,[88] but scattered reports throughout the literature document minimal success using this method in patients with inhalation injury when survival is used as the endpoint.[89-91] Although the technical limitations involving education, staffing and equipment preclude widespread use of this strategy, it remains an option for clinicians.

Appropriately trained respiratory therapists are invaluable in the management of burn patients and are a mainstay in specialized burn care units. Together with ventilatory management, other adjunctive therapies such as aggressive pulmonary toilet, nitric oxide, nebulized heparin, *N*-acetylcysteine, and/or bronchodilators may be used. Inhaled nitric oxide is an ultra short-acting vasodilator used in the treatment of pulmonary hypertension that works by increasing cyclic guanine monophosphate in smooth muscle.[92] Limited studies in burn patients have demonstrated variable improvement in Pao_2/FIo_2 ratios and improved survival in those patients who respond to treatment.[93] If a response is not demonstrated between doses of 5 and 20 ppm of nitric oxide within 60 minutes of treatment onset, the patient is unlikely to respond and therapy should be discontinued due to futility and cost.[93] Inhalation injury has been shown to result in fibrin deposition within the airways, solidifying and leading to obstruction (hence the need for aggressive pulmonary toilet).[94,95] Nebulized heparin and tissue plasminogen activation have demonstrated potential efficacy in both animal and human studies through breakdown of fibrin deposition with maintenance of alveolar structure and reduced airway obstruction.[95] The mechanisms by which aerosolized heparin exerts a beneficial effect in inhalation injury are as yet undetermined, but may be related to breakdown of fibrin casts and reduction in the inflammatory response from neutrophil migration into the airways.[96] *N*-acetylcysteine was noted to decrease leukocyte number in bronchoalveolar lavage and MPO in rat lung tissue, supporting the conclusion that *N*-acetylcysteine may ameliorate tissue damage after inhalation injury.[97] Although survival benefit has not clearly been demonstrated with use in ARDS and acute lung injury (ALI),[98] evidence exists for attenuation of lung inflammation.[99] β-Adrenergic agonists are widely used in treatment of lung conditions including asthma and ARDS/ALI. The aerosolized delivery of specific β_2-adrenergic agonists produces preferential effects including bronchodilation, attenuation of lung inflammation and potentially increased fluid clearance with limited systemic cardiac activation.[100] One retrospective review of burn children showed increased Pao_2/FIo_2 ratios, improved compliance and pH during treatment with continuous albuterol therapy.[100] Well-designed clinical trials are needed to further elucidate those adjunctive therapies most likely to improve morbidity and mortality in pediatric inhalation injury patients.

Perhaps most controversial in the management of inhalation injury is the use of corticosteroids. Although clearly beneficial for many chronic pulmonary diseases including asthma, benefits in acute pulmonary inflammation related to inhalation injury and ARDS have not been definitively demonstrated.[101-103] Corticosteroid therapy has been shown to increase mortality (from 13% to 53%) and complication rates (from 31% to 82%) in at least one study.[80] However, more recently Meduri et al.[104] demonstrated the potential utility of methylprednisolone given for 28 total days with fewer days on ventilator, a shorter ICU stay, fewer infections and increased survival. Until larger prospective studies are completed, corticosteroids for inhalation injury should be used with caution.

Nutritional Support in Burn Patients

Nutritional support of the pediatric burn patient is important for prevention of malnutrition, adequate wound healing, and moderation of the pro-inflammatory response induced by a hypermetabolic state. For the burn patient, a multitude of protocols exist for determining patient caloric requirements, onset of feeding, and choice of vitamin supplementation.

Box 111–2 Mayes Equations to Calculate Energy Requirement After a Burn

Mayes equation for a 5- to 10-year-old burn patient with injury <50% TBSA:

$$818 + 37.4\ (\text{weight in kilograms}) + 9.3 \times \%\ \text{TBSA burn}$$

Mayes equation for a 5.5-year-old patient with a 45% TBSA scald burn weighing 20 kg:

$$818 + 37.4\ (20\ \text{kg}) + 9.3 \times 45\ \%\ \text{TBSA scald}$$

$$818 + 748 + 481.5 = 2047.5\ \text{calories/day}$$

Burns induce a hypermetabolic state that may persist for up to 12 months after injury.[105,106] Although exact mechanisms remain unclear, levels of epinephrine and norepinephrine are known to be greatly amplified following a large burn with subsequent increases in stress hormones. Theories suggest the bulk of metabolic disturbances occur secondary to inflammation stimulating the hypothalamus with resultant increases in the temperature set point and production of catecholamines.[107] Pediatric patients are more susceptible to adverse changes in carbohydrate, lipid and amino acid metabolism, made worse by the propensity of children to lose more body heat via a thinner dermis. The systemic response to burn includes increased oxygen consumption, increased protein catabolism, increased lipolysis, culminating in decreased lean body mass, poor wound healing, and worsened host defense if appropriate nutrition is not maintained.

Calculating Nutritional Requirements

It is commonly assumed that hypermetabolism is directly related to burn size, but more than likely it is related to stress hormones as described previously.[107] In pediatric patients, plotting of weekly weights on an appropriate growth curve aids in estimating caloric requirements. Numerous equations have been developed to estimate the energy requirements of pediatric burn patients, although no single standard currently exists.[108-120] At our institution, we use the Mayes equation, which takes age, weight, and % TBSA burn into account (Box 111-2). Most formulas overestimate caloric requirements compared with indirect calorimetry, long considered the gold standard for calculating resting energy expenditure (REE). Indirect calorimetry is the preferred method to adjust nutritional support.[69] Total energy requirements can be estimated as 120% to 130% of REE.[69] Respiratory quotient, the measurement of VCO_2/VO_2 from indirect calorimetry, has proven unreliable in evaluating the nutritional status of burn patients with regards to under or overfeeding.[121] In children, carbohydrates should account for 60% to 70% of energy requirements while fats should account for 15% to 20%. Protein requirements vary from 2.5 to 4 g/kg/day.

The implications of correctly computing resting energy expenditure and caloric requirements involve prevention of overfeeding or underfeeding burn patients. Overfeeding results from excessive carbohydrate or fat intake, both of which are detrimental to the critically ill burn patient. Carbon dioxide production is increased following excessive carbohydrate consumption with subsequent respiratory abnormalities that interfere with pulmonary function and weaning from mechanical ventilation.[122,123] Excessive carbohydrates also lead to increased fat stores, hepatic dysfunction, hyperglycemia, dehydration via osmotic diuresis, and poor wound healing.[69,107,123] Although burns promote augmented protein catabolism, too much protein does not help offset catabolism, but may actually increase it.[123] Although some studies have demonstrated improved survival and reduced hospital stay with underfeeding of nonburned critically ill patients,[123] the bulk of burn literature supports early feeding to prevent malnutrition. Early feeding also promotes wound healing, mediation of inflammation, suppression of the hypermetabolic response, and reduction of sepsis-related morbidity and mortality.[124]

Monitoring Nutritional Status

A multitude of blood tests have been advocated together with indirect calorimetry for monitoring of nutritional status. Visceral proteins have proven better as prognostic markers than as indicators of protein status in acute burns.[120] Albumin is a poor surrogate for nutritional status as serum concentrations are known to fall as a result of burn. Albumin replacement below certain levels maintains no scientific basis as it does not stimulate production of endogenous albumin, nor has replacement been shown to have any clinical benefits regarding pulmonary function, wound healing, gastrointestinal function or mortality.[107] Prealbumin is advocated for long term monitoring of patient nutrition as it is a distinct marker for protein synthesis. It has a relatively short half-life, allowing the clinician a more sensitive marker for patient nutritional support. An absolute value lower than 15 mg/dL is consistent with malnutrition, but the physician must take into account the organ function of individual patients in interpreting prealbumin levels in pediatric patients. Static measurements of serum concentrations of nutritional markers such as transferrin, carotene, iron, and calcium are likely unreliable indicators of nutritional status in burn patients.[125]

A known aspect of the hypercatabolic response in burn injury involves an increased and sustained release of acute phase reactants from the liver, resulting in an exaggerated release of pro-inflammatory mediators that may contribute to multiple organ dysfunction.[126-128] Hyperglycemia occurs in most burn patients regardless of injury severity because of increased rate of glucose production and impaired tissue glucose extraction.[129,130] Insulin may serve dual functions in burn patients, both in its anabolic effects and ability to lower hyperglycemia. Jeschke et al. have demonstrated modulation of the inflammatory response with tight glucose control using insulin through mediation of hepatocyte apoptosis, which allows for improved hepatic function.[126]

Enteral Support

Enteral feeding is a mainstay of nutritional support in pediatric burn patients and is considered the ideal route for caloric and nutrient supplementation. Studies have shown enteral support helps maintain intestinal integrity following burn injury. Maintenance of gut integrity, in which glutamine plays a role,[131,132] is hypothesized to reduce the risk of bacterial translocation that may contribute to burn sepsis, while also

allowing for the appropriate absorption of nutrients required for wound healing.[131] The role of specialty amino acids, proteins and fatty acids present in commercial tube feed preparations for pediatric burn patients is controversial, as studies have both shown improvement in end point outcomes[133] and no effect on outcomes.[134] If the patient's caloric intake by mouth will be inadequate at 5 to 7 days after injury, the clinician should place a feeding tube. At our institution, nasoduodenal feeding tubes are routinely placed under fluoroscopic guidance to reduce the risk of perforation or incorrect positioning. After pyloric placement is confirmed, enteral feeds are then initiated at low rates, customarily 10 to 20 mL/hr. The speed at which tube feedings are increased is multifactorial. Working closely with a dietician will aid in starting the correct tube feed at the appropriate concentration and rapidly achieving the goal rate. The dietician is also invaluable in adjusting enteral supplementation based on clinical parameters and indirect calorimetry.

Although many clinicians anecdotally feel early enteral feeding is beneficial, some have questioned this practice in light of data suggesting lack of benefit and a possible increase in complications. In nonburn animal models and adult patients, calorie restriction has been demonstrated to be potentially beneficial.[123] Studies demonstrating reversal of hypermetabolism and hypercatabolism in burn animals have not been replicated in humans. Possible reasons for this include inability to realistically start "early" enteral feeding (i.e., within 1 to 2 hours of burn), or that the body's response to burn injury causes cellular changes in humans which are not present in the current animal burn models.[124] Mediation of inflammation from early enteral feeding has also been difficult to demonstrate in burn patients, contrary to animal experiments.[124] Studies evaluating improvement in clinical measures such as decreased length of stay, decreased incidence of infection and decreased mortality have also not conclusively been shown[120] when compared to later onset of enteral feeding (>72 hours). The risk of adverse events from technical errors in tube placement, aspiration, and intestinal necrosis must also be taken into account. In a prospective, randomized trial, Gottschlich et al.[124] found that four of five patients who developed an abdominal catastrophe from intestinal necrosis were in the early feeding arm of the study. Interestingly, intestinal necrosis has been shown to not always correlate with vasopressor support. This may be due to increased hypotensive episodes during early burn resuscitation, altered gut blood flow during burn shock, and increased blood flow requirement in the intestine when being fed.[124] Despite some of these concerns regarding early enteral feeding, initiation upon patient stabilization is considered standard of care in the pediatric burn patient.

Parenteral Support

Parenteral nutrition (PN) is considered a mainstay of therapy for many critically ill patients. In burn patients, central venous PN is reserved for individuals unable to tolerate enteral feedings from severe diarrhea or an organic gastrointestinal problem. Complication rates increase when burn patients are placed on PN because of line infections. Peripheral parenteral nutrition (PPN) is not an option because lack of adequate calorie delivery and high risk of peripheral access damage from PPN extravasation.

Vitamin and Anabolic Steroid Supplementation

Although supplementation is poorly understood in children, guidelines and dosages from the National Advisory Group/American Medical Association are customarily followed. Fat-soluble vitamins are more slowly depleted and less apt to be replaced compared to water-soluble vitamins such as B and C. The exceptions for fat-soluble vitamin replacement are vitamins A and D. Vitamin A has been shown to aid wound healing following burn injury.[135] Replacement of vitamin D, together with calcium supplementation, is required for adequate bone formation in children. Vitamin C plays a vital role in collagen synthesis and wound healing, necessitating its supplementation. There are some reports of replacing trace elements, often done when TPN support is given to critically ill patients. Interestingly, wound exudates were found to be the primary site of loss for trace elements,[136] suggesting burn patients may require replacement more than other critically ill patients. The trace element zinc is involved with wound healing and some reports suggest decreased zinc levels in septic patients are associated with subsequent adverse events.[69] For these reasons, zinc supplementation is often included as part of enteral nutrition. More studies are needed to determine the role of trace element supplementation in pediatric burn patients.

Because of hypercatabolism in burns, lean body mass is lost even with adequate nutritional support. Negative nitrogen balance is often seen during the first 1 to 2 weeks after burn.[120] To combat this, studies have demonstrated the effectiveness of anabolic agents such as oxandrolone in restoration of lost lean body mass and improved wound healing.[69] These results are controversial with regards to impact on the course of burn disease,[120] so anabolic steroids such as oxandrolone are not universally used in the management of pediatric burn patients.

Wound Care

Burn wounds will "evolve" over time based on factors ranging from mechanism of injury to fluid resuscitation, sometimes requiring 10 to 14 days for complete demarcation. It is not uncommon for previously diagnosed superficial partial burn wounds to demarcate as full thickness burns many days following the initial presentation. If the burn wound is improperly managed and allowed to desiccate or become infected it will convert to a deeper wound requiring definitive surgical management. Cleansing and debridement of the wound is absolutely essential for proper diagnosis of size and depth. This is accomplished with mild soap and water, or in the specialized burn center, chlorhexidine/normal saline washes may be used. Pain should be effectively controlled to allow for complete debridement of all necrotic tissue. Although there exists some controversy regarding the treatment of blisters, most burn experts recommend debridement of all blisters unless smaller than 0.5 cm or in a difficult to manage area. This reduces the risk of bacterial colonization or infection that will delay appropriate wound healing.

Burn wounds become colonized in the first few hours with gram-positive bacteria such as *Staphylococcus aureus* and *epidermidis,* and are predominantly colonized with gut flora such as *Pseudomonas aeruginosa, Enterobacter cloacae,* and *Escherichia coli* by 5 days. Health care workers involved with

the cleansing and debridement of burn wounds must be vigilant in hand washing and maintenance of a clean environment around the wound for prevention of cross-contamination in these immunocompromised patients. Culture swabs of all wound beds should be obtained on arrival and on a scheduled basis to monitor for changes in colonization. Quantitative cultures of burn wound invasion are best obtained by tissue biopsy, either in the operating room or at bedside. Bacterial colonization of burn wounds does not require systemic antibiotics, but should be managed with early debridement, appropriate topical and/or biologic dressings, and scheduled dressing changes. After cleansing and debridement, topical antimicrobial therapy is initiated even if early excision and grafting will be performed. Topical therapy is not intended to sterilize the burn wound, but to control colonization. Agents are applied twice daily after repeat cleansing and debridement. Upon placement of topical agent, several layers of gauze and sterile dressings are used for coverage with a resultant decrease in evaporative water losses and metabolic rate.[137] The choice of topical agent depends on the depth and extent of the wound being treated. Minor burns, including superficial and small superficial partial burns, can be managed with any triple antibiotic ointment, biologic dressing or silver-coated dressing. Superficial burns can also be treated with moisturizing creams such as Eucerin or aloe. Superficial partial-thickness burns to the face are treated in a similar fashion. Nonadherent gauze or petroleum gauze can be placed over tribiotic topical agents to provide a comfortable, protective environment that promotes epithelialization. Perhaps the most commonly used topical agents are silver sulfadiazine (Silvadene), mafenide acetate (Sulfamylon), and silver nitrate. Silvadene has been used in burns for decades and continues to demonstrate effective control of burn wound colonization against a continually widening spectrum of bacteria. It is easy and painless to apply, a benefit for both in- and outpatient treatment. Drawbacks include minimal eschar penetration and complications related to leukopenia and red blood cell hemolysis.[138] Mafenide acetate cream (Sulfamylon) is also easy to apply, but is rather painful in superficial partial burns. Eschar penetration is greatest using this agent, making it the topical of choice in burns where eschar will not be excised immediately. Its antimicrobial activity includes control of *Pseudomonas aeruginosa*, a common colonizing bacterium in pediatric burn patients. Sulfamylon is a carbonic anhydrase inhibitor so complications related to metabolic acidosis may occur. Although the above two agents are used most often in care of pediatric burns, silver nitrate 0.5% solution has fallen out of favor due electrolyte abnormalities and poor tissue penetration.

The use of topical antimicrobials has been called into question because of the need for frequent dressing changes resulting in traumatized epithelialization and delayed wound healing. Silvadene in particular has been shown to delay wound healing due to direct toxic effect on keratinocytes.[139,140] Newer agents such as hydrocolloid, hydrogel and polyurethane film dressings provide effective humidity and control of exudate, but are lacking in antimicrobial coverage. Silver-impregnated dressings such as Acticoat, Mepitel, and Mepilex provide combined antimicrobial coverage, adequate humidity for the wound, and decreased trauma to healing wounds with less frequent dressing changes. Biosynthetic substitutes such as Biobrane are marketed as epidermal substitutes that allow for faster reepithelialization.[141] These agents are useful for very superficial partial burns seen early in a burn center before bacterial colonization has taken place.

The previously described topical therapies are used in the outpatient pediatric burn setting. Inpatients, while often treated with similar therapies, are also managed with surgical excision and placement of xenograft, allograft, autograft or cultured epithelial autografts (CEA). Placement of skin substitutes and replacements requires adequate wound bed excision and preparation. Use of these materials on eschar or an improperly prepared wound bed will lead to graft loss and prolongation of definitive therapy. Although no consensus exists on the timing of burn wound excision, most experienced burn surgeons advocate early wound excision within the first 1 to 5 days after thermal injury to attenuate the inflammatory response of burn and reduce the risk of sepsis.[142-145] At our institution, a staged approach is often taken for more extensive injuries whereby the wound is excised and controlled on day one with subsequent donor site harvest and grafting on day two. The benefits of this approach include shorter operations, tighter temperature control and ability to perform sheet grafting through improved hemostasis. Prior to wound excision an operative plan is made dictating prophylactic antibiotic coverage, units of blood on hold, and type of wound coverage agent to be used.

Xenograft (pig skin) is a less expensive alternative to allograft (cadaver skin) for coverage of superficial partial burn wounds. It is incapable of engraftment and best used for temporary coverage, providing effective protection that allows for re-epithelialization. Allograft has revolutionized burn care by providing effective, medium term coverage for patients requiring excision without available autograft. Although burn patients demonstrate altered immunocompetence, allograft is typically rejected within 2 to 3 weeks after placement. Similar to xenograft, allograft placed in an infected or highly colonized wound will not engraft, necessitating re-excision and repeat placement. Autograft provides definitive coverage of deep partial and full thickness burns. Donor site selection depends on available areas and extent of burn to be covered. Autograft can be applied as sheet (85% of donor site provides coverage), or mesh 1:1 (110% coverage) and up to 4 or 6:1. Using large mesh grafts more than 2:1 is becoming uncommon even in treatment of large burns because of improved local wound management techniques and availability of synthetic skin substitutes. Cultured epidermal autografts are derived from the pediatric burn patient's own cells and were first successfully used in the 1980s.[146,147] However, these thin grafts are fragile, difficult to work with, take 2 to 3 weeks to grow and usually result in hypertrophic scarring and unstable epithelium. For these reasons, CEAs are considered only for burns involving greater than 85% TBSA. For the past two decades, our institutions has made use of a cultured skin substitute consisting of autologous keratinocytes and fibroblasts grown on a collagen-based scaffold.[148,149] Compared to CEA, there are fewer complications related to placement and healing postoperatively, as well as less hypertrophic scarring and improved aesthetic results. When compared to coverage provided only by autografting, cultured skin substitute allows for reduced autograft harvesting in coverage of burns more than 50% TBSA.[150]

References are available online at http://www.expertconsult.com.

VII Chapter 112

Evaluation, Stabilization, and Initial Management After Multiple Trauma

Steven Elliott and Randall S. Burd

PEARLS

- The primary survey, as defined by Advanced Trauma Life Support, is a prioritized evaluation and management protocol focused on identifying and treating the most life-threatening injuries first.
- Injured children who present to the emergency department can be divided into three categories with respect to initial airway management: those with a patent airway requiring no manipulation, those who have undergone interventions in the field or at another hospital to establish a patent airway, and those who will need intervention to establish a patent airway. The first group is the most common.
- The most effective, objective, and rapid steps in evaluating breathing and adequate ventilation are auscultation of the chest, application of a pulse oximeter for measurement of oxygen saturation, and assessment of respiratory rate.
- The greater physiologic reserve of children makes early identification of cardiovascular compromise more difficult in this group than in adults. Assessment and management of circulatory status in the primary survey is focused on early identification and treatment rather than defining the specific etiology of the shock state.
- Of the three main components of the Glasgow Coma Scale, the motor score has been shown to be the best predictor of outcome after injury.

Trauma is the leading cause of death and acquired disability in children and adolescents, resulting in more deaths in children than all other causes combined.[1,2] Because children with severe injuries can rapidly deteriorate, resources for rapidly identifying and treating injuries are needed immediately on arrival at the receiving hospital. The initial evaluation of injured children in the emergency department ("trauma resuscitation") has two main goals: (1) identify and immediately treat potentially life-threatening injuries, and (2) determine disposition after the trauma resuscitation based on known or suspected injuries. The trauma team must stabilize the child, determine the extent of the injury, and develop an initial treatment plan for the child's hospitalization.

Advanced Trauma Life Support (ATLS) is a protocol developed to standardize the initial evaluation and management of injured patients and avoid omission of potentially lifesaving interventions. The ATLS training program was initiated by an orthopedic surgeon in 1978 in response to suboptimal care that he and his family received in a rural hospital after an airplane crash in a Nebraska cornfield. After 30 years of refinement, ATLS serves as the standard for initial management of injured patients and is now taught to providers around the world.[2] The impact of ATLS on reducing morbidity and mortality after injury has been affirmed in several studies.[3,4] ATLS training is mainly focused on treating the injured adult, but includes modules that emphasis the anatomic, physiologic, and psychological features that make management of the injured child unique.

The first phase of ATLS is the *primary survey* and is a rapid evaluation for identifying life-threatening injuries. The steps include evaluation and treatment of airway injuries (A, *airway*) followed by evaluation of respiratory dynamics (B, *breathing*), evaluation of the patient's hemodynamic status (C, *circulation*), followed by a neurologic assessment (D, *disability*). The final phase of the primary survey (E, *exposure*) is removing the patient's clothing to identify concealed injures and to ensure that the patient is protected from environmental heat loss. The primary survey is then followed by the secondary survey—a detailed head-to-toe evaluation that identifies other injuries. The steps within the primary survey are repeated as needed if the patient's status changes and to monitor treatments given. The initial evaluation and treatment period can usually be accomplished within the first 20 to 60 minutes after arrival to the emergency department. The patient's disposition from the emergency department depends on the type of injuries and the need for treatment and may range from admission to an inpatient or intensive care unit to transport directly to the operating room, transfer to a higher level facility, or discharge.

The initial management of injured adults has been the domain of trauma surgeons; however, the jurisdiction of care for the injured child is not as well defined at many centers. Frequently, pediatricians have an active role in the initial

management and treatment of injured children.[5] While formal ATLS training is not needed for most pediatric providers, this training should be mandatory for those actively involved in the initial evaluation of injured children. At the least, a working knowledge of the evaluation and management steps of ATLS is needed for pediatricians and pediatric specialists who encounter injured patients in an acute care setting. The goal of this chapter is to provide a focused introduction to the initial resuscitation of injured children. This chapter does not serve as a replacement for ATLS training but will instead highlight aspects of the resuscitation that are unique to injured children or may not be emphasized in the ATLS curriculum.

Prehospital Care and Trauma Team Activation

Initial field care, appropriate triage and rapid transport are all aspects of prehospital care that can have an important impact on the outcome in pediatric trauma. Cities and regions have developed trauma systems that coordinate these aspects of care by creating networks of prehospital and hospital providers. The most severely injured children are triaged to the centers within each trauma system that have the personnel, facilities, and equipment to manage these patients. Equally important, minimally injured patients can be directed to nontrauma hospitals to avoid burdening pediatric trauma centers with these patients. Field triage is based on several components including physiological criteria, anatomic injury, mechanism of injury, and underlying medical conditions. Triage criteria have been designed to minimize inappropriate transport of severely injured patients to non-trauma hospitals (undertriage) but achieve this goal at the cost of directing some patients to trauma centers who are only minimally injured (overtriage). Because of the limited time and resources available for evaluation in the prehospital setting, overtriage is an unavoidable aspect of current trauma systems. Injured children who have met criteria for transport to high-level trauma centers by current criteria may be minimally injured and require no specific interventions before discharge from the emergency department. A key aspect of the initial management of the injured child in the emergency department is effectively continuing the care started in the field while avoiding unneeded care for those with minimal injuries.

One approach that has been used in many centers to address the problem of overtriage is the use of a tiered team response in the emergency department.[6] Based on prehospital criteria, patients who are identified as being most at risk for severe injury are met by a full team upon arrival, including a trauma surgeon, emergency department physicians, critical care physicians, anesthesiologists, nurses, and radiology technicians. Patients with a lower likelihood of severe injury are initially met by a smaller team with the option of summoning a larger team if the initial evaluation suggests a severe injury. Centers that have used this approach for team activation have significantly reduced the expenditure of resources on minimally injured patients without any impact on the care received for more severely injured patients.[7]

Trauma Resuscitation

Similar to medical codes, trauma resuscitations are among the most resource-intensive and time-pressured events in any hospital. The severity of the patient's injuries, the number of team members required, and the number of simultaneous evaluation and management steps needed contribute to the complexity of the environment. To manage the complexity of trauma resuscitation, a systematic team-based and process-focused approach is needed to rapidly identify and treat life-threatening injuries and minimize team errors.

Designating a specific room and team for trauma resuscitations helps ensure needed resources are immediately available. A single location ensures that supplies (e.g., emergency airway kits, chest tube and thoracotomy trays, and central or intraosseous vascular access kits) are available and that team members know to gather at a specific site. Physicians, nurses, radiography technicians, respiratory therapists, and other hospital personnel needed for trauma resuscitation are identified in advance as trauma team members and assemble and assume their roles in the resuscitation area upon arrival of the injured child (Figure 112-1). These seemingly simple preparations ensure that the arriving patient has the maximal resources available at the receiving hospital.

Before arrival to the hospital, prehospital providers transmit information to hospital providers about the mechanism of injury, the status of the patient, and initial treatments given. This information can alert the team to prepare specific equipment or resources or to summon other essential personnel. Before the patient arrives, it is good practice for the team to review prehospital information to ensure all team members are aware of the patient's status and anticipated needs. A "time out" or quiet period facilitates this information transfer. Upon arrival to the emergency department, an additional and final exchange of information between the prehospital providers and the trauma team occurs. Essential elements that should be obtained in this report include details about the injury event, vital signs obtained at the scene and during transport, pertinent physical findings, and the initial treatments administered and response to these treatments.[8] Allowing the prehospital providers to give their report before starting the patient evaluation or even transferring the patient to the emergency department gurney improves information exchange and prevents repetitive questions later in the resuscitation. Obtaining a record of the prehospital event completes the formal information exchange between prehospital and in-hospital providers. These records can contain critical information for early in-hospital management but often are not immediately obtained because prehospital providers are moving on to their next assignment and the trauma team is focused on direct care of the patient.

The Primary Survey

Overview

The primary survey, as defined by ATLS, is a prioritized evaluation and management protocol focused on identifying and treating the most life-threatening injuries first. This approach is different from the traditional initial evaluation in a patient where an extensive history and physical exam is performed before diagnosis and treatment. The steps of the primary survey are taught in the ATLS course as a sequence followed by one provider with one nurse assistant. In actual practice, most centers have a team of providers rather than only two, allowing the evaluation and management steps to proceed forward even if one step leads to a delay. For example, a relatively more time-consuming step such as placing an intravenous catheter

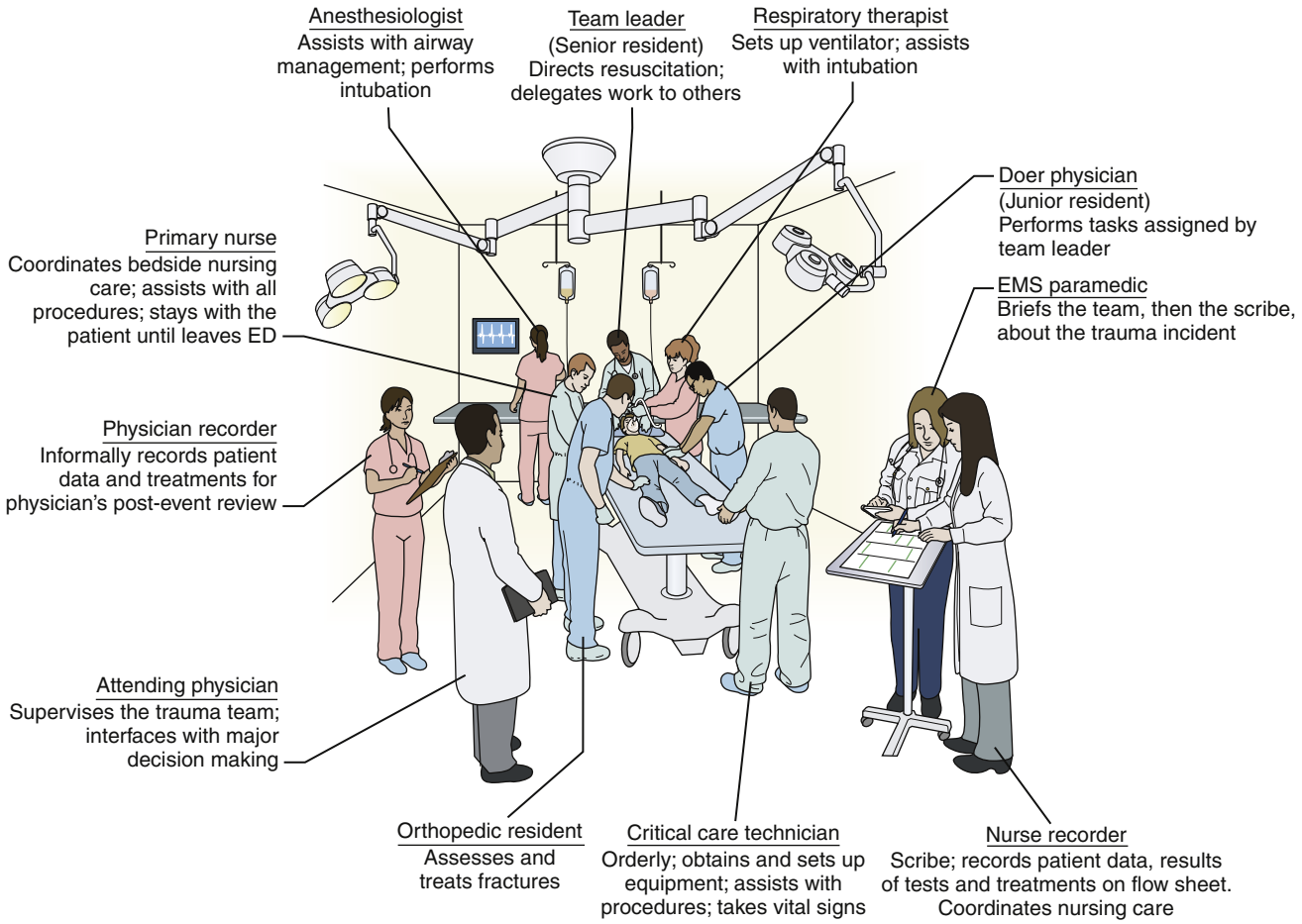


Figure 112–1. The trauma room and team. *(From Sacrevic A, et al:* Quantifying adaptation parameters for information support of trauma teams. *CHI 2008 Proceedings.)*

can be performed by one team member while others move on to subsequent steps in the primary survey. The typical model used at many trauma centers is to have a single provider on the team perform and report the components of the primary survey, supported by other team members as it is conducted. A designated team leader stands at the foot of the bed, receives information reported by the team and provides higher level direction of the conduct of the resuscitation. While the steps of the primary survey provide the framework for the initial assessment, new information may be obtained in later phases, or a patient's status may change, requiring iterative performance of each step. It is often a challenge to ensure the team retains its focus on the underlying prioritization scheme of the primary survey and does not omit or minimize steps in this process (Figure 112-2).[2] When resuscitations are evaluated, compliance with ATLS protocols is often low, mandating continued training and retraining to ensure the well-established benefits of this protocol are realized.[9]

Establish an Airway with Cervical Spine Stabilization (A)

Establishment of a patent airway with cervical spine stabilization is the first step of the primary survey. All patients should immediately receive oxygen as the evaluation is begun. After oxygen is placed, evaluation of the airway can proceed. Injured children who present to the emergency department can be placed into three categories with respect to initial airway management: (1) those with a patent airway requiring no manipulation, (2) those who have undergone intervention in the field or at another hospital to establish a patent airway, and (3) those who will need an intervention to establish a patent airway. Most children evaluated by the trauma team are in the first group. For these patients, evaluation should include several simple steps including asking the patient's name, inspection for craniofacial injuries, assessment for voice changes, and listening for obvious stridor. These steps can be performed easily and rapidly in most children. A simple statement that "the airway is patent" will communicate to the team these confirmatory steps have been accomplished. Because most injured children will not require any specific airway management, omission of elements of the airway assessment are common in pediatric trauma resuscitation. In a study of pediatric trauma resuscitations analyzed by video review, the most common omission in airway evaluation was not providing supplemental oxygen (omitted in 67% of resuscitations). Fewer than one quarter of resuscitations included a complete assessment of the airway along with assessment of 'breathing,' the second component of the primary survey.[10] Although the patency of the airway may seem "obvious" in many patients, subtle and early signs of pending airway compromise will be missed if a formal airway evaluation is not completed (Table 112-1).

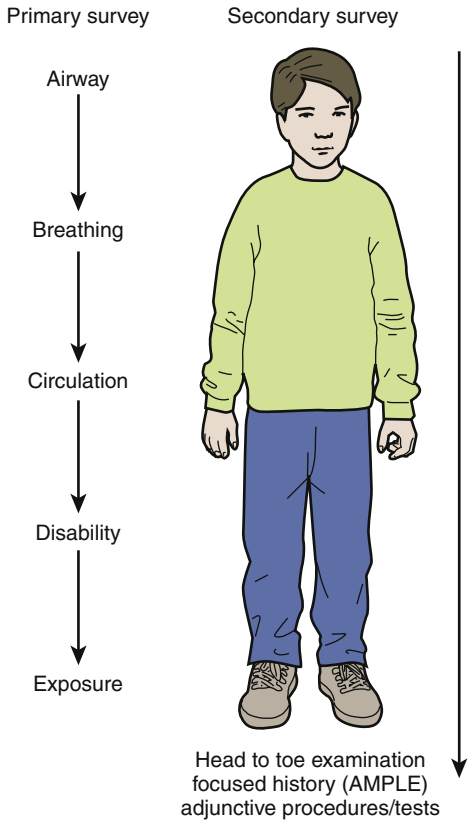


Figure 112–2. Schematic of initial trauma resuscitation.

The second category is children with an airway already established in the field or other hospital, usually by endotracheal intubation. Airway interventions performed prior to a patient's arrival should not be interpreted as an adequate airway and additional steps should be performed to assess airway patency, especially in light of the relative tenuous nature of pediatric airways placed under emergency situations.[11] The key steps to evaluating an endotracheal tube placed outside the emergency department are assessing the appropriateness of tube size, evaluating tube depth, assessing adequacy of ventilation by auscultation and inspection of the chest, measurement of end tidal CO_2, and confirmation of tube position with a chest radiograph. The appropriate tube size can be evaluated using age-specific formulas and charts or by comparing the tube with the child's fifth (little) finger. Deep placement of an endotracheal tube in a prehospital setting is common especially among younger children. Most prehospital providers have more experience with intubating adults, leading to a tendency toward deeper tube placement. In addition, the shorter airway of children increases the likelihood that an endotracheal tube will migrate from the proper position during transport. An easy rule for rapidly assessing tube depth is that the length of the tube at the teeth should be three times the tube size. Age-specific formulas for evaluating endotracheal tube depth are available and are more easily used by providers with greater experience in management of airways. Assessment that the endotracheal tube is an adequate airway should include steps that are more formally part of the breathing (B) phase of the primary survey, including assessment of ventilation by auscultation and inspection and measurement of end tidal CO_2. Because of a shorter airway and relatively less margin for movement of an endotracheal tube in younger child, correct endotracheal tube position cannot be reliably confirmed by auscultation of bilateral breath sounds alone.[12] Final confirmation of endotracheal tube position requires obtaining a chest radiograph. In most cases, the chest radiograph should be deferred until later in the resuscitation because simpler and more rapid evaluations can be performed to verify tube position that do not interrupt the conduct of the primary survey. However, a chest radiograph should be performed in the emergency department before transport to other areas of the hospital to avoid the need for airway management in less optimal hospital settings.

The final category of injured children undergoing airway evaluation is those who present with airway compromise requiring intervention. Because this category of injured children is least common, clearly defined personnel and procedures are needed to prepare the team to efficiently and safely establish an airway. Indications for endotracheal intubation in pediatric trauma include apnea, inability to maintain a patent airway by other means, need to protect the lower airway

Table 112–1 Missed Components of the Primary and Secondary Survey in Pediatric Trauma Resuscitation: Management Errors Among All Patients (N = 90)

Errors Identified	N (%)
AIRWAY AND BREATHING	
Delay in oxygen therapy	60 (67)
Chest not auscultated	40 (44)
Oxygen saturation not measured	33 (37)
Neck not adequately examined	71 (79)
CERVICAL SPINE	
No head stabilization on transfer	18 (20)
CIRCULATION	
Inappropriate intravenous access	18 (20)
Pulse not assessed	37 (41)
Central capillary refill not assessed	59 (66)
Blood pressure not measured	28 (31)
Fluid bolus not warmed	33 (89)
DISABILITY	
Pupils	22 (25)
Posture	22 (25)
SECONDARY SURVEY	
Perineum not examined	41 (45)
Head not examined	13 (15)
Ears not examined	16 (18)
Mouth not examined	41 (45)
Back not examined	13 (15)
Chest not examined	3 (3)
Abdomen not examined	2 (2)

Modified from Oakley E, Stocker S, Staubli G, et al: Using video recording to identify management errors in pediatric trauma resuscitation, *Pediatrics* 117: 658-664, 2006.

from aspiration of blood or vomitus, impending or potential compromise of the airway, presence of a closed head injury (Glasgow Coma Scale [GCS] score ≤8), and inability to maintain adequate oxygenation with face-mask oxygen supplementation.[2] An altered level of consciousness, usually due to an intracranial injury, is the most commonly observed reason for emergency airway intervention in the acutely injured child. Although a neurologic assessment is performed later in the primary survey, early recognition of children requiring a formal airway because of an altered level of consciousness is essential. The AVPU scale (***a***wake, responds to ***v***erbal stimuli, responds to ***p***ainful stimuli, and ***u***nresponsive) is one model for assessing consciousness that has been found to correlate with the GCS scale and which may be useful for identifying children who are at risk for a compromised airway because of an altered level of consciousness.[13] Patients with an AVPU score of "P" or "U" can be anticipated to have a GCS score of 8 or 3, respectively, and should receive early airway intervention.[14]

Once the trauma team has confirmed the need to establish an airway, the least invasive method for achieving this goal should be chosen. A chin lift and jaw thrust may be sufficient for initially opening the airway in some patients and are simple and rapid steps that can facilitate bag mask ventilation. However, in the presence of a suspected cervical spine injury, only a jaw thrust should be used. Because these maneuvers are not sufficient for long-term airway management, further interventions are usually needed to establish a definitive airway. Small children on a flat spine board may have a partially occluded airway because their proportionately large head forces the neck into a kyphotic position, resulting in upper airway obstruction. Simple manipulation of the young child's head to maintain the plane of the face with the plane of the spine board can improve airway patency, particularly among infants.

When a more definitive airway is needed, the preferred method for establishing an airway in pediatric trauma is orotracheal intubation. A rapid-sequence technique is preferred for most injured children, because intubation is made easier by eliminating protective airway reflexes and safer by preventing aspiration and decreasing physiological stress that can lead to increased intracranial pressure in children with severe head injuries.[15] During intubation, steps should be taken to account for the short length and narrow diameter of the trachea and the narrowing of the trachea at the cricoid ring, including choosing an appropriately sized tube and confirming tube position. While it can be a good option in other settings, nasotracheal intubation is usually not performed for injured children because this technique is more difficult due to the acute angle of the posterior pharynx of the child. Nasotracheal intubation has not been recommended in patients with facial trauma, cerebrospinal fluid leaks, or suggestions of basilar skull fractures, because these injuries suggest the possibility of a disruption between the cranial vault and nasopharynx.[16,17] Laryngeal mask airway (LMA) is also an option for emergency airway management in situations in which endotracheal intubation cannot be accomplished.[17-19] However, as the LMA does not protect against aspiration and cannot be used effectively to provide positive pressure ventilation in patients with altered respiratory compliance or resistance, it should be used only as a rescue technique if the patient cannot be intubated.[20]

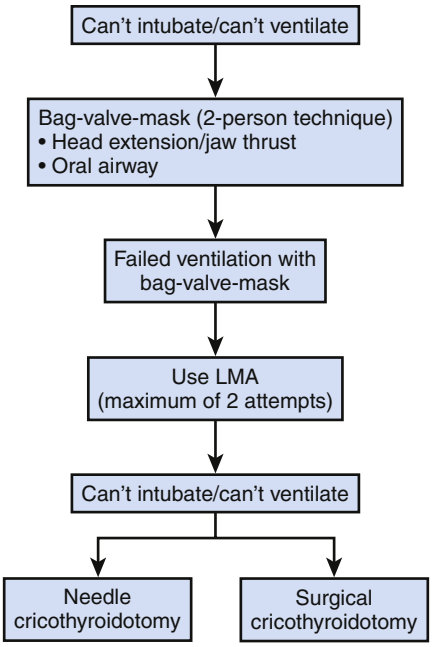


Figure 112–3. Flow chart for "can't intubate/can't ventilate" airway emergencies. *(Modified from Henderson JJ, Popat MT, Latto IP, et al: Difficult Airway Society guidelines for management of the unanticipated difficult intubation,* Anaesthesia *59:675-694, 2004.)*

Fewer than 1% of all adult patients who require an emergency airway in the emergency department require a surgical airway.[21] The percentage of children requiring an emergency airway after injury is likely to be even smaller. Among injured children with a comprised airway, endotracheal intubation may not be possible because of significant craniofacial injuries, massive bleeding from the nasopharynx or oropharynx, or preexisting anatomical features such as a short neck, micrognathia, or small mouth that make intubation more difficult. In this "cannot intubate/cannot ventilate" subset, a systematic approach is needed to rapidly secure a patent airway (Figure 112-3).[20]

If bag-mask ventilation is successful, the team has time to find alternative routes of securing an airway. Examples include attempting fiberoptic intubation or bringing a more experienced physician to the trauma bay to assist with establishing an airway. If bag-mask ventilation is not successful, an appropriate invasive procedure may be required. Among injured children, appropriate options include surgical or needle cricothyrotomy, depending on the child's size. Among children with a larger airway whose cricothyroid membrane is easily palpated, a surgical cricothyrotomy is preferred.[2] If small neck size or other anatomic features preclude the safe placement of a cricothyrotomy, a needle cricothyrotomy with needle jet insufflation of oxygen into the airway is the recommended approach. Surgical cricothyrotomy should be performed by members of the team with experience with this technique. This procedure has four main steps: (1) identification of the cricothyroid membrane, (2) making an incision through the skin and cricothyroid membrane, (3) stabilization of the larynx with a tracheal hook at the inferior aspect of the ostomy, and (4) placement of a tube in the trachea.[22] Training in this technique is now included as part of the ATLS course.

Although controversy surrounds whether needle cricothyrotomy should be used at all in pediatric patients, it is still

advocated by some authorities as a rescue technique in specific clinical scenarios. Needle cricothyrotomy can be performed using commercially available kits. When one is not available, the procedure can be carried out by inserting a large bore (12 to 18 gauge) angiocatheter in a caudal direction at a 30- to 45-degree angle through the cricothyroid membrane. During needle advancement, constant negative pressure is applied to the plunger of the syringe to aspirate air and confirm its endotracheal position.[23] After confirmation of endotracheal placement, the syringe and stylet are removed and the cannula is connected to an oxygen source. Among larger children and adolescents, the cannula should be connected to an unregulated oxygen supply of 50 psi, because ventilation cannot be adequately provided using an ambu bag.[24] While pediatric evidence is limited, a flow of 25 to 35 psi from a standard regulator set at 10 to 12 L/min for most children has been recommended. Another approach that can be used is based on flow rates and estimated tidal volumes (TV): 10 to 25 psi with TV of 340 to 625 mL for children 8 years and older; 5 to 10 psi with TV of 240 to 340 mL for children 5 to 8 years old; and 5 psi with TV of 100 mL for patients who are 5 years and younger.[23] Standard intravenous tubing can be connected to the cannula and a Y connector placed between the intravenous tubing and the oxygen tubing. Intermittent occlusion for 1 second and release of the Y-connector for 4 to 5 seconds provides some passive ventilation. A needle cricothyrotomy is a highly tenuous airway and should be carefully secured after placement and converted to a more stable airway as soon as possible. This approach is only sufficient for 30 to 45 minutes because of the progressive respiratory acidosis that results from underventilation.[2] Because surgical airway management is rarely performed in pediatric patients, centers that manage injured children should have the equipment and adequately trained personnel for performing these procedures when needed.

Cervical spine stabilization should be viewed as part of the "A" step and is included as part of airway management in ATLS. In contrast to intubation in other hospital settings such as the intensive care unit, intubation in the trauma bay should proceed with the assumption that a cervical spine injury is present until this type of injury has been formally ruled out. This step is needed in patients with any mechanism of injury that can be associated with cervical spine trauma. Many injured children present to the emergency department with a cervical collar that was placed in the field because of the mechanism of injury. The initial evaluation of the airway should be immediately followed or simultaneously performed with an assessment of the proper size and fitting of the cervical collar or placement of a cervical collar when one is not present. When endotracheal intubation is required, in-line cervical spine stabilization should be used. A member of the team holds the neck on each side with his or her hands and forearms maintaining the stability of the spine during airway manipulation. Despite the importance of this step, neck inspection and palpation while maintaining C-spine precautions and head stabilization during transfer to the trauma gurney are steps omitted in 80% and 20% of trauma resuscitation performed for injured children, respectively.[10]

Breathing (B)

Establishment of a patent airway is an important initial step but is not sufficient to ensure adequate oxygen delivery. The breathing (B) step of the primary survey is the immediate assessment of ventilation and performance of measures to establish adequate ventilation if it is compromised. The three most effective, objective, and rapid steps in evaluating ventilation are auscultation of the chest, application of a pulse oximeter for measuring oxygen saturation, and assessment of respiratory rate. Because patients are supine during the primary survey, auscultation is limited to sites on the anterior and lateral chest. Auscultation should be performed in both these areas to obtain the most accurate evaluation of ventilation. Localizing abnormal ausculatory findings to a specific region of the chest can be more difficult in younger children because of smaller chest size and the usual supine position of the injured patient during the primary survey. However, in most children, auscultation can be used to identify significant compromise in ventilation requiring lifesaving intervention. These steps can be supplemented by a subjective evaluation of the adequacy and symmetry of chest wall movement and an evaluation for evidence of chest wall trauma. Because of the pliability of the chest wall of younger children, significant chest injury may be present even in the absence of any chest wall deformity.

A main focus of the B phase of the primary survey is on identifying four specific thoracic injuries that can significantly impair ventilation and that require immediate treatment: (1) tension pneumothorax, (2) open pneumothorax, (3) flail chest with pulmonary contusion, and (4) massive hemothorax. The diagnosis of a tension pneumothorax should be made on clinical criteria, including tracheal deviation, unilateral absence of breath sounds, neck vein distention, tachycardia, hypotension, and respiratory distress. Delaying treatment to obtain a confirmatory chest radiograph should be avoided because of the time delay associated with processing, and interpreting this study. When the clinical diagnosis of a tension pneumothorax is made, the chest should immediately be decompressed by placing a 14 to 18 gauge, 5-cm needle into the second intercostal space at the midclavicular line. The needle should be sufficiently long to penetrate the chest wall and enter the pleural space. A minimum length of 5 cm is recommended in older children and adults, but shorter needles may suffice in infants and younger children.[2] Proper intrathoracic placement of the needle can be partly confirmed by an audible rush of air when entering the chest. Because needle decompression will convert a tension pneumothorax into a simple pneumothorax, a chest tube will be needed regardless of the response to needle decompression. Advanced prehospital providers are often trained in needle decompression of the chest in the field. If a child arrives after needle decompression, tube thoracostomy placement is also needed for definitive treatment.

An open pneumothorax or "sucking chest wound" occurs when the size of a chest wall injury approaches two thirds the area of the tracheal lumen, causing a preferential pull of air into the pleural space and out of the wound. This injury can lead to mediastinal shift, decreased venous return, and eventual cardiopulmonary collapse. Open pneumothorax is rare in children and is usually the result of a penetrating injury. Airflow through the wound will be audible or can be visualized by bubbling of blood at the wound. A rectangular petroleum jelly/gauze dressing that is occlusive on three sides beyond the wound edge will produce a one-way valve effect that will allow air to escape on expiration but inhibit air from entering the thoracic cavity on inspiration.[25]

Flail chest occurs when a segment of the chest wall has lost continuity with the movement of the thoracic cage, occurring

when two or more ribs are fractured in two or more positions. The pediatric thoracic cage is more compliant than adults and rib fractures are not always present when parenchymal injuries exist. When occurring in infants and young children, rib fractures suggest a significant amount of blunt force to the chest and the possibility of an underlying pulmonary injury. Because fractured ribs can lead to direct lung injury, the presence of a flail chest segment should raise the suspension of a pneumothorax and hemothorax. Due to compromised ventilatory function and underlying pulmonary injury, management of flail chest is focused on providing temporary ventilatory support until the injury heals. Intubation may be immediately needed in the emergency department when ventilation is significantly compromised by this injury.

Significant bleeding may occur with thoracic trauma from intercostal vessels, internal mammary vessels, lung parenchyma, or cardiopulmonary vessels, leading to massive hemothorax. Children with this injury will present with decreased breath sounds and dullness to percussion on the affected side. Eliciting the finding of dullness to percussion can be difficult in a noisy trauma resuscitation area but is a diagnostic feature that can be used to distinguish this injury from a pneumothorax. While the diagnosis is optimally made with a chest radiograph, the team should proceed with immediate chest tube placement if clinical evidence suggests the presence of a large amount of intrathoracic blood. When a massive hemothorax is present, fluid resuscitation or blood transfusion will often be needed. After chest tube placement, the amount of blood initially obtained and the rate of continued bleeding from the tube should be evaluated. A definitive thoracotomy for controlling bleeding from the chest wall, lung, or heart may be indicated if the initial volume exceeds 20% to 25% of estimated blood volume, bleeding continues at a rate exceeding 2 to 4 mL/kg/hr, the rate of bleeding is increasing, or the pleural space cannot be drained of blood and clots. The latter three criteria may be observed after the child is initially stabilized and has been admitted to the hospital.

About 75% of traumatic chest injuries can be treated expectantly or with placement of a chest tube and volume resuscitation.[26] While placement of a chest tube in an injured child is similar to placement in other settings, additional steps should be considered in the injured child. When placing a chest tube for trauma, the tube should be directed posteriorly to allow for adequate drainage of blood in a supine patient. A sufficiently large tube should be selected to allow drainage of blood and fluid without becoming clogged with blood clot. The fifth intercostal space in the anterior midaxillary line is ideal in most patients to prevent placement of the tube through the diaphragm or abdomen but allows sufficient length in the chest for drainage and avoiding later dislodgement. While it is often taught that the lung should be palpated with a gloved digit before tube placement, this verification step may be difficult to perform in infants and small children with smaller intercostal spaces. Confirmation of tube placement in the pleural space can be confirmed in infants and smaller children by the egress of air or blood after placement. Proper tube placement in the thoracic cavity can also be evaluated by observing air condensation on the internal surface of the tube and movement of fluid in the water-seal chamber in time with the patient's respirations when connected to a pressure regulated collection device. When palpating the lung in larger children, the use of double gloves will avoid cross contamination of the patient and the person placing the chest tube that may result from glove tears from broken ribs when palpating a track through the chest wall. A chest radiograph should be performed to verify placement of the tube before leaving the resuscitation area.

Circulation (C)

The "C" step of the primary survey is the assessment, recognition, and management of shock. Because of greater physiological reserve, early identification of cardiovascular compromise can be more difficult in children than adults (Table 112-2). Assessment and management of circulatory status in the primary survey is focused on early identification and treatment rather than defining the specific etiology of the shock state. Determining the site of internal hemorrhage and defining the specific type of shock state are steps that are deferred until after the primary survey. Objective assessment of circulation is done by measuring heart rate and blood pressure, and assessing pulses and capillary refill. In addition to cardiovascular compromise, tachycardia after injury can indicate pain, fear, or other psychological stress. Tachycardia therefore cannot be used as the sole criteria for diagnosing cardiovascular compromise and needs to be combined with other clinical criteria before treatment is initiated. A manual blood pressure measurement should be obtained, using the appropriate size cuff, upon arrival to the resuscitation area. Periodic reassessment of blood pressure should continue throughout the resuscitation to verify the child's hemodynamic status. Palpation of central and peripheral pulses is a rapid method for

Table 112–2 Systemic Response to Blood Loss in Pediatric Patients

System	Mild Blood Volume Loss (<30%)	Moderate Blood Volume Loss (30%–45%)	Severe Blood Volume Loss (>45%)
Cardiovascular	Increased heart rate, weak peripheral pulses	Low normal blood pressure, narrowed pulse pressure, tachycardia, absent peripheral pulses, weak central pulses	Hypotension, tachycardia then bradycardia
Central nervous system	Anxious, irritable, confused	Lethargic, dulled response to pain	Comatose
Skin	Cool, mottled, prolonged capillary refill	Cyanotic; markedly prolonged cap refill	Pale, cold
Urinary output	Minimal	Minimal	None

Data from Committee on Trauma, American College of Surgeons: *Advanced trauma life support for doctors, student course manual,* ed 7, Chicago, 2004, American College of Surgeons.

detecting hypotension and often can be accomplished before a cuff blood pressure is obtained. Because pulses are most likely to be lost in progressive hypotension in the wrist or feet followed by the groin followed by the neck, palpation for pulses in each of these areas can provide a crude estimate of the level of hypotension. Assessment of peripheral perfusion can also include an estimate of capillary refill in addition to a visual evaluation of skin perfusion. Because these latter assessments are more subjective, these should be used only in conjunction with more objective measurements in directing treatment. While assessment of circulatory status is essential to the initial evaluation of an injured child, these steps are often omitted or delayed until later in the resuscitation. During video review of pediatric trauma resuscitations, blood pressure was not measured in 31% of patients, pulses not assessed in 41%, and central capillary refill not assessed in 66% during the initial evaluation.[10]

The two main interventions for managing cardiovascular compromise during the primary survey are controlling external hemorrhage and administration of fluid. Active hemorrhage is easy to recognize and can usually be treated by direct manual pressure or the application of compression bandages. Scalp lacerations are a common source of external bleeding in injured children and the blood loss from this site should not be underestimated. A full evaluation for external hemorrhage, however, is only complete after the child has been exposed completely later in the primary survey.

Administration of fluids requires the establishment of intravenous access. In pediatric trauma, the preferred order of sites depends on the child's age and the urgency of establishing intravenous access. If a percutaneous peripheral intravenous line cannot be established, intraosseous access, percutaneous central venous access, or cutdown on a vein should be considered. Intraosseous access is achieved by placing a needle into the marrow cavity of a long bone in an uninjured extremity. This procedure is rapid, requires minimal training, and is the preferred alternate method of vascular access in infants and younger children. The availability of new equipment and techniques has expanded the use of intraosseous infusions to older children and even adults. Percutaneous placement of a central venous catheter can be pursued as alternate access in older children when equipment for intraosseous access in older patients is not available or when ossification of the long bones precludes placement of an intraosseous needle. Femoral placement of a central line in the injured child has advantages over placement in a jugular or subclavian vein position because it can be performed in most patients without interfering with ongoing assessment and management of other components of the primary survey. However, the femoral route is not recommended if there is a concern of the potential for intra-abdominal injuries. Despite the importance of establishing intravenous access in the injured child for fluid resuscitation and administration of medications, vascular access was not performed or inadequate access was obtained in 20% of recorded pediatric resuscitations.[10]

The goal of fluid resuscitation is to rapidly replace intravascular volume, initially with warmed crystalloid solution and then moving to blood products based on the child's response to crystalloid boluses (Figure 112-4). When cardiovascular compromise is detected, an initial bolus of 20 mL/kg of warmed isotonic crystalloid fluid (lactated Ringer's solution or normal saline) should be administered. Given that it

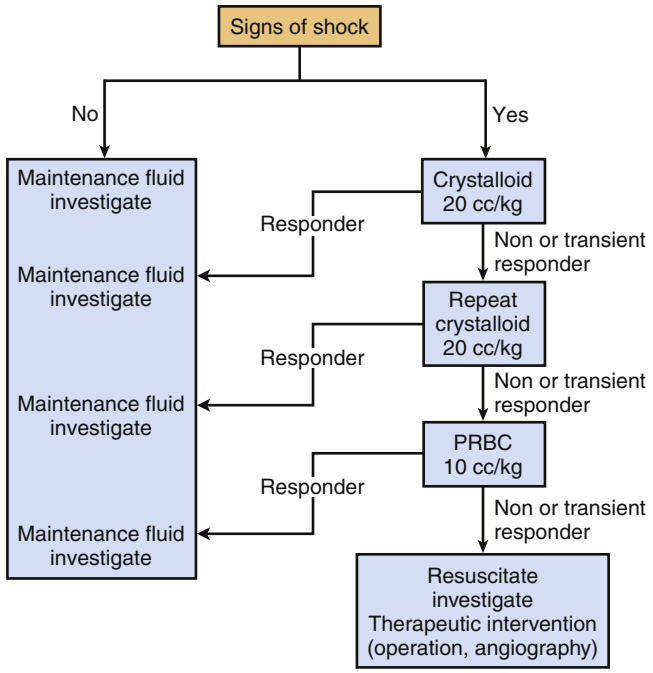


Figure 112–4. Algorithm for pediatric fluid resuscitation.

is relatively hypotonic, Ringer's solution is not recommended for fluid resuscitation in patients with evidence of traumatic brain injury. Fluid administration should not be delayed by slow-rate drip infusion, but instead should be administered as a bolus using a hand-pump device, a syringe, or a pressure bag to ensure that the effect of the bolus and assessment of need for additional fluid proceeds rapidly. If a second bolus of crystalloid is needed, preparations for the potential administration of blood products should begin. If the child responds to fluid administration, intravenous fluid is continued at a maintenance rate as further investigations concerning the need for fluid are performed. If there continues to be no response or transient response to crystalloid, blood administration should be considered. During the primary survey, cross-matched, type-specific blood is often not yet available, and O-negative blood should be administered. Blood should be administered in boluses of 10 mL/kg. The four sites of hemorrhage that can lead to major blood loss after injury include external sites (e.g., scalp laceration), intrathoracic injury, intraabdominal injury, and pelvic or multiple long-bone (usually femur) fractures. While external bleeding can be easily detected, bleeding in other sites is evaluated after the primary survey has been completed.

Disability (D)

The primary survey continues with a neurologic assessment of the child, the disability (D) component of the primary survey. This assessment includes two main components, calculating the GCS and assessment of pupillary responses (Figure 112-5). More extensive neurologic evaluation should be deferred to the secondary survey to avoid slowing the primary survey. As with airway assessment, a formal evaluation of GCS is often omitted when it is "obvious" that no neurologic injury is present. This practice should be avoided because subtle changes may be missed with only a cursory assessment. In addition,

INFANTS	CHILDREN	ADULTS
Best eye opening 4 – Spontaneous 3 – Opens to verbal stimulus 2 – Opens to painful stimulus 1 – No response	**Best eye opening** 4 – Spontaneous 3 – Opens to verbal stimulus 2 – Opens to painful stimulus 1 – No response	**Best eye opening** 4 – Spontaneous 3 – Opens to verbal stimulus 2 – Opens to painful stimulus 1 – No response
Best verbal response 5 – Coos and babbles 4 – Irritable cry 3 – Cries to pain 2 – Moans to pain 1 – No response	**Best verbal response** 5 – Orientated 4 – Confused 3 – Inappropriate words 2 – Incomprehensible words 1 – No response	**Best verbal response** 5 – Orientated (person, place, time) 4 – Confused, disorientated 3 – Inappropriate words 2 – Incomprehensible words 1 – No response
Best motor response 6 – Spontaneous purposeful movement 5 – Localizes to pain 4 – Withdraws to pain 3 – Flexion (decorticate response) 2 – Extension (decerebrate response) 1 – No response	**Best motor response** 6 – Obeys commands 5 – Localizes to pain 4 – Withdraws to pain 3 – Flexion (decorticate response) 2 – Extension (decerebrate response) 1 – No response	**Best motor response** 6 – Obeys commands 5 – Localizes to pain 4 – Withdraws to pain 3 – Flexion (decorticate response) 2 – Extension (decerebrate response) 1 – No response

Figure 112–5. Components of the GCS at different ages.

establishment of a baseline GCS may have prognostic value among children with an evolving intracranial injury. To account for variations in response related to age, the GCS should be calculated using age-specific criteria. Among the three main components of the GCS, the motor score has been shown to be the best predictor of outcome after injury.[27] Particular attention should be paid to ensure that this component is accurately assessed and recorded. Pupillary assessment includes an evaluation of pupil size and response to light and can easily and rapidly be assessed, reported, and recorded. Findings from the neurologic assessment are used to plan additional evaluation and management steps, including the need for endotracheal intubation, the requirements of additional imaging, and the final disposition after leaving the emergency department. Despite the importance of obtaining a GCS and assessing pupils, these steps were both omitted in 20% of observed pediatric trauma resuscitations.

Exposure (E)

The final step in the primary survey is exposure of the patient, the "E" component of the primary survey. In this phase, clothing is removed to visually inspect all body regions to minimize the chance of missing an obvious injury. A team-coordinated log roll of the child, maintaining cervical spine stabilization, can be used to assess the back and spine for external injury. When rolled on their side, patients are in an ideal position for assessing the spinal column for deformities and tenderness and for undergoing a rectal examination if indicated. While not all of these steps are formally part of the primary survey, the additional time required for them is minimal, leading to the inclusion of these steps as part of exposure in many centers. Immediately after exposing the injured child, the child should be covered again with warm blankets to minimize heat loss. Infants and younger children are particularly vulnerable to heat loss because of a relatively large surface area in relation to body volume. Other measures for warming or maintaining an injured child's temperature include warming the room and the use of overhead warmers or a Bair hugger. The patient's temperature should be obtained at this point, a step that is frequently omitted in the initial evaluation of the injured child.

The Secondary Survey

After completion of the primary survey, the secondary survey is then performed. This includes a medical and event history, a more complete physical examination, and additional adjunct interventions. The secondary survey is less structured than the primary survey and its components and sequence can be modified to reflect patient needs, provider preferences, and institutional practices. The secondary survey should not be performed until the components of the primary survey have been completed and interventions needed to address issues identified in the primary survey have been implemented. It is a common pitfall to move to components of the secondary survey or to mix components of the secondary survey during performance of the primary survey. This practice should be discouraged so as to avoid losing focus on the primary survey and the life-threatening injuries that it is designed to identify. During the secondary survey, attention should be intermittently refocused on vital signs and other monitoring steps of the primary survey. When changes are observed, the primary survey evaluation and treatment steps should be reinitiated to ensure that potentially life-threatening injuries are addressed.

In contrast to a typical history performed during evaluations in other settings, the history performed in the secondary survey is more focused and follows rather than precedes the performance of the physical examination. It is common practice to obtain this information while simultaneously performing the physical examination components of the secondary survey. The most important history elements to obtain are those that most directly impact injured patients and the evaluation and treatments needed for them. The acronym AMPLE is useful for remembering these key elements (***a***llergies,

medications, ***p***ast medical history, ***l***ast meal, and the ***e***nvironment and events related to the injury). Parents or other caregivers are often the best source of this information.

The physical examination contains elements similar to those performed in other settings but should be modified to include steps that identify common and important injuries. Examination of the entire scalp should be performed to identifying lacerations, contusions, or evidence of fractures. Posterior scalp lacerations can easily be missed because of hair or the position of the cervical collar. Massive facial injuries can produce significant facial edema making the eye examination difficult. Because facial swelling most often worsens with time, it is important to obtain an initial eye examination while the patient is in the emergency department. Fractures to the maxillofacial bones including nondisplaced fractures of the nasal bone, zygomatic arch, and orbital rim can be difficult to detect on physical examination and often require radiographic imaging. Examination of the chest in pediatric trauma can be misleading because severe intrathoracic injury may be present without evidence of obvious skeletal trauma. Abdominal injuries should be aggressively sought in children who have sustained a significant blunt injury to the torso. Repeated examinations are often needed to evaluate for the presence or absence of abdominal tenderness in the anxious child after injury.[28]

Examination of the perineum, rectum, and vagina should be focused on detecting direct trauma as well as for detecting evidence of a pelvic fracture. Digital rectal examination may often be omitted in children with no other signs of injury but should be included if the child sustained significant blunt trauma, has other findings suggesting a pelvic fracture, or has neurologic findings suggesting a spinal cord injury. While the rectal examination in adult trauma is used in part to detect the presence of a high-riding prostate that suggests a pelvic fracture, this physical examination finding is rarely detectable among infants and younger children. Any evidence of pain, swelling, or limitation of movement may suggest an underlying fracture and usually warrants radiographic evaluation. The secondary survey should include a more complete neurologic assessment than was performed in the primary survey as well as a formal assessment of sensory and motor functions.

While the secondary survey can be performed in a free-form fashion, a systematic strategy is needed to avoid missing key components of this evaluation. In reviews of pediatric trauma resuscitations, components of the secondary survey that are often omitted include examination of the mouth, ears, back, and perineum. As in the primary survey, findings in the secondary survey should be communicated to the team. The trauma team leader should address the need for tetanus administration (depending on child's vaccine requirements) and antibiotic administration (e.g., for open orthopedic fractures) during the secondary survey.

Missed injuries do occur in trauma resuscitations, which may lead to preventable morbidity during the patient's hospital stay. About 4% of injured children will have an injury missed in the primary and secondary survey. The risk of a missed injury is higher in children with more severe injuries, including those transported by air, those who undergo endotracheal intubation in the emergency department, those with a low admission GCS, and those with an injury severity score greater than 15.[29] Missed injuries have been shown to be reduced with the implementation of a designated pediatric trauma response team, supporting a focused and stepwise approach to the initial evaluation of the injured children.[30] Critical care providers should be alert to the possibility of missed injuries in patients admitted to their unit and not rely on the emergency department evaluation for detecting all injuries.

Diagnostic Assessment

The secondary survey is supplemented by diagnostic testing that focuses on identifying and treating injuries not found in the primary survey. Performance of a standard set of tests is discouraged to avoid unnecessary discomfort, exposure to radiation from excessive imaging, and cost. Injured children may be overtriaged to the resuscitation area and require no additional testing after the primary and secondary survey has been completed. Observation in the emergency department before discharge and close outpatient follow-up is an appropriate option for children identified as low-risk for injury.

Laboratory Studies

Routine laboratory evaluations in pediatric trauma have been shown to be of little value in the management of injured children.[31,32] Among children injured from a significant blunt mechanism, a focused screening set of laboratory studies to identify occult intraabdominal or retroperitoneal injury and hemorrhage has been shown to be sufficient. Based on the current literature, a screening panel that includes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), urinalysis, and hemoglobin will effectively screen for most intraabdominal injuries.[33] The ALT, AST, and urinalysis are screening tests to determine the need for an abdominal CT scan and can be omitted if other clinical indications suggest the need for abdominal imaging. Threshold values of greater than 100 U/L for AST and ALT and more than 5 red blood cells/hpf suggest the presence of an intraabdominal injury and suggest the need for abdominal imaging.

Among children with major head injuries, penetrating trauma, multiple extremity fractures, and significant mechanisms of injury, this panel of laboratory studies may be expanded to include coagulation studies, electrolytes, and blood for cross-matching. Coagulation studies in pediatric trauma are most often abnormal in the presence of severe traumatic brain injury. If obtained early after injury, electrolyte studies are most often normal and serve only as a baseline for a patient who will require aggressive management of severe head injuries or aggressive resuscitation. Blood should be obtained for cross-matching if significant fluid resuscitation has been required, the child has a preexisting condition causing a predisposition to bleeding, has a major head injury, or will undergo a surgical procedure with a potential for a blood loss. Early after injury, pancreatic enzymes do not need to be obtained as a screen for pancreatic injury because of the low diagnostic yield of these studies.[34] Screening tests for alcohol or drug use may be appropriate in older children and adolescent patients.

Radiographic Imaging

Radiographs may be needed to rule out specific injuries or to evaluate known injuries. Imaging in the resuscitation area is often performed with a portable system or with a built-in

system within the trauma room to avoid moving the child. The three most common radiographs obtained are cervical spine, chest, and pelvic radiographs. While these studies are commonly referred to as a *trauma series* and ordered as a set, the performance of all three is often not necessary. The need for each radiograph should be evaluated based on the mechanism of injury and patient symptoms and examination.[35]

A cervical spine injury should be suspected in any child sustaining a significant head injury or injured by a major blunt mechanism. Although cervical spine injuries are rare, these injuries can be devastating and can have worse outcomes when adequate spine precautions are not taken early after injury. A systematic and efficient approach using both clinical and diagnostic modalities is needed to ensure that a cervical spine injury is not present. Implementation of standards for cervical spine assessment and clearance have been shown to decrease the time for cervical spine clearance.[36] Each institution should develop an institution-specific protocol for managing the initial and subsequent imaging of the cervical spine to avoid either incomplete evaluations or excessive imaging. Criteria for cervical spine imaging include midline cervical tenderness, altered level of consciousness, evidence of intoxication, neurologic abnormalities potentially attributable to a spine injury, and presence of a distracting injury precluding a reliable clinical assessment.[37] The cervical spine evaluation in nonverbal children is particularly difficult to asssess. A recent study of this subgroup identified GCS less than 14, GCS eye component of 1, an injury sustained in a motor vehicle crash, and age less than 2 years as important variables associated with the presence of a cervical spine injury.[38]

A cervical spine series consists of a cross-table lateral, an anterior-posterior view, and an open-mouth view to assess the dens process of C1. With adequate films, a three-view series has a high sensitivity (89%) and a negative predictive value of 99.9%.[39] Among these views, the lateral cervical spine film is most useful and has been adopted as the initial screening film at many institutions.[40] If an injury is noted on screening cervical spine imaging, a cervical spine CT or MRI may be needed to further evaluate the injury. If either the clinical or radiographic findings cannot be used to safely rule out a cervical spine injury in the resuscitation area, the child should remain in a cervical spine collar and be evaluated later for the need for further imaging.

Chest radiographs can be often be omitted for children without physical examination findings or symptoms suggesting a thoracic injury.[35] This study, however, should be obtained for children who are injured by a major blunt mechanism such as a high-speed motor vehicle crash or those who have sustained other significant torso injuries. Pelvic radiographs can be safely omitted among children who are awake, alert, and have no physical examination findings or proximity injuries (e.g., a proximal femur fracture) to suggest a pelvic injury. Radiographs of the extremities or other areas may also be needed in the resuscitation area depending on the findings of the primary and secondary survey.

Computed tomography is a powerful and accurate diagnostic tool and has become an integral component of the evaluation of injured patients. Although CT scans can be essential in the evaluation of many children, excessive use is discouraged because of the higher radiation exposure associated with CT scans, rare but important complications such as contrast reactions, and added costs. CT scans are a growing source of medical radiation exposure in children and may contribute to the occurrence of radiation-related malignancy, particularly when performed among younger children.[41]

The two most common body regions imaged with a CT scan in pediatric trauma are the head and abdomen. A noncontrast head CT is performed to assess for closed head injuries and fractures that may require additional treatment such as a depressed skull fracture. The most common indication for a head CT scan after pediatric injury is a history of loss of consciousness or altered mental status. A head CT scan may also be needed for preverbal children whose injury was not observed or those who have received endotracheal intubation or are sedated as they cannot reliably be assessed for a potential head injury.[42-44] A large multicenter trial derived and validated predictive rules to identify children at very low risk of clinically important traumatic brain injury after blunt trauma where a head CT scan may be unnecessary. These prediction rules had a sensitivity of 100% in children less than or equal to 2 years old and 96.8% in children older than 2; negative predictive value was 100% for all ages (Figure 112-6).[45]

Recent emphasis on developing approaches to reduce the need for screening abdominal CT scans in pediatric trauma continues to evolve. Abdominal imaging is indicated when an injury is suggested by physical examination findings such as major abdominal ecchymoses or abdominal tenderness. Among children who sustain a significant blunt injury but do not have physical examination findings suggesting an abdominal injury, the yield of screening abdominal CT scans is low. Screening laboratory tests, however, can be used to reduce unneeded imaging for these children. A multicenter trial is underway that will define the specific studies and study parameters that are optimal for directing abdominal imaging.

While focused abdominal sonogram for trauma (FAST) has been widely adopted as a diagnostic tool for adult trauma patients, its value in pediatric trauma is less certain. FAST is focused on identifying fluid in four areas, the presence of which is suggestive of hemopericardium or intraabdominal injury: the pericardial sac, hepatorenal fossa, splenorenal fossa, and pouch of Douglas. Current evidence suggests that the role of FAST for evaluating children after blunt abdominal injury is limited. When used in children, FAST has only modest sensitivity (80%) for the detection of hemoperitoneum, and a negative ultrasound has questionable utility as the only test to exclude an intra-abdominal injury.[46] Recent studies have suggested that FAST may be combined with screening laboratory studies to increase sensitivity, specificity, positive predictive value, and negative predictive value.[47] The utility of FAST in the assessment of pediatric trauma still needs to be defined.

Emergency Department Thoracotomy

Emergency department thoracotomy can be a lifesaving intervention among some children presenting in extremis after injury. This procedure, however, should be used very selectively, because its effectiveness has been shown to be limited to specific patient subsets, including those who have received a brief period of cardiopulmonary resuscitation after sustaining a blunt injury or witnessed penetrating injury. Patients who sustain a penetrating injury are more likely to benefit from an emergency department thoracotomy, because the higher potential for identifying injuries that can be treated after a thoracotomy has been performed. Data defining the role of

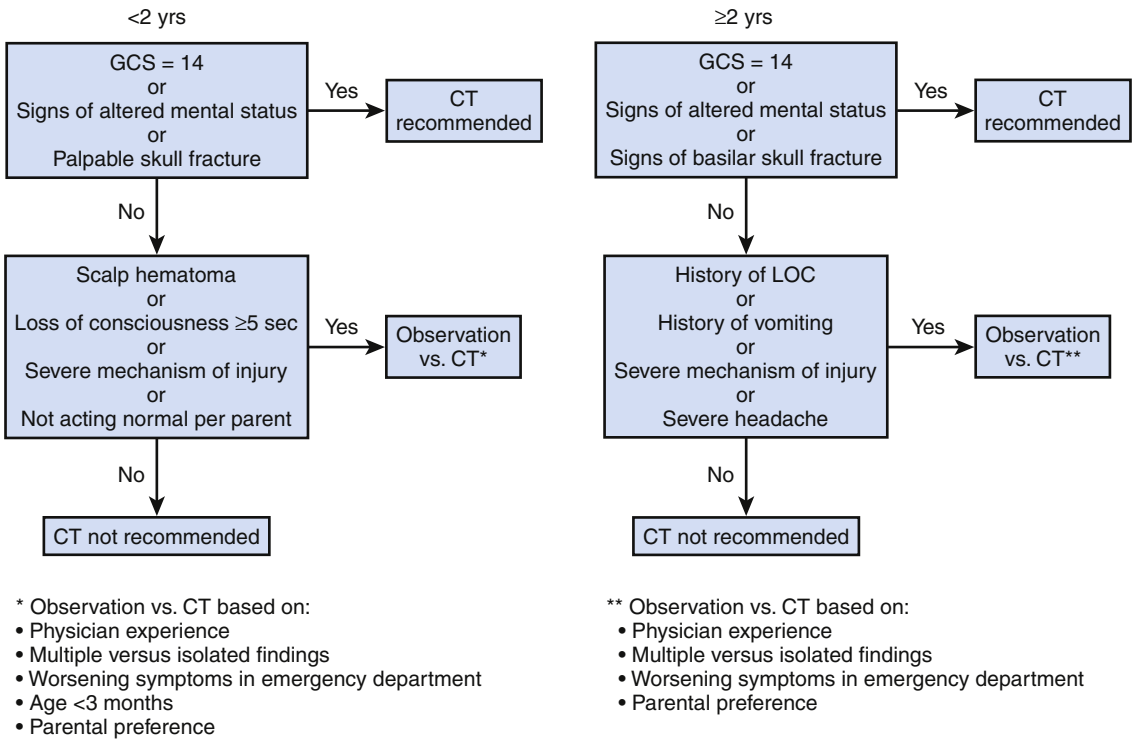


Figure 112–6. Algorithm for head CT using predictive rules. *(Modified from Kupperman N, Holmes JF, Dayan PS, et al: Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study,* Lancet *374:1160-1170, 2009.)*

emergency department thoracotomy in children are limited to small patient series and dated retrospective reviews. Available evidence suggests that this procedure should be reserved for pediatric patients who present with detectable vital signs and deteriorate despite maximal resuscitation.[48-51] Each institution should establish guidelines for the use of emergency department thoracotomy to aid in decision-making when this rare procedure needs to be performed.

Emergency department thoracotomy should only be performed by a surgeon with appropriate training in this technique. A left anterolateral thoracotomy incision is made extending from left of the sternum in the fifth intercostal space to the table. A large incision is needed to aid visualization and therapeutic interventions. This incision may be extended across to the right side of the chest if needed. The next step is to control hemorrhage by digital compression, suture control, or clamping of bleeding blood vessels. A pericardiotomy is performed using a longitudinal incision to evacuate blood and inspect the heart for injuries. Open cardiac massage can be performed if needed. Cross-clamping the descending aorta will stop blood loss below the diaphragm and allow cardiac filling to achieve cardiac and brain perfusion. The pulmonary hilum can be clamped or manually compressed to control bleeding from the lung and pulmonary vessels.

Stabilization and Definitive Care

Following the initial resuscitation, a plan for the next step in care is defined. Children can be discharged from the emergency department if no injuries requiring inpatient observation or management are identified and there is a low suspicion of injury based on the clinical evaluation and mechanism of injury. Other children may require inpatient admission to either the general hospital ward or intensive care unit depending on the injuries identified. Some children may have injuries that require immediate operative repair and need to be moved directly to the operating room. Transfer to a higher level of care facility after evaluation and stabilization may be needed if injuries are identified that cannot be treated at the receiving hospital. The period from the time of injury until a definitive emergency department disposition is an active period of medical decision-making in the care of all injured patients.

Conclusions

Pediatric trauma care requires an efficient team-based approach from prehospital care until the time of discharge. Within current trauma systems, patient care is optimized for efficiency and outcomes when each team member has a defined role and effective communication is established within the team. By understanding the prioritized sequence of ATLS, rapid recognition and treatment of life-threatening injuries will occur efficiently within the team and greatly improve the outcome of these injured patients. Pediatric critical care providers will continue to take an active role in the management of the most severely injured pediatric trauma patients. Pediatric critical care physicians proficient in emergent procedures and knowledgeable of resuscitative measures in trauma care will augment the multidisciplinary approach to pediatric trauma care.

References are available online at http://www.expertconsult.com.

VII Chapter 113

Child Abuse and Neglect

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PEARLS

- Accidental trauma differs from nonaccidental trauma in presentation, workup, treatment, and outcome. In child abuse, the history of trauma is withheld or falsified, and if the presenting symptoms are vague and nonspecific, the diagnosis and treatment of injuries may be delayed. This contributes to the increased death and long-term morbidity seen in abused children.
- Abusive head trauma is the most common nonaccidental injury seen in the pediatric intensive care unit. It is the most common cause of death in abused children. Abusive head trauma is more likely to be fatal and more likely to cause long-term morbidity in survivors than accidental head trauma.
- The infant brain is more vulnerable to injury, especially to shaking (shaken baby syndrome [SBS]). The infant's neck muscles are underdeveloped and the head is proportionately larger than that of the adult. Large cerebrospinal fluid spaces in the infant allow greater movement of the brain within the skull. The infant brain has greater water content and increased deformability. Neurons and axons are less protected because of incomplete myelinization. Increased cerebral vasoreactivity predisposes the infant brain to cerebral edema.
- Accidental head trauma generates translational forces that result in focal damage. Nonaccidental trauma (e.g., shaking) generates rotational forces from rapid acceleration/deceleration of the head. Rotational forces tear cerebral bridging veins (creating subdural hematoma) and axons (creating diffuse axonal injury).
- Signs of SBS include subdural hemorrhage, retinal hemorrhage, and skeletal injury. A small number of cases will have all three signs. The presence of subdural hemorrhage and retinal hemorrhage, alone or in combination, in the appropriate clinical setting, are suggestive of SBS.
- Posterior rib fractures, metaphyseal fractures, and spinous process fractures are highly specific for abuse because their proposed mechanisms of injury are unlikely to occur accidentally.
- Abdominal trauma is the second leading cause of fatal child abuse, with death rates approaching 40% to 50%. Inflicted abdominal injury is often occult, presenting without obvious signs or symptoms; thus recognition is delayed. Treatment may be delayed because of a delay in seeking medical attention or a failure to consider nonaccidental injury in the differential diagnosis.
- Two types of forces are generated in inflicted abdominal trauma. Compression forces crush viscera against the anterior spine, and this crush causes burst injuries of the solid viscera and perforation of air-filled viscera. Deceleration forces cause shear injuries at the site of fixed, ligamentous attachments, with tears and hematoma formation at the ligamentous attachments of the liver and small bowel. Children with inflicted abdominal injury often have concomitant injuries suggestive of child abuse (bruises, head trauma, long-bone and skull fractures).
- Abusive thermal burns are of uniform thickness and closely replicate the shape of the inflicting object. Accidental thermal burns have varying degrees of thickness and irregular shapes. Abusive scald burns have an immersion pattern with a burn that is circumferential, is of uniform depth with a well-defined edge, and spares body creases. Accidental scald burns have more random patterns, vary in depth, have poorly defined edges, and do not spare body creases.
- All cases of suspected child abuse must be reported to child protective services and law enforcement. All cases of fatal child abuse must be referred to the medical examiner. Detailed, legible medical documentation and good communication between the treating physician and the medical examiner are essential to secure evidence needed for successful prosecution of the case.

Only a small percentage of physically abused children require hospitalization in the pediatric intensive care unit (PICU), but these children have been shown to have higher morbidity and death rates than critically injured victims of accidental trauma.[1,2] The types of injuries that result from nonaccidental injury, coupled with delays in diagnosis and management, account for the worse outcome in abuse victims. Diagnosis and management of life-threatening injury is often delayed because the history of preceding trauma is not provided, or is so vague or the trauma is depicted as so minor that the physician is led away from a possible traumatic cause for the patient's condition. The "golden hour" allotted for successful trauma resuscitation is spent considering an infectious, neurologic, or metabolic cause for the child's illness. In addition, there can be considerable delay in seeking medical care. Several hours to days may elapse between time of injury and time of presentation to a medical facility.

Head trauma is the most common type of inflicted injury seen in the PICU, followed by abdominal trauma, burns, and thoracic trauma. Child abuse victims should be approached

like trauma patients. They may have occult multiple-organ injury. The discovery of one injury demands a thorough evaluation for additional trauma. A meticulous investigation for injury has obvious medical utility, but it also becomes an essential part of the forensic investigation that ensues once a report of suspected child abuse is filed with child protective services and law enforcement.

Recognition of Child Abuse

History of Injury

The history of an injury must account for the type and severity of injury that is seen on physical examination. Suspicion of abuse should arise when any of the following occur:

1. The caretaker is unable to explain the injuries or gives a mechanism of injury that does not match the degree of injury seen. For example, a minor fall would not explain the presence of life-threatening cerebral edema.
2. The timing of the injury does not fit with the time of presentation (e.g., a critical head injury cannot be attributed to a fall that occurred 1 week before presentation).
3. The child's developmental stage does not fit the history (e.g., rolling off a changing table should raise suspicion if the child is younger than 4 months).
4. The history of injury changes over time or from caretaker to caretaker. A careful review of all histories documented in the medical record may reveal discrepancies.

Patterns of Injury

Inflicted injury may be differentiated from accidental injury by its appearance, location, and distribution on the body (Table 113-1).

Bruising

Inflicted bruises are often bilateral, widely distributed, and located on soft tissue areas of the body that are unlikely to make surface contact during a fall. They may take the shape of the inflicting object (e.g., fingers, a hand print, linear whip marks from a belt, loop marks from a folded belt or cord). They are frequently found on the posterior trunk, buttocks, and the posterior side of the extremities because the victim would naturally be trying to run away from the perpetrator. Bruise color is not a reliable indicator of the time an injury occurred. Bruises resolve and therefore change color at different rates depending on their location and the force with which they were inflicted.[1] Nevertheless, documenting bruise color is important, particularly with the presence of bruises of markedly different colors at the same time, suggesting that the child may have been abused on more than one occasion. A simple gingerbread-man drawing of the child's body, marked with the locations of all the child's injuries, is a concise descriptive tool that will quickly jar a physician's memory before any legal proceeding.

Early photographic documentation of the child's injuries is essential. Thirty-five mm photography has been the standard for documentation, but digital cameras, both still and video, are replacing 35 mm photography. Polaroid photographs have been used in court, but they are inferior to 35 mm and digital photographs in both clarity and durability. Every effort should be made to obtain the best photographs; 35 mm photographs taken by a medical or law enforcement photographer are ideal. If a professional photographer is unavailable or if the attempt to obtain a professional is unsuccessful, any staff member familiar with the use of the camera should take photographs for the medical record.

Burns

Numerous researchers have attempted to describe the profile of an abused burned child and to characterize inflicted burns. In general, the child is often from a single-parent family of lower socioeconomic status on which previous suspicions of child abuse or neglect may have been filed. Compared with accidental burns, abuse burns are more extensive in degree and distribution, and often require management in a PICU.[2,3] Inflicted burns are of two types. Thermal injuries involve forced contact with a hot object, and scald injuries involve contact with a hot liquid, usually water. Abusive thermal burns are of uniform thickness and closely replicate the shape of the inflicting object. For example, an inflicted cigarette burn is approximately 8 mm round and uniform in depth. Accidental thermal burns have varying degrees of thickness and irregular shapes. If a child accidentally brushes against a hot cigarette, the burn will be more linear and of varying depth along its length.[1]

Abusive scald burns have an immersion pattern. Part of the child's body, usually the buttocks or limbs, are forcefully immersed and held in hot water. The resulting burn is circumferential and of uniform depth with a well-defined edge called a tide mark. Body creases are spared (withdrawal sign) during inflicted scald injury because the child pulls and folds his arms and legs inward to avoid immersion in the hot water. Accidental scald burns have more random patterns, vary in depth, have poorly defined edges, and do not spare body creases.[2]

Ideally, photograph documentation should be done before the initial burn dressing. Additional photographs taken 24 to 48 hours later, when the burn has fully evolved in depth and distribution, can also be valuable during litigation.

Fractures

Many of the characteristics used to recognize inflicted bruises and burns can be applied to fractures. The mechanism of injury described by the caretaker must remain consistent, be compatible with the child's developmental stage, and must account for enough force to break the child's bone. Inflicted fractures can be bilateral fractures of the same age or multiple fractures in different stages of healing. In his textbook *Diagnostic Imaging of Child Abuse,* Kleinman[4] divides fractures according to their degree of specificity for inflicted injury. Posterior rib fractures, metaphyseal fractures, and spinous process fractures are highly specific for abuse because

Table 113–1 Patterns of Injury

Accidental	Nonaccidental
Unilateral	Bilateral/symmetrical
Isolated injury	Multiple injuries
Amorphous shape	Well-defined shape
Prominent bone areas	Soft tissue areas
Posterior aspect of body	Anterior aspect of body
One age of injury	Multiple ages of injury

their proposed mechanisms of injury are unlikely to occur accidentally. Scapula and sternum fractures are highly specific for abuse if the caretaker's history does not account for a tremendous amount of force having been applied to these bones. Fractures of low specificity for abuse are fractures commonly seen after bumps and falls (e.g., clavicle fractures, linear skull fractures, long-bone fractures in ambulatory toddlers). Between high and low specificity for abusive trauma are acute, bilateral fractures, multiple fractures of different ages, widened (diastatic) or depressed skull fractures, and long-bone shaft fractures occurring in the young, nonambulatory infant.

It was long held that spiral fractures were highly suggestive of abuse because their spiral configuration implied that a forceful twisting motion had been applied along the length of the bone. Dalton et al.[5] looked at femur fractures in children younger than 3 years, dividing the fractures into three types (oblique, transverse, spiral), and into three age categories (0 to 1 year, 1 to 2 years, 2 to 3 years). Their results showed that the incidence of spiral fractures increased significantly with increasing age, whereas the incidence of abuse was highest in the youngest age group regardless of fracture type. Spiral fractures can occur accidentally in vigorous, ambulatory toddlers. The age of the child holds more significance than fracture type when the possibility of inflicted injury is considered.[5,6]

Posterior rib fractures and metaphyseal fractures are frequently seen in shaken or battered infants. Posterior rib fractures occur when the child's chest is compressed. This compression causes the rib to rock back over its articulation with the transverse vertebral process. The transverse process acts as a fulcrum for the rib, and a fracture occurs on the rib's pleural surface. Although this fracture has been seen in pediatric patients with major, high-speed trauma, it does not occur accidentally in healthy children during mild to moderate thoracic trauma. Cardiopulmonary resuscitation (CPR) has not been shown to cause posterior rib fractures. A detailed discussion of posterior rib fractures can be found in Kleinman's textbook, *Diagnostic Imaging of Child Abuse*.[4] Acute rib fractures are difficult to see on a plain film. They may only first be visible 2 to 3 weeks after injury, when a callus has formed around the fracture site. Therefore finding a callused fracture on x-ray film is discovering trauma that occurred at least 2 to 3 weeks before the radiograph.[4]

The periosteum of a pediatric long bone is loosely attached to its cortex. Any violent pull, tear, or twist on the shaft of a child's long bone displaces the periosteum. The results are subperiosteal hemorrhage and periosteal elevation that can be seen on x-ray film. Conversely, the periosteum is tightly attached at its point of origin, the metaphyseal plate. The metaphyseal plate, which is the most newly laid-down bone above the growth plate, has delicate trabeculations. Violent forces applied to the midshaft periosteum are transferred to its point of origin, the metaphyseal plate, and an avulsion fracture occurs through the delicate trabeculae. Depending on the angle at which the radiograph is taken, a metaphyseal avulsion fracture can appear as a thin line through the metaphysis, as "corners" broken off the edges of the long bone, or as a "bucket handle" attached to the end of the long bone. Like posterior rib fractures, metaphyseal fractures are pathognomonic for abuse. These corner fractures or bucket handle fractures are occult. There is no deformity or swelling, and they are not obviously tender to palpation. Like posterior rib fractures, metaphyseal fractures are usually found on a radiograph obtained for other reasons or on a skeletal survey done during the medical investigation of a suspected abuse case. Spinous process fractures are the remaining type of fractures listed under "high specificity" in Kleinman's text. They are thought to occur during infant shaking, when the spine is in hyperflexion, causing sudden stress on the posterior spinous ligament as it articulates with the posterior spinous processes.[4]

Skull fractures are the second most common fracture seen in abused children, but skull fractures are also commonly seen in accidental head trauma. A skull fracture is suspicious for abuse when there is no significant trauma to account for the fracture. An unexplained skull fracture obligates the physician to look for additional injuries that are pathognomonic for abuse. For example, a skeletal survey may reveal occult posterior rib or metaphyseal fractures. A noncontrast computed tomographic (CT) scan may reveal bilateral subdural hematomas, which are not commonly associated with accidental skull fractures.

The guidelines for dating fractures are broad. In general, periosteal elevation can occur acutely, within hours to days after injury. Callus formation is seen approximately 2 weeks after injury. Loss of the fracture line begins to occur 3 weeks after the injury, and remodeling of the fracture occurs anywhere from 3 months to a year after injury, depending on the child's age. Infants will heal and remodel faster than older children. Skull fractures and metaphyseal fractures are difficult to date because they do not show the same periosteal reactions that healing ribs and long bones do.[4] However, a diastatic skull fracture, which is a linear skull fracture greater than 3 mm wide, is not an acute injury. It takes time for a skull fracture to separate more than 3 mm.

Skeletal Survey

Finding one suggestive injury on a child necessitates a radiological evaluation of the entire skeleton. Skeletal survey is the most common screening tool used in child abuse investigation. Two views of every bone in the body, radiographed with orthopedic technique, is the gold standard. "Body grams" or "baby grams," in which the entire infant's skeleton is pictured on one x-ray plate, are unacceptable. We have been able to obtain adequate surveys at the bedside when the patient has been too unstable to move from the critical care area to the radiology department. We have also obtained postmortem skeletal surveys before transferring the child's body to the medical examiner (ME), because the quality of our surveys far surpasses radiographs performed in the morgue and therefore may serve to focus the ME on particular areas of the skeleton during autopsy.

The younger the child, the higher the yield of a skeletal survey. Because smaller children are easier to lift, shake, throw, or pull, it is possible to generate the forces required to create the classic abuse fractures previously discussed. In general, skeletal surveys have the highest yield in children younger than 2 years and are obtained in children up to age 5 years, after which the yield becomes low.[1]

Because fractures pathognomonic for abuse, such as posterior rib fractures or metaphyseal fractures, are difficult to see on initial radiographs, it is strongly recommended that a second skeletal survey be obtained approximately 2 weeks after the initial survey. The later survey may reveal callus formation of healing fractures that were not visible on the initial skeletal survey.

Occult fractures can be detected by bone scan, but bone scan is not specific for fracture. The radioactive isotope used in bone scan will also enhance areas of infection, neoplasm, and growth. Therefore positive bone scans cannot be used as evidence of injury in court. A positive scan serves to focus attention on a particular area of the skeleton in need of closer study, but the area of injury must always be verified by subsequent plain film. Bone scans are most useful in detecting occult rib fractures. They are not as useful in verifying metaphyseal fractures because the metaphysis lies next to an area of vigorous bone growth, and growth areas are normally enhanced in pediatric scans.[4]

Abusive Head Trauma

Abusive head trauma (AHT) is the most common form of child abuse seen in the PICU and is the number one cause of death in child abuse victims overall. Roughly 50% of all trauma in children younger than 1 year is head trauma. The median age of abusive head trauma victims is 2 to 4 months. When Bruce and Zimmerman[7] looked at a population of children younger than 2 years with head trauma, they found that 90% of the head injuries were accidental, and 10% were attributed to abuse. Eighty percent of the deaths from head trauma, however, occurred in the smaller percentage of abused children. Outcome studies comparing children surviving accidental and nonaccidental head trauma show significantly higher morbidity rates in the nonaccidental victims. Clearly abusive head injury differs vastly from accidental head injury.

Characteristics of the Infant Brain and Cervical Spine

The infant brain is more vulnerable to injury than the adult brain for several reasons. The neck muscles inadequately support the infant's head, which is relatively large compared with the rest of the body. Consequently, the head is put through a broad range of random motions during a traumatic event like shaking. The cerebrospinal fluid (CSF) spaces are large. These spaces allow greater movement of the brain within the skull, and the brain has greater water content, thereby increasing deformability. Open sutures increase skull flexibility so that an infant's skull can be pushed inward causing cortical damage without fracturing. Incomplete myelinization leaves neurons and their axons less protected, and increased cerebral vasoreactivity at the site of injured neurons predisposes the brain to cerebral edema.[8,9] The infant upper cervical spinal cord is predisposed to injury because of the increased ligament elasticity, poorly supportive paraspinal muscles, incompletely ossified vertebrae with flattened, horizontal facet joints, and increased cord mobility within the cervical canal. In addition, the large infant head causes traction injury to the upper cervical cord during acceleration-deceleration. These factors combined require that the infant with suspected AHT be immobilized in a cervical collar until the cervical spine can be thoroughly evaluated for injury.

Mechanisms of Head Injury

Accidental head trauma, such as a fall from height, generates translational forces, which are applied directly to the site of impact resulting in focal damage to the cerebral cortex. We may see a focal contusion, a coup-contre-coup injury, or an epidural hematoma. Nonaccidental trauma (e.g., shaking) generates rotational force as a consequence of rapid acceleration/deceleration movements of the head. Rotational force distorts both gross and microscopic cortical structure.[15] The tearing of cerebral bridging veins creates subdural hematoma. Axons that are torn at the microscopic level result in neuron death and global cerebral injury.[16] Although subdural hematomas are a hallmark of shaken baby syndrome (SBS), they are rarely life-threatening lesions. The increased morbidity and mortality associated with AHT is attributed to brain injury at the cellular level. This cellular injury has been called diffuse axonal injury (DAI) or traumatic axonal injury (TAI). Furthermore, increased vasoreactivity at the site of damaged axons causes a rapid onset of diffuse cerebral edema, which increases intracranial pressure (ICP) and compromises blood flow to vital areas of the brain. Therefore the child is placed at risk for seizures, respiratory compromise, herniation, and death. Within hours of a shaking injury, a CT scan will begin to show a "black brain" with diffuse edema and a loss of gray-white matter differentiation.[8]

Neuroimaging of Abusive Head Trauma

CT imaging is the universally accepted screening tool for suspected AHT. It is readily available, does not require sedation, and easily identifies subdural hemorrhage. CT scan does not reliably date a central nervous system (CNS) bleed. An acute subdural hematoma may contain both clotted and unclotted blood, each of which has different attenuation on CT. This falsely gives the impression that an acute bleed has occurred within a preexisting or chronic hemorrhage. Magnetic resonance imaging (MRI) is not readily available and requires sedation, but it is a better tool for identifying subarachnoid hemorrhage, petechial hemorrhage, infarction, hypoxic-ischemic encephalopathy, and axonal injury. Subtle evidence of AHT and its consequent secondary brain injury are more easily seen on MRI. In addition, MRI is a more useful forensic tool than CT scan during a child abuse investigation. Hemoglobin degradation within a CNS bleed occurs in a predictable sequence and can be roughly timed. Each hemoglobin degradation product has a unique appearance on T1- and T2-weighted images, and an experienced neuroradiologist may be able to narrow down the time of CNS injury. MRI should ultimately be used in all forensic child abuse investigations. Forensic interpretation of MRI findings should only be done by an experienced neuroradiologist. Ultrasound is not a useful screening tool for AHT.[10]

Retinal Hemorrhages

It is widely hypothesized that the eye is subjected to the same acceleration/deceleration forces that the brain endures. Retinal vessels, coursing through the 11 layers of retina, will randomly tear, forming hemorrhages of multiple shapes (e.g., dots, blots, flame hemorrhages). Hemorrhage shape is determined by the cell orientation in the particular retinal layer where tearing occurs. Intraretinal hemorrhages of multiple shapes in various retinal layers are a classic finding in shaken baby syndrome.[11] Controversy still surrounds the mechanism of retinal hemorrhage formation and there have been

scattered reports of scant retinal hemorrhage found after CPR, or in the face of increased ICP (Terson syndrome) or increased thoracic pressure (Purtscher retinopathy). These retinal hemorrhages, however, differ in appearance from the classic retinal hemorrhages of SBS.[11,12] Approximately 30% of healthy neonates will have retinal hemorrhages at birth, but these rapidly resolve by the third or fourth week of life. The retinal hemorrhages of SBS extend into the periphery of the retina, which can only be fully viewed by indirect ophthalmoscopy. The standard for investigation of SBS requires an indirect ophthalmoscopy evaluation by an ophthalmologist and photodocumentation of the retinal hemorrhages using a retinal camera.

Shaken Baby Syndrome

The diagnosis of SBS is made in the presence of a constellation of signs (i.e., subdural hemorrhage, retinal hemorrhage, skeletal injury). The mechanisms of injury proposed to cause subdural hematoma and retinal hemorrhage have been previously discussed. Posterior rib fractures occur when the infant's chest is compressed during shaking. Metaphyseal fractures are thought to occur as the legs and arms are flailed back and forth. Only a small percentage of cases will have all three signs of SBS (subdural hematomas, retinal hemorrhages, and skeletal injury). More than half the cases will show both subdural hematoma and retinal hemorrhage, but the presence of subdural hemorrhage or retinal hemorrhage alone still suggests the diagnosis of SBS.[13]

A proposed sequence of events in SBS would be as follows: The frustrated caretaker impulsively attempts to stop the infant's crying by violently shaking the infant. The infant immediately loses consciousness and becomes apneic, at which time the caretaker impacts the infant down onto the mattress or floor and leaves the child to recover on its own. The cerebral damage and ensuing edema lead to increased ICP, ischemia, seizures, and further respiratory compromise.[1] Eventually medical care is sought for the child. The clinical history is vague, although there is usually some history of altered mental status. The child has nonspecific symptoms such as lethargy, poor feeding, and irritability, or may have had a seizurelike episode. The differential diagnosis includes sepsis, meningitis, new-onset seizure, or a metabolic disorder. These children commonly have no external evidence of trauma. Trauma may only become part of the differential when a CT scan done for other purposes reveals intracranial hemorrhage or when a bloody spinal tap fails to clear. Bloody taps that fail to clear should be spun down within 2 hours to look for xanthochromic CSF, which is indicative of a preexisting intracranial hemorrhage. CSF that has a clear supernatant suggests the presence of blood for less than 2 hours, supporting a diagnosis of bloody tap. For early diagnosis and management of a potentially lethal injury to be facilitated, trauma must always be included in the differential when a young child is seen with altered mental status, seizures, or apnea. Jenny et al.[14] reviewed 174 children with abusive head injury who were seen at the Denver Children's Hospital over a 5-year period and found that, in 31% of these children, the diagnosis of abusive head trauma was missed on first presentation for medical evaluation. The most frequent misdiagnoses made were gastroenteritis, followed by accidental head injury, sepsis, increasing head size, otitis media, and seizure disorder. Examiners were most likely to make the correct diagnosis if one of the following was present: severe respiratory symptoms, seizures, facial or scalp injuries, or single-parent household. Cases were often missed in the youngest patients, white infants, infants with less severe symptoms, and two-parent households.[14]

Inflicted Abdominal and Thoracic Trauma

Abdominal Trauma

After head injury, abdominal trauma is the second leading cause of fatal child abuse. Death rates approach 40% to 50%.[17] Cooper et al.[15] reviewed 10,000 pediatric patients with trauma who were admitted between 1972 and 1986, identifying approximately 4400 victims of inflicted injury. Of these, only 22, or 0.5%, had abdominal trauma, but the death rate for this small subgroup was 45%. Several factors probably contribute to these high death rates. Inflicted abdominal injury is often occult, presenting without obvious signs or symptoms; this delays recognition. There is usually a delay between time of inflicted injury and time of presentation to a medical facility. Parents may not bring the child to medical attention until the secondary effects of severe abdominal trauma, namely, hemorrhagic shock and peritonitis, manifest. Health care personnel further delay treatment by failing to consider nonaccidental injury in the differential diagnosis. In the study by Cooper et al.[15] the mean time of delay between time of injury and time of presentation for medical care was 13 hours. Of significance, all the children with inflicted abdominal injury in the study by Cooper et al.[15] had concomitant injuries commonly seen in child abuse. Ninety-five percent had soft tissue injuries, 45% had head trauma, and 27% and 18% had long-bone fractures and skull fractures, respectively. Half of the families had been previously reported to child protective services for suspected abuse or neglect. The most recent abdominal injuries seemed to represent an escalation of abuse in the home. Therefore, any suggestive injury should prompt physicians to look for occult abdominal trauma and to contact child protective services for investigation of the child's social situation.

Children with nonaccidental abdominal trauma tend to be older (>1 year) than children with abusive head trauma. Because they are larger and ambulatory, they are more difficult to grab, lift, and shake, but they are still vulnerable to physical blows. Inflicted abdominal trauma is blunt force applied to the abdominal wall, usually a punch, kick, or blow to the midepigastrium. Two types of force are generated. Compression forces crush viscera against the anterior spine, and deceleration forces cause shear injuries at the site of fixed, ligamentous attachments. We may find burst injuries of the solid viscera, perforation of the hollow, air-filled viscera, or tears and hematoma formation at the ligamentous attachments of the liver and small bowel.[15] The spectrum of inflicted abdominal injuries varies from that seen in accidental abdominal injury because the force of an inflicted blow is concentrated in the midepigastrium. Most inflicted injury will involve the small bowel (duodenal hematoma), liver lacerations, and pancreatic injury. A wider array of injury is seen in accident victims, involving kidneys, spleen, liver, and, to a much lesser extent, small bowel and pancreas.[16,17] Pancreatitis is rare in childhood, and trauma is the primary cause. Unless there is a history of significant injury to the epigastrium, nonaccidental injury must be strongly considered when pancreatitis is found

in young children. Given the occult nature of nonaccidental abdominal trauma, CT scan of the abdomen is the evaluation of choice when intraabdominal trauma is being ruled out in child abuse victims.[4]

Child abuse consultants often screen for occult abdominal injury using hepatic transaminases. Lindberg et al.[18] recently conducted a multicentered prospective observational study of children less than 60 months of age who were referred to a child abuse consultant for a physical abuse evaluation. Of the 1676 patients recruited to the study, 1276 were screened with hepatic transaminases (76%). Fifty-four (3.2%) of the 1276 screened patients were found to have abdominal injury on CT. The authors concluded that 3.2% percent does not justify routine screening for abdominal injury using CT. Of the 54 patients with verified abdominal injury, 14 (26%) had no clinical signs of abdominal injury and the decision to screen the child with CT was influenced by the child's hepatic transaminases. The authors used a threshold of 80 IU/L for either alanine aminotransferase or aspartate aminotransferase, which is a lower threshold than has been used by previous authors studying the same question. Using a threshold of 80 IU/L, the sensitivity and specificity of hepatic transaminases as a screening tool for occult abdominal trauma was 77% and 82%, respectively.[18]

Thoracic Trauma

Beyond the pathognomonic rib fractures of child abuse, extensive thoracic trauma is rarely seen. A child's thoracic cage is so plastic and deformable, however, that, even in the absence of rib fractures, a child abuse victim could sustain compromising pulmonary injuries, namely, pneumothoraces, hemothoraces, or pulmonary contusions. As with abdominal trauma, the physician's index of suspicion must remain high to avoid delayed management of a life-threatening thoracic injury. The reader is referred to subsequent chapters of this text for detailed discussion of pediatric thoracic trauma.

Sexual Abuse

Physically abused children may also be sexually abused. When a patient is examined for evidence of physical trauma, a careful genital examination is warranted. Any evidence of old or new genital trauma must be documented with photographs. Genital trauma is usually subtle, difficult to recognize, and difficult to photograph. When possible, consult a physician who specializes in sexual abuse and who may be able to perform a noninvasive colposcopic examination of the external genitalia. The best photo documentation of genital injury is obtained with a colposcope. Of great significance, using colposcopy to videotape and photodocument a child's forensic exam eliminates the need for repeat examinations on the already traumatized sexual assault victim. If acute genital trauma is suspected or identified, a "rape kit" or forensic collection of evidence must be performed, and the police must be involved early. The forensic evidence becomes legal documentation of the sexual assault, and a chain of evidence must be carefully maintained between the hospital and the forensic laboratory. All cultures must be collected in culture medium or broth. DNA probes for gonorrhea and chlamydia cannot be used as evidence in court. Ideally, evidence collection should occur before any washing of the genitalia, including before the skin prep for insertion of a Foley catheter. Speculum and bimanual examination of sexually abused children is not warranted unless there is concern about internal lacerations in need of surgical repair. To avoid the need for repeat examinations, a sexual abuse expert or pediatric gynecologist should perform this examination with the patient under anesthesia.[1]

Box 113–1 Protocol for Medical Investigation of Child Abuse

Physical examination for skin and genital trauma
Photography of all injury
Skeletal survey for children <5 years
Bone scan (if skeletal survey results are negative)
CT head scan for children <3 years
Ophthalmology consultation to rule out retinal hemorrhage
Abdominal trauma laboratory values
Serum amylase/lipase
Liver enzymes
Urine analysis
CT abdomen scan
All nonverbal children
Positive findings from abdominal examination
Abnormal laboratory results
MRI of the head if AHT is identified on CT or is strongly suspected despite equivocal CT findings

Protocol for the Medical Investigation of Child Abuse

To ensure complete and objective evidence collection during the medical investigation of child abuse, we have established an investigative protocol for our institution that is based on the current medical literature. This protocol has worked well across all pediatric subspecialty services in our institution and has provided consistency when communication occurs with law enforcement, legal services, child protective services, and our community pediatricians (Box 113-1).

Fatal Child Abuse

Fatal child abuse is not merely a phenomenon of the twentieth century. There have been reports of fatal child abuse throughout history. Caligula's daughter died of inflicted head trauma in AD 41. The French literature records the fatal whipping of a 4-year-old girl in the 1850s. In 1860, Professor Ambroise Tardieu published a paper describing fatal physical and sexual abuse inflicted on infants and children by parents. Tardieu's account listed thermal burns, fingernail imprints, contusions due to pinching, intracranial hemorrhages, and other injuries similar to those seen today. Likewise, these parents and caretakers offered explanations for the injuries that were incompatible with the severity of injury, such as falls during play or by other minor accidents. Knight[19] concludes, in his historical review of child abuse, that fatal child abuse is nothing new.

Eighty percent of fatal child abuse is caused by head injury. Because many of these children undergo surgical intervention before their death, the forensic pathologist/ME is often faced with an autopsy in which the injuries have been altered by surgical procedures. An exact description of the injuries present before treatment is essential: for example, the extent (amount), location, and radiologic information (CT, MRI,

plain films) of all epidural, subdural, and subarachnoid hemorrhages. The chart must reference any biopsy specimens (usually blood clots) submitted to the pathology laboratory during surgical procedures. Documenting the extent and location of retinal hemorrhages may assist the forensic pathologist/ME during gross examination of the eyes. Although there are nontraumatic causes of retinal hemorrhage, CPR is not a common cause. The location and size (in inches/centimeters) and a brief description of any abrasions, lacerations, and contusions should be stated. With respect to contusions, the color on admission and on successive days should be recorded. Likewise, any skin breakdown following medical procedures, notably on the posterior scalp and neck, needs documentation.[20]

As previously stated, visceral trauma is the second leading cause of death in child abuse. Abdominal injuries include liver, spleen, intestinal, mesenteric, and renal contusions, lacerations, and rupture. There may be minimal external evidence of such catastrophic injuries. In the event that they are discovered during surgery, the amount of blood in the peritoneum and extent of organ damage should be carefully documented. Abdominal injuries resulting from CPR are extremely rare.[21]

Osseous Injury in Fatal Child Abuse

Fractures of bones in fatal child abuse are evidence. Documentation of the site of fracture (e.g., metaphyseal distal femur), type of fracture (e.g., transverse, spiral), and possible dating by x-ray analysis should be done on all cases. A head-to-toe approach with skeletal survey will aid the forensic pathologist/ME by locating injuries before the autopsy. During the autopsy, sections of these fractures are taken. Although some authorities consider histologic dating to be accurate, there are wide variations in the chronological healing of fractures. Only an approximate time frame can be assigned to a fracture.[22] Osseous injuries will also alert the staff to possible nontraumatic causes such as osteogenesis imperfecta.

Scene Investigation in Fatal Child Abuse

The scene is where the infant became unresponsive, became apneic, or sustained injuries that led to hospital admission. The scene typically belongs to and is secured by law enforcement officers, so the earlier they become involved, the more timely and accurate the scene investigation will be. Emergency medical service (EMS) providers or firefighters are often the first to arrive on the scene. Their narrative description of the immediate circumstances and surroundings is a crucial part of scene investigation. They are encouraged to describe the place and position in which the child was found; the type of bed and bedding the child was found in; the presence of body fluids (blood, vomit, urine, feces) at the scene; the tidiness of the environment; and the presence of drugs, medications, drug paraphernalia, or alcohol at the scene. They often record the initial reactions of caretakers, identify potential witnesses to the preceding events, and discover other vulnerable children within the household. Talking to EMS providers on their arrival with the critically injured child can provide a wealth of information leading to early suggestions of child abuse/neglect, timely medical interventions, and early law enforcement and child protective services involvement.

Box 113–2 Scene Investigation Information

Law enforcement jurisdiction
Date, time, address of place of injury
Witnessed by whom (or unwitnessed)
First responders to scene
Field interventions (CPR, intubation, drugs)
Description of victim as found
Description of environment
Scene diagram (supplied by law enforcement)
Interviews with parents, caretakers, witnesses
Cardiopulmonary resuscitation

Autopsy

The successful identification of tragic fatal child abuse cases depends on a team approach. Box 113-2 lists the minimal information desired by the forensic pathologist/ME before autopsy.[23] Clearly this list is best assembled as a collaborative effort of EMS, law enforcement, and physicians. Ideally, representatives of the pediatric team, law enforcement, and the district attorney's office would attend the autopsy examination. Although law enforcement attendance is routine in all fatal child abuse cases, numerous constraints interfere with pediatric presence at autopsy. Minimally, a phone conversation between the ME and the pediatric attending physician is strongly recommended.

Organ Procurement Organization and Fatal Child Abuse

The limited supply of organs for transplantation is well known. Although all age groups are represented, there is a lower organ donation percentage in the pediatric age group because this group has a lower relative death rate. Thus the use of organs from the pediatric age group is critical. When a child or infant sustains injuries leading to brain death, organ procurement is sought by organ procurement organizations (OPOs). Initially, some forensic pathologists/MEs may deny the use of organs on the basis that it may cause problems with judicial procedures.[24] This is not absolute. All three agencies must examine each individual case. The district attorney, forensic pathologist/ME, and the pediatrician must work with the OPO to see if organs not damaged by injury may be used in transplantation. If all parties are satisfied, then a representative of the ME's office (ideally the forensic pathologist/ME who will do the autopsy) should be present when the organs are retrieved for transplantation. The interacting groups are listed in Box 113-3.

Documentation and Testifying in Court

Testimony of medical personnel begins with thorough and legible documentation in the medical record. Complete, rather than brief, documentation is strongly recommended, because trials may be delayed for months to years. Handwritten notes will become a memory lifeline during testimony. One must document information objectively. Be specific about where information is coming from. When recording conversations with caretakers, place their exact words in italics and write "per conversation with…." Months to years later,

Box 113–3 Key Groups Needed for Tissue Procurement

Pediatrician representing family's request
OPO representative
ME office
District attorney's office

one will not remember exactly who was interviewed or who actually said what is written in the chart. Written words may be misconstrued as opinion, and defense attorneys frequently make this an issue when witnesses testify to confuse or discredit testimony.

Testifying on behalf of a child who has been abused or murdered is emotional. Stick to the facts and remain objective. Remember that medical personnel are not the judge in this case. Stay calm, particularly when being cross-examined by the defense attorney, and remember that medical personnel and their work are not on trial. There is no urgency in court. Take the time you need to formulate answers. Responses should be brief and limited to the questions asked, unless one is specifically told to elaborate further. If a question is not understood, ask that it be clarified before an answer is given. If a detail (e.g., a date, a time, a person's name) cannot be recalled, simply state so. One is allowed to refer to the medical records once they have been entered into medical evidence. If a witness does not think that he or she possesses the expertise to answer a question, then the witness should simply state so.

The more prepared one is, the less stressful the experience in court will be. It is the responsibility of medical personnel to review the medical records, laboratory reports, and radiological studies before trial. If the prosecuting attorney is properly preparing the case, the attorney will meet with each witness before testimony is given. This meeting gives both the attorney and the witness a chance to clarify specific issues that will be raised in court and to discuss the limits of the testimony. One may be asked to submit an updated curriculum vitae to establish credentials. If one is being called as a fact-finding witness, the court will not solicit opinions. During the trial, one may be qualified as an expert witness in his or her medical subspecialty. Then, one will be allowed to express opinions more freely.

If one is called to testify again regarding the same case or if a deposition was given before trial, then previously recorded statements should be reviewed so that testimony remains consistent. It serves to keep the witness from becoming uncomfortably entangled in unintended contradiction and legal rhetoric on the stand. Included in the following reference list are suggested readings that may be helpful in preparation trial.[25-27]

References are available online at http://www.expertconsult.com.

VII Chapter 114

Thoracic Injuries in Children

Mauricio A. Escobar Jr. and Michael G. Caty

PEARLS

- Thoracic injuries in children are uncommon but result in significant morbidity and mortality, mainly from the frequently associated head trauma and abdominal trauma.
- Most thoracic injuries in children result from blunt trauma.
- The most common manifestations of thoracic trauma in children are rib fractures, pneumothoraces, hemothoraces, and pulmonary contusions.
- Traumatic asphyxia and commotio cordis are more common in children than in adults.

Thoracic injuries in children are relatively uncommon, but result in disproportionate morbidity and mortality compared with other traumatic injuries, mainly because thoracic injuries often are associated with other life-threatening conditions and injuries. Children, unlike adults, undergo constant growth and change. Any consideration of the injured child must take into account several factors including age-related limitations in their ability to communicate and to understand their injuries, a limited ability to cooperate with care, and their potential for recovery, growth, and life-long productivity.[1] Children with significant thoracic injuries require intensive monitoring and hemodynamic and respiratory support. It is important to establish an accurate diagnosis. High-resolution imaging techniques such as helical computed tomography (CT) are indicated to detect intrathoracic lesions. This chapter discusses the epidemiology, diagnosis, and immediate approach to children with thoracic injuries and the current management of specific injuries to the thorax.

Epidemiology

The National Pediatric Trauma Registry (NPTR) was created in 1994 and has collected information from 94 trauma centers in the United States. From 1994 to 2001, 3721 patients with thoracic injuries were reported, which corresponds to 7.7% of all pediatric trauma.[2] Interestingly, isolated thoracic injuries accounted for only 0.7% of all pediatric trauma patients. Thoracic trauma occurs more frequently in males, with a male/female ratio of approximately 2:1. No differences in age distribution are noted. Blunt trauma is the most frequent cause of injury (92%). The incidence of penetrating chest injury in urban areas is increasing with the escalating use of firearms in society. However, penetrating injuries (gunshot wounds and stab wounds) currently account for only 8% of all thoracic injuries in the pediatric patient.[2]

An analysis of consecutive pediatric patients treated at a Level 1 trauma center found that the most common thoracic injuries were pulmonary contusion (48%), pneumothorax/hemothorax (39%), and rib fractures (32%).[3] Thoracic injuries most commonly present concomitantly with other injuries.[2-4] From 60% to 85% of children with thoracic injuries have significant injury to at least one other organ system, most notably the central nervous system (CNS), the abdominal cavity, or the musculoskeletal system.[3,4] The most common mechanisms of injury are motor vehicle-related accidents (40.7%), children as pedestrians struck by a motor vehicle (19.2%), bicycle accidents (6.6%), and falls (5.8%). Additionally, abuse accounts for 7% to 8% of blunt trauma in children.[5] The pediatric traumatologist must also be aware of other modes of blunt injury including skateboarding, skiing, snowboarding, sports injuries, fights, and suicide. The advent of "extreme sports" in geographically risky areas must also be kept in mind. Finally, the role of alcohol and drugs in injury must be addressed.[1]

The clinical importance of thoracic injuries is reflected in the greater severity of injury observed in children with thoracic injuries (Trauma Score [TS] 11, Injury Severity Scale [ISS] 27) compared with that seen in children without thoracic injuries (TS 15; ISS 7).[4] According to the NPTR, the overall mortality for trauma in the pediatric population is 3%. Thoracic injuries are present in 33% of fatal cases. The mortality rate for thoracic trauma is 12.2%. In patients with thoracic trauma, CNS injuries are the major cause of death (63.1%), followed by uncontrollable hemorrhage (13.5%).[2] The number and severity of associated injuries are important determining factors in the eventual outcome and survivability of the injury.[3-6] Stratification of mortality rates according to the number and type of associated injuries illustrates this point. In isolation, thoracic trauma in children carries a 5% mortality rate. Children with abdominal and thoracic injuries have a 20% mortality rate; children with chest and head injuries have a 35% mortality rate; and children with all three injuries have a 39% mortality rate.[4] Fortunately, immediately life-threatening chest injuries are infrequent; consequently, emergency thoracotomies in the operating room are required in only 3% to 6% of all

pediatric thoracic trauma.[7] Indications for emergency thoracotomy include victims of penetrating thoracic trauma who had signs of life at some point during the resuscitative efforts.[8] The indication for emergency thoracotomy in blunt trauma (witnessed cardiac arrest in the emergency department) is controversial.

Anatomic and Physiologic Considerations with Chest Injuries

The injured child is not a small injured adult. The thoracic organs in a child exhibit different physiologic characteristics than in an adult. Increased cartilage content and incomplete ossification of the ribs make the thoracic cage more compliant than that of an adult, permitting the anterior ribs to be compressed against the posterior ribs.[9] This compliance results in more kinetic energy being transmitted to intrathoracic organs without bony injury. Therefore pulmonary contusions without concomitant rib fractures are more common than in adults. Rib fractures and flail segments become more common as ossification occurs. The flail segment responds to changes in intrathoracic pressure rather than to the pull of respiratory muscles, resulting in retraction with inspiration and bulging with expiration. This paradoxical movement results in inefficient thoracic expansion and increased energy expenditure. Hypoventilation and subsequent atelectasis result from the associated pain.

The trachea is more compressible and narrower (narrowest at the level of the cricoid cartilage) early in life. Therefore children are susceptible to profound respiratory embarrassment from seemingly inconsequential insults (foreign body aspiration, etc.). A decreased functional residual capacity coupled with higher oxygen consumption per unit body mass leads to rapid development of hypoxemia in the traumatized child. This equalizes to adult values by age 8 to 10 years. Cardiac output in children is determined by heart rate and stroke volume. Contractility is largely fixed in early life. Children may compensate hemodynamically and maintain a normal blood pressure with up to a 40% blood loss. Additionally, the less complete fixation of the mediastinum in children allows more visceral shift, greater compromise of preload, and profound hypotension.[1]

Diagnosis and Immediate Management of Chest Injuries

The initial evaluation of the child with known or suspected thoracic trauma conforms to standard trauma protocols.[10] Life-threatening diagnoses should be sought in the unstable child at each step of the evaluation during the primary survey (Box 114-1). First, the patency of the airway is established. The inability to maintain an airway because of anatomical obstruction or depressed level of consciousness (Glasgow Coma Scale [GCS] ≤8) warrants endotracheal intubation. All patients with suspected cervical injuries should have manual in-line cervical stabilization maintained during intubation. If endotracheal intubation is not possible, an age-appropriate surgical cricothyroidotomy should be performed.

After the airway is secured, breathing is assessed. Both hemithoraces are observed for symmetrical motion and auscultation is performed to evaluate breath sounds. In the intubated patient the position of the endotracheal tube should be checked, looking for asymmetric chest expansion or decreased breath sounds, before any invasive procedures are performed. Arterial Pao_2 analysis and pulse oximetry are useful for assessing oxygenation whereas $Paco_2$ level and capnography, where available, are extremely helpful for assessing ventilation. Capnography is being used increasingly in the emergency care of critically ill infants and children. It not only documents the correct intratracheal position of the endotracheal tube, but may also help to guide ventilation during transport. The stable child with decreased breath sounds on one side should undergo immediate chest radiography. A chest tube should be placed if either a pneumothorax or hemothorax is demonstrated. In an unstable child, needle thoracentesis should be performed immediately on the side with decreased breath sounds (Figure 114-1).

Assessment of the circulation begins with recording the pulse rate and blood pressure. Observation of capillary refill provides an approximation of tissue perfusion. Appropriate intravenous access is established and fluid resuscitation is initiated. Cardiac tamponade should be suspected in the child with equal breath sounds and a normal chest x-ray film but hemodynamic instability. Pulsus paradoxus and jugular venous distension are inconsistent findings. Their absence should not be used to rule out the presence of cardiac tamponade.

Additional clues to the nature of injuries are obtained by observation and palpation. Specifically, looking at the patterns of abrasions and contusions may suggest the mechanism of injury and allow prediction of potential intrathoracic injuries. One example is the child with a sternal contusion, who should

Box 114–1 Acute Thoracic Conditions Requiring Immediate Correction

Airway obstruction
Tension pneumothorax
Massive hemothorax
Cardiac tamponade

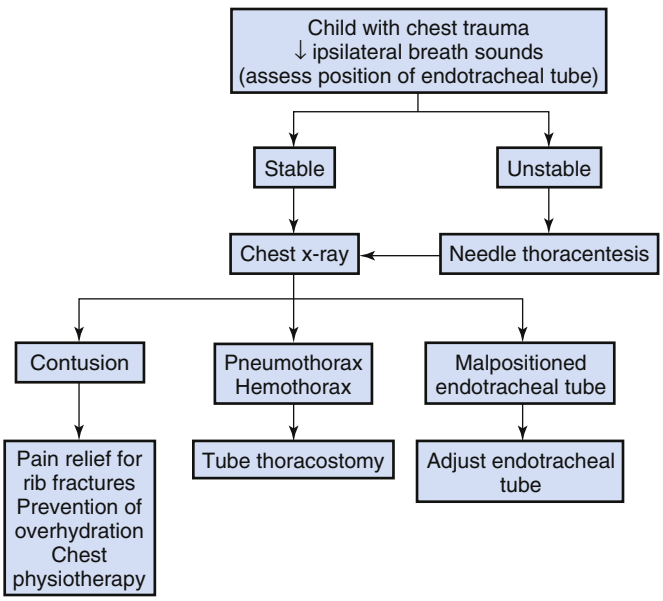

Figure 114–1. Management of the child with decreased breath sounds.

be assessed for a cardiac contusion. The thoracic cage should be palpated from under the arms to the abdomen in a sequential fashion, looking for rib tenderness and/or flail segments. Chest radiography completes the initial evaluation. The physician checks the x-ray film for evidence of pneumothorax, hemothorax, pulmonary contusion, and rib fractures. First and second rib fractures do not seem to be reliable indicators of aortic injury in children, but may be related to other significant vascular injuries (subclavian artery).[11-13] In general, approximately 60% of patients with a thoracic trauma diagnosis are admitted to the pediatric intensive care unit for further monitoring and management.[3,14]

Rib Fractures

Fractures of the bony thorax, specifically rib fractures, are more common than previously suspected.[3,6,15] In one large study, rib fractures were noted in 32% of all children with thoracic injuries.[4] However, in the context of all injured children admitted, rib fractures were infrequent and were observed in only 1.6% of injured children. Again, the pediatric experience stands in sharp contrast to the adult experience, in which rib fractures are frequently seen and are present in 33% of injured adult patients.[6] The importance of rib fractures as a marker of injury severity has been emphasized.[11] In one study, rib fractures were noted in only 1.6% of children admitted. However, the mortality rate of children with rib fractures was 42%, compared with a 2.1% mortality rate in children without rib fractures. When a head injury is associated, children with rib fractures have a disproportionately higher mortality rate of 71%. In addition, head injury and the number of ribs fractured correlate with risk of mortality in children.[14]

The mechanisms of injury resulting in rib fractures parallel those seen in other pediatric thoracic injuries, with the notable exception of the high incidence of intentional injury in younger children. Traffic injuries accounted for nearly 70% of all rib fractures, whereas child abuse accounted for 21%. The mean age of children with rib fractures is 4.7 years, and nearly 60% of children with rib fractures are 4 years or younger. It is noteworthy that child abuse accounts for nearly two thirds of rib fractures in children younger than 3 years.[14] The number of fractured ribs in both injured adults and children correlates directly with the severity of injury (assessed by the Revised Trauma Score [RTS] and the ISS), the likelihood of multisystem and intrathoracic injury, and higher mortality rates.[14,16] Presence of three or more rib fractures in a child reliably identifies him or her as having a significant likelihood of intrathoracic, as well as other organ involvement, and a significantly higher probability of dying.[6]

First and second rib fractures in children do not correlate with the presence of concomitant injury to the mediastinal great vessels and, in isolation, do not warrant aortography.[3,14,17] Additionally, neither posterior rib fractures nor scapular rib fractures were indicative of great vessel injury. However, first and second rib fractures are associated with pulmonary contusions, cervical spine injuries, and injuries to intrathoracic vessels and nerves.[13-19] Moreover, evidence suggests that the presence of thoracic spine fractures should heighten the suspicion of great vessel injury.[20] Lower rib fractures may be associated with liver and spleen injuries.[21]

The key to successful management of chest wall injuries is adequate pain control to promote effective air exchange and to facilitate pulmonary toilet.[6,22,23] The goal is to prevent atelectasis and pneumonia. Regional anesthetic techniques, such as epidural and intercostal nerve blockade, play an expanding role in pain control and are increasingly viewed as effective and safe adjuncts to traditional analgesia techniques.[22,23]

Flail segments result from multiple contiguous ribs with more than two points of fracture, fracture of the sternum and multiple costochondral junctions, or midaxillary fracture with fracture or dislocation of rib heads.[1,24] A 17-year review of 225 children treated for chest trauma revealed no incidences of flail chest.[24] These injuires are quite rare in children. For flail chest injury patients, an ISS greater than 23, the need for blood transfusions within the first 24 hours, and the presence or development of shock on admission are suggested as factors that predict the need for ventilatory assistance.[22] These assertions stem from an analysis of adult patients. Their validity in the treatment of children awaits further evaluation. Fortunately, the majority of children with fractured ribs do not require ventilatory assistance and have a good overall prognosis.[14]

Clavicle, Sternal, and Scapular Fractures

The medial physis of the clavicle does not typically close until 23 to 25 years of age.[25] Because of this, falls on the shoulder may lead to posterior sternoclavicular physeal fracture-dislocations in children. These injuries can be associated with dysphagia, dyspnea, and brachiocephalic compression.[26] The clinician must evaluate for esophageal and great vessel injuries in this population. Sternal fractures in children can occur from motor vehicle collisions, direct blows, or flexion-compression of the spine.[27-29] Although rare, these types of fractures may be associated with blunt cardiac injury.[30,31] All patients with sternal fractures or sternal bruising should be assessed for a cardiac contusion.

Scapular fractures are uncommon in children.[32] A significant amount of force is required to fracture the scapula. Scapular fractures are associated with rib fractures, pulmonary contusion, and head injury. Axillary artery or brachial plexus injury may also occur.[33]

Children with symptomatic chest wall injuries should have imaging performed to identify the fractures and associated intrathoracic injuries. Children with suspected posterior sternoclavicular fractures/dislocations, first rib fractures, and sternal fractures should be evaluated with CT imaging to evaluate the great vessels and intrathoracic organs.[34] Additionally, an electrocardiograph should be obtained in children with sternal fractures.[35] Any abnormal rhythm should lead to an echocardiogram and cardiac enzyme analysis to exclude blunt cardiac injury.[31]

Pulmonary Contusion

Pulmonary contusion rivals pneumothorax/hemothorax as the most common childhood thoracic injury. It is present in as many as 48% of children with thoracic injuries.[3,4] Pulmonary contusion is defined as nonanatomical areas of consolidation on chest radiograph or CT. Evidence suggestive of pulmonary contusion, such as external chest wall abrasions, tachypnea, and abnormal breath sounds, is frequently absent in children. Automobile crashes represent the most common mechanism

of injury. Pulmonary contusion is usually associated with other potentially more life-threatening conditions such as pneumothorax/hemothorax or other systemic injuries.[4,14,36-38]

Rib fractures are present in up to 32% of children with intrathoracic injuries.[4,14,36-38] Up to 40% of cases of pulmonary contusion and other intrathoracic lesions were not radiographically evident until 48 hours after injury.[36] Thus rib fractures are important markers of internal injuries because the radiographic manifestations of other intrathoracic injuries are often delayed. When pulmonary contusion is accompanied by rib fractures, serial chest radiographs should be performed during the initial 48 hours after injury to promptly identify other intrathoracic injuries.[36] Although most patients with pulmonary contusion are identified by sequentially obtained chest radiographs, CT imaging may be of greater value in demonstrating posttraumatic intrathoracic pathology in patients requiring endotracheal intubation and mechanical ventilation. For patients with an oxygenation index (Pao_2/Fio_2) less than 300, a CT scan may be helpful in defining the extent of pulmonary contusion and identifying those patients at higher risk for acute respiratory failure or those with unsuspected or incompletely treated hemothoraces or pneumothoraces.[39]

Management of pulmonary contusion centers on oxygen supplementation, judicious fluid management, pain control, adequate pulmonary toilet, and respiratory support. Many children with thoracic trauma exhibit wet lung, a syndrome characterized by a combination of pulmonary contusion, pneumonia, and atelectasis.[24,40] However, concern for wet lung should *not* compromise appropriate volume resuscitation during the initial evaluation. Corticosteroids are ineffective and probably harmful.[36] Prognosis for most children with pulmonary contusion is excellent, because the majority of these injuries are mild to moderate in severity, and children recover without the need for ventilatory support. For severe pulmonary contusions, differential lung ventilation may be valuable.[41-43] Early success of synchronized independent lung ventilation using a double-lumen endobronchial tube connected to two ventilators indicates a potentially lifesaving treatment option for the child with a significant pulmonary contusion.[37] Early institution of synchronized independent lung ventilation may increase survival in the severely injured patient with pulmonary contusion.[3,4,37,38,44] Extracorporeal life support measures may increase the risk of posttraumatic bleeding complications.[1] Approximately 20% of children with pulmonary contusion develop pneumonia, a risk factor for developing respiratory failure. Half of the children who develop respiratory insufficiency do so in the first few hours after injury.[40] Few develop true adult respiratory distress syndrome (Pao_2/Fio_2 <200), and death primarily related to the pulmonary contusion is rare in children.[40,45]

Traumatic Asphyxia

Traumatic asphyxia results from direct compression of the chest from crushing injury in conjunction with a deep inspiration and closed glottis. This results in a marked increased in intrathoracic pressure that is transmitted from the right atrium directly through the valveless superior and inferior vena cava, causing rupture of venules and capillaries of the face and head. A rapid increase in intracranial pressure may also occur.[44] Clinical manifestations include conjunctival hemorrhage, facial edema and cyanosis, ecchymotic or petechial hemorrhages of the chest and face, hemoptysis, epistaxis, hemotympanum, and exophthalmos.[46] Retina, vitreous body, or optic nerve hemorrhage may result in loss of vision. Associated neurologic symptoms include altered mental status, brachial plexus injuries, quadriplegia (without evidence of spinal cord injury), and coma.[47] Interestingly, while clinical manifestations of traumatic asphyxia can be quite dramatic, morbidity and mortality are generally due to associated injuries. For those children that survive the initial traumatic insult, the dramatic clinical manifestations usually resolve with no neurologic sequelae.

Pneumothorax/Hemothorax

Pneumothorax and hemothorax collectively represent the second most common intrathoracic injuries seen in children.[3,4,36] Together, they account for 39% to 50% of childhood intrathoracic injuries. Among all children who sustain thoracic trauma, approximately one third will develop a pneumothorax.[3,4] One third of the pneumothoraces occur in isolation.[3] The remainder will have associated intrathoracic and extrathoracic injuries. The majority (76%) of chest injuries resulting in pneumothorax or hemothorax require only a tube thoracostomy for successful management.[3,4,48] One of the most common mistakes in managing a significant hemothorax is placing a chest tube that is not large enough to adequately evacuate the blood (Table 114-1). Tube thoracostomy is best performed with the upper extremity fully abducted. This position elevates the ribs and widens the intercostal space, facilitating the placement of the chest tube, which may be both diagnostic and therapeutic. The chest tube is inserted more caudally and more posteriorly for a suspected hemothorax than for a pneumothorax. Ideally, the fifth intercostal space is used along the midaxillary line. At this level, there is little danger to the long thoracic nerve, and relatively little risk to the liver or spleen. More posterior placement of the tube can result in obstruction of the tube when the child lies in the supine position.

Because of the low arterial pressure in the pulmonary circulation, bleeding from tears in the lung parenchyma is slow and hemostasis occurs early after the lung is reexpanded. Prompt drainage of blood in the thorax is necessary for several reasons, including prevention of lung entrapment secondary to hemothorax organization, prevention of infection (empyema), and

Table 114–1 Chest Tube Sizes by Patient Weight

Age	Weight	Chest Tube Size
Newborn to 1 year	3–5 kg	10–12 Fr
≥1 year to 2 years	6–9 kg	12–16 Fr
3 years to 4 years	10–11 kg	16–20 Fr
	12–14 kg	20–22 Fr
5 years to 7 years	15–18 kg	22–24 Fr
	19–22 kg	24–28 Fr
8 years to 11 years	23–30 kg	28–32 Fr
≥12 years	>30 kg	32–42 Fr

Data from Bliss D, Silen M: Pediatric thoracic trauma, *Critic Care Med* 30(11): S409-S415, 2002.

accurate quantification of the amount of hemorrhage.[1] Exsanguinating hemorrhage usually involves intercostal, hilar, or mediastinal vessels. Thoracotomy is indicated when the initial thoracostomy tube output is greater than or equal to 20% to 30% of the blood volume, when the output is greater than 2 to 3 mL/kg/hr over the following 6 hours, or when significant rebleeding occurs.[49]

It is widely accepted that the erect chest radiograph with posteroanterior and lateral projections is highly accurate in demonstrating major intrathoracic pathology. However, with the overriding concern for possible cervical spine injury, chest radiographs during trauma resuscitation usually are taken with the child in the supine position. In that position, small and even modest collections of air may not be readily demonstrated. Although the portable chest x-ray film has a well-defined role during assessment of thoracic injuries, its limitations must be borne in mind.[48]

Whenever possible, standing anteroposterior and lateral chest x-ray images should be obtained as soon as the clinical condition allows. Some authorities, noting the lower sensitivity of chest radiographs, recommend that emergent chest CT scans be performed in stable patients with blunt high-energy torso trauma, cross-body injury patterns, or mechanisms of injury suggestive of chest trauma.[16,38,50] The focused assessment sonography for trauma (FAST) in the setting of thoracic trauma is useful for detecting fluid in the pleural cavity and has 95% sensitivity in detecting pneumothoraces compared with chest radiographs.[51] However, a recent meta-analysis evaluating FAST for abdominal injuries in children noted a sensitivity of 80% and specificity of 96%. When only the most methodologically stringent articles were used (six studies), the combined sensitivity of the FAST exam for identifying children with hemoperitoneum was 66%. Sensitivity for detection of all children with intra-abdominal injuries (including those without hemoperitoneum) was even lower at 50%.[52,53] The continued role of FAST in evaluating the child with thoracic injuries remains to be seen.

The increased mobility of the child's mediastinum places the pediatric patient at increased risk for the physiologic consequences of a tension pneumothorax, which may occur in 25% of children presenting with a pneumothorax.[3] However, as the mediastinum becomes more fixed, shifting is less likely. In older children and adolescents, tension physiology may be due to progressively less effective ventilation and oxygenation caused by increased intrathoracic pressure.[54] The traumatologist must also keep in mind other causes of hypoxemia and hypotension including cardiac tamponade, right mainstem position of the endotracheal tube (ETT), ETT obstruction, and gastric distension.[1] Fortunately, in the majority of cases, pneumothorax results from small disruptions of the lung parenchyma. These disruptions are associated with small to modest air leaks and are effectively treated with a tube thoracostomy.[4,11,55,56]

Tracheobronchial Injuries

Persistent air leaks suggest disruption of a major airway. If ventilatory support is necessary and if the size of the child's airway allows, a double-lumen tube can be used for selective management of the uninjured and injured lungs, thus minimizing the severity of the air leak and optimizing ventilation.[4,55-58] Single-lung intubation is an efficient alternative maneuver if double-lumen ventilation cannot be accomplished.

Severe tracheobronchial disruptions usually are seen after high-energy impact injuries, most frequently motor vehicle crashes. Consequently, these injuries in children likely have associated multisystem injuries that may require emergent treatment. Because of the increased compliance of the child's chest wall, tracheobronchial injury may occur without the suggestive chest wall injuries usually present in the adult patient with a similar mechanism of injury.

The most common presenting signs and symptoms are subcutaneous emphysema, dyspnea, sternal tenderness, and hemoptysis.[4,55-58] The typical radiographic findings are subcutaneous emphysema, pneumomediastinum, pneumothorax, air surrounding the bronchus, and an abnormal appearance of the endotracheal tube. These findings, in association with upper thoracic fractures, are highly suggestive of tracheobronchial disruption. An uncommon finding, but one that is nonetheless highly specific for tracheobronchial injury, is collapse of the lung toward the chest wall.[11,59] When the constellation of a likely mechanism of injury, a suggestive clinical picture, and radiographic findings are present, diagnostic bronchoscopy is a priority. In a stable patient, either flexible or rigid bronchoscopy should be performed to confirm the location and the extent of airway disruption. If possible, a flexible bronchoscope is passed through the ETT with the tube withdrawn enough to inspect the entire trachea. If size disparities between the ETT and the bronchoscope preclude passing the flexible bronchoscope through the ETT, the trachea should be examined with a ventilating (rigid) bronchoscope.

Tracheobronchial injuries range from irregular tears to complete transections. Major sternal injuries have been associated with partial or complete horizontal transections of the trachea. An associated esophageal laceration must be promptly recognized to avoid esophageal fistula and fatal mediastinitis. Esophagoscopy is mandatory in this setting. The site of the injury influences the choice of thoracotomy incision.[60] Injuries to the left main stem bronchus or parenchyma are managed best through a left thoracotomy. A right thoracotomy affords the best exposure for injuries to the right lateral or posterior aspect of the trachea or to the right bronchi or parenchyma. The anterior or left lateral aspect of the mediastinal trachea is best approached through a median sternotomy. Principles of bronchial surgery include conservative debridement of irregular ends; precise end-to-end approximation using interrupted, absorbable sutures; proportional placement of all sutures before tying; and layered coverage to provide an airtight seal and to prevent pleural-bronchial fistulas.[61] Primary reconstruction of the tracheobronchial tree should be performed as soon as possible to ensure the best results. Delayed operations have a high incidence of late scar formation, necessitating further operations.[57] Distal bronchial injuries are amenable to anatomic pulmonary resection.[1] Approximately one third of children with tracheobronchial injuries die, and 50% of these patients die within the first hour after injury.[9] Airway compromise is the primary cause of death. Long-term sequelae in patients with bronchial injuries may include bronchial stenosis, bronchopleural fistulas, or infection.

Rarely, pneumomediastinum without damage to the mediastinal organs is seen after blunt trauma to the torso.[62] The explanation offered for this phenomenon is that blunt trauma induces a sudden rise in intrapulmonary pressure, leading to passage of air from the perihilar alveoli into the mediastinum

along the peribronchial and perivascular spaces. Nevertheless, the clinical priority when pneumomediastinum is recognized on radiographic examination is to exclude, by whatever means deemed appropriate, the presence of aerodigestive tract injury. Video-assisted thoracoscopic surgery is suitable in cases of residual hemothorax, persistent air leaks, or posttraumatic empyema.[63,64]

Cardiac Injuries

Most cardiac injuries in children result from blunt trauma. These injuries have inconsistent manifestations, making diagnosis problematic. The incidence of trauma-related cardiac injuries in children is less than 3%.[50] For those who reach a hospital, cardiac injuries are discovered at autopsy in up to 15% of cases. Of these patients, 46% die at the scene of the accident; the rest die in the emergency department or later during hospitalization.[65] Myocardial contusion is by far the most common cardiac injury.[66] In a multicenter review, myocardial contusion represented 95% of the cardiac trauma in patients with a mean ISS of 27.[67] Cardiac contusion may resemble a myocardial infarction, with depressed myocardial function, or it may present as supraventricular and ventricular arrhythmias. Cardiac contusions in the pediatric population are more common than was previously appreciated.[15] Associated injuries include pulmonary contusions (50.5%) and rib fractures (23%). Cardiac contusion is more commonly diagnosed in the context of severe multiple system trauma rather than an isolated event.[67] Diagnosis of myocardial contusion depends on a high index of suspicion. Although the electrocardiogram (ECG) is generally accepted as a reliable screening tool,[35] its sensitivity in children has been questioned.[67]

Other studies of varying utility in identifying cardiac contusion are serum creatinine kinase and its isoenzymes, troponin, radionuclide angiography, and echocardiography.[68-75] Attempts to reliably identify patients at high risk for cardiac complications after blunt chest trauma have been challenging and have explored the predictive validity of a number of tests. One study identified an abnormal ECG and ISS greater than 10 as predictive of a myocardial contusion. However, this same study was unable to identify other factors predicting the development of complications of myocardial contusion.

Although a plethora of studies have addressed ways to diagnose myocardial contusion, it is important to recognize that, in most instances, cardiac contusion has limited clinical significance.[68-75] Indeed, the incidence of cardiac sequelae among patients with myocardial contusion is low.[71] Cardiac complications usually occur within 12 hours of injury and are forewarned by an abnormal ECG in most cases.[76] Patients with isolated chest wall contusions, a normal admission ECG, and normal rhythm 4 hours after injury rarely develop any cardiac-related complications during the course of their hospitalization.[72]

Other recognized trauma-related cardiac injuries are valvular dysfunction from papillary muscle or chordae tendineae rupture, cardiac rupture, pericardial effusion, and cardiac dysrhythmia.[15,66,72,76-85] Echocardiography is valuable for identifying pericardial effusions and global or segmental defects in heart wall motion. Conduction abnormalities noted on the admission ECG may be predictive of subsequent serious dysrhythmias, warranting close monitoring and possible treatment.[75] Echocardiography and isoenzyme levels, although frequently positive, do not predict cardiac-related morbidity. Ultimately there is no standard diagnostic test for the diagnosis of cardiac trauma in pediatric patients. Those who develop life-threatening complications can be identified in the emergency department setting using modalities readily available in most hospitals (e.g., 12-lead ECG) in most instances.[75] The mortality rate among patients with cardiac injury is 13%, mainly as a result of associated head or intra-abdominal injuries. Approximately 5% of survivors will have significant cardiac sequelae, most commonly valvular insufficiency and ventricular septal defects. Follow-up of children with cardiac injury should be ensured.[67]

Commotio Cordis

Commotio cordis is a unique phenomenon in pediatric trauma. It is defined as sudden cardiac arrest in the absence of apparent structural heart disease after a nonpenetrating chest injury.[86] It is characterized by the absence of pulmonary contusion, coronary artery abnormalities, structural anomalies, or conduction system pathology.[1] The rare occurrence of commotio cordis is largely explained by its mechanism, which requires the rare confluence of several determinants such as location of the blow directly over the heart and precise timing to the vulnerable phase of repolarization (just prior to T-wave peak).[86] These blunt, nonpenetrating chest blows, often innocent in appearance, cause virtually instantaneous sudden death, most commonly in young males. Ventricular tachyarrhythmias seem to be most associated. Sports-related commotio cordis deaths have triggered considerable interest in chest barriers to protect young sports participants from catastrophic precordial blows. However, many case reports have surfaced of commotio cordis even in the setting of protective gear.[86,87] Commotio cordis is a survivable phenomenon. The identification of ventricular tachyarrhythmias at the scene and in the emergency department resulted in shockable rhythms with survival due to the availability and use of an automated external defribillator.[86,88]

Aortic and Great Vessel Injuries

The overall mortality rate observed in children with aortic and great vessel injuries is 75%.[4] Of these children, approximately 85% die at the scene and 15% die after arrival to the hospital. Fatal hemorrhage in the 25% of patients who survive is avoided because the surrounding tissue contains the bleeding. However, left undiagnosed and untreated, 30% of those who arrive alive at the hospital will exsanguinate within 24 hours after admission.[89] Fortunately, these injuries are uncommon in children and are seen in only approximately 1% to 3% of injured children.[3,4] The most common and lethal of these injuries is traumatic aortic disruption, characteristically seen in the older adolescent population.[3,4] The well-recognized signs and symptoms associated with traumatic aortic rupture are midscapular back pain, unexplained hypotension, upper extremity hypertension, bilateral femoral pulse deficits, and large initial chest tube outputs.[90-92] Early recognition of these signs can prevent tragic delays in diagnosis. However, acute traumatic aortic rupture remains a highly lethal injury with no change in prognosis during the past two decades.[93]

The findings on chest radiographic examination include a widened mediastinum, deviation of the nasogastric tube or central venous lines, blurring of the aortic knob, abnormal paraspinous stripe, rightward tracheal deviation, or upward

shift of the left main stem bronchus.[90-92] Transverse mediastinal width and mediastinal width/chest width ratio on supine chest films have been suggested as useful tools for identifying the patient with possible traumatic aortic rupture.[14] However, their clinical usefulness is limited by considerable overlap between normal and abnormal measurements as is seen in infants with an enlarged thymus. This has prompted others to suggest that subjective assessment of anatomical mediastinal abnormality is more reliable in determining the need for aortography.[14]

The role of CT scan and angiography in ruling out a potential intrathoracic vascular injury remains debatable. Traditionally, invasive aortography has been considered the test of choice to rule out such injuries. Authors in favor of this technique find aortography more accurate and expeditious with high sensitivity (98%) in detecting aortic and major branch vessel injuries.[94-96] Both cut film arteriography and digital subtraction arteriography are used, with similar results and enhanced visualization.[97] On the other hand, helical CT scan is a noninvasive procedure that can be used as the initial diagnostic tool, with a sensitivity and negative predictive value of 100%, equivalent to that of aortography.[98] Helical CT scanning prevents unnecessary aortography, expedites patient care, and reduces costs. Some scanners are capable of performing CT aortography, which creates a three-dimensional reconstruction of the aorta. Using helical CT scan to exclude a mediastinal hematoma and to evaluate the cause of an abnormal aortic contour promotes more selective use of aortography.[98-100]

Another useful diagnostic tool is multiplane transesophageal echocardiography (TEE). In patients with severe blunt chest trauma, TEE and helical CT scan have similar diagnostic accuracy for identifying acute traumatic aortic injury. TEE also allows functional and anatomic assessment of the heart and identifies intimal or medial lesions of the thoracic aorta more readily.[101,102] Additional randomized studies comparing these techniques are required.

The issue of treatment priorities in patients with traumatic aortic rupture is evolving. The most common cause of death is hemorrhage, and 95% of these patients have associated injuries requiring surgery. The most common associated injuries requiring emergent treatment are serious closed-head injuries and intra-abdominal hemorrhage. The hemodynamically unstable patient with known intra-abdominal hemorrhage should undergo laparotomy before any other procedure. The hemodynamically stable patient with intra-abdominal hemorrhage should undergo aortography followed by laparotomy. Left hemothorax, pseudocoarctation, and/or supraclavicular hematoma can be found in patients at high risk for sudden free rupture and exsanguination. Patients demonstrating these characteristics may benefit from immediate thoracic exploration rather than waiting for aortography.[90] Repair of an aortic rupture using simple aortic cross-clamping alone is feasible in the majority of patients without increased mortality or spinal cord injury.[93] Although the traditional therapy for blunt traumatic rupture of the thoracic aorta is immediate repair, in some patients with concomitant head trauma, respiratory failure, cardiac dysfunction, or sepsis, this injury can be managed conservatively with selective delayed operative repair without increasing the risk for exsanguinating hemorrhage.[103] While experience with β-adrenergic antagonists in children with traumatic aortic injuries is limited, some authorities argue that the approach to pediatric traumatic rupture of the thoracic aorta should be identical to that in the adult.[104]

Finally, the advent of endovascular repair in adults makes this a tantalizing treatment modality in children. There have been case reports of endovascular aortic stent grafts being used in younger patients.[104] The known complications of stents include occlusion of the left main stem bronchus, erosions, perigraft leak, graft migration, limb ischemia, arch perforation, entrapment, infection, pseudoaneurysm, distal embolization, and femoral artery complications.[105] Long-term follow-up in these patients is mandatory to determine how the child's future growth affects outcome.

Other Miscellaneous Injuries

Significant injury from thoracic trauma may occur in less common sites in the thorax. Although infrequent, these injuries have equal capacity to result in morbidity and mortality. Among these injuries are diaphragmatic and esophageal rupture, posttraumatic lung cysts, and intercostal hernias. Diaphragmatic ruptures occur most commonly on the left side as a result of severe thoracoabdominal compression or by penetrating injury. The incidence in children is 4%.[106] A large diaphragmatic rupture can cause immediate respiratory compromise because of displacement of intra-abdominal viscera into the chest. However, most diaphragmatic injuries are initially asymptomatic and cause problems later because of incarcerated viscera. The key to diagnosis is a high index of suspicion for any abnormal chest radiograph. Radiographic findings that suggest diaphragmatic rupture include displacement of the nasogastric tube tip into the chest, abnormal gas patterns in the chest, and haziness of the diaphragm.[107] Herniated abdominal organs may be damaged when tube thoracostomy is performed in the hemithorax of an undiagnosed diaphragmatic injury. Most diaphragmatic injuries are best repaired through the abdomen. The lacerated diaphragm is repaired primarily and a chest tube is placed. If the injury results in loss of diaphragmatic tissue, a prosthetic patch may be necessary to close the defect.

Esophageal rupture rarely occurs after blunt trauma. It is more likely to occur after penetrating trauma. It should be suspected in the patient with pneumomediastinum or hydrothorax after thoracic trauma. Water-soluble esophagram and rigid esophagoscopy is indicated to make the diagnosis and identify the site of the injury. If the rupture is detected early, primary repair of the esophagus usually is possible. Broad-spectrum antibiotics, nasogastric decompression, and fluid resuscitation are indicated.

Lung cysts may present immediately after blunt thoracic trauma. They are thought to occur as a result of lung laceration. Although there are exceptions, most undergo slow resolution without surgical intervention. Injury to the intercostal muscles during blunt trauma may create an area of weakness, leading to an intercostal hernia. The weakness in the thoracic wall can be detected soon after injury or late in the course, up to 4 years after the initial injury. When detected, intercostal hernias should be closed with muscle or fascia from the adjacent thoracic cavity. A prosthetic mesh is required in some instances.[108,109]

Penetrating Trauma

Penetrating thoracic wounds are a challenge for the surgeon and often carry a high mortality rate. The vast majority of penetrating trauma occurs in patients older than 12 years, mainly in males. In a review of an urban Level 1 trauma center, 55%

of penetrating injuries resulted from stab wounds, while the remainder were caused by gunshot wounds. Isolated injuries were present in 69% of cases, whereas 31% incurred additional extrathoracic injuries.[110] Although most penetrating injuries are isolated, any chest injury at or below the nipple line anteriorly, or at or below the tip of the scapula posteriorly, is better classified as a thoracoabdominal injury. In children with penetrating injuries of this type, the presence of intra-abdominal injuries must be excluded. For a patient with an open chest wound, placement of an occlusive dressing (taped on three sides) may prevent development of an open pneumothorax.[111] Diagnostic aids include peritoneal lavage, triple-contrast CT scan, and laparoscopy. The last has been found to be effective in assessing disruption of the diaphragm in hemodynamically stable patients.[63] In patients with suspected penetrating cardiac injury, pericardial focused ultrasound has 100% sensitivity and 97% accuracy in detecting pericardial blood.[112]

Use of autotransfusion devices in children with significant hemothoraces may be beneficial. Patients with ISS of 25 or greater and blood pH of 7.3 or less at admission are more likely to require an operation. Additionally, these two parameters are good predictors for mortality in both gunshot wounds and stab wounds. The overall mortality rate for penetrating trauma is 17%, largely as a result of cardiac and intrathoracic great vessel injuries.[110] Almost all patients will require intensive monitoring after surgery.

Functional Outcome

Among all patients with pediatric thoracic trauma, more than 75% leave the hospital without serious disabilities, but approximately 15% will require some sort of rehabilitation. In terms of functional status, the assessment of the Functional Independence Measure for children older than 7 years has shown that 68% will achieve complete independence, 7% will require minimal to moderate assistance, and 7% will be completely unable to recuperate their abilities. Most of these limitations are related to extrathoracic injuries, especially intracranial sequelae.[2]

Summary

Thoracic injuries are a rare but potentially lethal subset of childhood injuries. Because they are so uncommon, the timely implementation of diagnostic and therapeutic measures may be less than satisfactory. The framework for successful management of pediatric chest injuries includes the widely held principles of establishing and managing the patient's airway, assessing breathing, and monitoring the adequacy of circulation. A detailed primary and secondary survey for the extent of thoracic and associated nonthoracic injuries is essential. Rapid resuscitation and institution of definitive therapy minimizes morbidity and mortality.

References are available online at http://www.expertconsult.com.

VII Chapter 115

Abdominal Trauma in Pediatric Critical Care

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PEARLS

- In the initial resuscitation of trauma victims, the first priority remains the ABCs of ***a***irway, ***b***reathing, and ***c***irculation.
- When in doubt about the reliability of the airway, perform endotracheal intubation.
- The standard of care in treating hemodynamically stable children with hepatic or splenic injury is nonoperative observation.
- Patients who are hemodynamically stable may undergo further radiographic workup, whereas patients with evidence of an abdominal injury who remain clinically unstable after resuscitation with 40 mL/kg of fluid should be taken to the operating room for exploration.
- Splenic preservation is more important in younger children and is usually possible with nonoperative management or embolization.
- Vigilance and reexamination are necessary to detect a small bowel injury, which results in increases morbidity if missed for greater than 24 hours after trauma.

Trauma is the leading cause of morbidity and mortality in the pediatric age group. An estimated 1.5 million pediatric injuries occur each year, resulting in 500,000 hospitalizations and 20,000 deaths.[1] Thus trauma exceeds all other causes of death combined. Abdominal injuries are a marker of severe trauma, and evaluation of the child with an abdominal injury must include a thorough examination of the entire child. Failure to accurately assess the abdomen is the single most common error in the early treatment of the injured patient. Management of pediatric trauma requires a multidisciplinary approach with emergency department physicians, critical care specialists, anesthesiologists, and surgeons working as a multidisciplinary team to provide prompt stabilization, assessment, and treatment. Performing the primary and secondary survey, instituting fluid resuscitation, and arriving at a decision as to the most appropriate management plan are the principal goals of the trauma team leader.

The vast majority of abdominal injuries in children are preventable. Health care providers must work with the broader community to identify and alleviate causes of pediatric trauma. Education, public safety measures, and legislation will serve to prevent many cases of pediatric injury. Intentional abdominal trauma to children must be considered and, if suspected, must be reported to the appropriate agency. New developments in pediatric abdominal trauma include use of imaging modalities such as Focused Abdominal Sonography for Trauma (FAST) and embolization of solid organ injuries, which allows for increased utilization of nonoperative management. Laparoscopy can be applied in select scenarios. As part of disaster preparedness, clinicians providing trauma care for children should have an awareness of wartime and mass casualty injury management.

Mechanisms and Patterns of Injury

The severity and pattern of abdominal injury correlate with the mechanism of injury. Blunt injury accounts for 90% of abdominal trauma in children. The most common mechanisms are motor vehicle accidents, motor pedestrian accidents, falls from heights, bicycle accidents, and nonaccidental trauma. In pediatric blunt abdominal trauma, solid viscus organs such as the liver, spleen, and kidney are more frequently injured than hollow viscus organs. Children suffering lap belt injury, handlebar injury, or kicks may suffer small bowel perforation. Pedestrians struck by motor vehicles can have a pattern of head injury, splenic fracture, and left femur fracture (Waddell triad). In addition, urban violence and the high prevalence of firearms result in penetrating abdominal injuries in children. Although the mechanism of injury may correlate with the extent of injury, ongoing clinical assessment is a more sensitive indicator of the extent of blood loss and hemodynamic instability, and determines the resuscitation and management of the child with an abdominal injury.

Penetrating Abdominal Trauma

A national decrease in violent crime has reduced the incidence of penetrating trauma since the 1980s. Penetrating abdominal injuries are most commonly caused by firearm use or stabbings. In children, abdominal gunshot wounds result in more severe injuries than stab wounds because of the increased energy delivered by firearms, particularly shotguns and military rifles.[2] Significant intraperitoneal injuries are present in most children who sustain gunshot wounds, suggesting the

need for abdominal exploration in all gunshot victims. There is a controversial trend toward selective exploration of penetrating injuries in adults. For example, computed tomography has been successfully used to determine the use of selective laparotomy in penetrating torso trauma.[3] However, most trauma centers continue to perform mandatory laparotomy on all patients with gunshot wounds to the abdomen, although some nontherapeutic explorations will occur. Abdominal stab wounds that are found to penetrate the transversalis fascia on local wound exploration should undergo laparotomy or laparoscopy. Expectant observation of stab wounds in children should rarely be applied because the true extent of injury is not always appreciated on local exploration.

Recreational and Sports Injury

Specific recreational activities commonly practiced by children, such as bicycling, all-terrain vehicle (ATV) use, skiing, snowboarding, and horseback riding result in predictable injury patterns that guide evaluation. Snowboard injuries are increasing and include abdominal injuries in 25% of cases.[4] ATV crashes produce a particularly damaging pattern of injury as the ATV has the weight of a car and the lack of protection of a motorcycle. This results in a combination of an ejection and rollover mechanism of injury with the worst of both. The majority of deaths involve head and spine injuries. Lack of helmet use is associated with a higher mortality. ATV abdominal injuries include crush injuries to liver, spleen, and kidney. Child drivers are more susceptible to crash and it is alarming that child-sized ATVs are in production. Even where laws restrict ATV use by children, they are frequently injured and have a high rate of missed injuries.[5] Blunt impalement on a bicycle handlebar can result in a predictable pattern of injury to bowel, mesentery, or pancreas.

Wartime Trauma

It is unfortunate to note that children can also be victims of wartime trauma causing abdominal and other injuries. In contrast to wars of the past, modern warfare is often conducted in urban areas with a civilian population present and the frequent involvement of children. Additionally, medical infrastructure is disrupted in a war zone and many residents suffer malnutrition and infections which makes them more debilitated in the face of a new injury. Military high-energy rifles cause penetrating wounds in which the pressure wave of the projectile results in a cone of tissue destruction. In abdominal injuries, this necessitates wide debridement of soft tissues, and often a second-look laparotomy is required to detect evolving intestinal necrosis. It is common for children to suffer blast and fragmentation injuries from land mines, bombs, indirect fire weapons (rockets and mortars), improvised explosive devices, and suicide bombings.[6] Land mines and air-delivered cluster bomblets are particularly insidious because their interesting colors and shapes attract children's curiosity. Wounds include pressure wave blunt injury, shrapnel penetration, and burns. These injuries in children often require a damage-control laparotomy, wide debridement of soft tissues, temporary abdominal closure, and multiple operations. Vacuum-assisted wound dressings are particularly useful.[7] Wide-bore feeding tubes allow improvised feeds such as eggs, milk, honey, and grains. Long hospital stays are needed to ensure that the child can survive at home with little medical attention.

Evaluation and Resuscitation

Evaluation and resuscitation occur simultaneously when a child presents with an abdominal injury. The Advanced Trauma Life Support (ATLS) protocols developed by the American College of Surgeons should be used. The initial assessment, or primary survey, includes stabilization of the cervical spine while evaluating for airway patency, function of breathing, and adequacy of circulation (the ABCs). Prompt endotracheal intubation should occur in any patient in whom the stability of these functions is in doubt. Intravenous access in the small child can be particularly challenging, and skilled personnel should be employed. Pediatric Advanced Life Support (PALS) guidelines suggest utilizing an intraosseous line after three failed attempts to establish intravenous access or 90 seconds have expired and access has not been obtained. Basic neurologic function is assessed. The patient must be completely exposed for examination and then covered with blankets to maintain body temperature. Children are more susceptible to heat loss and dehydration because of their greater surface area/mass ratio.

Physical Examination

Abdominal examination includes observation of external signs, then palpation for tenderness, distension, or firmness. Children swallow a large amount of air when they cry and gastric distension may require nasogastric tube decompression. Upper quadrant ecchymosis, tenderness, and associated rib fractures suggest the presence of liver or spleen injury. Midabdominal ecchymosis from a seat belt suggests the possibility of a small bowel injury. Stability of the pelvis is assessed with lateral and axial manual compression of the pelvic ring. Extraperitoneal bladder ruptures may cause localized suprapubic tenderness, whereas an intraperitoneal bladder rupture may present as generalized abdominal distension.

Laboratory Tests

Laboratory examinations, including complete blood counts, serum chemistries, and urinalysis, should be obtained on all trauma patients. Additional studies, such as liver function tests and pancreatic enzymes, are indicated in certain injuries. Elevated transaminase levels suggest nonspecific parenchymal liver injury whereas elevated amylase and lipase levels suggest a pancreatic injury. A base deficit of greater than 6 meq/L is a strong indicator of intraabdominal injury in blunt trauma. Hematuria is associated with intra-abdominal injury and renal injury. Urinalysis demonstrating more than five red blood cells per high-power field combined with clinical assessment accurately predicts intra-abdominal injury. Hemoglobin concentrations as low as 7 g/dL are well tolerated in children after blunt abdominal injury, provided intravascular volume is repleted.

Radiographic Assessment

Prompt plain radiographs of the chest, lateral cervical spine, and pelvis should be obtained during the initial assessment. Patients who are hemodynamically stable may undergo

further radiographic workup, while patients with evidence of an abdominal injury who remain clinically unstable after resuscitation with 40 mL/kg of fluid should be taken to the operating room for exploration.

Computed Tomography

Computed tomography is the procedure of choice for definitive radiographic assessment after blunt abdominal trauma in children. Clinical impression remains the most sensitive indicator of the need for computed tomography. Computed tomography can be used to identify hepatic, splenic, intestinal, pancreatic, renal, and bladder injuries in children and can even detect intestinal and mesenteric injury with sensitivities of 94% and 96%, respectively.[8] Serial clinical assessments must be made before computed tomography. If the patient deteriorates, stabilization in the PICU or immediate operative intervention must be considered. Findings on computed tomography suggestive of intestinal injury are unexplained free fluid without solid visceral organ disruption, abnormal distribution of bowel loops, contrast extravasation, and contrast enhancement of intestinal wall.[9] The Organ Injury Scaling Committee of the American Association for the Surgery of Trauma has developed a grading system to estimate the extent of abdominal injury.[10,11] Short of operative exploration, computed tomography is the most accurate method used to grade the extent of injury.

Sonography

FAST is a rapid, noninvasive, and portable method to evaluate the abdomen. Various reports note that sonography for abdominal trauma has a sensitivity of 55% to 86% and a specificity of 95% to 98%.12-14 Sonography accurately identifies intraperitoneal free fluid, but it does not accurately identify the source of that fluid. Sonography is comparable to diagnostic peritoneal lavage (DPL) as a method for detecting free peritoneal fluid, but is less invasive. However, it does not supplant computed tomography in its ability to define the specific nature and extent of abdominal injury.

Additional Assessment Tools

Diagnostic Peritoneal Lavage

Refinement in the nonoperative management of pediatric abdominal trauma makes DPL unnecessary in stable patients, because the presence of free intraperitoneal blood is not an absolute indication for surgery in children. In addition, performing a DPL can be difficult in small children due to the decreased domain of the smaller abdomen. However, DPL is a useful triage tool for selectively applying laparotomy for blunt intestinal trauma in children. In one series, the cell count, amylase activity, and particulate matter in the DPL specimen were able to identify small bowel perforation with a sensitivity of 100%.[15]

Diagnostic Laparoscopy

Diagnostic video-assisted laparoscopic evaluation has been suggested as a safe and effective modality for evaluating the abdomen in the stable patient after penetrating trauma. Diaphragmatic injuries can be diagnosed and repaired laparoscopically.[16] Alternatively, thoracoscopy in hemodynamically stable penetrating-trauma patients can be used to avoid nontherapeutic laparotomy by ruling out penetration of the abdominal cavity and can identify thoracic and diaphragmatic injuries.

Management of Specific Abdominal Injuries

Children often demonstrate surprising hemodynamic stability in the face of significant hemorrhagic loss, until their capacity for compensatory vasoconstriction is surpassed. Although fluid resuscitation and blood transfusion is far and away the primary therapy, a select few children may require inotropic support after major trauma. Frequent serial abdominal examinations are performed to determine the need for surgical exploration for a missed hollow viscus injury. Operative intervention should not be delayed, because hypotension and decreased cerebral perfusion pressure worsen morbidity and mortality. Although abdominal compartment syndrome has a low reported incidence of 0.6% to 4.7% in critically injured children, it will only be detected through a high index of suspicion and frequent measurement.[17] In stable patients, early enteric feeding maintains immune function and shifts the patient to a more anabolic balance.

Nonoperative Management of Solid Organ Injuries

The standard of care in treating hemodynamically stable children with hepatic or splenic injury is nonoperative observation. Management of these injuries varies widely between adult and pediatric facilities, and splenectomy can be avoided if a child is taken to a facility that utilizes this nonoperative strategy. The American Pediatric Surgical Association Trauma Committee has proposed guidelines for care based on radiographic severity of injury (Table 115-1). Although this observation traditionally has taken place in the intensive care unit, evidence gathered to determine these recommendations suggests that observation on a patient ward is safe.[18]

Table 115–1 Proposed Guidelines for Resource Utilization in Children with Isolated Spleen or Liver Injury

CT Grade	I	II	III	IV
ICU stay (days)	None	None	None	1
Hospital stay (days)	2	3	4	5
Predischarge imaging	None	None	None	None
Postdischarge imaging	None	None	None	None
Activity restriction (weeks)*	3	4	5	6

*Return to full contact, competitive sports (e.g., football, wrestling, hockey, lacrosse, mountain climbing) should be at the discretion of the individual pediatric trauma surgeon. The proposed guidelines for return to unrestricted activity include "normal" age-appropriate activities.

Data from Stylianos S and the APSA Trauma Committee: Evidence-based guidelines for resource utilization in children with isolated spleen or liver injury, *J Pediatr Surg* 35:164–169, 2000.

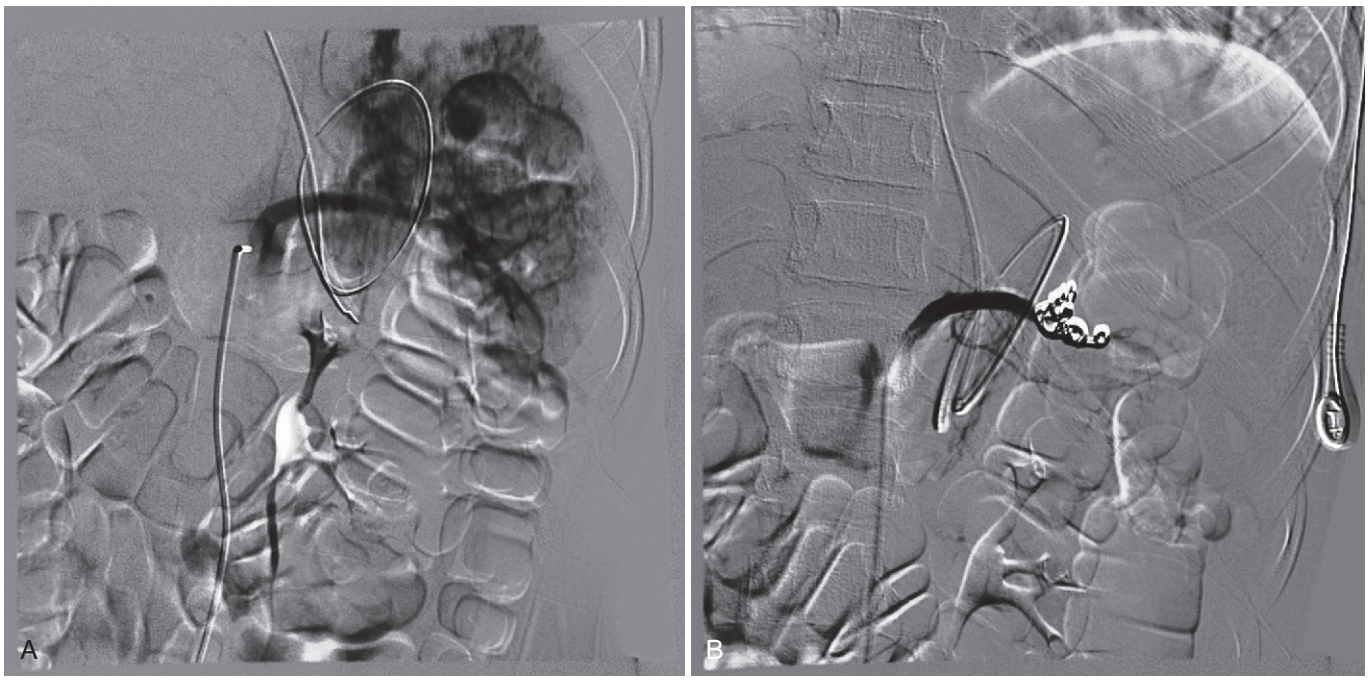

Figure 115–1. Nonselective splenic embolization. **A,** Angiography demonstrates splenic injury with active extravasation of blood. **B,** Postembolization image demonstrating coil in splenic artery and resolution of hemorrhage.

Embolization of Solid Organ Injuries

Computed tomography can identify active extravasation from splenic and hepatic injuries. Angiography is able to map out the specific site of hemorrhage and embolization coils can be used to selectively occlude the bleeding vessel. This therapy reduces the need for transfusion and can help avoid the need for a laparotomy. Nonselective embolization of the main splenic artery has also been shown to reduce bleeding (Figure 115-1). Angiography should be reserved for children with active extravasation who are still hemodynamically stable. Unstable patients with solid organ injury require laparotomy.

Injury to the Spleen

The spleen can extend below the costal margin in children and is the most commonly injured abdominal organ in blunt trauma. Treatment of splenic injury has evolved from routine splenectomy to a strategy of nonoperative management that is successful greater than 90% of the time.[19] Splenic injuries are most often caused by a direct blow to the left upper quadrant and manifest as localized tenderness, abrasion, or ecchymosis. Splenic injury is graded by computed tomography (Figures 115-2 and 115-3, Table 115-2). Operative intervention for splenic trauma usually results in splenectomy. For this reason, nonoperative management should be attempted in stable children, regardless of the severity of injury. If a stable child with a splenic injury requires laparotomy for injury to another organ, splenorrhaphy and autotransfusion increase splenic salvage, which reduces risk of infection.[20] Angiography and embolization of splenic vessels can control hemorrhage without laparotomy. At pediatric trauma centers, operating on a child with an isolated splenic injury is very rare. The indications for operative intervention are generally limited to persistent hypotension, greater than 50% blood volume replacement, or additional life-threatening abdominal injuries.

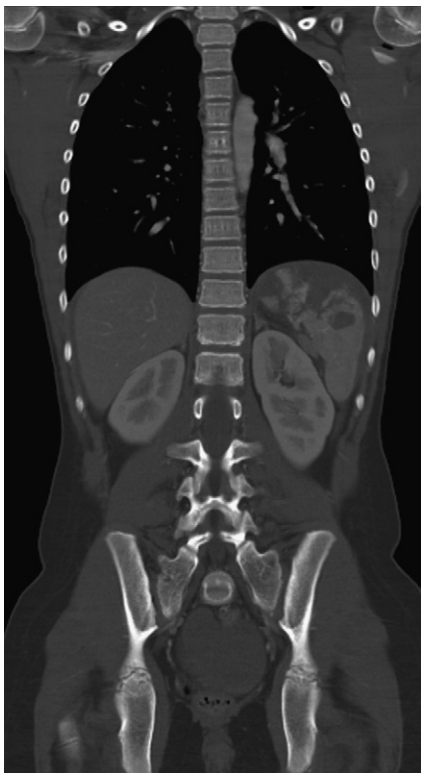

Figure 115–2. CT scan of a patient with a grade IV splenic laceration.

Nonoperative management generally consists of large-bore venous access for fluid resuscitation, a nasogastric tube for gastric decompression, intensive care unit monitoring, frequent hematocrit values, serial physical examinations, and bed rest. Recommendations from the American Pediatric Surgery Association Trauma Committee indicate only short periods of

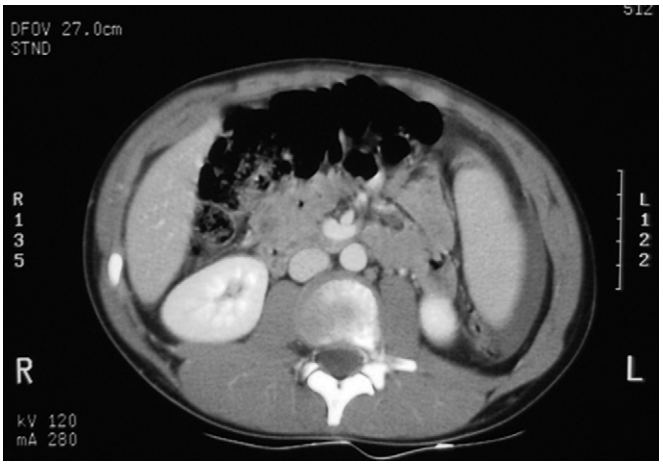

Figure 115–3. CT scan of a patient with a grade IV splenic laceration demonstrating free fluid around the tip of the spleen.

observation are necessary.[18] This abbreviated observation of 1 day bed rest for Grade I and II injuries and 2 days of bed rest for higher grade injuries has been validated to be safe.[21]

Injury to the Liver

The liver, which also extends below the costal margin in children, is the second most commonly injured organ in blunt abdominal trauma. Liver injuries are associated with the highest mortality and may require surgical correction of injuries to the hepatic veins or vena cava. Liver injuries in stable patients can be managed nonoperatively. Ecchymosis, bruising, or abrasions over the right upper quadrant suggest significant injury. Liver injury is graded by appearance on computed tomography (see Table 115-2). However, the clinical course of the patient, not the appearance on computed tomography, should determine treatment (Figures 115-4 and 115-5). Elevated serum transaminase concentrations are associated with liver trauma and other intraabdominal injury.[22] The mortality associated with operative management of hepatic injuries is higher than in the nonoperative group. Late complications of liver injuries include bile peritonitis, abscess formation, hemorrhage, and hematobilia. Operative treatment is required for major hepatic trauma associated with hepatic vein or retrohepatic canal injuries. Often, definitive repair is not possible at the time of initial exploration, necessitating damage-control surgery with packing, stabilization, resuscitation, and repeat laparotomy. Select patients with ongoing bleeding from a hepatic injury can be stabilized with embolization of hepatic blood vessels.

Injury to the Small Bowel

Bowel injuries resulting from blunt trauma are relatively rare. However, a high index of suspicion must be maintained to avoid a delayed diagnosis, which is more common in children. The incidence of small bowel injury increases with increasing number of other organs injured.[23] The mechanisms of injury associated with blunt bowel trauma include motor vehicle/pedestrian accidents, handlebar injuries, lap belt injuries, and child abuse. Deceleration injuries in children restrained with a lap belt may occur as a constellation that includes intestinal injury, abdominal wall ecchymosis, and flexion-distraction injury (Chance fracture) to the lumbar spine (Figure 115-6). Intestinal injuries include bowel disruption, mesenteric avulsion, and bowel wall contusion. (Figure 115-7) Areas of the small bowel particularly prone to injury are the points of retroperitoneal fixation, such as the proximal jejunum at the ligament of Treitz or the terminal ileum near the junction with the cecum. A perforation may be present even without free air or significant spillage of succus on DPL. Delayed perforations may occur as a result of mesenteric disruptions and subsequent bowel necrosis. In some instances, a prolonged ileus that fails to resolve may be the only evidence of intestinal injury.

The mechanism of injury and abdominal wall ecchymosis can suggest the diagnosis of intestinal injury. Abdominal tenderness may be present on physical examination. Until spinal injuries are ruled out, a lateral decubitus film is preferred over an upright chest film for detection of free air. Findings on computed tomography consistent with small bowel injury are free air, contrast extravasation, focal bowel thickening, free fluid, and fat stranding or fluid in the mesentery.[24] Once diagnosed, bowel injuries are treated by laparotomy, exploration, and repair. Excision of injury and primary anastomosis to reestablish gastrointestinal continuity are usually possible. Morbidity and mortality are not increased if the delay in diagnosis is less than 24 hours.[15]

Injury to the Duodenum

Duodenal injuries are rare in children but occur more commonly than in adults. Children may have localized right upper quadrant tenderness, but the presentation may be subtle. The majority of duodenal injuries in children result in a duodenal hematoma without disruption of the lumen. When there is perforation, computed tomography demonstrates extraluminal gas or oral contrast extravasation in the right anterior pararenal space. Thickening of the duodenal wall is seen when a duodenal hematoma is present. Duodenal injuries are classified from grade I to V based on severity (see Table 115-2). The majority of pediatric duodenal injuries are grades I and II. Overall, mortality is 18% for patients with duodenal injuries. For grade I lesions, the mortality is 8%, with associated injuries as the usual cause of death.

A duodenal hematoma is treated with observation and parenteral hyperalimentation. Resolution generally occurs in 2 to 4 weeks. In some cases of duodenal hematoma, placement of a nasojejunal tube will allow enteral feeding distal to the point of obstruction. Repair of full-thickness duodenal injury may require duodenorrhaphy, pyloric exclusion, duodenoduodenostomy, duodenojejunostomy, pancreaticoduodenectomy, or simple drainage (Figure 115-8). The majority of injuries are treated with debridement and primary closure with drainage. Pyloric exclusion is recommended for complex duodenal injuries. Duodenostomy and regional drains are useful. In children, pancreaticoduodenectomy is rarely required to treat a duodenal injury.

Injury to the Pancreas

Injuries to the pancreas may require operative intervention depending on severity of injury and integrity of the pancreatic duct (see Table 115-2). Upper abdominal tenderness, elevated amylase level, edema of the gland, and unexplained fluid in the lesser sac on computed tomography suggest pancreatic

Table 115–2 Abdominal Organ Injury Computed Tomography Grading Scales*

Injury	Grade I	Grade II	Grade III	Grade IV	Grade V	Grade VI
Splenic hematoma	Subcapsular, <10% surface area	Subcapsular, 10%–50% surface; intraparenchymal, <5 cm diameter	Subcapsular, >50% surface or expanding; Intraparenchymal >5 cm or expanding; ruptured			
Splenic laceration	<1 cm depth	1–3 cm depth	>3 cm depth or involving vessel	Segmental vessel >25% devascularization	Shattered spleen	
Splenic vascular					Hilar injury 100% devascularization	
Hepatic hematoma	Subcapsular, <10% surface area	Subcapsular, 10%–50% surface; intraparenchymal, <10 cm diameter	Subcapsular, >50% surface or expanding; Intraparenchymal >10 cm or expanding; ruptured			
Hepatic laceration	Capsular tear, <1 cm depth	1–3 cm depth, <10 cm length	>3 cm depth	Disruption 25%–75% of lobe or 1–3 Couinaud segments in lobe	Disruption >75% lobe or >3 Couinaud segments in lobe	
Hepatic vascular					Injury to cava or hepatic vein	Avulsion
Duoenum hematoma	Single portion	>1 portion				
Duodenum laceration	Partial thickness	<50% circumference	50%–75% circumference second portion	>75% circumference second portion, ampulla, or common bile duct	Disruption duodenopancreatic complex	
Duodenal vascular					Devascularization of duodenum	
Pancreas hematoma	Minor contusion	Major contusion				
Pancreas laceration	Superficial	Major	Distal transaction or duct injury	Proximal transaction or ampulla injury	Massive disruption of head	
Kidney contusion	Hematuria					
Kidney hematoma	Subcapsular, nonexpanding	Confined to retroperitoneum				
Kidney laceration		<1 cm depth	>1 cm depth	Through cortex, medulla, and collecting system	Shattered kidney	
Kidney vascular					Avulsion	

*Add one grade for multiple injuries up to grade III.
From Moore EE, Cogbill TH, Malangoni MA, et al: Organ injury scaling, II: pancreas, duodenum, small bowel, colon, and rectum, *J Trauma* 30:1427-1429, 1990; and Moore EE, Shackford SR, Pachter HL, et al: Organ injury scaling: spleen, liver, and kidney, *J Trauma* 29:1664-1666, 1989.

injury. Handlebar injury, lap belt injury, direct blow to the abdomen, and motor vehicle crash are the most common mechanisms (Figure 115-9). When the gland is fractured, this generally occurs where it crosses the vertebral column (Figure 115-10). Pancreatic transection is best treated by early distal pancreatectomy and drainage. When the main pancreatic duct is intact, nonoperative treatment with an extended course of bowel rest and parenteral nutrition should be attempted. Devascularization of the pancreas and duodenum in blunt abdominal trauma is rare in children. When it does occur, laparotomy, pyloric exclusion, drainage, and repeated debridement with an open abdomen may be required. After pancreatic injury, pseudocysts may develop and require internal or external drainage after maturation. Operative drainage of a pseudocyst to the stomach or a roux-en-Y loop of intestine should be delayed for at least 6 weeks until the pseudocyst wall is mature. An infected pseudocyst with fevers may require urgent percutaneous drainage. Endoscopic retrograde cholangiopancreatography is useful to diagnose pancreatic duct disruption, and a pancreatic stent can be placed across the disrupted duct, which potentially prevents pseudocyst formation[25] (Figure 115-11).

Blunt Abdominal Aortic Injury

The majority of aortic injuries after blunt trauma are in the chest, with only 6% in the abdomen.[26] Pedestrians struck by a motor vehicle and unrestrained passengers are more likely to

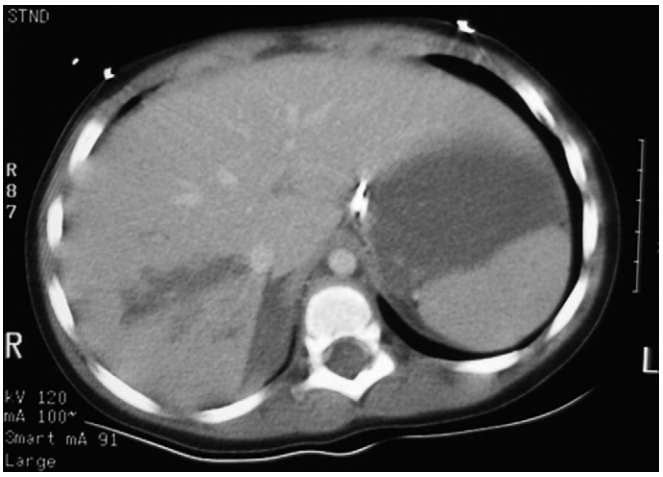

Figure 115–4. CT scan of patient with grade II hepatic hematoma.

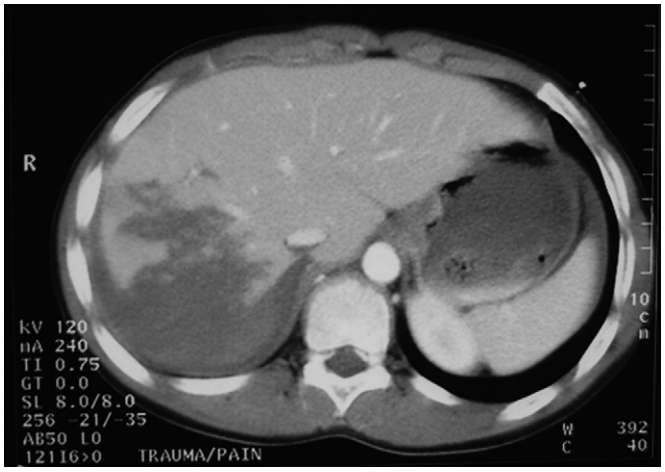

Figure 115–5. CT scan of patient with a grade IV hepatic laceration.

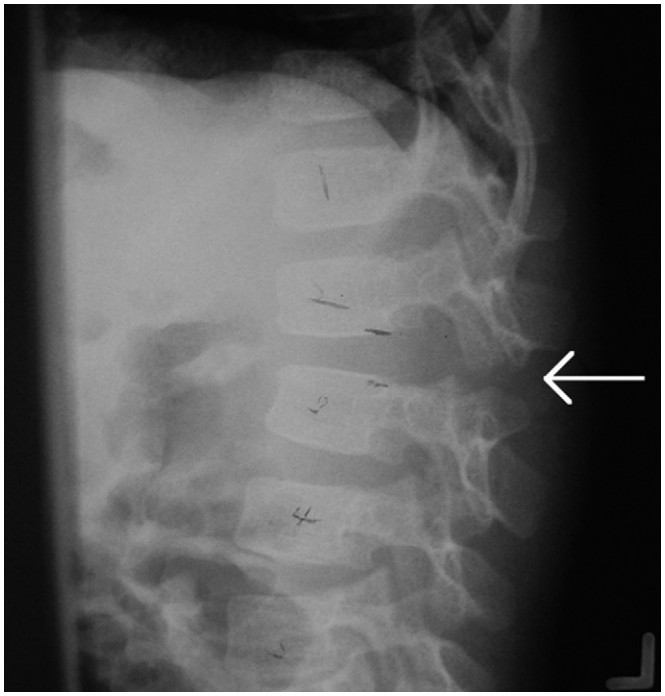

Figure 115–6. Plain lateral lumbar spine radiograph. *Arrow* indicates distraction injury to posterior spine secondary to lap belt injury.

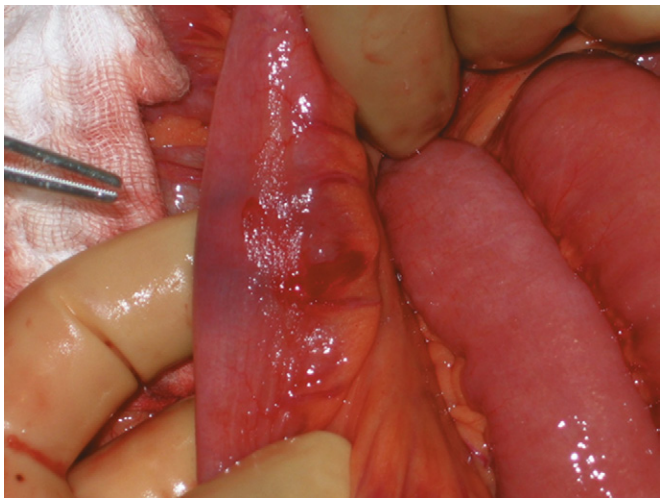

Figure 115–7. Small bowel contusion after blast injury.

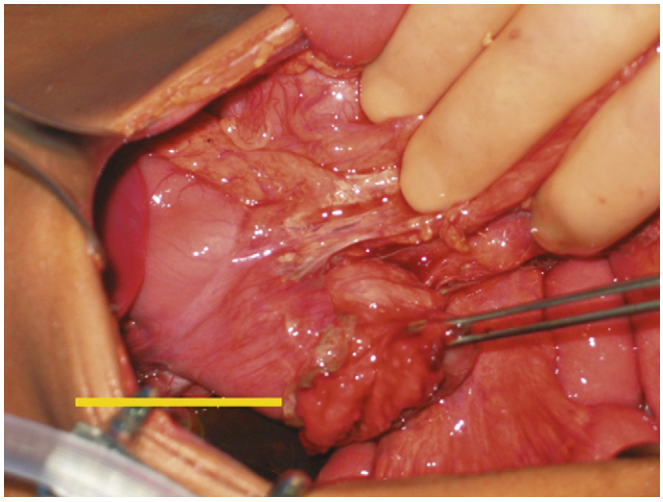

Figure 115–8. Grade III duodenal laceration blowout injury after fall onto a hand rail.

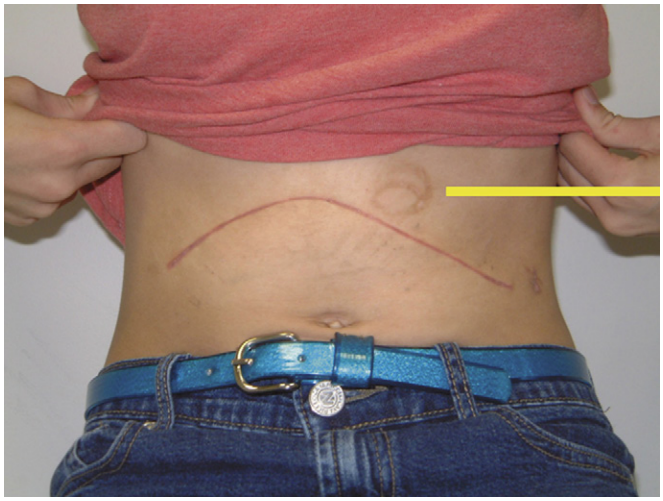

Figure 115–9. Handlebar injury in patient who required distal pancreatectomy.

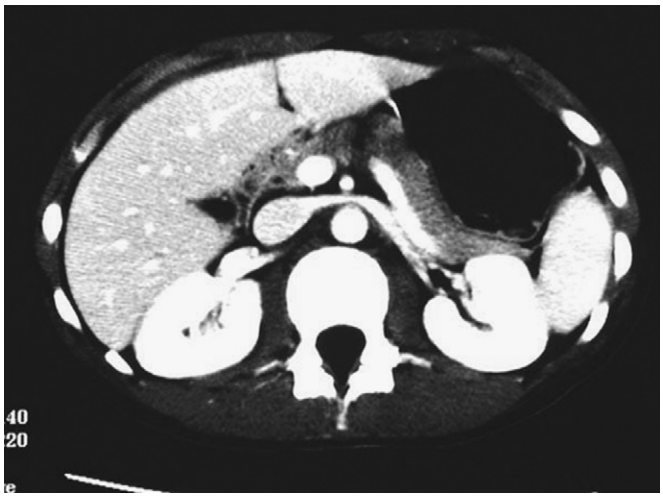

Figure 115–10. CT scan of patient with a grade III pancreatic laceration. *(Courtesy Martin Eichelberger, MD, and Patrick McLaughlin, MD.)*

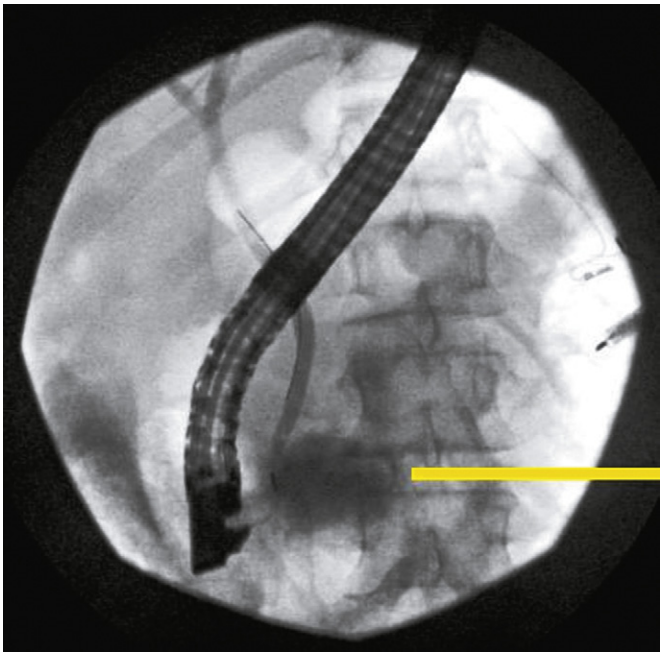

Figure 115–11. Endoscopic retrograde cholangiopancreatography demonstrates pancreatic duct leak after kick to abdomen.

have thoracic injuries, while passengers with lap belt injuries are more likely to injure the abdominal aorta.[27] Injury to the renal artery or mesenteric artery is more common than aortic injury.[28] Computed tomographic angiography is capable of definitive diagnosis; however, angiography may be required in some children. Aortic injuries include contusion, intimal dissection, and complete disruption. The most frequent site of disruption is at the inferior mesenteric artery or the renal arteries. Patients present with diminished or absent distal lower extremity pulses. Neurologic deficits may result from aortic compromise. Associated injuries are present in 65% of cases. When blunt abdominal aortic injury is recognized early, surgical intervention can dramatically lower mortality. A pseudoaneurysm can develop as a late complication. Major abdominal venous injuries resulting from blunt trauma are usually fatal.

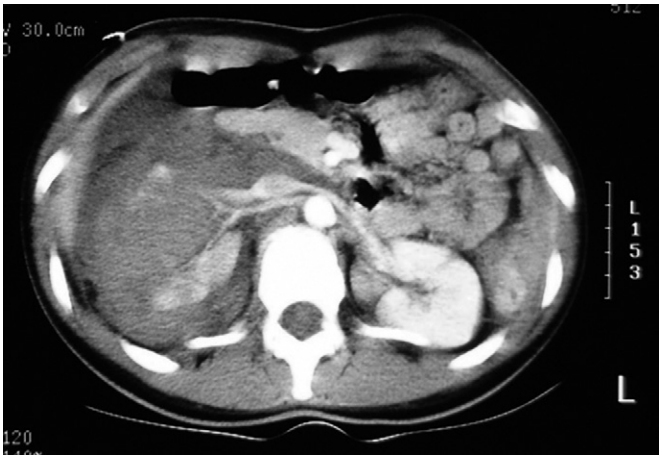

Figure 115–12. CT scan of patient with a grade IV renal laceration and vascular injury.

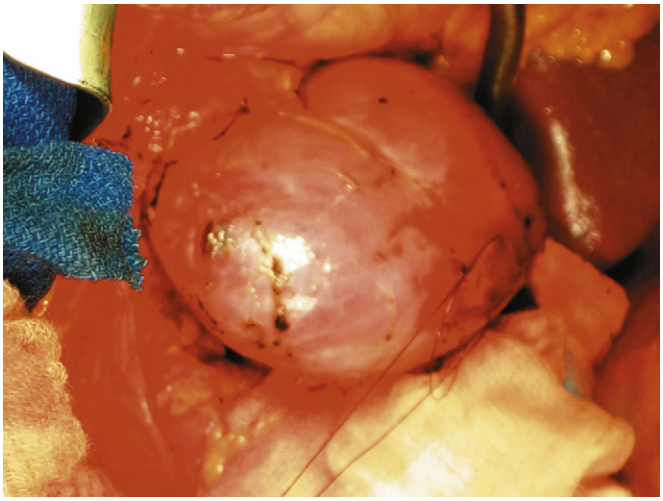

Figure 115–13. Repair of grade II renal laceration after penetrating trauma.

Renal Trauma

Renal injury rarely occurs as an isolated injury. Findings suggestive of renal injury include flank tenderness, flank or abdominal mass, or ecchymosis. Hematuria, either gross or microscopic, is the best indicator of serious renal injury. However, serious injury, especially renal pedicle injuries, may be present even without hematuria. In hemodynamically stable patients, computed tomography with intravenous contrast allows for a very accurate diagnosis of renal injury and function (Figure 115-12). Sonography also provides accurate diagnosis of extrarenal fluid collections.[29] Renal trauma can result in a hematoma, laceration, or vascular injury (see Table 115-2). Children who are hemodynamically stable may be safely managed nonoperatively. Angiography with embolization can control hemorrhage when contrast extravasation is seen on computed tomography.[30] Exploration is warranted in children who are hemodynamically unstable, have an expanding hematoma, or have an associated abdominal injury necessitating exploration. In unstable patients, nephrectomy is the safest choice; however, the surgeon must ensure that the contralateral kidney is present before proceeding. Renal repair or partial nephrectomy is possible in select cases (Figure 115-13). Isolated urinary extravasation

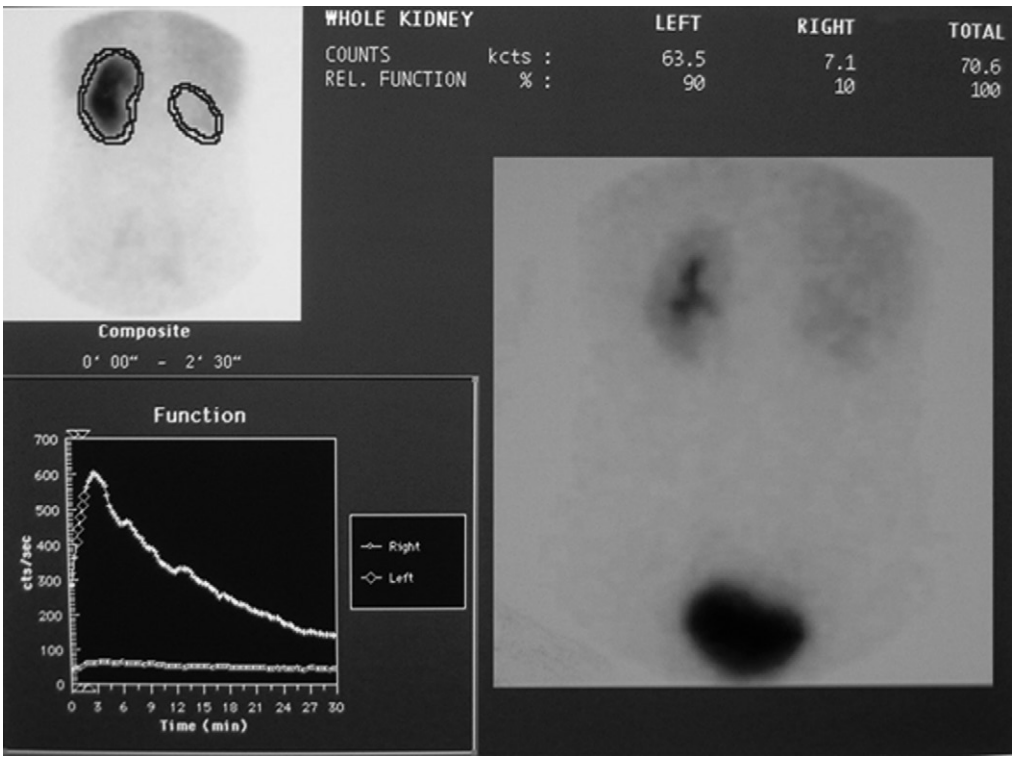

Figure 115–14. Renal scan of patient with grade IV renal laceration and vascular injury.

is not an indication for emergent exploration, but delayed operation or percutaneous drainage may be required for persistent extravasation or infection. If urinary extravasation is present, antibiotics should be administered. Patients with extravasation and devascularized segments on computed tomography have a higher incidence of delayed complications. Observation and bed rest usually result in excellent outcome, even with deep parenchymal lacerations associated with urinary extravasation. Patients with gross hematuria are kept on bed rest until the urine is grossly clear. Reevaluation is necessary for persistent hematuria, tenderness, or mass. All patients with renal injuries, regardless of severity, should be monitored for the delayed onset of hypertension. A captopril-furosemide DTPA (technetium-99m diethylenetriamine pentaacetic acid) renal scan is used to verify function after injury (Figure 115-14).

Renal pedicle injuries are rare and are suggested by lack of renal contrast enhancement on computed tomography. Renal angiography definitively establishes the diagnosis and directs operative management. Ureteral injuries require operative repair, but diagnosis of ureteropelvic junction disruption may be delayed because of a lack of clinical signs on presentation. Absence of contrast in the ureter indicates that ureteral stent placement will likely be necessary.[31]

Bladder Injuries

Bladder injuries are most often associated with blunt trauma. The bladder is predominantly intra-abdominal in children. Therefore, burst injuries are more common than in adults. Bladder rupture is associated with pelvic fractures. Clinical presentation of bladder rupture may be subtle, with only mild suprapubic tenderness. The severity of associated injuries may mask signs of a bladder injury. Hematuria is the most consistent finding. Recognizing the injury and identifying it as intraperitoneal or extraperitoneal are important. Cystography is best for establishing the diagnosis. Lack of extravasation on computed tomography does not exclude a bladder injury. Peritoneal fluid located in the lateral perivesical recess, superior to the bladder, and in the pouch of Douglas is suggestive of intraperitoneal bladder rupture. Extraperitoneal bladder rupture is noted by fluid extending superior and anterior to the level of the umbilicus and by fluid in the retrorectal presacral space. The distinction between intraperitoneal and extraperitoneal bladder rupture is important for treatment purposes. Controlled extraperitoneal ruptures are treated nonoperatively with urinary catheter drainage. Extensive extraperitoneal rupture and intraperitoneal injuries require operative intervention.

Pelvic Fractures

The most common mechanism resulting in pelvic fracture in children is a pedestrian struck by a motor vehicle. Single fractures of the pelvis are rarely associated with significant abdominal injury. Children with multiple fractures of the pelvis are at significant risk for abdominal injury even if hemodynamically stable (Table 115-3). Pelvic fractures are usually evident on the initial physical examination. Findings include abrasions, bruising, hemorrhage, instability, or swelling. Asymmetry of the bony structure, pain on palpation, or crepitus can be present. After recognition, attention should be directed toward stabilization and assessment of hemodynamic status. Pre-hospital providers may use inflatable pneumatic anti-shock garments, but they should be replaced with another method of stabilization after arrival

Table 115–3 Associated Injury by Location of Pelvic Fracture

Fracture site	Number (%)	Number with Abdominal Injury (%)	Number with Genitourinary Injury (%)
Unifocal	44 (81.5)	5 (11)	0
Pubic ramus	32 (59.3)	2 (6)	0
Iliac/pelvic rim	9 (16.7)	3 (33)	0
Sacrum	3 (5.60	0	0
Multiple	10 (18.5)	6 (60)	4 (40)
Total	54	11 (20)	4 (7.4)

Data from Bond SJ, Gotschall CS, Eichelberger MR: Predictors of abdominal injury in children with pelvic fracture, *J Trauma* 31:1169, 1991.

to the hospital. An anteroposterior radiograph of the pelvis is obtained in the trauma bay to determine the anatomy of the fracture. Opening of the pelvic ring, associated with fracture at two points, should be stabilized with a sheet wrapped around the pelvis, a C-clamp, or an external fixator. Vertical shear injuries usually are not amenable to this treatment and will require operative reduction. Hemodynamically unstable patients should be aggressively resuscitated. Early angiography and embolization of bleeding vessels helps to stabilize patients and avoid the need for operative intervention. Hemodynamically stable patients should undergo computed tomography to evaluate for associated injuries. Special attention should be directed toward the rectum and urethra, which are especially susceptible to injury by bony fragments.

References are available online at http://www.expertconsult.com.

VII Chapter 116

Principles of Drug Disposition in the Critically Ill Child

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PEARLS

- Studies devoted to the disposition of drugs in critically ill patients and children are limited.
- Therapeutics is the branch of pharmacology concerned with the use of drugs for their therapeutic effects. It focuses on four fundamental questions that can serve as an outline for the clinician designing any pharmacotherapeutic plan: what drug, what dose, what route, and how long?
- Drug disposition is controlled by pharmacokinetics and pharmacodynamics. Pharmacokinetics is the discipline within clinical pharmacology that broadly describes the changes in the quantity of drug and/or drug metabolite in various body compartments over time. Whereas pharmacokinetics describes what the body does to the drug, pharmacodynamics encompasses the pharmacologic aspects that impact how the drug affects the body.
- Pharmacokinetic processes that influence drug disposition include absorption, distribution, metabolism, and excretion. Both ontogeny and critical illness may significantly impact any of these processes. Metabolism may be further affected by genetic differences in involved enzymes.
- Ontogeny and critical illness affect pharmacodynamics in infants and children, although formal study of these effects is limited.
- Pharmacotherapeutic strategies that can be used in the critically ill patient include the target concentration and target effect strategies. The target concentration strategy relies on concentration of drug in blood or plasma (usually) to guide therapy; this approach is best applied to drugs used chronically for signs or symptoms that manifest intermittently. The target effect strategy, the strategy most commonly used in the pediatric intensive care unit, relies upon an accepted clinical endpoint to determine drug dosing; clinical evidence of toxicity also impacts dosing. The latter strategy probably is the most reliable means by which to administer the "right amount" of drug to a highly variable patient population.

Pharmacology is the study of the interaction between chemical agents and biologic systems. When these chemical agents are used with the intent of palliating or curing disease, the agents are termed *drugs*. Perhaps nowhere is drug therapy more important than in critical care. In this setting, however, drug response often is difficult to predict. Physiologic aberrations and coincident pharmacologic and nonpharmacologic therapies may thwart intended drug effects. For the pediatric intensive care physician, pharmacotherapeutic decisions are further complicated by ontogenetic differences in drug processing and response. Finally, experience upon which to base pharmacotherapeutic expectations or prescription is sparse. Most drugs used in the intensive care setting have never been formally investigated in critically ill patients, let alone in children. As such, it is imperative that the pediatric intensive care physician have an understanding of the pharmacologic and related developmental constructs that influence drug response in patients.

The discipline of therapeutics provides a useful outline by which to design and monitor drug treatment. *Therapeutics* is the branch of pharmacology concerned with the use of drugs for their salubrious effects. It focuses on four fundamental questions pertaining to drug therapy as it relates to patient care: what drug, what dose, what route, and how long? The task of answering these important questions is facilitated by an understanding of the general pharmacologic principles that dictate drug response and the factors that lead to variation among patients.

Drug Disposition in Infants and Children

It should come as no surprise that controversy exists regarding drug dosing in pediatric patients. Over the years, a number of dosing rules been developed with the intent that drugs be safely administered to young children. All these rules depend on the standard adult dose with a scale-down factor based on body weight or age. However, distinct differences in pharmacokinetics and pharmacodynamics (Box 116-1) distinguish the pediatric patient from the adult patient. Critical illness may further alter pharmacokinetics and pharmacodynamics in children. These differences must be recognized before providing safe and effective dosing and during the initial selection of the drug itself.

Determinants of Effective Therapy

Effective therapy results when the drug(s) selected for a given condition has both favorable pharmacokinetic and favorable pharmacodynamic properties (see Box 116-1). Moreover,

Box 116–1 Determinants of Effective Therapy

Pharmacokinetics
Absorption
Distribution
Metabolism
Excretion

Pharmacodynamics
Drug/receptor interactions
Structure/activity relationships
Receptor/effector coupling
Safety profile

Box 116–2 Factors Affecting Drug Absorption

Physicochemical Factors
Disintegration of tablets or solid phase
Dissolution of the drug in gastric or intestinal fluids, and number of ionizable groups
Degree of lipid solubility of the lipid-soluble form
Molecular weight

Patient Factors
Surface area available for absorption
Gastric and duodenal pH
Gastric emptying time
Bile salt pool size
Bacterial colonization of the gastrointestinal tract
Underlying disease states

administration to the patient must be individualized based on (1) a realistic clinical endpoint determined before administration; (2) sound knowledge of the quantitative aspects of the disposition of the drug selected; and (3) an understanding of the impact on the patient's illness of both the dosing regimen to be used and the anticipated therapeutic effect.

Pharmacokinetics

Pharmacokinetics is the discipline within clinical pharmacology that broadly describes the changes in the quantity of drug and/or drug metabolite in various body compartments over time. These changes can be described by four processes: absorption, distribution, metabolism, and excretion. Each of these processes can be affected by both development and disease. A clear understanding of pharmacokinetic processes and the factors affecting them will permit the clinician to design an effective treatment plan or to troubleshoot when an undesired response to treatment occurs. In other words, an understanding of basic pharmacokinetic principles will increase the likelihood that any treatment goal will be successfully accomplished with minimal adverse effects.

Drug Absorption

Absorption refers to the translocation of a drug from its site of administration into the bloodstream. When drugs are administered intravenously, as often occurs in the intensive care unit (ICU), the need for absorption is bypassed. When intravenous administration is not possible or convenient, several other routes of administration can be effectively used. Physicochemical properties of the drug and specific factors related to each route determine the rate and magnitude of absorption. Knowledge of these factors increases the likelihood that the clinician will be able to predict, if not control, this component of drug disposition.

Absorption of drugs from the gastrointestinal tract is affected by a number of factors (Box 116-2).[1,2] In general, enteral absorption depends on gastric emptying, intestinal surface area and motility, and hepatic first pass. Ontogeny and critical illness may significantly affect these and other patient factors (Figure 116-1 and Box 116-3).

Bioavailability (F) describes the fraction of a dose of drug that reaches the systemic circulation. Bioavailability of a single drug may vary significantly depending on the route of administration. By routes other than intravenous, absorption is a primary determinant of F. In enteral administration, an additional factor influences F. Excluding drugs primarily absorbed by the oral mucosa, drugs administered into the gastrointestinal tract may undergo metabolism by intestinal mucosal cells and/or metabolism and/or biliary excretion when they pass through the liver, before reaching the systemic circulation. This is known as the *first-pass effect*. With affected drugs, this phenomenon may significantly reduce F. This accounts for the fact that the enteral dose for many drugs is significantly greater than the intravenous dose. The susceptibility of a drug to hepatic first-pass metabolism may influence how the drug is administered; for example, nitroglycerin is given sublingually to circumvent a considerable first-pass effect in this drug.[3] Aside from the physicochemical nature of the drug itself, other factors may influence the extent of hepatic first-pass metabolism. Changes in hepatic blood flow may alter this action.[4] Age likely further influences the extent of hepatic first pass. As described later in the chapter, maturation of hepatic enzyme systems and transporters appears to occur postnatally.[7] Although the data dedicated to the ontogeny of metabolizing enzymes and transporters in the liver are limited, particularly as they relate to drug bioavailability, F probably decreases with age as these systems mature.[7]

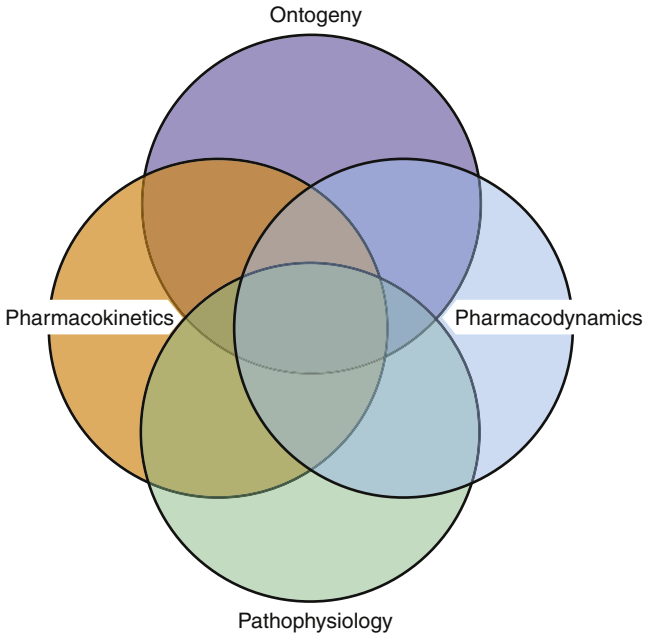

Figure 116–1. Determinants of effective therapy.

Box 116–3 Selected Disease States Affecting Gastrointestinal Absorption of Drugs

Gastric Acid Secretion
Proximal small bowel resection

Delayed Gastric Emptying
Pyloric stenosis
Congestive heart failure
Protein calorie malnutrition

Intestinal Transit Time
Protein/calorie malnutrition
Thyroid disease
Diarrheal disease

Bile Salt Excretion
Cholestatic liver disease
Extrahepatic biliary obstruction

Decreased Surface Area
Short bowel syndrome
Protein/calorie malnutrition

Box 116–4 Drugs Demonstrating Effective System Absorption After Intramuscular Administration

Antibacterial
Amikacin
Ampicillin
Benzathine penicillin
Benzyl penicillin (penicillin G)
Cefazolin
Cefotaxime
Ceftazidime
Ceftriaxone
Clindamycin
Gentamicin
Kanamycin
Methicillin
Oxacillin
Nafcillin
Piperacillin
Ticarcillin ± clavulanate
Tobramycin

Antituberculous Agents
Isoniazid
Streptomycin

Anticonvulsants
Diazepam ± midazolam
Phenobarbital

Sedatives/Tranquilizers
Chlorpromazine
Promethazine

Cardiovascular Drugs
Hydralazine
Procainamide
Pyridostigmine

Diuretics
Acetazolamide
Furosemide
Bumetanide

Endocrine
Corticotropin (ACTH)
Cortisone
Desoxycorticosterone
Glucagon

Pituitary
Vasopressin (tannate oil)

Vitamins
D
K

From Blumer JL: Therapeutic agents. In Fanaroff AA, Martin RJ, editors: *Neonatal-perinatal medicine: diseases of the fetus*, ed 4, St Louis, 1987, Mosby.

Intramuscular Administration. The parenteral route of drug administration is important when a patient's disease state precludes oral therapy or when the bioavailability of an oral formulation is poor. The intravenous route for drug delivery is preferred over intramuscular (IM) injection. However, in children with poor intravenous access, IM injection is a viable and effective alternative for the administration of many drugs. Both physicochemical and physiologic factors affect the rate of drug absorption from the IM injection site.[8] Lipophilicity of a drug favors rapid diffusion into the capillaries; however, the drug must retain a degree of water solubility at physiologic pH to prevent precipitation at the injection site. For example, the sodium salt of phenytoin is principally an acid and thus is insoluble in the extracellular milieu of skeletal muscle. This explains the poor IM absorption of phenytoin. By contrast, phenobarbital and benzathine penicillin are well absorbed after IM administration. Both of these drugs are weak acids with pKa values close to physiologic pH and are therefore unlikely to precipitate in muscle under most physiologic conditions. By having knowledge of the physicochemical properties of a drug preparation, the clinician can predict, even control to some extent, how the drug is absorbed. While aqueous preparations will undergo rapid absorption, drugs in a solution of oil or other repository vehicles will be absorbed at a slower and more continuous rate.[9]

Another important factor that influences absorption of drug from an IM injection site is local blood flow, which may be compromised in patients with poor peripheral perfusion.[10] Rate and extent of absorption from an IM injection site also are influenced by the total surface area of muscle in contact with the injected solution, similar to the dependency of oral absorption on the total available absorptive area in the intestines.[8]

A final consideration in IM absorption is muscle activity, which may affect the rate of absorption and therefore affect the peak serum concentration. Sick, immobile infants and children or those chemically paralyzed may show reduced absorption rates after IM drug administration. Use of this route of administration in the ICU may be limited by actual or induced (anticoagulant therapy[9]) bleeding diatheses in some patients. A list of intramuscularly administered drugs used frequently in the pediatric intensive care unit (PICU) is provided in Box 116-4.

Subcutaneous Absorption. As with absorption of drugs from IM sites, absorption of subcutaneously administered drugs is influenced by local blood flow, as well as by proximal scarring or injury.[4] The pattern of absorption varies similarly to that following IM injection, depending on the physicochemical properties of the preparation. Frequently, drugs given by the subcutaneous route undergo slow and sustained absorption.[9] As such, the rate of absorption can be regulated by the drug formulation. For example, when drugs are administered in solid pellet form, absorption may occur over weeks to months.[9] Absorption can be slowed by the addition of a vasoconstrictor.[9] This route of administration is not appropriate for large volumes or for drugs that are irritating to tissues.

Percutaneous Absorption. Percutaneous absorption is inversely related to the thickness of the stratum corneum and directly related to skin hydration.[11] The stratum corneum is generally assumed, but not proven, to be thinner in children than in adults. The integument of the full-term neonate possesses intact barrier function.[12] This is not assured in the case of the premature infant.[6] Another important factor dictating percutaneous absorption is the surface area/body weight ratio, which is much larger in the full-term neonate than in an adult. Theoretically, if a newborn receives the same

percutaneous dose of a compound as an adult, the systemic availability per kilogram body weight is approximately 2.7 times greater in the neonate.

The percutaneous route of drug administration is taking on greater importance in the ICU setting. Historically, the most commonly used cutaneous preparation for systemic therapy is nitroglycerin.[13] More recently, advances in the technology associated with drug delivery systems have resulted in the common use of clonidine as a percutaneous preparation for treatment of hypertension and narcotic withdrawal. In addition, a number of narcotics exist as cutaneous preparations so that essentially "continuous infusions" of these drugs can be safely administered outside the ICU.[14] Finally, even drugs such as nitroglycerin ointment are finding potential new uses in the PICU, for example, treatment of the distal ischemia associated with purpuric injuries.

Rectal Absorption. Rectal administration of drugs is of potential therapeutic importance if a patient cannot take an agent orally and intravenous access for drug administration is impracticable. Because of the routes of the respective venous drainage systems, drugs administered into the superior aspect of the rectum are susceptible to hepatic first pass, whereas drugs administered lower into the rectum initially bypass the liver.[15] This may be an advantage for drugs such as lidocaine or propranolol that demonstrate a significant hepatic first-pass effect. The predominant mechanism for drug absorption from the rectum probably is similar to that observed in the upper gastrointestinal tract (i.e., passive diffusion). Theoretically, the physicochemical and host factors discussed earlier with respect to oral drug absorption also influence rectal drug absorption. In general, absorption from aqueous or alcoholic solutions is more rapid than from suppositories.

Lipophilic drugs with pK_a between 7 and 8, such as barbiturates and benzodiazepines, seem to be ideally suited for rectal administration because they exist mostly in unionized form and readily cross cell membranes. Rectal use of drugs such as thiopental and diazepam may be effective when intravenous access is a problem and rapid induction of anesthesia is desired or when a child is convulsing. Dulac et al.[16] showed that rectal administration of 0.25 to 0.5 mg/kg of a diazepam solution to children aged 2 weeks to 11 years produced serum concentrations comparable with those observed after intravenous administration. Additionally, peak serum concentrations occurred within minutes of administration. Potentially effective anticonvulsant serum concentrations were maintained for 1 to 3 hours in most of the study patients. Knudsen[17] demonstrated similar results in 20 children aged 1 to 2 years and further ascertained the clinical efficacy of rectal diazepam in preventing recurrent febrile seizures. In a similar fashion, Burckart et al.[18] reported rapid and effective sedation after rectal administration of thiopental suspension to 36 infants and children undergoing computed tomographic scanning.

Drug Distribution

Knowledge of drug distribution is important for selecting the appropriate drug and dose to be administered. Distribution of most drugs in the body is influenced by a variety of age-dependent factors, including protein binding, body compartment sizes, hemodynamic factors such as cardiac output and regional blood flow, and membrane permeability.[19,20] Any of these factors also can be altered by disease. This section briefly reviews the pharmacokinetic description of distribution and the effect of ontogeny and critical illness on several factors that determine drug distribution.

The primary pharmacokinetic parameter representative of drug distribution is the volume of distribution (V_d). V_d reflects the apparent space within the body available to contain drug and relates the amount of drug in the body to its concentration in a biologic fluid, usually blood or plasma.[9] V_d varies among drugs, based on the drug's extent of protein and tissue binding and its partition coefficient in fat.[9] Additionally, for any given drug, V_d varies among patients because of differences in protein stores or binding and body composition as a result of age or illness. For example, in neonates and infants, a relatively increased extracellular fluid volume, decreased protein binding, and increased brain and liver size all contribute to increased weight-normalized V_d for most drugs.[21] An understanding of the factors influencing V_d is of paramount importance to the clinician caring for critically ill children. V_d relates the administered dose of drug to its plasma or blood concentration, which determines therapeutic effects, both favorable and adverse. Alterations in V_d produce reciprocal changes in drug concentration.[21] Familiarity with the concept of V_d and the ontogenic and other factors influencing its variation will assist the intensive care physician in understanding why a standard drug dose might be inappropriate for a given patient.

Developmental Aspects of Protein Binding. Plasma protein binding of drugs depends on the concentration of binding proteins available, the affinity constant of the drug for the protein(s), the number of available binding sites, and the presence of pathophysiologic conditions or endogenous compounds that may alter drug-protein interaction.[22] The affinity of albumin for acidic drugs increases, as do total plasma protein levels, from birth to early infancy.[23] These values do not reach normal adult levels until age 10 to 12 months. In addition, although plasma albumin may reach adult levels shortly after birth, the neonatal albumin level in blood is directly proportional to gestational age, reflecting placental transport and fetal synthesis.[24] Binding of basic drugs by α_1-acid glycoprotein also is affected.[21,25] Studies in cord blood suggest that decreased levels of α_1-acid glycoprotein cause this decreased binding.[25] Some of the drugs that have exhibited decreased protein binding in the infant include diazepam, furosemide, propranolol, thiopental, phenytoin, and some antibiotics.[21] The comparative binding of some of these drugs in neonates and adults is given in Table 116-1. The impact of decreased binding of many of these drugs on efficacy has not been determined.[21] For drugs that are highly protein-bound and subject to therapeutic monitoring (e.g., phenytoin), however, any decrease in protein binding may result in a lower measured total drug concentration.[21] In such cases, monitoring of free drug concentration (if possible) will prove more clinically relevant.

Developmental Aspects of Fluid Compartment Sizes. Alterations in body water compartment sizes affect the volume of distribution of a drug. Age-dependent changes in the various fluid compartments (Table 116-2) were reviewed in detail by Cheek et al.[27] and Friis-Hansen.[28] Regardless of age, critical illness and related therapies may alter total body water and other fluid compartment volumes.

Table 116–1 Comparative Protein Binding of Some Representative Drugs

Drug	% Bound	
	Newborn	Adult
Acetaminophen	37	48
Ampicillin	10	18
Diazepam	84	99
Lidocaine	20	70
Morphine	46	66
Phenobarbital	32	51
Phenytoin	80	90
Propranolol	60	93
Theophylline	36	56

Data from Kurz H, Mauser-Ganshom A, Stickel HH: Differences in the binding of drugs to plasma proteins from newborn and adult man, *Eur J Clin Pharmacol* 11:463, 1977.

Table 116–2 Fluid Compartment Size as a Function of Age

Age	Total Body Water*	Extracellular Fluid*	Intracellular Fluid*
Fetus <3 mo	92	65	25
Term gestation	75	35-44	33
4–6 months	60	≈23	37
12 months		26-30	
Puberty	60	≈20	40
Adult	50-60	20	40

*As a percentage of body weight.

At 40 weeks of gestation, measurements of extracellular fluid volume have ranged from 350 to 440 mL/kg body weight. Cassady[29] demonstrated that the extracellular fluid volume of newborn infants correlated more closely with body weight than with gestational age. By age 1 year, extracellular fluid volume decreases to approximately 26% to 30% of body weight. After the first year, it decreases slowly and gradually approaches the adult value of 20% body weight by puberty. Intracellular fluid volume increases from 25% of body weight in the young fetus to 33% at birth to approximately 37% of body weight at age 4 months. Except for a sudden increase during early childhood, the intracellular fluid volume remains relatively constant thereafter, approximating 40% of body weight. The clinical relevance of this gradual reduction in the size of extracellular body water compartments with age cannot be overemphasized. To achieve comparable plasma and tissue concentrations of drugs distributing into extracellular fluid, higher doses per kilogram body weight must be given to infants and children than to adults.[30]

Developmental Aspects of Body Composition. The percentage of body weight composed of adipose tissue approximately doubles over the first year of life.[21] Additionally, the liver and brain account for a higher percentage of body weight in the neonate than in the adult.[6,21] All of these factors may lead to significant differences in weight-normalized V_d between infants and adults, depending on the drug. Differences in the amount of adipose tissue may alter clearance of some drugs.

Critical Illness and Drug Distribution. Because of impaired production or increased losses, respectively, conditions such as liver disease and nephrotic syndrome reduce circulating albumin concentrations, resulting in an increase in apparent V_d. Diseases that induce an acute phase reaction (e.g., malignancy, myocardial infarction, inflammatory bowel disease) may provoke increased binding of basic drugs because of increased levels of α_1-acid glycoprotein.[9] Additionally, accumulation of extravascular fluid collections (e.g., pleural effusions and ascites) results in the development of a reservoir for drugs that are distributed into the total body water.[31]

Drug Clearance

Clearance reflects the removal of drug from the body. Clearance occurs by two processes: biotransformation (i.e., metabolism) and excretion. Metabolism occurs primarily in the liver. Excretion is predominately facilitated by the kidney, although excretion also can occur via exhalation, saliva, sweat, or the gastrointestinal tract.[6,9] Redistribution of drug can contribute to total clearance if the reference compartment is blood or plasma, as is often the case.[4] When reflected in the blood or plasma, clearance quantitatively describes the volume of blood or plasma from which all drug is removed per unit of time.[4,6] Clearance is an important pharmacokinetic parameter to consider when the goal is maintenance of steady-state drug concentration, which correlates with therapeutic efficacy. Once steady state is achieved, clearance of the drug determines the quantity of drug that must be administered in order to maintain that concentration (i.e., Drug out = Drug in).[4,7] The clinically relevant pharmacokinetic concepts related to clearance are discussed later in this chapter. The ontogeny of systemic clearance mechanisms probably accounts for a significant portion of the difference in pharmacologic response between infants and adults.[7] These developmental factors also produce variability among pediatric patients. Critical illness may have an additional profound impact on clearance mechanisms.

Hepatic xenobiotic metabolism assumes an extremely important role in determining the pharmacokinetic and pharmacodynamic properties of many drugs. Clearance of a drug (Cl) by an individual organ depends on blood flow to the organ (Q) and the organ's extraction ratio (E) and can be described as follows[32]: $Cl = Q \times E$, where E is the ratio of the arteriovenous concentration difference divided by the arterial concentration (extraction) as expressed by $E = (C_a - C_v)/C_a$, where C_a and C_v are the arterial and venous concentrations, respectively. Organ clearance concepts are best described for the liver and kidneys. Hepatic clearance depends on hepatic blood flow, plasma free drug concentration, cellular uptake, hepatic metabolism, and biliary excretion. The hepatic clearance of a drug can be expressed by the following equation:

$$Cl_H = \frac{Q \times f_B \times Cl_{int}}{Q + (f_B \times Cl_{int})}$$

where Cl_H is hepatic clearance, Q is hepatic blood flow; f_B is fraction of free drug; and Cl_{int} is intrinsic clearance, which is a measure of hepatocellular metabolism. Drugs that are primarily cleared by the liver can be classified as flow limited or

capacity limited.[33] If a drug displays a high Cl_{int} and E, then doubling the Cl_{int} will have little effect on Cl_H, whereas a change in blood flow will produce a proportional change in Cl_H. In other words, for drugs that are highly extracted (>80%) and metabolized by the liver, Cl_H reflects the amount and rate of drug delivered to the liver.[34] The considerable declines in hepatic blood flow and oxygen delivery that occur immediately following birth do not appear to translate to significantly reduced clearance of flow-limited drug in the newborn compared with the adult.[7] Drugs with high extraction ratios are subjected to the first-pass effect when administered enterally.

Capacity-limited drugs display low extraction ratios (<20%) and a low intrinsic metabolic clearance. Therefore hepatic clearance depends on the degree of hepatic uptake and metabolism of the drug and is independent of hepatic blood flow. Capacity-limited drugs can be further subdivided into binding-sensitive and binding-insensitive drugs. Binding-sensitive drugs, such as clindamycin, have extraction ratios that approach the free drug concentration ($E = f_B$). Therefore factors that increase f_B, such as decreased protein binding, increase hepatic clearance. In contrast, other drugs may display extraction ratios that are much less than the free drug concentration. In these cases, an increase in f_B does not enhance extraction of the drug, and therefore the hepatic clearance is a function of the intrinsic clearance and is independent of protein binding. These drugs are referred to as binding-insensitive (e.g., chloramphenicol).

At every level, from the ontogenetic changes in hepatic blood and portal oxygen tension to the developmental alterations in protein binding and xenobiotic metabolizing enzyme activities, there is the potential for age to affect the processes associated with hepatic clearance. Very little investigative effort has been expended to elucidate these effects; however, some of the important available data are discussed further. For detailed reviews of this data, the reader is referred to articles by Alcorn and McNamara[7] and Leeder and Kearns.[35]

Biotransformation: Phase I Reactions. The biotransformation of endogenous and exogenous substances occurs primarily in the liver, although the adrenal gland, placenta, kidney, gut, and skin also are capable of metabolizing compounds. Once a drug enters the hepatocyte, it may be transformed by one or more enzymatic reactions. These pathways, or phase I reactions, include oxidation, reduction, hydrolysis, and hydroxylation.[36,37] In general, these reactions are responsible for transforming compounds into more polar, less lipid-soluble molecules that are more rapidly eliminated by the kidney, biliary system, or lung. However, parent compounds may be transformed into pharmacologically active intermediates, such as theophylline to caffeine, or into toxic metabolites, as occurs with oxidation of acetaminophen. In addition, pharmacologically inactive parent compounds (prodrugs) may be converted to active moieties, as occurs with hydrolysis of chloramphenicol succinate to chloramphenicol. The ontogeny of human enzyme systems differs dramatically from most animal species, especially for oxidation and glucuronidation pathways.[38] Therefore extrapolating data for enzyme system maturation from animals to humans is difficult. Of the enzyme systems capable of metabolizing drugs, the hepatic cytochrome P450 (CYP) mixed-function oxidase system has been studied in greatest detail. It is responsible for most of the phase I reactions catalyzed in the human liver.

Yaffe et al.[39] first demonstrated drug-oxidizing enzymes in the human fetal liver. During fetal life, these enzymes are present at 30% to 60% of adult activity in vitro.[40] Following birth, total CYP levels increase, approaching adult range by age 1 year.[7] Activity of all CYP enzymes is generally thought to be considerably lower in children, particularly neonates and infants, than in adults. In truth, the developmental aspects of expression and function vary among CYP enzyme families and isoforms. Although data delineating these variations are limited, particularly for specific families or isoforms, some insight into the ontogeny of select enzymes has been gleaned from immunochemical studies in hepatic microsomes and tissue, pharmacokinetic studies of known enzyme substrates, and studies evaluating the biotransformation of pharmacologic "probes" (e.g., carbamazepine in the case of CYP3A4). The ontogeny and the drugs affected by some of the important CYP isoforms are outlined in Table 116-3. A limited discussion of the most clinically relevant isoforms in pediatric patients follows.

CYP1A2. Cytochrome P450 1A2, the only CYP1A isoform found in human liver, is involved in the biotransformation of many drugs, including the methylxanthines.[35] Immunohistochemical studies have suggested that this protein is sparse, if present at all, in fetal liver.[41] These studies also demonstrate that levels of CYP1A2 do not appreciably increase until several weeks to months after birth, remaining below adult levels well into childhood. These findings are reflected in studies examining enzyme activity as assessed by biotransformation of theophylline. Nassif et al.[42] reported a significant correlation between a decreasing elimination half-life for enterally administered theophylline and increasing age. Decreased elimination was further suggested by a marked difference in dosage requirement, with patients younger than 4 months requiring approximately half the daily dose needed in patients age 8 to 13 months to maintain therapeutic levels. Tateishi et al.[43] evaluated biotransformation of intravenous theophylline, quantifying three metabolites (1-methyluric acid [IMU], 3-methylxanthine [3MX], and 1,3-dimethyluric acid [DMU]) in urine. The ratios of metabolites to theophylline in urine increased dramatically from the neonatal period to age 3 years, when they appeared to essentially plateau. However, a greater variation in these ratios was seen among patients older than 3 years. This study also established that the relative production of DMU, a product of reactions catalyzed by other CYP enzymes, including CYP2E1 and CYP3A4, was higher in the youngest patients compared with those older than 3 years. The relative production of the other two metabolites, which result from CYP1A2 activity alone, is similar between the groups. After age 1 year into early childhood, rates of theophylline clearance appear to exceed the rates in adults, prompting the need for an increased dose to maintain therapeutic levels.[35]

CYP2C9. The CYP2C family comprises a substantial portion (approximately 20%) of CYP enzymes in the adult liver and has comparable importance in the metabolism of drugs.[7] CYP2C9 is the principal isoform in this family. Enzyme protein is undetectable[44] to low[35,41] in fetal liver. In vitro studies in fetal hepatic microsomes suggest comparably low enzyme activity. Demethylation of diazepam, which is mediated by the CPY2C family, occurs at a level less than 5% that in adult microsomes.[44] On the other hand, hydroxylation of tolbutamide, which is catalyzed specifically by CYP2C9, is

Table 116–3 Ontogeny of Select Hepatic Enzymes

Enzyme	Representative Substrates	Developmental Evolution
PHASE I		
CYP1A2	Acetaminophen, caffeine, theophylline, warfarin	Negligible in fetal liver. Adult levels of activity by approximately age 4 months. Activity exceeds that in adults after age 1 year; gradually declines to adult levels by end of puberty.
CYP2C9	Diazepam, phenytoin, NSAIDs, tolbutamide, S-warfarin	Undetectable to low in fetal liver. Adult levels of activity by age 1–6 months. Activity exceeds that in adults from age 3–10 years; gradually declines to adult levels by conclusion of puberty.
CYP2D6	Numerous, including captopril, codeine, dextromethorphan, haloperidol, metoprolol, propranolol, ondansetron, tricyclics	Undetectable in fetal liver. Expression and activity appear to be stimulated by parturition. Complete maturation may occur by age 1 year, although acquisition of adult activity levels has been reported to occur as late as age 5 years.
CYP3A4	Numerous, including acetaminophen, amiodarone, budesonide, carbamazepine, cyclosporine, erythromycin, lidocaine, nifedipine, tacrolimus, theophylline, verapamil, R-warfarin	Low in fetal liver; replaces CYP3A7 as the predominant isoform following birth. Based on pharmacokinetic and drug disposition studies, activity in children thought to be greater than that in adults. Decline toward adult levels begins at approximately age 4 years. Adult levels reached by end of puberty.
PHASE II		
Uridine 5′-diphosphate glucuronyltransferases (UGTs)	Numerous, including acetaminophen, benzodiazepines, bilirubin, chloramphenicol, dextromethorphan, morphine, naloxone, NSAIDs, propofol, thyroxine	Varies by isoform; difficult to characterize individual isoforms because of overlapping substrate specificities. As a group, activity appears to be deficient in the neonate and infant. Variably reported acquisition of adult levels of activity; anywhere from age 2–30 months, depending on the proposed isoforms involved.
N-acetyltransferase-2 (NAT2)	Caffeine, clonazepam, hydralazine, ioniazid, procainamide	Low activity in neonates and infants. Movement toward adult phenotypes (≈50% fast and 50% slow acetylators) after nearly 3 months of age.
Methyltransferase group (MT)	Catecholamines, captopril, serotonin, spironolactone	S-methylation capacity (TPMT) approximately 50% greater in infants than in adults. Limited evaluating maturation after this point; one Korean study demonstrated adult level activity by age 7–9 years.
Sulfotransferase group (ST)	Acetaminophen, bile acids, chloramphenicol, cholesterol, dopamine, polyethylene glycols, salicylates	At least some isoforms well developed in the infant; compensates for deficient glucuronidation of certain substrates (e.g., acetaminophen).

Substrate listings from Leeder JS, Kearns GL: Pharmacokinetics in pediatrics: implications for practice, *Pediatr Clin North Am* 44:55, 1997. Additional data related to substrates and all remaining data derived from references cited in the text.
NSAID, Nonsteroidal antiinflammatory drug.

not at all evident in fetal microsomes.[44] Several studies, both in vitro and in vivo, suggest an increase in enzyme expression and activity within the first month of life. Following sedation with diazepam, levels of desmethyl diazepam in urine are very low at age 1 to 2 days and increase within the first postnatal week.[44] CYP2C9 protein reaches adult levels in hepatic tissue after age 6 months.[41] Enzyme activity corresponds. By age 1 to 6 months, production of the phenytoin metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin is comparable to that seen in adults.[45] In fact, CYP2C9 activity appears to supersede that observed in adults by age 3 to 10 years, declining to adult range by the conclusion of puberty.[45] This explains the frequent need for a relatively increased dose of phenytoin in this age group.

CYP2D6. A number of drugs undergo biotransformation by CYP2D6, and some are more relevant to critically or chronically ill children than well children. Enzyme protein levels are undetectable in fetal liver except for those obtained from fetuses delivered by spontaneous or induced abortion. These specimens are far more likely to contain detectable enzyme, suggesting that parturition stimulates expression.[46] Enzyme activity, as evidenced by O-methylation of dextromethorphan, is negligible in fetal hepatic microsomes. Enzyme protein levels increase rapidly after birth, but the time at which they reach adult levels is variably reported in the literature. Levels in hepatic tissue from subjects aged 1 month to 5 years reportedly were only approximately two thirds the adult levels,[7] but another study reported no difference in expression between patients younger than 1 year and those older than 1 year, suggesting that development of this isoform is complete by age 1 year.[47]

CYP3A4. The CYP3A family comprises the largest fraction of measurable CYP450 enzymes in adult liver.[7] In the fetal liver, CYP3A7 is the predominant isoform. After birth, there is a shift between CYP3A7 and CYP3A4, levels of which are negligible in fetal hepatic tissue. The mechanisms of this transition have not been elucidated. In infants and children, the activity of CYP3A4 is generally increased above that in adults. The biotransformation of carbamazepine demonstrates this developmental difference. Studies in children demonstrate that both clearance and production of the metabolite carbamazepine-10,11-epoxide significantly

decrease with increasing age.[48-50] The role that other enzymes, particularly microsomal epoxide hydrolase, which further transforms carbamazepine-10,11-epoxide, play in these developmental differences is uncertain.[35] In addition, although these age-related differences have been described in pediatric patients on monotherapy, coadministration of anticonvulsants that are known to induce CYP3A4 are speculated to skew these findings. Nonetheless, these developmental differences in CYP3A4 activity have been suggested by study of other substrates, among them cyclosporine, which also exhibits increased clearance in children compared with adults.

The development of other phase I enzyme systems has been studied much less extensively. Alcohol dehydrogenase activity is detectable in 2-month fetuses at levels no greater than 3% to 4% of adult activity.[51] Moreover, the level of activity does not approach adult values until after age 5 years.

Aromatic nitroreductase activity is detectable in fetal livers by 7 to 8 weeks of gestation; however, the hepatic activity at midgestation remains low, and no specific postnatal pattern of development has been described. Also, few data exist on the ontogeny of hydrolytic enzymes. Echobichon and Stephens[52] found low levels of blood esterase activity in the fetus and neonate.

Biotransformation (Phase II Reactions). Conjugation reactions, or phase II reactions, synthesize more water-soluble compounds by combining a substance with an endogenous molecule to enhance excretion of that substance. Glucuronide, sulfate, and glycine are the common endogenous molecules to which drugs are bound. A drug must possess a specific functional group, such as a carboxyl, hydroxyl, amine, or sulfhydryl, in order to be conjugated. Alternatively, a drug must acquire one of these functional groups by undergoing phase I metabolism. Phase II enzyme groups have been studied far less than CYP450 enzymes; therefore the ontogeny of phase II enzymes remains relatively elusive.

Glucuronidation is the most common conjugation pathway because of the availability of glucuronic acid and the variety of functional groups with which it can combine. The uridine 5′-diphosphate glucuronosyltransferases (UGTs) participate in the biotransformation of at least 100 drugs (e.g., acetaminophen, morphine, nonsteroidal antiinflammatory drugs [NSAIDs]) and endogenous compounds, including bilirubin and thyroxine. Ready elucidation of the ontogeny of UGT isoforms has been precluded by overlapping specificities. For a detailed summary of available information about the UGT enzyme family, the reader is referred to the review by de Wildt et al.[53]

The activity of a number of UGTs is decreased in the fetus and neonate, as assessed by in vitro studies.[53-55] In addition, there is ample in vivo evidence of deficient glucuronidation in infants and particularly neonates. A profound example of this is the association of "gray baby syndrome" with the drug chloramphenicol, which normally undergoes glucuronidation. Morphine glucuronidation serves as a "probe" for isoform UGT2B7 activity. Studies have demonstrated significantly decreased clearance[56,57] and biotransformation[56] of morphine in neonates. Depending on how values are standardized between pediatric and adult subjects, morphine clearance approximates adult levels at anywhere from age 2 to 30 months.[7,57] Reduced UGT activity during infancy is also reflected in the biotransformation of acetaminophen. Levy et al.[58] demonstrated that 2- to 3-day-old term infants had a limited ability to conjugate acetaminophen with glucuronide, which is the major conjugation pathway in adults. However, this limitation in glucuronidation was compensated for by a well-developed sulfation pathway. This supports the findings of Alam et al.,[59] who showed that rates for glucuronidation are much lower and sulfation much higher with salicylamide and acetaminophen as substrates in children 7 to 10 years old compared with adults.

Studies evaluating bilirubin and chloramphenicol glucuronidation have reported low rates at birth, with adult rates achieved by age 3 years.[59] However, some evidence indicates that phenobarbital may induce glucuronidation in newborns and older children. Talafant et al.[60] administered phenobarbital 10 mg/kg/day to healthy full-term infants for their first 3 days of life. One group received phenobarbital intramuscularly and one group received phenobarbital orally; one group served as a control. These authors described significantly higher urinary glucaric acid concentrations on day 7 in the IM group than in the controls. This finding correlated well with a downward trend in serum bilirubin in the group receiving IM bilirubin. The ontogeny and potential substrates of other phase II enzymes is summarized in Table 116-3.

Additional Factors Affecting Hepatic Biotransformation. Several factors in addition to those of a developmental nature may affect hepatic biotransformation. Although the impact of each on hepatic enzyme systems is incompletely characterized, factors such as genetics, concomitant drug therapy, and critical illness may alter drug biotransformation and, hence, patient response. Genetic variation of a number of hepatic isoenzymes has been described, with corresponding variation in phenotype. For example, 7% to 8% of Caucasian children are characterized as "poor metabolizers" with reference to the enzyme CYP2D6, which may manifest as insufficient metabolism of several categories of drugs, including β-agonists, antidepressants, antipsychotics, antiarrhythmics, and derivatives of morphine.[35] Variants of CYP2C9 have been described, affecting metabolism of drugs such as tolbutamide, NSAIDs, warfarin, and phenytoin.[35] Polymorphism of the phase II enzyme N-acetyltransferase-2 (NAT2) affects half of the Caucasian and African-American populations in North America. In this case, "slow metabolizers" are at increased risk for several adverse drug responses, including drug-induced lupus erythematosus following procainamide or isoniazid therapy and Stevens-Johnson syndrome or toxic epidermal necrolysis following sulfonamide exposure.[35] Finally, several UGT isoforms are subject to genetic mutation. The best known of these genetic variations occur in UGT1 and UGT1A1, producing absent or reduced bilirubin glucuronidation in the case of the former isoenzyme and reduced bilirubin conjugation in the latter. Phenotypically, these mutations manifest as Crigler-Najjar and Gilbert syndrome, respectively. The effect of these UGT polymorphisms with respect to drug metabolism has not been substantially studied.[35] However, sparse data suggest that glucuronidation of drugs may also be affected in these patients.[35,61]

The frequent need for polytherapy in the ICU increases the possibility that hepatic biotransformative enzyme systems will be induced or inhibited, affecting the metabolism of any substrate of that system. A list of drugs known to induce or inhibit hepatic metabolic enzymes was compiled by Leeder

and Kearns.[35] Even less is known about the effect of critical illness on hepatic enzyme function than that of development. Several factors may contribute to altered hepatic metabolism in critically ill patients. Decreases in cardiac output and, consequently, hepatic blood flow reduced clearance of lidocaine in adult patients; in these patients, treatment with dobutamine improved plasma clearance.[62] In vivo studies suggest that certain CYP isoforms, including those in the CYP3A family, are exquisitely vulnerable to hypoxia, demonstrating alteration of activity after as few as 8 hours of hypoxia.[62] The systemic inflammatory response appears to potentially alter CYP activity as well. Mice infected with *Listeria monocytogenes* experienced decreased expression of some CYP450 enzymes, which returned to normal levels after 96 hours.[63] Many inflammatory mediators reduce expression of CYP isoforms, including CYP1A1, CYP2C, CYP2E1, and CYP3A in human hepatocytes.[64] Decreased metabolism of a number of known substrates of CYP450 has been demonstrated in patients with fever induced by infection and drugs and with hypothermia following cardiopulmonary bypass.[62] Of course, linking pharmacokinetic variations in the critically ill patient to impaired hepatic metabolism is difficult in the face of other pathophysiologic alterations.

Drug Elimination

The elimination half-life ($t_{1/2\beta}$) of a drug is commonly used to describe its disappearance from the blood and is measured as the time required for half the amount of drug present in the blood to disappear. As such, $t_{1/2\beta}$ can be used to reflect drug clearance, although changes in V_d also affect this parameter. This and related pharmacokinetic principles are discussed more thoroughly later in the chapter.

Renal Excretion. Most drugs and/or their metabolites are excreted from the body by the kidneys. Renal excretion depends on glomerular filtration, tubular reabsorption, and tubular secretion.[65] The amount of drug that is filtered per unit of time is influenced by the extent of protein binding and renal plasma flow. When the latter is constant, the greater the extent of protein binding, the smaller the fraction of circulating drug that is filtered. The degree of protein binding also influences drug elimination in patients undergoing dialysis in a similar manner; drugs that are highly protein bound are less easily dialyzed.[66,67] This section also examines developmental aspects of renal function and their influence on renal drug excretion.

Renal blood flow and renal plasma flow increase with age as a result of increased cardiac output and reduced peripheral vascular resistance.[68-70] The kidneys of neonates receive only 5% to 6% of the cardiac output compared with 15% to 25% in adults. Renal plasma flow averages 12 mL/min (0.72 L/hr) at birth and increases to 140 mL/min (8.4 L/hr) by age 1 year. If renal plasma flow is corrected for body surface area, adult values are reached before 30 weeks of extrauterine life. Using clearance of para-aminohippurate to estimate renal plasma flow, Calcagno and Rubin[71] demonstrated adult rates by age 5 months.

At birth, glomerular filtration rate (GFR) is directly proportional to gestational age.[72] However, a linear relationship is not evident before 34 weeks of gestation. Inulin clearance rates below 10 mL/min have been described in newborns under 34 weeks of gestation, reflecting a significantly reduced GFR. This process must be considered when administering drugs or fluid to the premature newborn.[72] At birth, GFR for term infants ranges from 2 to 4 mL/min. In the first 2 to 3 days of postnatal life, GFR in term babies increases markedly to rates between 8 and 20 mL/min. During the first several weeks of life, increases in GFR correlate with postconceptual age, not postnatal age.[72] Adult values for GFR (127 mL/min) are reached by age 2.5 to 5 months.[73] The postnatal increase in GFR most likely results from the combined effects of increased cardiac output, decreased peripheral vascular resistance, increased mean arterial blood pressure, increased surface area available for filtration, and increased membrane pore size.[74] In fact, the finding that increases in GFR correlate with postconceptual age suggests that maturational changes are an important factor in the observed increase in glomerular function. The clinical implications for maturation of GFR become apparent when considering drugs that are primarily eliminated by glomerular filtration. Several studies have investigated the pharmacokinetics of aminoglycosides in preterm and term infants. Szefler et al.[75] demonstrated a decreasing $t_{1/2}\beta$ for gentamicin with increasing gestational age in infants younger than 7 days.

Proximal convoluted tubules in the normal kidney of a full-term infant are small in relation to their corresponding glomeruli. This glomerulotubular size imbalance is reflected by functional differences in the transport capacity (secretion) of the proximal tubular cells.[76] Therefore tubular function matures at a slower rate than does glomerular function. Reasons for this reduced functional capacity include not only the small size of the tubules but also a smaller mass of functioning tubular cells, reduced blood flow to the outer cortex, and immaturity of energy-supplying processes. This imbalance continues for the first year of life, after which function of both glomerular and tubular components is comparable to that in healthy, young adults.[5] Processes of both active absorption (i.e., secretion) and passive absorption (i.e., reabsorption) are impacted in the immature kidney.

Many drugs rely on either the organic anion or cation transport systems present in the proximal tubules for renal excretion. Penicillin is actively secreted. Results of pharmacokinetic studies of ampicillin, ticarcillin, benzylpenicillin, and methicillin show that the $t_{1/2\beta}$ for the penicillins varies inversely with gestational and postnatal age.[77-80] In all the studies cited here, $t_{1/2\beta}$ for penicillins was highly variable, but generally decreased to 1 to 2 hours by 2 weeks postnatal age. These observations may be partially explained by findings in animals that the capacity of the pathways responsible for penicillin secretion may undergo substrate stimulation. Substrate stimulation has not been formally studied in human neonates, but evidence indicates that it does occur. Kaplan et al.[78] showed a reduction in $t_{1/2\beta}$ for ampicillin in both preterm and term infants after multiple doses compared with a single dose.

Furosemide is another drug secreted by the proximal tubules. In addition to being filtered, evidence for tubular secretion is inferred from adult data describing reduced rates of plasma clearance and urinary excretion after probenecid administration.[81] Aranda et al.[82] found an eightfold prolongation in $t_{1/2\beta}$ and an eightfold reduction in the elimination rate constant for furosemide in fluid-overloaded term and preterm neonates with normal renal function compared with adults. Peterson et al.[83] evaluated single-dose kinetics for furosemide in preterm and term infants and found a mean $t_{1/2\beta}$ of 19.9 and 7.7 hours, respectively. This is in contrast to a $t_{1/2\beta}$ of 30

minutes in healthy adults. These prolonged plasma half-lives correspond with the prolonged duration of diuretic and saluretic effect seen in infants,[84] although the response to furosemide most likely is dependent on its rate of urinary excretion.

The sensitivity of the kidney to hypoxic and ischemic insult is well known. Because this is one of the most important final common pathways for serious illness in infants and children, it follows that renal functional impairment is relatively frequent in patients in the PICU. Kidney function may be further impaired by the frequent use of nephrotoxic drugs such as amphotericin B and aminoglycosides in PICU patients. Clearly, varying degrees of renal functional impairment seen in critically ill infants and children can seriously complicate drug therapy in this setting.[26,85]

Drug Delivery Systems

As discussed previously, the maintenance of steady-state drug concentration requires that the amount of drug being administered match the amount of drug being cleared from the body. Several factors determine how much of a drug can be administered to any given patient at any given time. Although uncommon in the ICU, the available routes of administration may limit bioavailability and, hence, ultimate drug concentration. In the patient who requires fluid restriction, limitations in the maximal concentration of drugs may prove problematic. In the smallest of patients, full delivery of intravenous drug doses contained in diminutive volumes of vehicle may not be assured. Administration of a drug as a bolus generally ensures that the patient has received the full dose, provided any tubing between the site where the drug is given and where it enters the vein is adequately flushed. In the case of drugs given over a discrete interval or by continuous infusion, the drug delivery system influences the amount of a given drug dose received by the patient. Regardless of the technology used, the amount of drug delivered by a system depends upon the designated flow rate and the amount of tubing between where the drug is introduced and the patient's bloodstream.[21] When a drug is added to a fluid reservoir, delivery also depends on the volume of drug added.[21] An example of the impact of these factors on drug delivery is as follows. If a drug is added to the reservoir in a system where the flow rate is 25 mL/hr, drug delivery may not begin for almost 2 hours and would require nearly 4 hours for completion.[21] Consequently, administering drug in this manner could result in delayed and/or incomplete drug delivery. Additionally, an inability to pin down the timing of drug delivery complicates interpretation of drug levels when monitored.[21]

Fortunately, considerable advances in drug delivery technology have been made over the past 20 years[86] and have been of particular benefit in the PICU. Infusion pumps that provide greater volumetric accuracy have facilitated full delivery of small volumes. In some cases, improvements in infusion continuity have enabled uninterrupted delivery of continuously administered drugs, a fact that is of particular importance for drugs with very short $t_{1/2\beta}$ values (e.g., nitroprusside).[86] It is important that the intensivist have some familiarity with the technology used in his or her unit; this knowledge may be helpful when an unintended response to pharmacotherapy occurs. For a comprehensive review of this technology, the reader is referred to the chapter by Kwan.[86]

Effect of Extracorporeal Therapies on Drug Disposition. Extracorporeal therapies, including hemofiltration, dialysis, and extracorporeal membrane oxygenation (ECMO), can alter drug disposition in affected critically ill patients. Although relatively little study has been devoted to drug disposition in patients on ECMO, evidence supports the idea that this treatment modality alters pharmacokinetics. In neonates and infants, the largest number of studies have looked at the disposition of gentamicin and vancomycin.[87] Increased V_d, increased $t_{1/2}$, and decreased clearance compared with control or post-ECMO values were demonstrated in the majority of these studies.[87-89] In one study investigating vancomycin, only an increased $t_{1/2}$ differentiated ECMO patients from non-ECMO controls.[90] Other drugs, including theophylline,[91] morphine,[92,93] tobramycin,[87] bumetanide,[87] and ranitidine[87] have been shown to increase V_d, decrease clearance, and/or increase $t_{1/2}$ in patients on ECMO. The addition of an extracorporeal reservoir contributes to the increase in V_d, and alterations in hepatic and renal function in ECMO patients impact clearance. Additionally, adhesion of some drugs to circuit hardware may alter serum or blood concentrations. The age of the circuit appears to influence this factor to some extent. Dagan et al.[93] evaluated the "elimination" of drugs following direct injection into two circuits: a new one and a circuit that had been used by a patient for 5 days. A relatively increased elimination of several drugs by the new circuit was described (vancomycin, 36% vs. 11%; gentamicin, 10% vs. 0%; phenobarbital, 17% vs. 6%; phenytoin, 43% vs. 0%; morphine, 36% vs. 16% in the new vs. used circuit).[93] Several other drugs are subject to this phenomenon, including heparin, furosemide, fentanyl, benzodiazepines, propofol, and perhaps morphine.[87] Propofol appears particularly susceptible to this effect. In vitro studies using entire circuits and various individual components report recovery of propofol has been 10 percent or less.[87] In the in vitro studies, priming of the circuit with albumin appears to reduce adsorption of at least some of these drugs.[87] This method of priming may have contributed to the maintenance of serum morphine concentrations in an in vivo study as well.[94] Drug concentrations may be altered when a circuit containing some fraction of that drug is discarded and replaced.[87] Finally, pharmacokinetics may be altered by in-line hemofiltration, which is required in approximately 12% of neonates on ECMO, and by dialysis, which is required by approximately 3% to 4% of these patients.[87]

Pharmacodynamics

In contrast to pharmacokinetics, which operationally describes what the body does to the drug, pharmacodynamics deals with what the drug does to the body.[95] As such, this discipline within pharmacology deals with the mechanisms of action of drugs, their safety profiles, drug-receptor interactions, and receptor-effector coupling phenomena. Infants and children have been described to exhibit different clinical responses to several medications than do adults. One example of this difference is the hyperexcitability children may experience following exposure to antihistamines and barbiturates in contrast to the sedation normally observed in adults.[96] Children also have a greater incidence of dystonic reactions following the administration of dopamine antagonists (e.g., haloperidol, chlorpromazine, metoclopramide), which has been speculated to result from an increased concentration of DA-2 receptors in the young brain.[96] When no pharmacokinetic explanation for different drug responses between children

and adults has been offered, a difference in "sensitivity" has been proclaimed. Variable sensitivity to drugs, including some of the nondepolarizing neuromuscular blocking agents (e.g., pancuronium) and the catecholamines, has been described in infants compared with adults. For example, a decreased sensitivity to dopamine has been observed in infants, manifested by an insignificant change in any physiologic variable (including heart rate) below a dose of 15 μg/kg/min.[96] The formal study of ligand-receptor interactions and their consequences is covered comprehensively in two referenced texts.[97,98] However, the translation of these principles into the practice of medicine is embodied in the discipline of therapeutics. Just as important developmental changes determine the related absorption, distribution, metabolism, and excretion of drugs, ontogenetic changes in drug responsiveness account for both the qualitative and quantitative differences observed in efficacy and toxicity when drugs are used in infants and children. Unfortunately, the latter have not been evaluated with the same intensity that has characterized our assessment of developmental changes in pharmacokinetics.[99,100] Actions of drugs in the immature individual may be altered for a variety of reasons, including altered numbers of receptor sites compared with mature individuals, altered affinity of the receptor for its primary ligand or agonists, and/or altered receptor-effector coupling resulting in altered drug responsiveness. Additional work is necessary to bring this level of sophistication to the clinical setting.

Effect of Disease on Drug Action

During serious illness, substantial changes may occur in receptor function, tissue architecture, and postreceptor function that ultimately are responsible for changes in drug action. These often result from vascular volume or electrolyte derangements and from the effects associated with derangements in acid-base status. Nevertheless, conditions such as pulmonary fibrosis and cardiomyopathy may be associated with diminished responsiveness to drugs acting on the affected organ. Infection with *Haemophilus influenzae* type B has been associated with decreased pulmonary β_2-receptor function with a resultant increase in airway resistance.[101,102] Protracted use of catecholamines may result in down-regulation of functional β-receptors in target organs, requiring frequent dose increases to achieve the maintained desired pharmacologic effect.[103-105]

Finally, remember that most drugs used in the PICU are potent agents that have the potential to cause serious side effects.[106] Unfortunately, drug toxicity in a critically ill patient may be an amplified event. Such patients are the least likely to be able to tolerate such effects. Thus the therapeutic index for most of the drugs used commonly becomes increasingly narrow as the patient's condition warrants more aggressive therapy.[107]

Pharmacokinetic Principles

Evaluation of the Plasma Concentration-Time Curve

The application of pharmacokinetic principles to patient care should permit rational drug dosing and result in effective pharmacotherapy. Most of the drugs used in clinical medicine are metabolized via linear first-order kinetic processes (Figure 116-2). This means that a constant percentage of drug is removed from the body per unit of time. Virtually all of the pharmacokinetic parameters used on a routine basis can be derived from a plot of serum/plasma concentration versus time, which then is converted to a semilogarithmic display (Figure 116-3). The straight, terminal portion of the former represents the elimination phase for the drug, and its slope is the elimination rate constant K_e (Table 116-3 and Figure 116-4). The elimination half-life for the drug $t_{1/2\beta}$ (see Figure

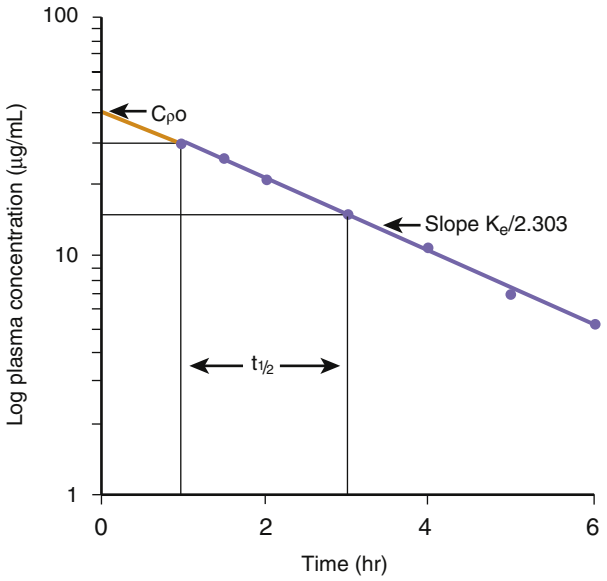

Figure 116–2. First-order elimination. Plasma concentration versus time curve for a drug eliminated via first-order kinetics. Note the elimination half-life is depicted as the time required for the drug concentration to be reduced by half. A constant fraction of the drug in the body is eliminated in each equal interval of time.

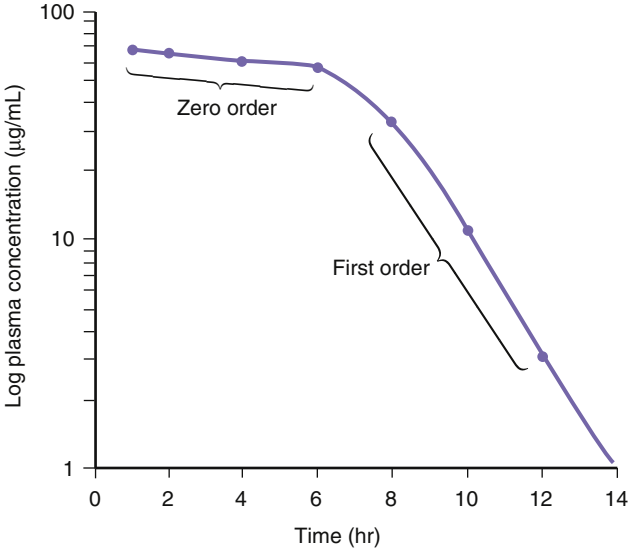

Figure 116–3. Michaelis-Menten kinetics. Log plasma concentration versus time curve for a drug showing saturation of the elimination mechanism. Initially, a constant amount of drug is eliminated per unit time rather than a constant fraction of drug per unit time. This initial phase is said to show zero-order elimination. Later, the plasma concentration falls below the saturating level and the elimination process becomes first order.

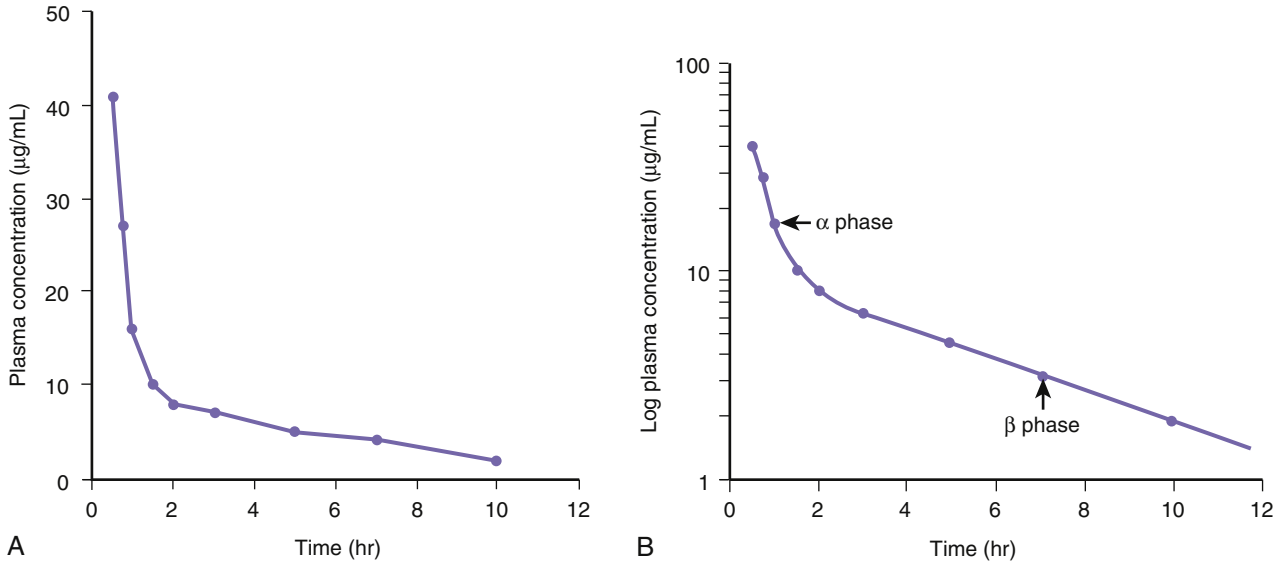

Figure 116–4. Two-compartment model. **A**, Plasma concentration versus time curve presented using rectangular coordinates. **B**, Semilogarithmic transformation of the data shows a biphasic curve rather than a straight line. This is thought to represent the interaction between two compartments: plasma and extracellular fluid space. The upper portion of the curve is called the α *phase* and is thought to represent drug distribution. The lower portion is termed the β *phase* and is thought to represent actual drug elimination. Slope of the β phase = –K/2.303.

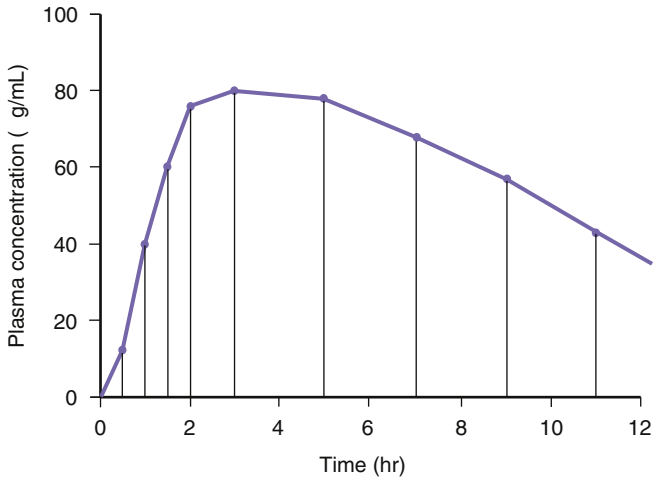

Figure 116–5. Trapezoidal rule. Plasma concentration versus time curve for a drug after oral administration. The area under the curve (AUC) represents the total amount of an individual dose that is absorbed. This area can be calculated by dividing the curve into a series of trapezoids, calculating the area for each, and summing all of the areas.

116-2) then can be determined directly by inspection of the semilogarithmic graph as the time required for the concentration to decrease by half, or it may be calculated from the exponential decay curve considerations once K_e is determined:

$$t_{1/2\beta} = \frac{0.693}{K_e}$$

The area under the serum concentration versus time curve (AUC) can be determined by applying an approximate integration formula, most commonly the trapezoidal rule.[108] This method involves the description of a given plasma concentration-time curve as a series of straight lines, which enables the curve to be divided into a number of trapezoids (Figure 116-5). The area of each trapezoid can be easily calculated, and the sum of all such areas equals the area under the AUC. The latter value is important in deriving two other values of clinical importance: bioavailability and clearance of the drug. Finally, by extrapolating the terminal elimination phase of the curve b to time 0, the intercept on the Y axis denotes the concentration that would have resulted if the total dose of the drug had instantaneously distributed throughout the body (Figure 116-6). This concentration, termed C_o, can be used to determine the apparent volume of distribution of the drug V_d, using the following equation:

$$V_d = \frac{D}{C_o}$$

where *D* is the dose administered.

In children, a number of important compounds demonstrate saturation kinetics at clinically useful doses (Box 116-5). In this case, the drugs appear to have longer half-lives at higher concentrations. For these drugs, the relationship between serum concentration and time is better described by the values V_{max} and K_m than by V_d and Cl.[19,109] The most important drug demonstrating this type of biodisposition is phenytoin.[110] With this drug, a small increase in dose may result in a large increase in serum concentration. Disease states and drug interactions can pose particular problems for patients receiving drugs cleared by saturable processes. A patient with liver dysfunction may have decreased V_{max} for a given drug compared with a healthy child. Consequently, saturation of metabolic elimination may occur at a lower concentration than normal.

Applied Pharmacokinetics

Use of pharmacokinetic parameter estimates is essential to the development of proper dosing regimens, the effective use of the drug analysis laboratory, and ultimately in optimization of drug therapy. Among the available parameters, the most important in the PICU are clearance (Cl), volume of distribution (V_d),

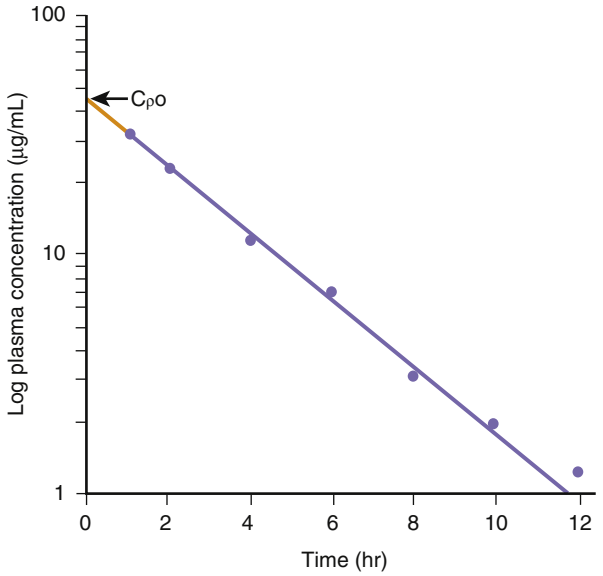

Figure 116–6. Log plasma concentration versus time curve depicting Cp_0. This is a semilogarithmic plot of plasma drug concentration versus time after intravenous infusion of drug. This drug shows one-compartment, first-order elimination as indicated by the single straight line. Extrapolation of the line back to time zero yields an estimate of Cp_0 or the drug concentration that would result if the total dose was administered and distributed immediately throughout the body. If the dose administered is known and the C_0 ascertained, the apparent volume of distribution V_d of the drug administered can be calculated.

Box 116–5 Drugs Demonstrating Saturation Kinetics in Infants and Children

Caffeine
Chloramphenicol
Diazepam
Ethanol
Furosemide
Indomethacin
Mezlocillin
Phenytoin
Salicylate

and half-life ($t_{1/2\beta}$). In addition, if oral therapy is contemplated, bioavailability (F) must be considered. Each of these parameters can be used for mathematically describing the biodisposition of a drug under steady-state conditions.

Bioavailability

The concept of bioavailability was discussed extensively in the section related to drug absorption. For most drugs administered intravenously, the bioavailability is 100% and F = 1. In clinical terms, the "relative" bioavailability of a drug is most important. Bioavailability F is defined as the ratio of the AUC for the drug given by a nonintravenous route (AUC_{Oral}) to the AUC of the same drug administered intravenously (AUC_{IV}):

$$F = \frac{AUC_{Oral}}{AUC_{IV}}$$

Relative bioavailability can be used to convert from one route of administration to another. For example, the relative bioavailability of theophylline is 1. Therefore in switching from intravenous to oral dosing, the same total daily dose of theophylline should be administered. In contrast, relative bioavailability of furosemide is approximately 0.5. Thus in switching from intravenous to oral administration, the dose of the drug should be doubled to maintain the same diuretic effect.

Half-Life

Elimination half-life of a drug is a hybrid term that is a function of both clearance and volume of distribution:

$$t_{1/2\beta} = \frac{0.693}{K_e} = \frac{0.693 V_d}{Cl}$$

This is the pharmacokinetic parameter most commonly used by clinicians, but it is often misconstrued to signify drug elimination. However, as shown in the equation, either a change in Cl or a change in V_d can result in a change in $t_{1/2\beta}$. The therapeutic implications of these alterations are clearly different. It is also apparent that if pathophysiologic changes result in offsetting changes in V_d and Cl, the elimination half-life could remain unaffected in the face of significant disease. The most important clinical application of half-life is as a determinant of drug dosing. Four to five half-lives are required for a drug to reach steady-state plasma concentration at any given dose. This is true whether therapy is being initiated or the dose is being changed.

Apparent Volume of Distribution

The volume of distribution V_d describes the apparent volume of the compartment into which the drug distributes. It must be emphasized that this value has no physiologic significance. Rather, it serves as a parameter estimate that permits the calculation of the dose of drug (i.e., loading dose) required to achieve a desired plasma concentration:

$$C_p = \frac{Dose}{V_d}$$

It should be noted that calculation is independent of the drug's clearance and half-life.

Total Body Clearance

As previously noted, clearance is a useful parameter for determining the amount of drug needed to maintain a desired steady-state plasma concentration. Because by definition the rate of drug elimination at steady state is equal to the rate of drug administration, then[20,33,108]

Elimination rate = $C_p \times Cl$, where C_p is the average steady-state plasma concentration:

$$\text{Administration rate} = (F \times D) / \tau$$

where D = dose and τ = dosing interval.
At steady state:

$$C_p \times Cl = (F \times D)/\tau$$

or, rearranging:

$$C_p = (F \times D)/(Cl \times \tau)$$

where the solutions provide the average steady-state plasma concentration. It is obvious from the equation that to maintain a steady-state plasma concentration, disease-associated changes in Cl must be compensated by changes in dose D or interval τ.

Critical Care Therapeutics

In the treatment of critically ill infants or children, consideration must be given to both developmental and disease processes. Thus at first glance it seems an overwhelming task to develop therapeutic strategies that would be both safe and effective in treating these patients. Nevertheless, two approaches can be identified that lend themselves to the rational care of these patients: target concentration strategy and target effect strategy.[111]

Target Concentration Strategy

The target concentration strategy can be considered for drugs that are used chronically to treat clinical problems that manifest themselves intermittently (Box 116-6). Such problems include reversible reactive airway disease, seizures, and cardiac dysrhythmias. Application of this therapeutic strategy requires recognition that certain target serum concentrations are associated with either the therapeutic or the toxic effects attributed to a given pharmacologic agent. It is important to remember that these target concentration ranges are determined using population-based data rather than individual patient data. Therefore the so-called therapeutic or toxic ranges may not be strictly applicable to the patient currently being treated. However, they serve as useful guides for the initiation and ongoing monitoring of therapy. As part of this ongoing monitoring, effective use of the drug analysis laboratory is essential. To apply the target concentration strategy, physicians must have some knowledge of the pharmacokinetics of the drug being used (Box 116-7). Such knowledge includes an awareness of any active metabolites that may be involved in the expression of the drug's therapeutic activity.

The approach to treatment of the patient in whom the target concentration strategy is to be used requires that the physician have an expectation regarding the clinical manifestations of drug efficacy and drug toxicity before any therapy is initiated. This should be accompanied by an awareness of the appropriate sampling times for the various drugs and an overall understanding that drug "levels" are guides to therapy rather than therapeutic endpoints in themselves. Therapeutic drug monitoring does not substitute for other means of patient evaluation. Effective drug dosing using the target concentration strategy requires a familiarity with the pharmacokinetic parameters previously described and the effective use of the drug analysis laboratory. When a target plasma concentration is known, an initial dose can be chosen. Under some circumstances, it may be desirable to achieve the target concentration immediately. In these instances, the initial dose is termed a *loading dose* and calculated as:

$$\text{Loading dose} = \frac{C_p \times V_d}{F}$$

where C_p is the target concentration.

Use of a loading dose is not always appropriate. Under certain circumstances, the calculated loading dose can result in toxic plasma concentrations before tissue distribution. The alternative is to begin therapy with what is termed the *maintenance dose*:

$$\text{Maintenance dose} = \frac{C_p \times \tau \times V_d}{F}$$

Box 116–6 Principles of the Target Concentration Strategy in Drug Therapy

- Strategy may be effective for drugs used on a chronic basis to treat diseases that manifest signs and symptoms intermittently.
- Caregivers must have some knowledge of the pharmacokinetics of the drugs being used.
- A relationship between drug or metabolite concentration in the sampled biologic fluid and therapeutic efficacy or clinical toxicity must have been established.
- Appropriate sampling time must be known and a reliable assay must be available.
- Target concentrations must be used as guides; treat patients, not drug levels.

Box 116–7 Drugs Used in the Target Concentration Strategy

Antiarrhythmic agents: amiodarone, procainamide, quinidine, lidocaine
Anticonvulsant agents: phenytoin, phenobarbital, valproic acid, carbamazepine, pentobarbital
Antibiotics: aminoglycosides, chloramphenicol, vancomycin (±)
Methotrexate
Cyclosporine
Antipyretics: acetaminophen, salicylate
Theophylline

When therapy is initiated with a maintenance dose, dosing for a total of four to five half-lives will be required to reach the desired steady-state plasma concentration. In contrast, when used in conjunction with a loading dose, the maintenance dose should maintain the plasma concentration attained with the loading dose.

Effective use of therapeutic drug monitoring in the critical care setting requires integration of certain characteristics of the drugs to be used, the laboratory where drug analysis occurs, and physician behavior. The drug selected for therapeutic drug monitoring should be one from which a relatively sustained and constant effect is expected over a comparatively long period of time. Monitoring should be limited to drugs characterized by wide interindividual variation in pharmacokinetics, as well as those that manifest a narrow therapeutic index. Finally, it is imperative that a set of data exists to relate the clinical effects of the drug directly to its concentration in the serum.

For drugs fulfilling these criteria, sensitive and specific assays for determination of their concentrations in various types of biologic fluids must be available. Moreover, this service must be provided with a turnaround time that is appropriate to the type of therapy being rendered. Thus it may be appropriate to provide aminoglycoside serum concentration determinations with a 24-hour reporting schedule; however, the safe and effective adjustment of theophylline dosing requires that serum concentrations be available within 1 hour from the time the blood is drawn. In addition, the results provided by any laboratory must be internally consistent. Standard curves must be checked frequently, and this quality assurance information must be available to all physicians on request.

Use of the target concentration strategy places heavy demands on the physician. Values for commonly used pharmacokinetic parameters describing absorption, distribution, and elimination should be known or readily available. The physician must be aware of conditions in which these pharmacokinetic parameter estimates may be altered and the extent to which these alterations may affect therapy. The physician must have a working knowledge of the average steady-state concentrations of drug in serum associated with both drug effectiveness and drug toxicity. Moreover, the pathophysiologic conditions that may alter these concentration-response relationships must be understood. Finally, clinical experience and sound judgment must prevail. Therapy must consist of an ongoing commitment to treat patients and not drug levels.

Target Effect Strategy

The target effect strategy embodies the therapeutic approach most commonly practiced in the PICU. In fact, the therapeutic strategy allows for rational application of most of the drug classes required in the intensive care setting to the pediatric patient (Box 116-8). Application of the target effect strategy requires that the clinician determine a therapeutic endpoint before initiating drug treatment and accept a commitment to monitor for both drug effectiveness and toxicity. In using this approach, the clinician must have a reasonable understanding of the pharmacodynamic actions of the drugs to be used, including their side-effect profiles. Moreover, the impact of both ontogeny and disease on drug action must be considered. Once therapy is started, the dose is increased until the desired effect is achieved, unless the sequential increase in drug dose results in no increase in therapeutic benefit and the desired effect is not achieved or drug toxicity supervenes. The amount of time taken in dosage escalation is dictated by the clinical circumstance at hand. In some circumstances, days of adjustments may be acceptable, whereas in others minutes may be too long. Nevertheless, inherent in this strategy is a belief that responses to drugs are dose-related and that any concept of a preexisting maximal dose is precluded. Thus if either lack of efficacy or toxicity becomes apparent, the mandated response is to *change* the drug.

Box 116–8 Classes of Drugs Used in the Target Effect Strategy for Critically Ill Children

Anticoagulants
Catecholamines
β-Lactam antibiotics
Diuretics
Corticosteroids
Oxygen
Anxiolytics, sedatives
Neuromuscular blockers
Vasodilators
Antihypertensives
Inotropes: amrinone

In summary, rational therapeutics for the critically ill child must account for the impact of development and disease on drug action. The scenario suggests use of short-acting drugs with large therapeutic indexes and requires that expectations regarding drug effects be ascertained prospectively. This approach mandates rigorous attention to monitoring but ultimately ensures that the dosage used will be sufficient to achieve the desired response.

References are available online at http://www.expertconsult.com.

Molecular Mechanisms of Drug Actions: From Receptors to Effectors

Catherine Litalien and Pierre Beaulieu

PEARLS

- Receptors play a central role in determining the nature of the pharmacologic effects produced by a drug.
- Most drugs and endogenous compounds (e.g., hormones, neurotransmitters) exert their action by binding to a receptor or by modulating an ion channel.
- G proteins are a superfamily of proteins that allow transduction between activated receptor (by an agonist) and different intracellular effectors, such as enzymes or ion channels, relaying signals from more than 1000 receptors. G protein–coupled receptors represent the target, directly or indirectly, of approximately 50% of all current therapeutic agents.
- Continued exposure of a receptor to an agonist often results in progressive loss of receptor responsiveness, with a diminished receptor-mediated response over time. This is called *desensitization*.
- Calcium is critically important as a regulator of cell function. It exerts its control on cellular function through its ability to regulate the activity of many different proteins, such as channels, transporters, and transcription factors. In the majority of cases, a calcium-binding protein serves as an intermediate between Ca^{2+} and the regulated functional protein.
- The role of inheritance in the individual variation of drug response is increasingly recognized with the identification of polymorphisms in genes encoding drug-metabolizing enzymes, drug targets, and proteins involved in signal transduction. Studies evaluating the effects of single nucleotide polymorphisms (SNPs) for a given gene will need to consider specific haplotypes or combination of haplotypes because individual SNPs may have poor predictive power as pharmacogenetic loci.

Optimizing drug response is a challenging task that clinicians confront on a daily basis. This is particularly true for those caring for critically ill patients, in whom many factors influencing drug response are being more commonly recognized. These include reduced absorption, variable drug distribution, decreased metabolism and elimination, as well as alterations in drug receptors, signaling mechanisms, and effectors.[1-3] In recent years, advances in molecular pharmacology have shed more light on the processes that transduce extracellular signals into intracellular messages that control cell function. This has led to the elucidation of multiple points at which modulation of signal transduction, either by pharmacologic agents or diseases, can occur. Also, there has been an ongoing recognition of the role of inheritance in the individual variation of drug response with the identification of polymorphisms in genes encoding drug-metabolizing enzymes, drug targets (e.g., receptors, enzymes), and proteins involved in signal transduction.[4-6]

This chapter provides a detailed overview of how drugs work at the molecular level and how this complex system is influenced by genetic factors, developmental changes, disease processes, and the environment (Figure 117-1). Ultimately, the objective is to help pediatric intensive care physicians better tailor the pharmacotherapy they use: that is, choose the right drug, or combination of drugs, for the right patient to achieve maximal efficacy with no or minimal toxicity. This chapter does not address signaling pathways involved in diseases per se.

Targets For Drug Action

The initial step in the cascade of biochemical events resulting in drug action mostly consists in the binding of drugs to specific cellular targets. These can be broadly divided into four categories: (1) receptors, (2) ion channels, (3) enzymes, and (4) carrier proteins (Figure 117-2). The vast majority of important drugs act on one of these types of proteins.

Receptors

Receptors are the most frequent drug target. They can be defined as the sensing elements in the system of chemical communication that coordinate the function of all different cells in the body, the chemical messengers being the various hormones, neurotransmitters, other mediators, or drugs. Ligands

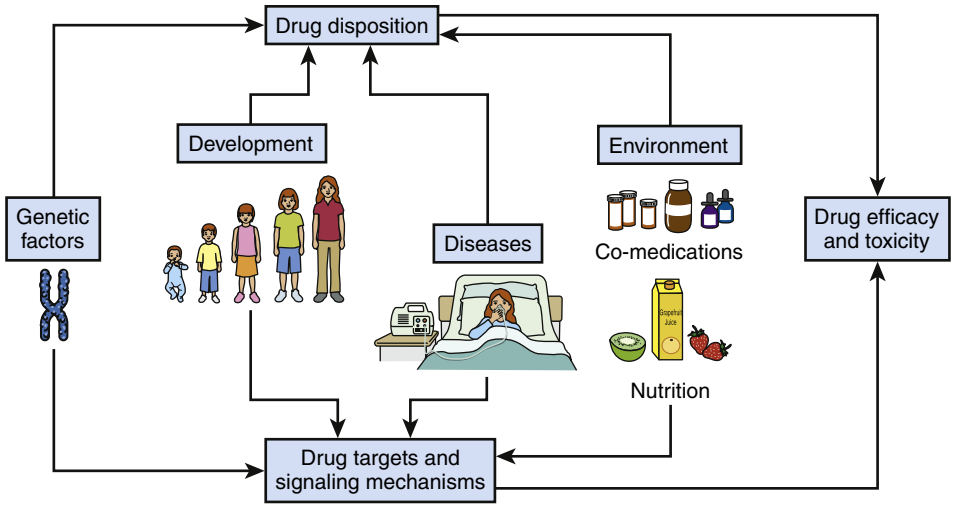

Figure 117–1. Relationships among genetic factors, development, diseases, and the environment and drug efficacy and toxicity.

(e.g., hormones, drugs) that bind with receptors are termed *agonists* if their binding results in the expected effect and are termed *antagonists* if binding stops or decreases an agonist-induced activity.[7] Administration of a receptor antagonist in the absence of agonist results in no effect because antagonists bind to receptors but do not activate them. An antagonist is said to be *surmountable* when maximal response to the agonist can be restored by raising the agonist concentration (parallel displacement of the agonist dose-response curve to the right). Likewise, an antagonist is said to be *insurmountable* when even high concentrations of the agonist are not able to elicit the maximal expected agonist response (Figure 117-3, *A*). The terms *competitive* and *noncompetitive* do not describe a pharmacologic behavior per se; rather, they refer to the receptor binding site of the antagonist with regard to that of the agonist. A competitive antagonist binds to the same site as the agonist on the receptor, whereas a noncompetitive antagonist has its own binding site separate from that of the agonist and makes the receptor refractory to the agonist. Both *competitive* and *noncompetitive* antagonists can be *insurmountable.*

The duration of action of an *insurmountable* antagonist depends mostly on synthesis of new receptors, which can take several days. This may have clinically important consequences. For example, phenoxybenzamine, an *insurmountable* α-adrenergic receptor antagonist sometimes used in stage I Norwood procedures to balance the pulmonary and systemic circulations, can produce symptomatic hypotension in some patients. The attenuation or reversal of the decrease in systemic vascular resistance it produces may not be achieved with an α-adrenergic receptor agonist such as dopamine (high dose) or norepinephrine, depending on the dose of phenoxybenzamine given. In such circumstances, the use of a pressor agent that does not act through the α-adrenergic receptor such as vasopressin, which binds on V_1 receptors of smooth muscle cells, must be considered.[8]

Partial agonists are ligands that bind to the same receptor as full agonists but have less intrinsic capacity to produce a response as strong as full agonists, despite full receptor occupancy (Figure 117-3, *B*). The exact mechanism that accounts for the blunted maximal response seen with partial agonists is unknown. Simultaneous administration of a partial agonist and a full agonist prevents the maximal response usually observed with the full agonist alone because partial agonists have the ability to occupy the receptor population (Figure 117-3, *C*). Finally, inverse agonists are ligands that reduce the level of constitutive activation encountered in some receptor systems (Figure 117-3, *D*).[9]

Receptors play a central role in determining the nature of the pharmacologic effects a drug produces. First, receptors bind with only one or a limited number of structurally related ligands, thus ensuring that the final effect seen in a normal setting occurs only in response to defined stimuli. Second, for a given dose or concentration of a drug, the drug's affinity to bind to the receptor and the total number of available receptors directly influence the maximal effect a drug can produce. Third, drugs differ in their intrinsic activity in regard to their receptors (e.g., partial agonist vs. full agonist). Thus the magnitude of the response to any drug is proportional to both the extent of receptor occupancy and the intrinsic activity of the receptor itself, resulting in different dose or concentration relationships for different agonists.

Ion Channels

Ion channels are molecular machines that serve as principal integrating and regulatory devices for the control of cellular excitability. Different types of ion channels have been described: channels responding to electrical (voltage-dependent ion channels), mechanical, or chemical (ligand-gated ion channels) stimuli; ion channels controlled by phosphorylation/dephosphorylation mechanisms; and G protein–gated ion channels. Most ion channels are of the voltage-dependent type and consist mainly of Na^+, K^+, and Ca^{2+} channels. Drugs can affect ion channel function directly by binding to the channel protein and altering its function or indirectly through G proteins and other intermediates. Lidocaine is a good example of a drug that directly affects voltage-gated Na^+ channels by blocking the channel and thus Na^+ entry into the cell. Channel-linked receptors (ligand-gated ion channels) are discussed below.

Enzymes

Enzymes are a specialized class of proteins responsible for catalyzing chemical reactions within the cell and thus are ideal drug targets. Most drugs that alter enzymes activity are

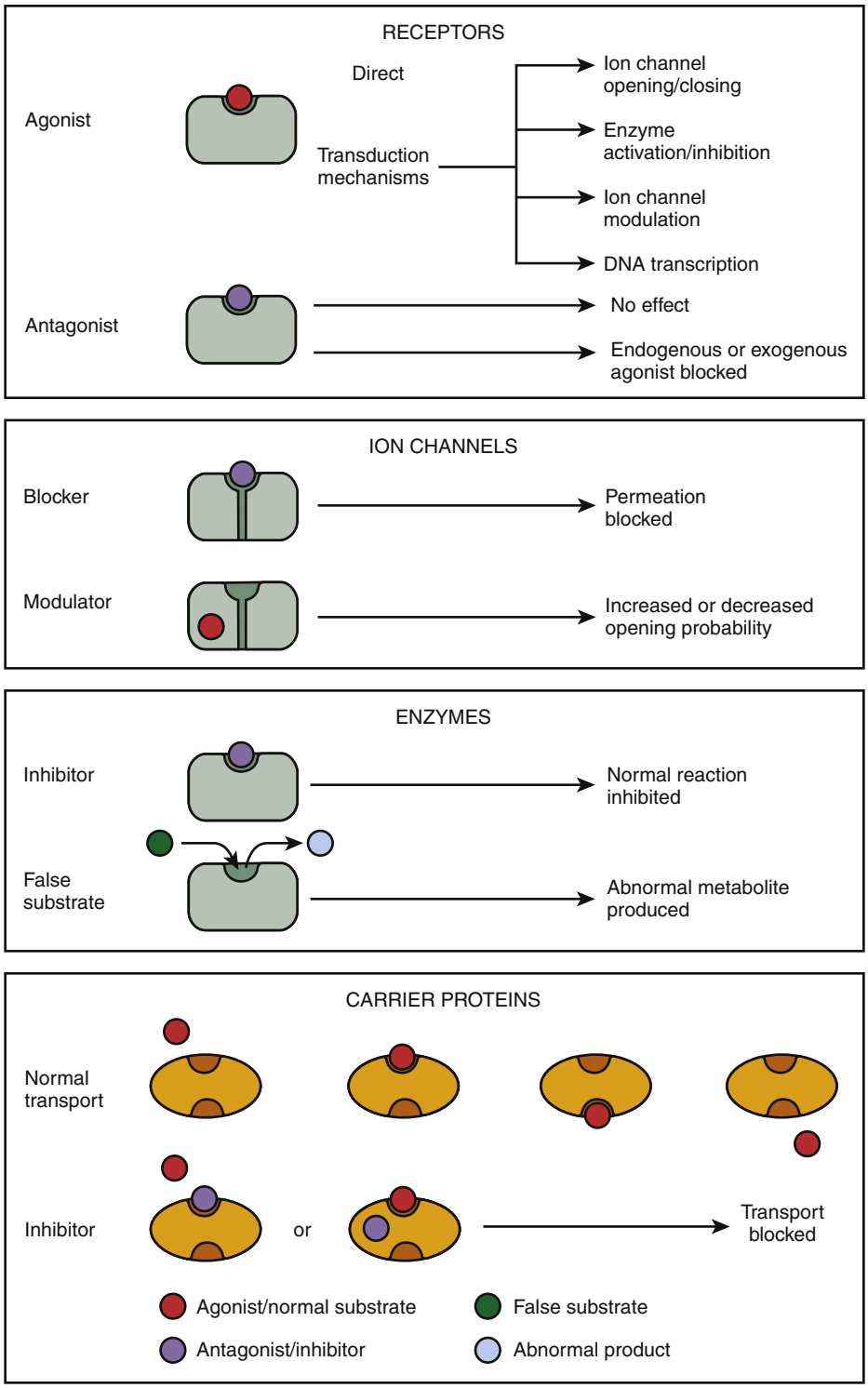

Figure 117–2. Targets for drug action. *(Modified from Rang HP, Dale MM, Ritter JM, et al:* Rang and Dale's pharmacology, *ed 6, Philadelphia, 2007, Churchill Livingstone.)*

substrate analogues of enzymes that inhibit their activity either reversibly (e.g., angiotensin-converting enzyme inhibitors acting on peptidyl dipeptidase) or irreversibly (e.g., acetylsalicylic acid acting on cyclooxygenase). Drugs may also prevent the normal functioning of enzymes. Fluorouracil, an anticancer drug, is a good example of such drug; it is converted into an abnormal nucleotide that inhibits thymidylate synthetase, thus blocking DNA synthesis.

Carrier Proteins

Several biologic elements, such as ions and small organic molecules, are not lipid soluble enough to cross the plasma membrane and require a carrier protein to be transported. In most cases, the transport of organic molecules is coupled to the transport of ions (usually Na^+), either in the same direction (symport) or in the opposite direction (antiport). The carrier

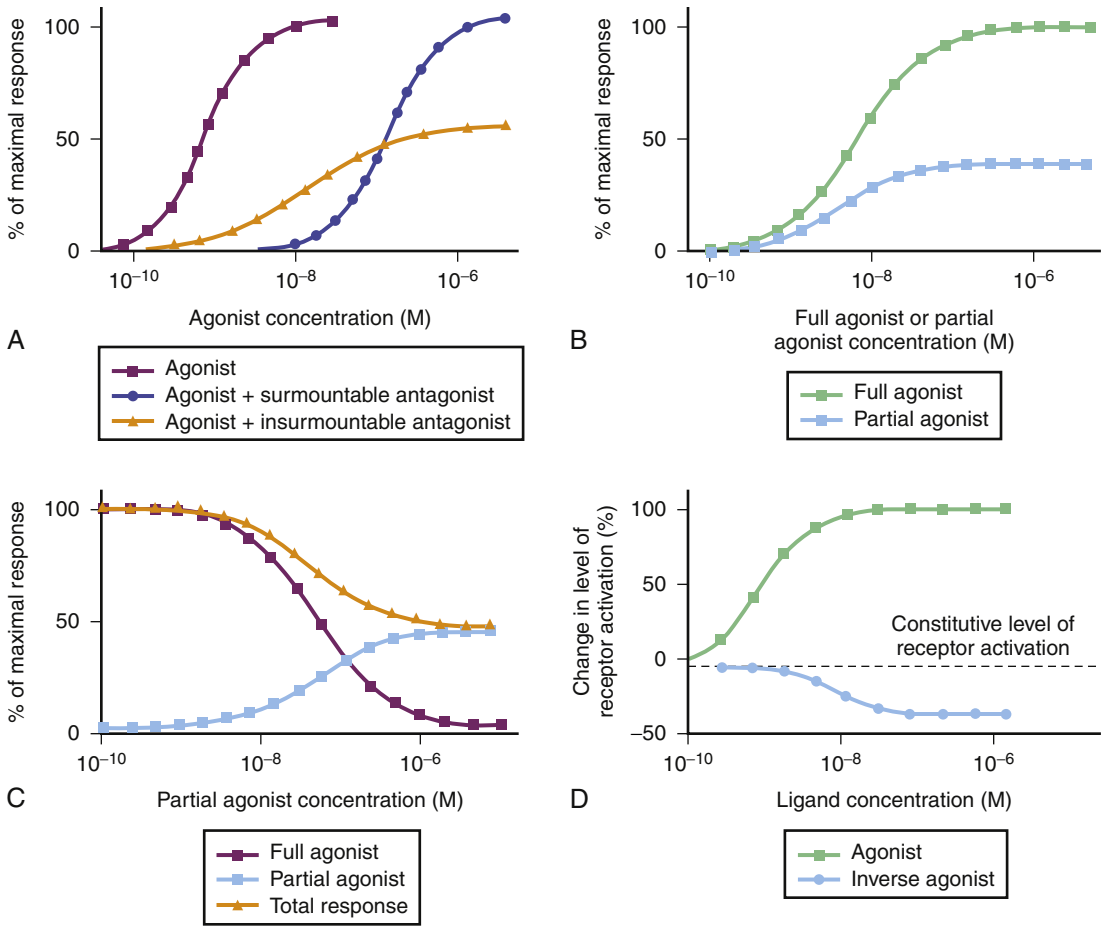

Figure 117–3. **A,** Concentration-response curves for an agonist in the absence or the presence of a surmountable or insurmountable antagonist. **B,** At similar concentrations, a partial agonist produces a lower response than does a full agonist. **C,** Response pattern observed during simultaneous treatment with a single concentration of a full agonist and increasing concentration of a partial agonist. **D,** When an appreciable level of activation of a receptor exists in the absence of an agonist (constitutive activation), the presence of an inverse agonist decreases the degree of receptor activation. *M*, mol/L. (**A,** *Modified from Brunton LL, Lazo JS, Parker KL:* Goodman & Gilman's the pharmacological basis of therapeutics, *ed 11, New York, 2006, McGraw-Hill.* **B** *and* **C,** *Modified from Katzung BG, Masters SB, Trevor AJ:* Basic & clinical pharmacology, *ed 11, New York, 2009, McGraw-Hill.* **D,** *From Rang HP, Dale MM, Ritter JM, et al:* Rang and Dale's pharmacology, *ed 6, Philadelphia, 2007, Churchill Livingstone.)*

proteins embody a recognition site that makes them specific for a particular permeating species; these recognition sites can also be targets for drugs whose effect is to block the transport system.[25] Indeed, some drugs, such as cardiac glycosides (e.g., digoxin), bind to these carrier proteins and interfere with the transport system. Digoxin is a typical example of drugs that produce their effect by inhibition of an ion pump: blockade of the Na^+/K^+ ATPase pump.

Table 117-1 shows the targets of some pharmacologic agents commonly used in the pediatric intensive care unit.

Receptor Type and Regulation

Classification of Receptors

Four families of receptors, three cell surface receptor types and one nuclear receptor, have been described (Figure 117-4).

Most transmembrane signaling is accomplished by only a few molecular mechanisms, each of which has been adapted to transduce many different signals. These protein families include cell surface receptors and receptors within the cell as well as enzymes and other components that generate, amplify, coordinate, and terminate postreceptor signaling.

G Protein–Coupled Receptors. In 1994, Alfred G. Gilman and Martin Rodbell were awarded the Nobel Prize in Physiology or Medicine for their discovery of G proteins and their role in signal transduction in cells.[10] G proteins are a superfamily of propeller proteins that allow the transduction between the activated receptor (by an agonist) and different intracellular effectors such as enzymes or ion channels, relaying signals from more than 1000 receptors.[11] G protein–coupled receptors (GPCRs), also known as *metabotropic receptors*, are in fact the first component of the cellular amplification cascade (Figure 117-5). Indeed, the activation of target enzymes through GPCRs leads to the synthesis of numerous second messengers, which in turn activate other enzymes. The intervention of the second messenger system allows for the diversity of the cellular targets (see below). GPCRs represent the target, directly or indirectly, of approximately 50% of all current therapeutic agents.[12]

Three major families of GPCRs are defined based on their amino acid sequence: family 1, the largest one, includes receptors for rhodopsin, monoamines (such as β-adrenergic receptors), neuropeptides, opioids, and chemokines. Family 2 consists mainly of receptors for peptides with a large molecular weight, such as calcitonin and secretin. Family 3

Table 117–1 Targets of Drugs Commonly Used in Critically Ill Children

Drug	Receptor	Agonist	Antagonist
RECEPTORS			
Adenosine	Adenosine	√	
Atropine	Muscarinic		√
Bosentan	ET_A, ET_B		√
Clonidine	α_2-Adrenergic	√	
	D_1	√	
Dopamine	α- and β-adrenergic	√	
Dobutamine	β-Adrenergic	√	
Epinephrine	α- and β-adrenergic	√	
Glucorticoids	Glucocorticoid	√	
Haloperidol	D_2		√
Insulin	Insulin	√	
Isoproterenol	β-Adrenergic	√	
Neuromuscular blockers (depolarizing and nondepolarizing)	Nicotinic		√
Nitric oxide	Soluble guanylate cyclase	√	
Norepinephrine	α- and β-adrenergic	√	
Opioids	μ, δ, κ Opioid	√	√
Phenoxybenzamine	α-Adrenergic		√
Phenylephrine	α_1-Adrenergic	√	
Propranolol	β-Adrenergic		√
Ranitidine	H_2		√
Vasopressin	V_1, V_2, V_3	√	
Salbutamol	β_2-Adrenergic	√	
Spironolactone	Mineralocorticoid		√
ION/RECEPTOR CHANNELS			
Adenosine	Ca^{2+}		√
Amiodarone	Na^+, K^+, Ca^{2+}		√
Barbiturates	$GABA_A$-gated Cl^-	√	
Benzodiazepines	$GABA_A$-gated Cl^-	√	
Flumazenil	$GABA_A$-gated Cl^-		√
Ketamine	Glutamate-gated (NMDA) cation		√
Lidocaine	Na^+		√
ENZYMES			
Acetazolamide	Carbonic anhydrase		√
Captopril	Angiotensin-converting enzyme (peptidyl dipeptidase)		√
Milrinone	Phosphodiesterase III		√
Nonsteroidal antiinflammatory drugs	Cyclooxygenase-1 and -2		√
Sildenafil	Phosphodiesterase V		√
CARRIER PROTEINS			
Digoxin	Na^+/K^+-ATPase pump		√
Loops diuretics	$Na^+/K^+/Cl^-$ cotransporter		√
Omeprazole	H^+/K^+-ATPase pump		√
Thiazides	Na^+/Cl^- cotransporter		√

D, Dopaminergic; *ET*, endothelin; *GABA*, γ-aminobutyric acid; *H*, histamine; *NMDA*, *N*-methyl-D-aspartate; *V*, vasopressin.

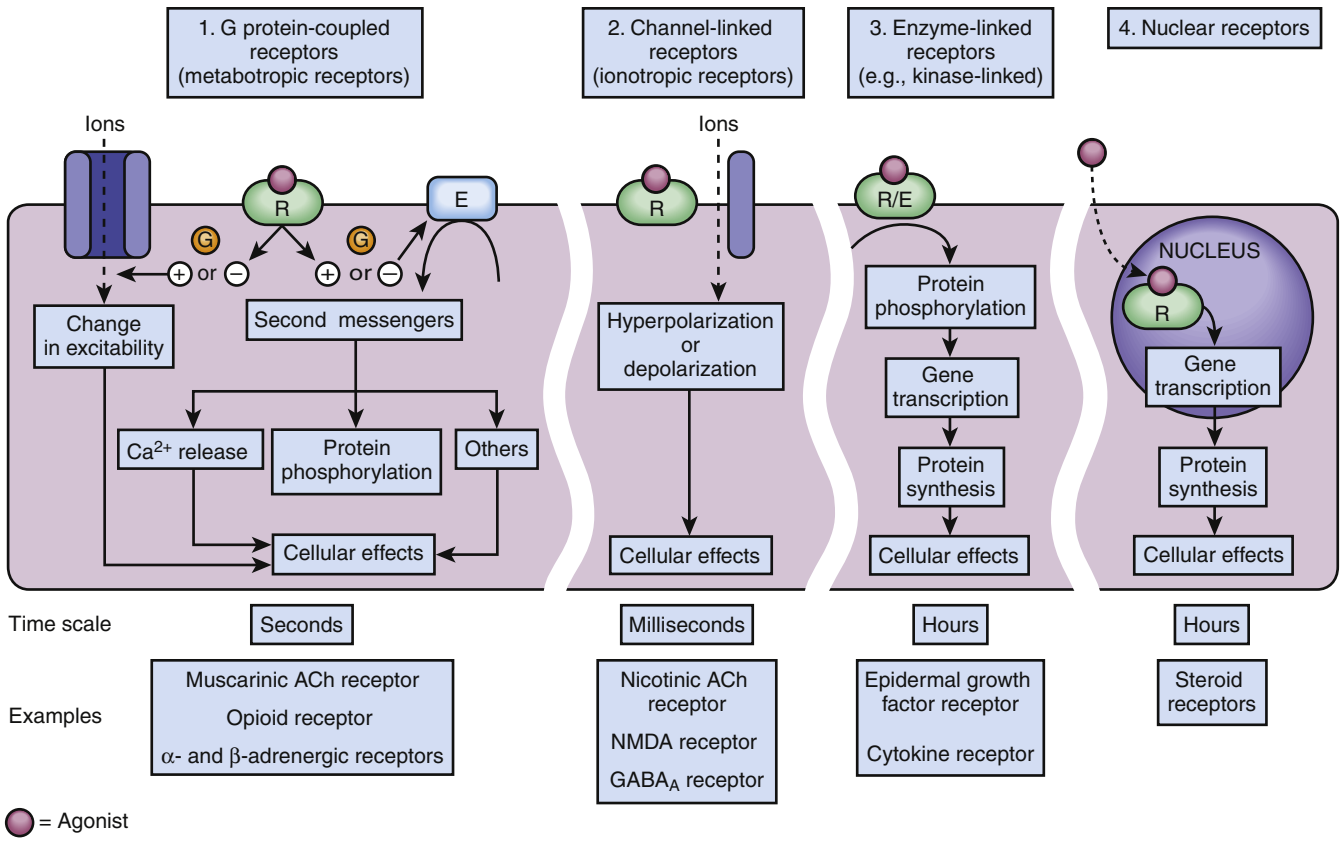

Figure 117–4. Four families of receptors are classically described: G protein–coupled receptors, channel-linked receptors, enzyme-linked receptors, and nuclear receptors. *ACh*, Acetylcholine; *E*, enzyme; *G*, G protein; *GABA*, γ-aminobutyric acid; *NMDA*, *N*-methyl-D-aspartate; *R*, receptor. *(Modified from Rang HP, Dale MM, Ritter JM, et al:* Rang and Dale's pharmacology, *ed 6, Philadelphia, 2007, Churchill Livingstone.)*

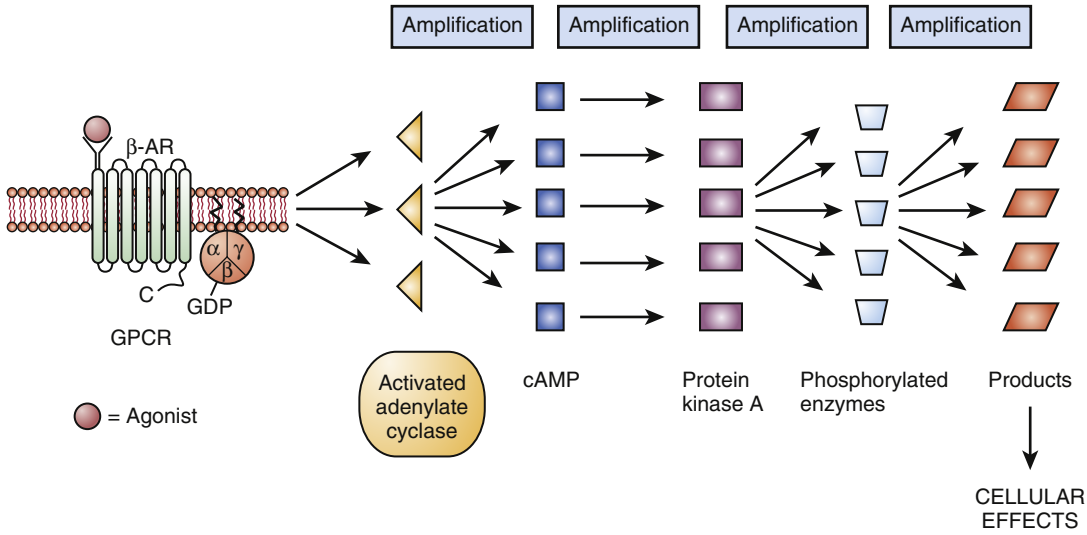

Figure 117–5. Cellular amplification cascade. After binding to a G protein–coupled receptor (*GPCR*), a ligand (agonist) activates a target enzyme (adenylate cyclase), which synthesizes a second messenger (*cAMP*). The latter then activates other enzymes (protein kinases) that phosphorylate proteins and mediate specific cellular effects. *β-AR,* β-adrenergic receptor; *GDP,* guanosine diphosphate.

has, among others, receptors for glutamate (metabotropic), γ-aminobutyric acid$_B$ (GABA$_B$), and extracellular calcium. Despite these differences, the families of GPCRs share characteristic structural and functional features. All GPCRs share a common serpentine structure consisting of seven transmembrane domains with three extracellular and three intracellular loops. The extracellular regions are involved in ligand binding, and the intracellular regions are primarily involved in signaling.[13] The latter are coupled to a heterotrimeric guanine-nucleotide-binding regulatory protein (G protein) located on the cytoplasmic portion of the cell membrane and are made of three subunits. Each G protein is composed of an α-subunit

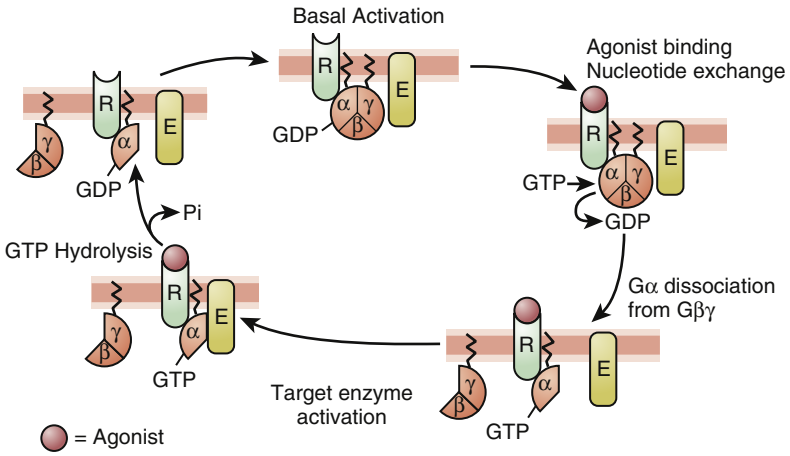

Figure 117–6. Functional cycle of the G proteins. The receptor (*R*) becomes activated after binding of an agonist. Guanosine diphosphate (*GDP*) bound to the G protein is replaced by guanosine triphosphate (*GTP*), and the α-subunit of the G protein dissociates from βγ-subunit complex. The α-subunit/GTP complex binds to the target enzyme (*E*) or ion channel, whereas the βγ-subunit complex stimulates several other downstream effectors. The GTPase activity of the α-subunit is increased when the target enzyme or ion channel is bound, leading to hydrolysis of the bound GTP to GDP, whereupon the α-subunit reunites with βγ-subunit complex and the agonist dissociates from the receptor.

that is loosely bound to a tightly associated dimer made up of β- and γ-subunits. The activity of a trimeric G protein is regulated by the binding and hydrolysis of guanosine triphosphate (GTP) by the α-subunit (Figure 117-6).

Each of the three subunits is encoded by a separate gene selected from at least 20 α, six β, and 12 γ genes, respectively. The α-subunit is essential in the "receptor-effector" coupling. Various α-subunits define different G protein trimers (G_s = stimulatory G protein, G_i = inhibitory G protein, G_o = other G protein, etc.), each of which regulates a distinctive set of downstream signaling pathways. Table 117-2 shows some examples of GPCRs with their trimeric G protein along with their target enzymes or ion channels and second messengers. Some receptors act by way of more than one type of G protein trimer (e.g., μ opioid receptor). Approximately 50% of the GPCRs couple to G_i/G_o proteins, approximately 25% couple to G_s, and about the same amount couple to G_q proteins.[14] G_s proteins (made of α_s-subunits) can activate adenylate cyclase and are inhibited by the cholera toxin. In contrast, G_i proteins (made of α_i-subunits) can inhibit adenylate cyclase and open K^+ channels and are inhibited by the pertussis toxin.

Small G proteins are monomeric G proteins with molecular weight of 20 to 40 kDa. As with heterotrimeric G proteins, their activity depends on the binding of GTP. More than 100 small G proteins have been identified. They are classified into different families: Ras, Rho, Rab, Rap, Ran, and ARF. They play key roles in numerous cellular functions such as cell division, proliferation, differentiation, vesicle trafficking, cytoskeletal reorganization, and gene expression.[15]

Channel-Linked Receptors. Also known as *ligand-gated ion channels* or *ionotropic receptors,* channel-linked receptors mediate fast responses, affecting ion fluxes and membrane potential. These receptors possess four distinct characteristics: (1) activation by an agonist or inactivation by an antagonist; (2) flux of ions across a central pore; (3) ion selectivity, and (4) fluctuation among open, closed, and inactivated states. Broadly speaking, two types have been identified: receptors of excitatory mediators and receptors of inhibitory mediators.

Receptors of excitatory mediators (glutamate, aspartate, and acetylcholine), which comprise the *N*-methyl-D-aspartate [NMDA] (Figure 117-7, *A*) and the nicotinic acetylcholine receptors, are receptors whose activation provokes depolarization of the cell, leading to propagation of the action potential and ultimately secretion of a neuromediator and muscular contraction, for example. These receptors are permeable to monovalent and divalent cations, mainly Na^+, K^+, Ca^{2+}, and magnesium (Mg^{2+}). Ketamine, a dissociative anesthetic, is a noncompetitive surmountable NMDA receptor antagonist that acts by preventing the opening of ion channels by glutamate. In addition, the potential neuroprotective effects of ketamine appears to be mediated via NMDA receptor blockade.

Receptors of inhibitory mediators, the activation of which provokes hyperpolarization of the cell and therefore decreases

Table 117–2 Examples of GPCRs with their Trimeric G Protein, Target Enzyme and/or Ion Channel, and Second Messengers

GPCR	G Protein	Target Enzyme/Ion Channel	Second Messengers
β_1- and β_2-adrenergic	G_s	↑ Adenylate cyclase	↑ cAMP
D_1			
H_2			
V_2			
α_2-Adrenergic	G_i	↓ Adenylate cyclase	↓ cAMP
$M_{2,4}$			
μ Opioid			
AT_1			
α_1-Adrenergic	$G_{q/11}$	↑ Phospholipase C	↑ IP_3, DAG, $[Ca^{2+}]_i$
$M_{1,3,5}$			
$ET_{A,B}$			
AT_1			
H_1			
V_1			
μ Opioid	$G_{i/o}$	Opens K^+ channels	
μ Opioid	G_o	Closes voltage-dependent Ca^{2+} channels	↓ $[Ca^{2+}]_i$

AT, Angiotensin; *cAMP*, cyclic adenosine monophosphate; *D*, dopaminergic; *DAG*, diacylglycerol; *ET*, endothelin; G_s, stimulatory G protein; G_i, inhibitory G protein; G_o, other G proteins; *GPCR*, G protein–coupled receptor, *H*, histamine; *IP3*, inositol 1,4,5-triphosphate; *M,* muscarinic; *V*, vasopressin.

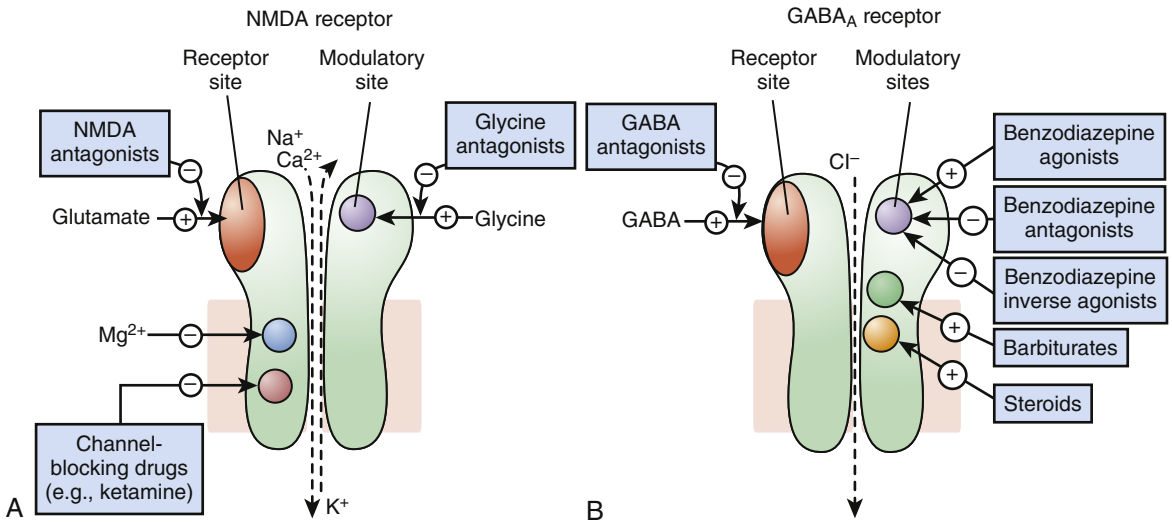

Figure 117–7. Two important members of the channel-linked receptors, the NMDA receptor (**A**) and the $GABA_A$ receptor (**B**). The main sites of drug action on these receptors are shown. *GABA*, γ-Aminobutyric acid; *NMDA*, *N*-methyl-D-aspartate. *(Modified from Rang HP, Dale MM, Ritter JM, et al:* Rang and Dale's pharmacology, *ed 6, Philadelphia, 2007, Churchill Livingstone; and Nestler EJ, Hyman SE, Malenka RC:* Molecular neuropharmacology, *New York, 2001, McGraw-Hill.)*

cellular excitability, are a group that includes $GABA_A$ (Figure 117-7, *B*) and glycine receptors. These ligand-gated ion channels are selective for anions such as chloride (Cl^-) or phosphorus (PO_4^{3-}). GABA is the major inhibitory neurotransmitter in the central nervous system, and drugs that potentiate GABAergic inhibition in the brain, such as benzodiazepines and barbiturates, result in sedation and hypnosis.[7] Benzodiazepine agonists enhance Cl^- ion conductance induced by GABA by increasing the frequency of channel-opening events, whereas barbiturates seem to do so by increasing the duration of the GABA-gated channel openings. Both classes of agents bind to sites on the $GABA_A$ molecule that are different from each other and also from the GABA receptor site.

Enzyme-Linked Receptors. Enzyme-linked receptors have an extracellular ligand-binding domain linked to an intracellular domain that possesses an intrinsic catalytic activity. This large and heterogeneous group of membrane receptors can be divided into four subfamilies according to their catalytic activity (tyrosine kinase, guanylate cyclase, tyrosine phosphatase, and serine/threonine kinase). Cytosolic enzymes presenting an activity similar to that of enzyme-linked receptors are also considered to belong to this family of receptors (e.g., soluble guanylate cyclase receptors activated by nitric oxide [NO]).

Tyrosine kinase receptors include receptors for neurotrophin,[16] growth factors (epidermal growth factor [EGF], platelet-derived growth factor [PDGF]), as well as insulin and many other trophic hormones. These receptors shift from an inactive monomeric state to an active dimeric state upon agonist binding (dimerization). This is followed by autophosphorylation of the intracellular domain of each receptor and binding of SH2-domain proteins that are themselves phosphorylated. Depending on the receptor subtype, SH2-domain proteins allow the phosphorylated receptor to activate other functional proteins, which eventually results in stimulation of gene transcription, or are enzymes such as phospholipases, leading to the formation of second messengers (see below). One important pathway involved in the transduction mechanisms of tyrosine kinase receptors include the Ras/Raf/mitogen-activated protein (MAP) kinase pathway which is important in cell division, growth, and differentiation (Figure 117-8).

Unlike tyrosine kinase receptors, cytokine receptors do not usually possess intrinsic kinase activity; instead, they associate with cytosolic Janus kinases (JAKs). After dimerisation of the receptors that occurs after binding of the cytokine, JAKs phosphorylate tyrosine residues on the receptor, which then result in the binding of another set of proteins called *signal transducers and activators of transcription* (STATs). The bound STATs are themselves then phosphorylated by the JAKs and dimerize and dissociate to migrate in the nucleus and activate gene expression to regulate diverse biologic processes controlling the synthesis and release of many inflammatory mediators, growth, development, and homeostasis.

Guanylate cyclase–linked receptors are unique because they synthesize their own second messengers upon agonist binding. The natriuretic peptide receptors, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) receptors, belong to this family (Figure 117-9). The extracellular NH_2-terminal constitutes the binding domain. There is a short transmembrane segment whose role is to anchor the receptor protein to the membrane. The intracellular domain is made of two different entities: (1) a protein kinase homology domain whose function is to control and relay receptor activation to the catalytic domain, and (2) a guanylate cyclase catalytic domain, also known as *particulate guanylate cyclase,* involved in the synthesis of cyclic guanosine monophosphate (cGMP) from GTP.[17] In addition to this particulate guanylate cyclase (the membrane form of the enzyme), an intracellular soluble form exists. It is a heterodimer consisting of α- and β-subunits, both of which are necessary for enzyme activity, and is expressed in most tissues, though not uniformly.[18] It is activated by intermediate substances derived from the biosynthesis of eicosanoids (prostaglandins and leukotrienes) and by NO and NO donors such as sodium nitroprussate and nitroglycerin (see below). Guanylate cyclases and cGMP-mediated signaling cascades play a central role in the regulation of diverse

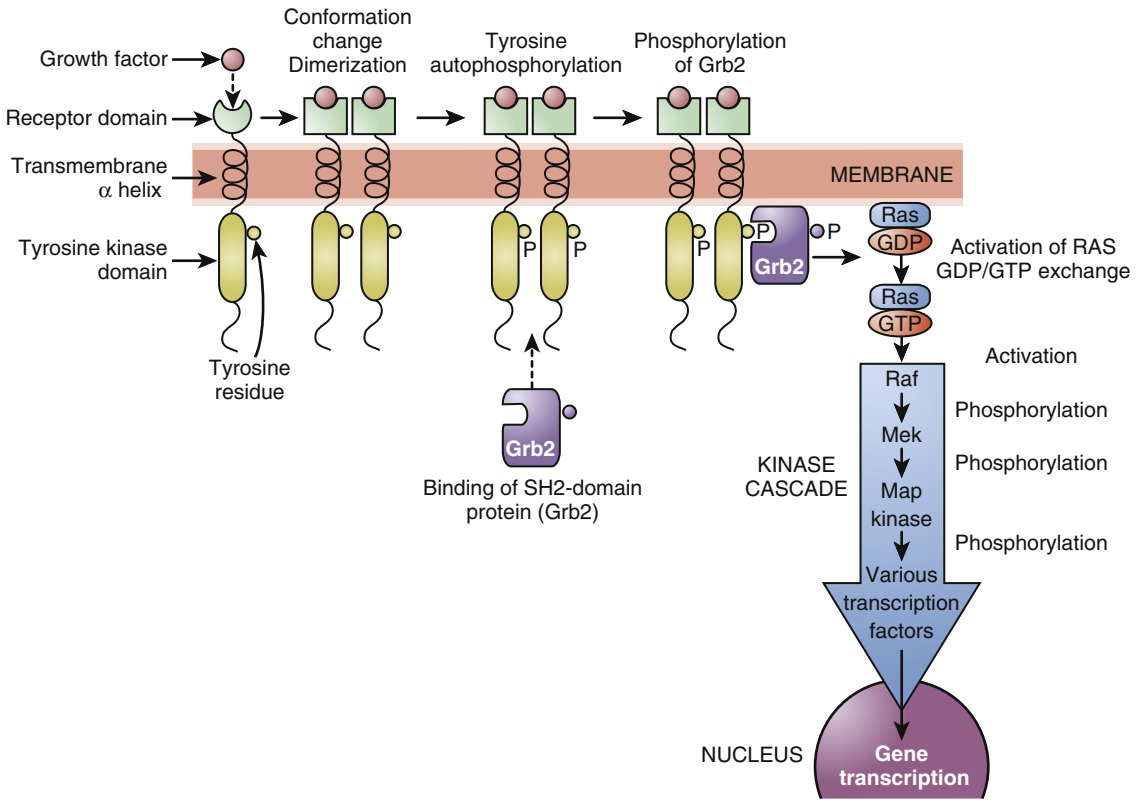

Figure 117–8. Functioning of kinase-linked receptors. The main steps are dimerization of the receptor, autophosphorylation, and phosphorylation of targeted proteins. The growth factor pathway is shown with the kinase cascade involving the successive phosphorylation of many enzymes (Raf, Mek, Map kinase), eventually leading to gene transcription. *GDP*, Guanosine diphosphate; *GTP*, guanosine triphosphate. *(Modified from Rang HP, Dale MM, Ritter JM, et al:* Rang and Dale's pharmacology, *Philadelphia, ed 6, 2007, Churchill Livingstone.)*

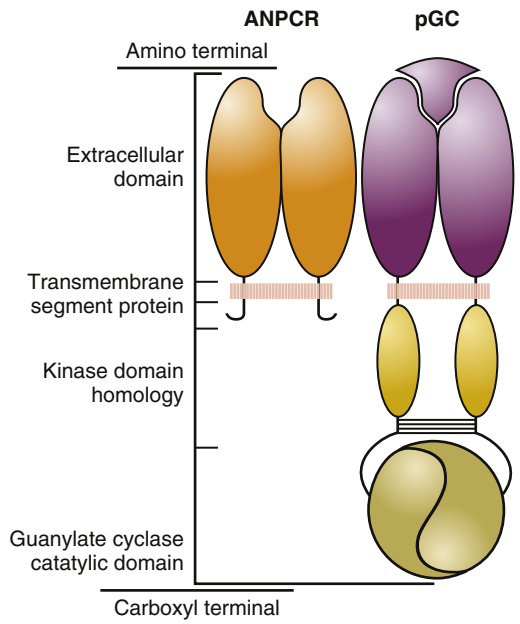

Figure 117–9. Molecular structure of the natriuretic peptide receptors. *Left*, Atrial natriuretic peptide–C receptor (*ANPCR*) is a clearance receptor that does not possess the kinase and guanylate cyclase domains. It plays a role in the catabolism of natriuretic peptides. *Right*, Typical particulate guanylate cyclase receptor (*pGC*) (ANP-A or -B receptor) is shown with its extracellular dimeric protein-binding domain. The intracellular domain consists of a protein kinase homology domain and a guanylate cyclase catalytic domain.

pathophysiologic processes, including vascular smooth muscle motility, intestinal fluid and electrolyte homeostasis, and retinal phototransduction.[19]

Nuclear Receptors. Nuclear receptors belong to a family of functionally and structurally related proteins. They regulate gene expression and are not associated with a membrane. Their principal mechanism of action is shown in Figure 117-10. The agonist, which must be lipid soluble, diffuses into the cell and binds to the nuclear receptor located either in the cytosol or in the nucleus. The complex agonist-activated receptor then binds on high-affinity sites on DNA, hormone response element (HRE), situated on the promoter region of genes whose transcription can then be induced or suppressed. Because gene transcription is at their origin, these effects are slow to develop.

Endogenous agonists for these receptors include steroid and thyroid hormones as well as agents such as retinoic acid and vitamin D. The most commonly used drugs that target these receptors include exogenous steroids and lipid-lowering agents. For many of theses receptors, the corresponding hormone or vitamin has not been identified; these receptors are therefore referred to as *orphan nuclear receptors.*

Receptor Regulation

Continued exposure of a receptor to an agonist often results in a progressive loss of receptor responsiveness, with a diminished receptor-mediated response over time. This is called *desensitization* (or tachyphylaxis) and is classified into two forms. Homologous desensitization is a process in which only

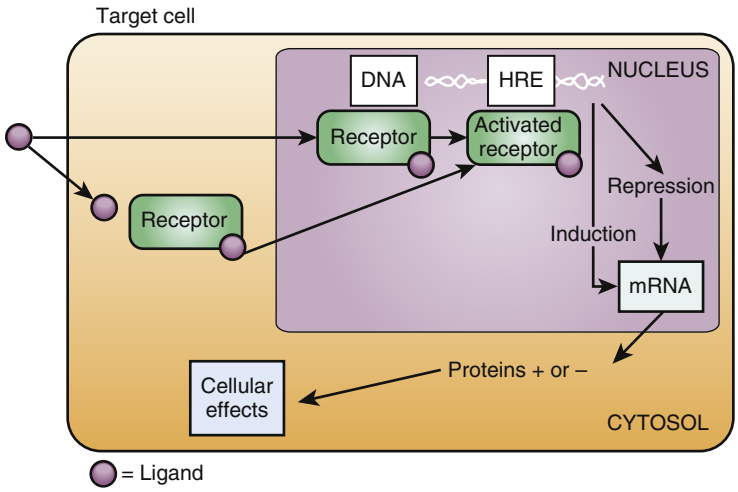

Figure 117–10. Activation and action of nuclear receptors, located either in the cytosol (e.g., steroid receptors) or in the nucleus (e.g., vitamin D receptor). *DNA*, Deoxyribonucleic acid; *HRE*, hormone response element.

the activated receptor is "turned off" or desensitized, whereas heterologous (cross-) desensitization refers to processes in which the activation of one type of receptor can result in the desensitization of other types of receptors. Interaction of the receptor with an antagonist prevents the occurrence of desensitization.

In general, desensitization occurs in three ways (Figure 117-11, *A*): (1) inactivation or uncoupling of the receptor, which is usually the result of receptor phosphorylation and occurs within seconds to minutes of agonist exposure; (2) sequestration of the receptor in endosomes (from there, the receptor is recycled to the cell membrane); and (3) downregulation, which is characterized by receptor endocytosis and destruction in lysosomes with a net loss of receptors in the cell (at the cell membrane and within the cell). It develops more slowly than uncoupling, taking hours to days.[20] In addition to receptor degradation, decreased synthesis of the receptor also contributes to this process. Downregulation is responsible for the decreased responsiveness to prolonged exogenous catecholamine infusion frequently seen in the critical care population.[21] Desensitization is usually reversible, within minutes (inactivation) to hours (sequestration/downregulation) of removal of the agonist depending on the specific receptor and cell type, the concentration of the agonist, and the duration of the exposure to the agonist.

Homologous desensitization of GPCRs results from these three distinct and coordinated processes (Figure 117-11, *B*).[22] It begins within seconds of exposure to the agonist and is initiated by phosphorylation of the receptor by G protein–coupled receptor kinases (GRKs) and second messenger–dependent protein kinases (protein kinase A [PKA], and protein kinase C [PKC]). Once phosphorylated, the receptor binds with high affinity to members of the arrestin gene family, the β-arrestins. The β-arrestin binding prevents the receptor–G protein interaction, leading to termination of signaling by G protein effectors (receptor inactivation or uncoupling). The receptor-bound β-arrestin can also act as an adapter protein to couple the receptor to clathrin-coated pits, inducing receptor-mediated endocytosis or sequestration. Subsequently, the receptor is either recycled to the cell membrane or degraded (receptor downregulation). Resensitization of a GPCR requires its dephosphorylation and dissociation from its agonist. In contrast to homologous desensitization, heterologous desensitization of GPCRs occurs when inhibition of one GPCR is induced by the activation of another GPCR. One well-recognized mechanism is the phosphorylation of one GPCR by second messenger–dependent protein kinases (PKA and PKC) activated by any other GPCRs. Such phosphorylation of the receptor impairs receptor–G protein coupling and leads to the inactivation of the receptor. However, it is becoming increasingly clear that receptor phosphorylation is not the exclusive mediator of heterologous desensitization and that events downstream are involved.[23]

As GPCRs, channel-linked and enzyme-linked receptors are desensitized following prolonged or repeated agonist exposure. Channel-linked receptors are phosphorylated by second messenger–dependent protein kinases while tyrosine kinase receptors are internalized.

Upregulation refers to the increase in receptor sensitivity seen in the setting of lack of agonist stimulation or prolonged presence of a receptor antagonist. This is best exemplified by a phenomenon seen when a β-adrenergic blocking agent such as propranolol is administered for a long period of time and abruptly discontinued. Because a greater number of sensitized β-adrenergic receptors become available for stimulation by endogenous agonists, rebound hypertension is observed.

Signal Transduction Mechanisms: Intracellular Messengers and Effectors

After binding of an agonist to receptors such as GPCRs or enzyme-linked receptors, the signal transduction mechanisms from the membrane first involve the production of second messengers such as cyclic adenosine monophosphate (cAMP), cGMP, arachidonic acid and its metabolites, diacylglycerol (DAG), inositol 1,4,5-triphosphate (IP_3), and Ca^{2+}. These, in turn, activate protein kinases and calcium-binding proteins, all of which result in different biologic effects (Figure 117-12). Thus the synthesis and degradation of intracellular second messengers are described first, followed by a review of the role of protein kinases and calcium-binding proteins in the transduction mechanisms.

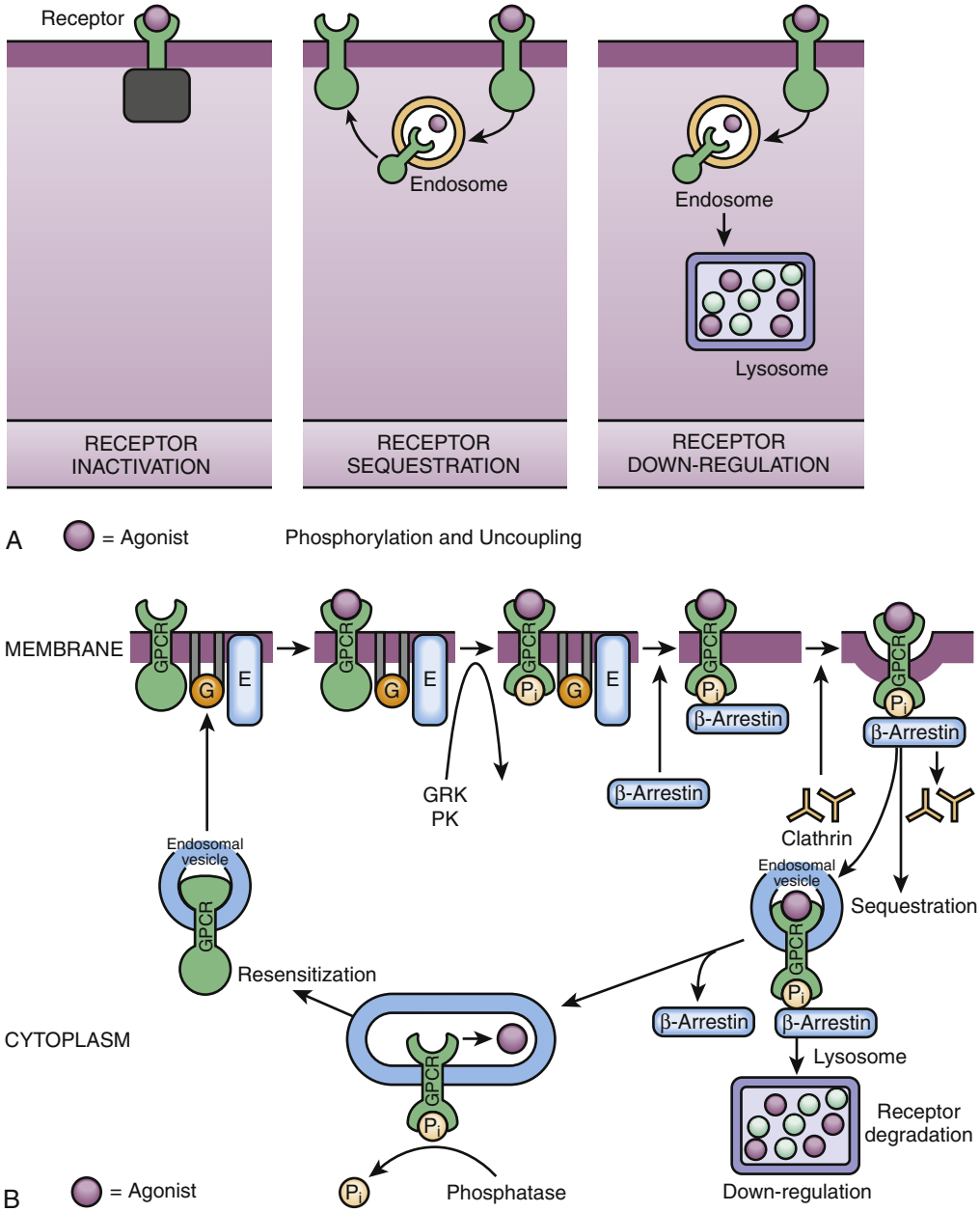

Figure 117–11. Desensitization in response to an agonist. **A,** Ways in which receptors can become desensitized to an agonist. **B,** Homologous desensitization of GPCR. *E*, G proteins effectors; *G*, G protein; *GPCR*, G protein-coupled-receptor; *GRK*, G protein-coupled receptor kinase; *PK*, second-messenger-dependent protein kinases. (***A,*** *Modified from Alberts B, Johnson A, Lewis J, et al: Molecular biology of the cell, ed 4, London, 2002, Garland Science. B Modified from Luttrell LM, Lefkowitz RJ: The role of beta-arrestins in the termination and transduction of G-protein-coupled receptor signals,* J Cell Sci *115:455–465, 2002.)*

Second Messengers

Cyclic Adenosine Monophosphate

This pathway is involved in signal transduction initiated by binding of agonists to GPCRs. cAMP is synthesized from adenosine triphosphate (ATP) after the action of adenylate cyclase, which is a transmembrane glycoprotein of the cell membrane. To date, nine forms of adenylate cyclase (types I to IX) have been identified by molecular cloning, and several have described features that are hypothetical.[24] cAMP regulates many aspects of cellular function (cell division and differentiation, ion transport, etc.) by one common mechanism involving activation of protein kinases. These, in turn, regulate the function of many different cellular proteins by catalyzing the phosphorylation of serine and threonine residues. Phosphorylation can then either activate or inhibit target enzymes or ion channels.[25] As previously mentioned, receptors coupled with G_s proteins stimulate adenylate cyclase and produce an increase in cAMP, whereas receptors coupled with G_i proteins inhibit adenylate cyclase and reduce cAMP.

The degradation of cAMP is catalyzed by phosphodiesterases leading to the production of 5′-AMP, an inactive product. Phosphodiesterases are a complex family of enzymes divided into 11 groups according to mechanism of regulation, selectivity for the substrate (cAMP and/or cGMP), preferential localization, and sensitivity to various inhibitors.[26] In critically

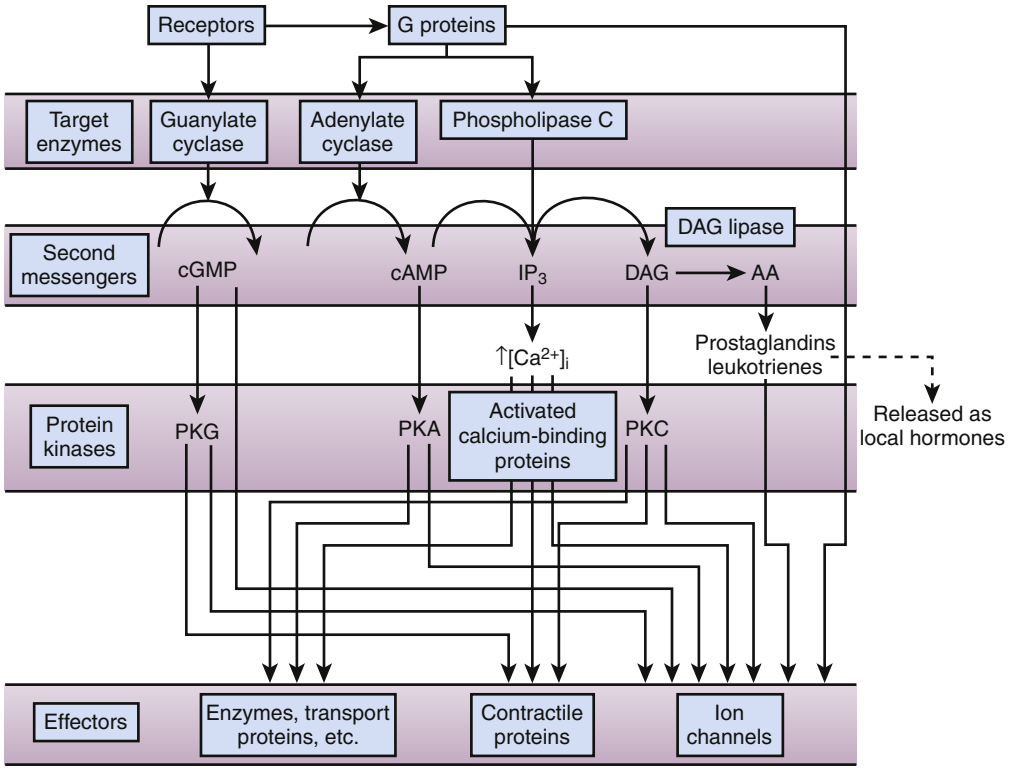

Figure 117–12. Transduction mechanisms of membrane signaling. *AA*, Arachidonic acid; *cAMP*, cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; *DAG*, diacylglycerol; *IP_3*, inositol 1,4,5-triphosphate; *PKA*, protein kinase A; *PKC*, protein kinase C; *PKG*, protein kinase G. *(Modified from Rang HP, Dale MM, Ritter JM, et al:* Rang and Dale's pharmacology, *Philadelphia, ed 6, 2007, Churchill Livingstone.)*

ill children, milrinone, used for its positive inotropic effect and vasodilating properties, is a phosphodiesterase inhibitor selective for the type III isoenzyme.

Cyclic Guanosine Monophosphate

As discussed above, guanylate cyclase is part of the cytosolic portion of some transmembrane receptors (membrane form) but also exists as a cytosolic enzyme (soluble form) activated by various molecules, including NO. Stimulation of guanylate cyclase results in the accumulation of cGMP. This second messenger then regulates complex signaling cascades through immediate downstream effectors, including cGMP-dependent protein kinases (e.g., protein kinase G [PKG]), cGMP-regulated phosphodiesterases (mainly type II and III), and cyclic nucleotide-gated ion channels (cells of the retina), which eventually leads to a variety of physiologic effects.[27] For example, NO readily passes across the target cell membrane and activates soluble guanylate cyclase in vascular smooth muscle, resulting in increased cGMP production with the regulation of various downstream targets such as protein kinases and ion channels, which culminates in vasodilatation.

As with cAMP, the degradation of cGMP into inactive GMP is catalyzed by phosphodiesterases. In pulmonary and penile vascular smooth muscle cells, phosphodiesterase type V is responsible for the degradation of cGMP; inhibition of this enzyme results in an accumulation of cGMP in the cytosol with smooth muscle relaxation and vasodilatation. As such, phosphodiesterase type V inhibitors (e.g., sildenafil) are widely recognized as efficacious for the treatment of erectile dysfunction in men and have been shown to induce pulmonary vasodilatation both in children and adults and are part of the new strategies available for the treatment of pulmonary hypertension.[28-30]

Arachidonic Acid and Its Metabolites

Arachidonic acid and its metabolites (prostaglandins and leukotrienes) are now considered intracellular messengers.[31] Arachidonic acid is a component of membrane phospholipids released either in a one-step process, after phospholipase A_2 (PLA_2) action, or a two-step process, after phospholipase C and DAG lipase actions. Arachidonic acid is then metabolized by cyclooxygenase (COX) and 5-lipoxygenase, resulting in the synthesis of prostaglandins and leukotrienes, respectively. These intracellular messengers play an important role in the regulation of signal transduction implicated in pain and inflammatory responses. Corticosteroids inhibit PLA_2 activity, whereas nonsteroidal antiinflammatory drugs inhibit COX activity.

Diacylglycerol and Inositol Triphosphate

Phospholipase C is the target enzyme for some GPCRs (phospholipase C-β) as well as enzyme-linked receptors such as tyrosine kinase receptors (phospholipase C-γ). It splits phosphatidylinositol, a membrane-bound phospholipids, into DAG and IP_3, both of which function as second messengers. The most important function of DAG is to activate the membrane-bound PKC, which catalyzes the phosphorylation of a variety of intracellular proteins. IP_3 binds to and opens an IP_3-gated Ca^{2+} release channel on the endoplasmic reticulum membrane, which results in an increase in free intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$).

Calcium ions

$[Ca^{2+}]_i$ is critically important as a regulator of cell function. Indeed, an increase in $[Ca^{2+}]_i$ is the most important intracellular messenger signaling pathway known in biologic

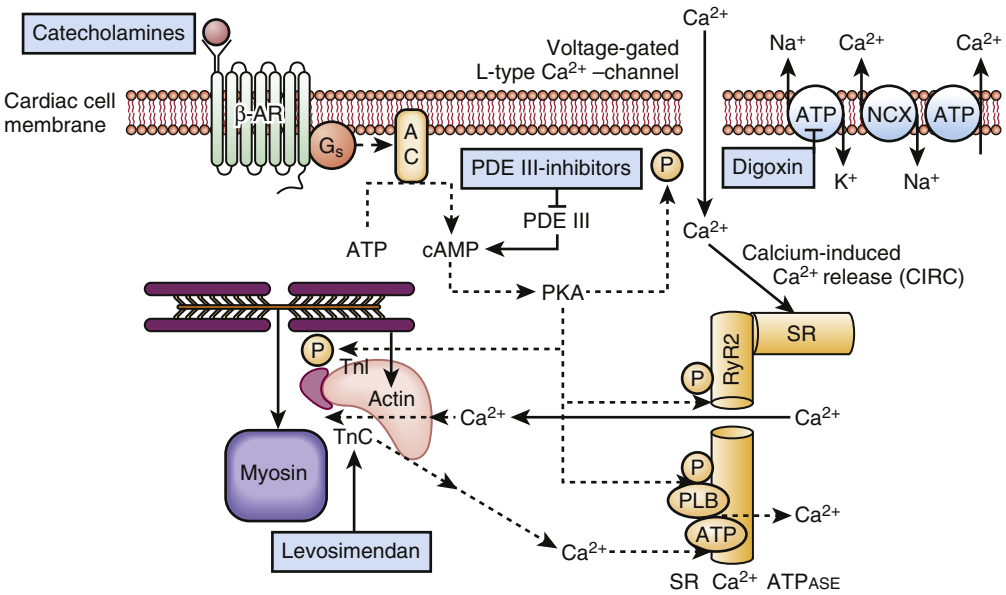

Figure 117–13. Cardiac excitation-contraction coupling and molecular targets of therapeutic agents with positive inotropic and lusitropic effects. (*Note:* Under physiologic conditions, NCX works mainly in the Ca^{2+} extrusion mode; however, if intracellular Na^+ concentration is elevated, as it is the case with digoxin, it can work in the Ca^{2+} influx mode.) *AC*, Adenylate cyclase; *ATP*, adenosine triphosphate; *β-AR*, β-adrenergic receptor, *cAMP*, cyclic adenosine monophosphate; G_s, stimulatory G protein; *NCX*, Na^+/Ca^{2+} exchanger; *P*, phosphorus; *PDE*, phosphodiesterase; *PKA*, protein kinase A; *PLB*; phospholambam; RyR_2, cardiac/isoform 2 ryanodine receptor; *SR*, sarcoplasmic reticulum; *TnI*, troponin I; *TnC*; troponin C. *(Modified from Toller GT, Stranz, C: Levosimendan, a new inotropic and vasodilating agent,* Anesthesiology *104:556–569, 2006.)*

systems. When $[Ca^{2+}]_i$ is at its baseline value, few proteins have an affinity sufficient to bind to Ca^{2+}. Once membrane signaling occurs, an increase in $[Ca^{2+}]_i$ results, derived from either the extracellular space or from the lumen of the endoplasmic reticulum, and allows binding of proteins to Ca^{2+}. Finally, this binding can trigger contraction, secretion, a modification in metabolism regulation, or several other effects depending on the cell type involved. To maintain a low resting $[Ca^{2+}]_i$, Ca^{2+} is permanently expulsed from the cytosol into the extracellular compartment or into the endoplasmic reticulum via a Ca^{2+}-ATPase and Na^+/Ca^{2+} exchanger.

Phosphorylation of Proteins

Many receptor-mediated signals produce variations in the concentration of second messengers, such as cAMP, cGMP, arachidonic acid, DAG, IP_3, and Ca^{2+}, as previously discussed. These can then modify the activity of other proteins, mainly protein kinases and calcium-binding proteins.

Protein Kinases

Protein kinases are enzymes located in the cytoplasm that phosphorylate proteins. The main protein kinases consist of PKA, PKG, and PKC[32] as well as tyrosyl protein kinases (part of tyrosine kinase receptors). They are distinguished from each other by the different intracellular second messengers involved in their regulation and by the selective substrates they use. They all have a binding site for Mg^{2+}-ATP (phosphate donor) and for substrate protein as well as various regulatory sites. Phosphorylation of these proteins is short lived because protein phosphatases rapidly dephosphorylate proteins previously phosphorylated by protein kinases, thus terminating the intracellular signal.

Calcium-Binding Proteins

Calcium exerts its control in cellular function by virtue of its ability to regulate the activity of many different proteins, such as channels, transporters, and transcription factors. In the majority of cases, a calcium-binding protein serves as an intermediate between Ca^{2+} and the regulated functional protein. Calcium-binding proteins represent a large group of cytosolic proteins and include the calmodulin and annexin (or lipocortin) families.

Multiple Drug Targets Within an Organ System: The Myocardium

To understand the molecular mechanisms behind therapeutic agents that increase contractility and accelerate relaxation within the myocardium, cardiac excitation-contraction coupling, where Ca^{2+} is the essential second messenger, should be reviewed (Figure 117-13).[33] During the depolarization phase of the cardiac action potential, Ca^{2+} enters the cell through voltage-gated L-type Ca^{2+} channels. Ca^{2+} entry triggers Ca^{2+} release from the sarcoplasmic reticulum (SR) through a SR membrane ion channel—the cardiac/isoform 2 ryanodine receptor (RyR2). This process is known as *calcium-induced Ca^{2+}release* (CICR). The combination of Ca^{2+} influx and release raises $[Ca^{2+}]_i$, allowing Ca^{2+} binding to troponin C (TnC), which permits cross-bridging between actin and myosin and ultimately contraction. For relaxation to occur $[Ca^{2+}]_i$ must decline, allowing Ca^{2+} to dissociate from TnC. This requires Ca^{2+} transport out of the cytosol by four pathways: SR Ca^{2+}-ATPase (the main one), sarcolemmal Na^+/Ca^{2+} exchanger, sarcolemmal Ca^{2+}-ATPase, and mitochondrial Ca^{2+} uniport. SR Ca^{2+}-ATPase activity is modulated by phospholamban, an endogenous inhibitor. Under physiologic conditions, there is no net gain or loss of cellular Ca^{2+} with each contraction-relaxation cycle.

There are two main ways to pharmacologically increase the strength of cardiac contraction (see Figure 117-13)[33,34]: (1) by increasing the amount of $[Ca^{2+}]_i$ available for binding to TnC or (2) by increasing the sensitivity of myofilaments to Ca^{2+}.

1. *Catecholamines and phosphodiesterase type III inhibitors (PDEIII inhibitors).* β-Adrenergic receptor stimulation by catecholamines activates a GTP-binding protein (G_s), which stimulates adenylate cyclase to produce cAMP, whereas PDEIII inhibitors (e.g., milrinone) prevent cAMP degradation. The resulting increase in cAMP activates PKA, which, in turn, phosphorylates intracellular targets, including voltage-gated L-type Ca^{2+} channels, RyR2, phospholamban, and troponin I (TnI). Phosphorylation of voltage-gated L-type Ca^{2+} channels enhances Ca^{2+} entry into the cytosol with subsequent increase in CICR from the SR and contraction (positive inotropic effect of catecholamines and PDEIII inhibitors). In contrast, phosphorylation of phospholamban activates SR Ca^{2+}-ATPase with increase Ca^{2+} transport from the cytosol back to the SR and thus promotes relaxation (positive lusitropic effect of catecholamines and PDEIII inhibitors). This action also contributes to the overall gain in cardiac excitation-contraction coupling by increasing the SR Ca^{2+} content available for the next contraction. However, such increased loading of the SR with Ca^{2+} may be a key factor in the development of Ca^{2+}-mediated arrhythmias.[35] The lusitropic effect of catecholamines and PDEIII inhibitors is also mediated by phosphorylation of TnI, which decreases the affinity of myofilaments for Ca^{2+}.
2. *Digoxin.* Digoxin enhances myocardial contractility, although modestly, by inhibiting the Na^+/K^+-ATPase pump with a resultant mild increase in intracellular Na^+. This increase of Na^+ subsequently inhibits the extrusion of Ca^{2+} from the cytosol outside the cell by the sarcolemmal Na^+/Ca^{2+} exchanger. Ca^{2+} not extruded from the cytosol is stored in SR and allows increased release of Ca^{2+} during the next contraction.
3. *Ca^{2+}sensitizers.* More recently, Ca^{2+}sensitizers (e.g., levosimendan), a new class of inotropic agents, have been developed. They improve cardiac contractility by binding to TnC and stabilizing its interaction with Ca^{2+}, which results in prolonged interaction of actin-myosin filaments. One possible limitation of some Ca^{2+} sensitizers is worsening diastolic function due to facilitation of cross-bridging at diastolic Ca^{2+} concentrations. However, this does not appear to be the case of levosimendan because its binding to TnC depends on $[Ca^{2+}]_i$ (i.e., when $[Ca^{2+}]_i$ increases during systole, it facilitates actin-myosin interaction, and when $[Ca^{2+}]_i$ decreases during diastole, it does not). One potential beneficial effect of theses agents compared with catecholamines and PDEIII inhibitors comes from the fact that they do not increase $[Ca^{2+}]_i$ and, as such, have neutral effects on myocardial oxygen demand and heart rhythm.[34]

Drug Response and Genetic Polymorphisms

The same medication, at a given dose, can produce different responses in different patients in regard to both efficacy and toxicity. This is termed *interindividual variability.* It is estimated that genetic factors can account for 20% to 95% of variability in drug disposition and effects.[36] Most genetic variations involve single-nucleotide polymorphisms (SNPs); that is, the exchange of a single nucleotide in the DNA sequence. Small insertions and deletions, variable-number tandem repeats, gene deletions, and gene duplications can also take place. Depending on where SNPs occur, they can result in no change in the protein amino acid sequence (silent polymorphism or synonymous SNP) or in a change in the coded amino acid sequence (nonsynonymous SNP) that can have no functional consequence or can result in altered protein function. The latter can have significant clinical and/or therapeutic implications. In addition, given that genes often present many SNPs, it has become increasingly recognized that single SNPs fail to predict drug responses, whereas combinations of SNPs on a given chromosome (specific haplotype) are clinically more significant and can better determine drug effects.[37]

Each person has two alleles for each gene, one from each parent. One form of the allele that is the dominant wild-type allele (functional allele) from one parent may be expressed more than the recessive mutant allele (allele with reduced function or nonfunctional allele) from the other parent. Two identical alleles result in a homozygous dominant or recessive trait of that gene, whereas a combination of two different alleles leads to a heterozygous trait. Thus a particular protein, such as an enzyme or a receptor, encoded by a gene with polymorphism may be expressed in different amounts. Therefore it is easy to comprehend that a drug response can be altered by genetic polymorphisms occurring in genes that encode drug-metabolizing enzymes, drug targets (e.g., receptors, enzymes), drug transporters, and/or proteins involved in signal transduction.[38] An example of how genetic variants in multiple genes might affect drug dose or drug therapy selection is shown in Figure 117-14.

Genetic Polymorphisms and Drug Disposition

Many major enzymes involved in phase I and phase II drug metabolism have known polymorphisms leading to phenotypic differences (i.e., clinically significant alteration in drug-metabolizing enzyme activities).[36] For a specific polymorphic drug metabolizing enzyme, homozygous individuals for the wild-type allele exhibit normal enzymatic activity (extensive metabolizers), heterozygous individuals may have reduced enzymatic activity (heterozygous extensive/intermediate metabolizers), and homozygous individuals with the mutant allele have low enzymatic activity (poor metabolizers). For some enzymes (e.g., CYP2D6), individuals have ultrarapid metabolism as a result of gene duplications of functional alleles (ultrarapid metabolizers). The clinical consequences of such polymorphisms may be fourfold: (1) poor metabolizers can have an enhanced drug effect, either therapeutic or toxic, resulting from higher plasma concentrations of a given drug; (2) poor metabolizers can experience a diminished drug effect resulting from the inability of a prodrug to be converted into the active metabolite due to low enzymatic activity; (3) ultrarapid metabolizers can experience diminished drug effect resulting from markedly lower plasma concentrations of a given drug; and (4) ultrarapid metabolizers can experience enhanced drug effect from an excessive conversion of a prodrug into the active metabolite as a result of supranormal enzymatic activity. Codeine is a good example of the clinical impact of CYP2D6 polymorphism. CYP2D6 catalyses

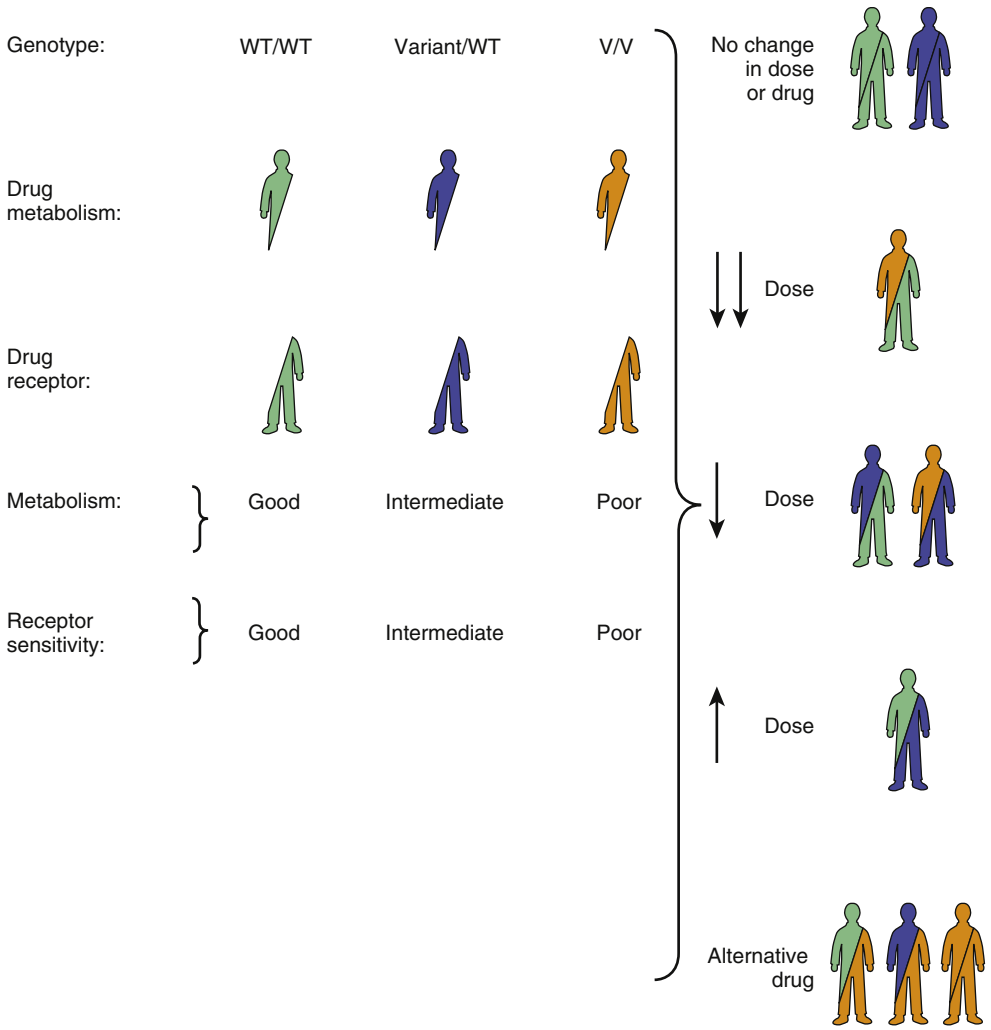

Figure 117–14. Patient genotypes and treatment modifications. The simplest form of polygenic drug response is illustrated, in which the genes encoding the predominant pathway for drug inactivation and the principal receptor for pharmacologic effects exhibit genetic polymorphism that has functional consequences. For the purpose of illustration, both are assumed to be inherited as autosomal codominant traits, with the variant form of each gene (*V*) encoding a protein that is nonfunctional or less sensitive to the prescribed medication. Thus those who inherit wild-type alleles (*WT*) have the highest rate of metabolism (drug inactivation) and therefore require the standard dose to achieve optimal concentrations, assuming they comprise the majority of patients (i.e., were the population studied when establishing the standard dose). This example also assumes that drug receptors encoded by the variant allele are less responsive to treatment and that patients heterozygous for the receptor gene would benefit from exposure to higher drug concentrations and that those who are homozygous for the variant receptor allele will be refractory to any concentration of the medication. *(Modified from Johnson JA, Evans WE: Molecular diagnostics as a predictive tool: genetics of drug efficacy and toxicity,* Trends Mol Med *8:300–305, 2002.)*

the biotransformation of codeine into morphine, the active compound. CYP2D6 poor metabolizers are at increased risk of experiencing inadequate analgesia as a failure to convert codeine into morphine, whereas CYP2D6 ultrarapid metabolizers may be at increased risk for opioid-related adverse effects as a result of increased formation of morphine from codeine.[39,40]

Genetic Polymorphisms and Drug Targets and Signaling Mechanisms

More recently, genetic polymorphisms in signaling mechanisms involving GPCRs and enzymes have been identified.[41-43] These polymorphisms can result in either decreased or enhanced agonist efficacy and can influence drug response. Mutations in G proteins have also been shown to cause certain diseases.[44] The genetic variation occurring in the genes of β_1-adrenergic receptors is a good example of how polymorphisms in drug target and signal transduction genes can alter drug effects. These polymorphisms can potentially affect the pharmacologic response of drugs commonly used in the pediatric intensive care unit, such as catecholamines, and are discussed further below.

As mentioned previously, the β_1-adrenergic receptor is coupled to the stimulatory G_s, which mediates chronotropic and inotropic responses to catecholamines by an increase in cAMP. Two nonsynonymous SNPs (a serine [Ser] to glycine [Gly] substitution at codon 49 and an arginine [Arg] to glycine [Gly] substitution at codon 389) occur in the gene encoding the β_1-adrenergic receptor.[4] In vitro studies suggest that both polymorphisms have functional consequences with the Gly49 form of the receptor, resulting in greater agonist-promoted downregulation than the Ser49 form and the Arg389 form of the receptor, resulting in slightly greater basal and twofold to threefold higher agonist-stimulated adenylate cyclase activity than the Gly389 form. Recent in vivo

studies have demonstrated that these polymorphisms, either as single SNP or haplotype, are important determinants of antihypertensive response to β-adrenergic receptor blockade. Individuals homozygous for Arg at codon 389 experience a significantly larger decrease in blood pressure in response to atenolol and metoprolol compared with those who carry the variant allele.[45,46] The underlying hypothesis is that hypertensive patients who are homozygous for Arg389 have hypertension predominantly mediated through the adrenergic nervous system and thus have a greater antihypertensive response to β-adrenergic receptor blockers.

Of specific interest for the care of critically ill patients, an in vitro study using isolated human myocardial tissue expressing receptor variants of the Arg389Gly polymorphism showed significantly increased inotropic potency to norepinephrine in tissue from individuals homozygous for Arg at codon 389 compared with individuals homozygous for Gly at codon 389. Tissue cAMP levels were also greater in the former group, whereas cAMP-dependent protein kinase activity was the same in both variants.[47]

Drug Response and Development

From birth through puberty, dramatic developmental changes occur that can have a profound impact on drug disposition and action. Most studies have evaluated the effect of age on pharmacokinetics, revealing clinically important differences compared with adults.[48,49] The ontogenesis of important drug-metabolizing enzymes, the cytochrome P450 enzymes, is a good example of how development affects drug disposition and how age is an important determinant in selecting appropriate doses (see Chapter 110 and Table 117-3). Even though developmental changes are also expected to affect the different players involved in pharmacodynamics, scarce data concerning the ontogenesis of specific drug targets, signal transduction mechanisms, and intracellular messengers are currently available. To date, human studies have mainly dealt with receptor expression (and not function), mostly in the brain and have found age-related differences in terms of receptor density and regions of the brain where receptors are expressed.[50-52] The exact consequences of all these differences are unknown, but it is speculated that they may play a role in organ maturation as well as in the pathophysiology of diseases and drug response.

Drug Response and Disease

Although a vast literature exists regarding the effects of diseases on drug pharmacokinetics, limited data are available about pharmacodynamic changes occurring as a consequence of illness. Of particular interest for the critically ill population is the myocardial hyporesponsiveness to catecholamines observed during sepsis. Sepsis, which is associated with elevated circulating catecholamine levels, induces a disruption at various levels of the β-adrenergic signaling cascade (Figure 117-15).[3] Postulated mechanisms, mainly derived from animal studies, include inactivation of catecholamines by superoxide, decreased β-adrenergic receptor density, decreased stimulatory G-proteins (G_s), and increased inhibitory G-proteins (G_i) (β_2-adrenergic receptor

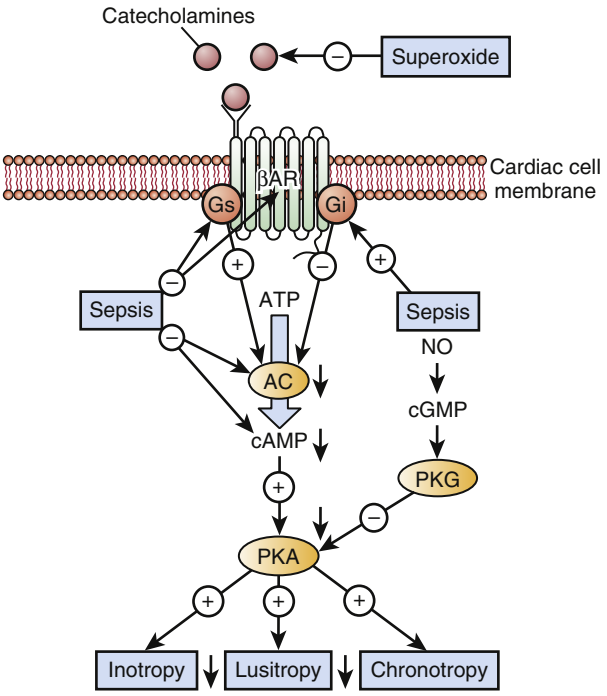

Figure 117–15. Sepsis-induced alterations in the the β-adrenergic signaling cascade. *AC*, Adenylate cyclase; *ATP*, adenosine triphosphate; *βAR*, β-adrenergic receptor, *cAMP*, cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; G_i, inhibitory G protein; G_s, stimulatory G protein; *NO*, nitric oxide; *PKA*, protein kinase A; *PKG*, protein kinase G. *(Modified from Rudiger A, Singer M: Mechanisms of sepsis-induced cardiac dysfunction,* Crit Care Med *35:1599–1608, 2007.)*

in rat ventricular cardiomyocytes can couple to G_i; whether human cardiac β-adrenergic receptors can do the same is unknown[53]). These changes result in decreased activity of adenylate cyclase and reduced levels of cAMP. In addition, NO released during sepsis activates soluble guanylate cyclase with increased cGMP and activation of PKG, which in turn inhibits PKA. These alterations ultimately lead to decreased contractility, impaired myocyte relaxation, and reduced chronotropy.

Conclusion

Even though knowledge of how drugs work at a molecular level has grown tremendously over the past decade, continued elucidation of normal signal transduction physiology and of the effects of genetics, development, and disease states on the functional integrity of receptors, signaling pathways, and effectors should improve and refine pharmacologic interventions administered to critically ill children. To optimize the efficacy/toxicity ratio, both genetic and nongenetic factors, including the patient's age, sex, organ function, ethnicity, concomitant therapy, drug interactions, nature and severity of the disease, comorbid conditions, and the use of extracorporeal device (e.g., extracorporeal membrane oxygenation) should be taken into account to individualized pharmacotherapy in the PICU setting.

References are available online at http://www.expertconsult.com.

Adverse Drug Reactions and Drug-Drug Interactions

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PEARLS

- Although adverse drug events in ambulatory pediatric patients may be relatively uncommon, epidemiologic studies in inpatient settings confirm that the problem is just as important for children as it is for adults. Overall, the incidence of adverse events in pediatric inpatients can range from 5% to 21% of hospital admissions, which is higher than the estimated incidence of approximately 4% in adults.
- The pediatric intensive care provider is confronted daily with potentially hazardous drug-drug interactions in the critical care setting. The ability to recognize every potential drug-drug interaction in the pediatric critical care setting is nearly impossible; however, in most cases, drug-drug interactions are predictable and preventable, with appropriate dosage modifications or avoidance of combinations.
- Prescription medications are the most common cause of iatrogenic seizures. Drug-related factors that may contribute to seizures are the intrinsic epileptogenicity of the agent, factors that influence serum levels (dose, schedule, route), and factors that affect central nervous system drug levels (lipid solubility, molecular weight, ionization of the drug, protein binding, transport by endogenous systems).
- Parenteral administration of drug therapy poses a potential source of drug-drug interactions in the pediatric/neonatal intensive care unit. In this scenario, polypharmacy arising from an extensive problem list and limited intravenous access conspire to force the mixing of various drug solutions. However, disparate physicochemical properties and varying administration times preclude the indiscriminate admixing of numerous drugs.

Adverse drug reactions in the pediatric critical care setting are a potential contributor to the morbidity and mortality of patients.[1-5] Although adverse drug reactions in ambulatory pediatric patients may be relatively uncommon, epidemiologic studies in inpatient settings confirm that the problem is just as important for children as it is for adults.[3-7,9] There is substantial evidence that suggests the incidence of adverse drug reactions may be more common than in adults. Many of the therapeutic agents used in the pediatric critical care setting have not been studied and evaluated for safety and efficacy. Intensive care physicians should have a heightened awareness of the incidence of adverse drug reactions so they can assist with recognizing and ultimately preventing adverse drug reactions. Patients in the intensive care unit are predisposed to adverse drug reactions due to the incidence of single and multiple organ failure. Impairment in metabolism (hepatic function) and clearance (renal function) of therapeutic agents increases the incidence of adverse drug reactions. In order to alleviate adverse drug reactions, pediatric intensivists need to be aware of the complications associated with drug therapy in the pediatric critical care patient.

Steps are now being taken to help prevent adverse reactions caused by the lack of knowledge of how a given drug affects children, but remaining issues still cause children to be more susceptible to adverse drug reactions. It is common practice to use weight-based dosing, which adds another layer of complexity to drug therapy in children. For example, many parenteral therapies require dilution of stock solutions, providing an opportunity for errors. Finally, sick infants and children may have reduced ability to survive iatrogenic events if and when they occur. Publications have brought to light the importance of adverse drug events in adults and their impact on the health care system in general.[9] Although adverse drug events in ambulatory pediatric patients may be relatively uncommon, epidemiologic studies in inpatient settings confirm that the problem is just as important for children as it is for adults.[3-7,9] Overall, the incidence of adverse events in pediatric inpatients can range from 5% to 21% of hospital admissions,[2-5] which is higher than the estimated incidence of approximately 4% in adults.[10,11]

Defining Adverse Drug Reactions

One of the difficulties in reviewing the literature on adverse drug reactions is how they are defined. There are many different examples of what constitutes an adverse drug reaction. Many professional organizations have tried to standardize exactly how an adverse drug reaction is defined. The World Health Organization (WHO) defines an adverse drug reaction as any response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiologic function.[12] The Joint Commission on Accreditation of

Healthcare Organizations (JCAHO) defines an adverse drug reaction as an undesirable response associated with use of a drug that compromises therapeutic efficacy, enhances toxicity, or both.[13]

For reporting purposes, the Food and Drug Administration (FDA) categorizes a serious adverse event (events relating to drugs and devices) as one in which "the patient outcome is death, life-threatening (real risk of death), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage."[14] The American Society for Health-System Pharmacists (ASHP) defines a significant adverse drug reaction as any unexpected, unintended, undesired, or excessive response to a drug that[15]:

- Requires discontinuing the drug (therapeutic or diagnostic)
- Requires changing drug therapy
- Requires modifying the dose (except for minor dosage adjustments)
- Necessitates admission to a hospital
- Prolongs stay in a health care facility
- Necessitates supportive treatment
- Significantly complicates diagnosis
- Negatively affects prognosis
- Results in temporary or permanent harm, disability, or death

The ASHP also defines what is not an adverse drug reaction as follows:

- Side effects
- Drug withdrawal
- Drug abuse syndrome
- Accidental poisoning
- Drug overdose complications

The mechanisms by which adverse drug reactions occur can be divided into type A and type B. Type A mechanisms usually are thought of as preventable, predictable, and related to the pharmacologic action of the medication. Knowledge of the effects caused by the medication can predict the likelihood of an adverse drug reaction occurring. Appropriate monitoring of the medication can assist in preventing adverse drug reactions.[16-18] Type B mechanisms usually are considered to be unavoidable and not predictable. These reactions normally are uncommon and not related to the pharmacologic action of the medication. Idiosyncratic and hypersensitivity reactions are common type B reactions.[16-18]

A critical factor in assessing adverse drug reactions is establishing a causal relationship between the suspected drug and the adverse reaction.[19] Identification of adverse drug reactions can be arbitrary. Some of the confounding factors are the ambiguous characteristics of the reactions, the fact that patients usually are taking more than one medication at the time of the reaction, and the inability to perform definitive cause and effect tests.[19] There have been numerous attempts to try to formalize the process.[18-21] Karch and Lasagna[19] designed decision tables that can identify a potential reaction, assess the certainty of a link between the drug and the event, and evaluate the underlying cause of the reaction. These provide a framework for systematic evaluation of potential adverse drug reactions and reduce the ambiguity that, at present, characterizes the assessment of adverse drug reactions. Kramer et al.[21] devised an operational assessment using an algorithm with six axes to assess the probability of an adverse drug reaction occurrence. A scoring system for each axis and an overall score help delineate the likelihood that an adverse drug reaction has occurred. Similarly, Naranjo et al.[18] developed an adverse drug reaction probability scale using 10 questions answered positively (yes), negatively (no), or unknown to determine the likelihood that an adverse drug reaction had occurred. The Naranjo method has been shown to improve the reproducibility of adverse drug reactions assessments.

An FDA algorithm that assesses the characteristics of the event (temporal relationship, dechallenge, rechallenge, and relationship to disease) has been presented.[20] The algorithm contains four questions to assess the likelihood that an adverse drug reaction had occurred:

1. Did the reaction follow a reasonable temporal sequence?
2. Did the patient improve after stopping the drug?
3. Did the reaction reappear on repeated experience (rechallenge)?
4. Could the reaction be reasonably explained by known characteristics of the patient's clinical state?

The categories *remote, possible, probable,* and *highly probable* are used based on the answers to the four questions.

Comparisons of the different methods have been conducted. Michel and Knodel[22] compared the Kramer, Naranjo, and FDA methods. The Kramer method was considered to be the standard of practice at the time, and Naranjo and FDA methods both compared favorably. The Naranjo method was shown to be simpler and less time consuming. The lack of a numerical score in the FDA algorithm caused the authors to decide there was a need for more data to recommend its use over Naranjo method, even though the FDA algorithm was less time-consuming than either method.[22] Busto et al.[23] compared the Kramer and Naranjo methods. The two methods were determined to be equal in terms of reproducibility, but the Kramer method was more complex.

Once an adverse drug reaction is identified, appropriate reporting is critical. Reporting can occur by several mechanisms. The event can be reported through the health care systems adverse drug reaction program as mandated by the JCAHO. This program usually is coordinated by the pharmacy department. Another avenue is to contact the drug manufacturer, as all companies have a mechanism for documenting adverse drug reactions. Finally, severe and significant reactions can be reported to the FDA through the MedWatch program.

Adverse Drug Reactions by Organ System

Renal

Nephrotoxicity accounts for nearly 7% of all adverse drug reactions.[11] Several factors place the renal system at risk for adverse drug reactions. The renal system is responsible for elimination of many drugs and metabolites, of which several are known nephrotoxins. Additionally, the renal vascular system receives approximately 20% to 25% of resting cardiac output. Therefore the kidneys are exposed to high concentrations of drugs and diagnostic agents. Although the renal system is highly vulnerable to nephrotoxicity, there are only a few mechanisms by which nephrotoxins can induce injury. These mechanisms include hemodynamically mediated nephrotoxicity, tubular necrosis, interstitial nephritis, obstructive nephropathy, and vascular toxicity. Many nephrotoxins can injure the kidney through more than one mechanism.

A variety of drugs are associated with acute tubular necrosis, including aminoglycosides, cisplatin, amphotericin B,

radiocontrast media, cyclosporine, and intravenous (IV) immunoglobulins.[24-26] Acute tubular necrosis is one of the most common renal disorders associated with drug therapy. Minimizing risk factors for nephrotoxicity with these agents is imperative (i.e., administration of a saline load and repletion of volume have proved beneficial in reducing toxicity).[27] Table 118-1 provides a more complete list of medications associated with tubular necrosis.

Several drugs are implicated in alteration of renal blood flow. Some of the most common include angiotensin-converting enzyme inhibitors (ACEIs) (e.g., enalaprilat), nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., ketorolac), β-adrenergic antagonists (e.g., propranolol), and calcineurin inhibitors (e.g., cyclosporine).[7,28-35] ACEIs can induce renal insufficiency in patients suffering from any process that decreases renal blood flow, including bilateral renal artery stenosis or unilateral stenosis with a single kidney.[36] The mechanism involves inhibiting the conversion of angiotensin I to angiotensin II, which results in dilation of the efferent arterioles, with resultant decreased glomerular capillary hydrostatic pressure and reduced glomerular filtration. The incidence of ACEI-induced renal failure in patients with renovascular hypertension ranges from 20% to 38%.[34] NSAIDs inhibit prostaglandin synthesis, which leads to reduced renal blood flow and reduced glomerular filtration. The incidence of renal insufficiency is most common in patients with chronic renal disease, hypovolemia, sepsis, and use of concomitant nephrotoxic drugs.[28,30-33,35] NSAID-induced renal toxicity is reversible if the toxic agent is discontinued immediately.[36] Table 118-1 provides a more complete list of drugs associated with hemodynamic renal failure.

Acute interstitial nephritis is another common source of drug-induced nephrotoxicity. It is reported to cause 3% to 8% of all cases of acute renal failure.[37] The clinical presentation of acute interstitial nephritis can appear anywhere between 2 and 44 days after initiation of the offending therapy.[38,39] Typical clinical symptoms include fever, skin rash, and flank tenderness.[38,39] Common laboratory findings include hematuria, sterile pyuria, and eosinophilia.[37] Histologic findings of acute interstitial nephritis include interstitial infiltrate of lymphocytes, plasma cells, eosinophils, and neutrophils.[37-39] Prompt discontinuation of the offending drug from therapy is recommended, and administration of corticosteroids may improve recovery.[40] Table 118-1 lists some medications associated with acute interstitial nephritis.

Renal tubular obstruction is associated with renotubular precipitation of endogenous products, drugs, and their metabolites. Formation of uric acid precipitates after chemotherapy can result in renal obstruction. Hydrating patients prior to chemotherapy, urinary alkalinization, and use of allopurinol or rasburicase can help prevent uric acid precipitation. Rhabdomyolysis can cause intratubular precipitation of myoglobin and lead to acute renal failure. Terbutaline overdose has resulted in rhabdomyolysis-induced renal failure.[41] Drugs associated with formation of crystals include acyclovir, sulfonamides, mannitol, pentobarbital, methotrexate, and dextran.[42-45]

Aminoglycosides are used frequently for treatment of gram-negative infections. All aminoglycosides have been shown to be toxic to the proximal renal tubules.[50] Aminoglycoside nephrotoxicity is related to dose, high trough concentrations, and prolonged therapy.[50] The drug-induced nephrotoxicity normally manifests as nonoliguric renal failure.[47] Several risk factors for developing aminoglycoside nephrotoxicity include the need for intensive care, decreased albumin, poor nutritional status, prolonged therapy, hypovolemia, pneumonia, shock, preexisting liver or kidney disease, and elevated initial steady-state drug concentrations.[47,48] In addition, vancomycin, piperacillin, furosemide, amphotericin B, and cephalosporins when administered concomitantly with aminoglycosides are associated with an increased risk for developing nephrotoxicity.[47] Predicting nephrotoxicity based on the risk factors stated is an extremely complicated, inexact task.[47,49] Typically, aminoglycoside nephrotoxicity is reversible upon discontinuation of the offending agent.[50,51]

Drug-induced nephrotoxicity is a common serious adverse drug reaction that can lead to morbidity and lengthen hospital stays.[52] It is important to recognize potential nephrotoxins before initiating therapy and to evaluate therapeutic options. It is also important to monitor therapy appropriately for signs of toxicity and to modify therapy as needed.

Table 118–1 Drugs Causing Nephrotoxicity

Tubular Necrosis	Interstitial Nephritis	Hemodynamic-Mediated Renal Failure
Aminoglycosides	Allopurinol	Angiotensin-converting enzyme inhibitors
Amphotericin	Aminoglycosides	Cyclosporine
Carboplatinum	Aztreonam	Mannitol
Cephalosporins	Captopril	NSAIDs
Cisplatin	Carbamazepine	Propranolol
Cyclosporine	Cephalosporins	Radiologic contrast agents
Mannitol	Cimetidine	Tacrolimus
Methoxyflurane anesthesia	Ciprofloxacin	
NSAIDs	Cyclosporine	
Pentamidine	Erythromycin	
Radiologic contrast agents	Interferon-α	
	NSAIDs	
	Penicillins	
	Phenobarbital	
	Phenytoin	
	Ranitidine	
	Rifampin	
	Sulfonamides	
	Tacrolimus	
	Thiazide and loop diuretics	
	Valproic acid	
	Vancomycin	
	Warfarin	

NSAID, Nonsteroidal antiinflammatory drug.

Hepatic

The liver is the most critical organ in drug toxicity due to its major role of metabolism and elimination of foreign substances. This renders it a target for drug toxicity. It is well documented that acetaminophen causes intrinsic hepatotoxicity following acetaminophen overdose. However, a variety of medications cause drug-induced hepatotoxicity. It often is difficult to determine the source of unexplained liver injury, so detailed examination of past and current drug therapies is needed to rule out possible drug-related causes. Most hepatotoxicity associated with drugs is idiosyncratic in nature and has a rate usually less than 1 per 10,000 exposed patients. The pathogenesis of drug-induced liver disease is mediated either

through an immune response or direct cell damage.[53,54] In many cases, this hepatotoxicity is idiosyncratic, meaning not predictable or dose-related, in contrast to drugs like acetaminophen and isoniazid/iproniazid, for which toxicity is related to dose.[53,54]

The mechanism of toxicity for drug-induced liver injury generally involves the accumulation of drugs or their metabolites which cause direct cell damage, target mitochondrial function, or trigger an immune response. The initial stress or immune reaction leads to mitochondrial permeability transition, which is either a direct pathway (intrinsic) mediated by cell damage or is triggered by the death receptor amplified pathway. The mitochondrial impairment will determine if the hepatocytes dies by apoptosis or necrosis. Measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin are important measurements in assessment of drug-induced liver injury. It has been estimated that one tenth of the Hy's law cases (defined as bilirubin elevated to twice the upper limit of normal [ULN] and transaminase three times ULN) with hyperbilirubinemia or jaundice die or require transplant.[55,56] In severe cases of drug-induced hepatic injury, jaundice and hepatic failure may ensue.[54] Typically drug-induced hepatic disease occurs expectedly as a result of high-dose therapy of a known hepatotoxin or unexpectedly as a result of an idiosyncratic reaction to a drug not associated with hepatotoxicity. Overall, children are less prone to drug-induced liver disease than are adults.[58] However, specific hepatotoxins have been shown to afflict children more than adults. Reye syndrome is a hepatocellular disease that has been associated with aspirin use in children.[59] Valproate hepatotoxicity occurs more frequently in children younger than 2 years who have preexisting neurologic or physical defects.[60]

Drug-induced hepatic disease can occur by a variety of mechanisms, including hepatocellular, cholestatic, and vascular. These injuries are associated with intrinsic or idiosyncratic hepatotoxins. Intrinsic hepatotoxins typically show a dose-related toxic effect. Idiosyncratic hepatic disease is an unpredictable reaction that can occur by immune-mediated hypersensitivity, metabolically or both. Hypersensitivity reactions in the liver can cause cell injury to hepatocytes. The reactions do not correlate with dosage and are difficult to anticipate. This immune-mediated reaction results from antigenic complexes that stimulate T lymphocytes, which can result in hepatic injury. These reactions can be accompanied by fever, skin rash, lymphadenopathy, and eosinophilia.[54] The reactions typically resolve upon discontinuation of therapy and resurface when therapy is rechallenged.[54] Metabolic idiosyncrasy occurs when a compound that is metabolized to nontoxic metabolites and eliminated in the majority of patients is metabolized to a toxic metabolite in a small number of patients because of genetic differences in metabolism (such as with isoniazid).[60] Box 118-1 lists a number of agents that are associated with drug-induced hepatotoxicity.

Box 118–1 Drugs that Cause Hepatotoxicity

Acetaminophen
Amoxicillin-clavulanic acid
Carbamazepine
Erythromycin
Isoniazid
Ketoconazole
Labetalol
Nitrofurantoin
NSAIDs
Phenobarbital
Phenytoin
Rifampin
Sulfonamides
Terbutaline
Tetracyclines
Trazodone
Valproate
Voriconazole

Cardiovascular

Adverse cardiovascular reactions have been noted to be one of the most common types of adverse drug event in pediatric patients.[61] Several medications are associated with adverse cardiovascular effects and the mechanisms are often thought to be related to the agents' pharmacologic action. These effects are potentiated by four general physiological pathways: electrolyte and fluid imbalances; receptor-mediated sympathomimetic effects; alterations of the electrophysiology of the cardiac tissue; and drug-induced cardiotoxicity.

Medications can affect electrolyte and volume status by direct action on electrolyte receptors or indirectly by affecting prostaglandin release or the renin-angiotensin-aldosterone system. Dramatic changes in fluid and electrolyte status caused by these medications can lead to severe changes in blood pressure, heart rate, or cardiac rhythms. Nonsteroidal antiinflammatory drugs, corticosteroids, diuretics, nesiritide, fenoldopam, and certain immunosuppressant agents, such as cyclosporine and tacrolimus, are all medications that can alter fluid and electrolyte balance.[62-67]

Pediatric patients in the intensive care unit often require vasopressive medications; however, it is important to be aware that many cardiovascular toxicities have been observed with use of vasopressors and most of these toxicities stem from their receptor-mediated effects (Table 118-2). The α-adrenergic agonism of the sympathomimetics produces palpitations, ectopic heartbeats, sinus tachycardia, and ventricular arrhythmias.[68] The direct effect on myocardial tissues may be manifested as electrocardiographic (ECG) changes, such as a reduction in T-wave amplitude, which have been reported during epinephrine infusions in normal individuals. Increased myocardial oxygen demand may precipitate an infarction, especially in individuals with underlying cardiac disease. A dramatic rise in heart rate and peripheral vascular resistance may produce severe hypertension, which could lead to cerebral hemorrhage or hemiplegia. Excessive α-adrenergic stimulation may produce vasoconstriction so severe in the extremities, kidneys, or liver that tissues become ischemic or necrotic. Gangrene of the extremities is reported with high doses of dopamine in patients with underlying occlusive vascular disease. Vasopressin can cause severe vasoconstriction and has been associated with digital loss and splanchic ischemia.[69] Extravasation of most sympathomimetic agents may lead to tissue necrosis.[70] The sedative dexmedetomidine, though not classified as a vasopressor, has α_2-adrenergic agonistic properties and has effects similar to the medication clonidine. When

Table 118–2 Adverse Effects of Vasopressor Medications by Adrenergic Receptor Affinity

Medication	Affected Adrenergic Receptor	Associated Adverse Effect
Dopamine	<10 μg/kg/min: β_1 >10 μg/kg/min: β_1 and α	Vasoconstriction, tachycardia, arrhythmias Extravasation causes ischemia
Dobutamine	β_1: selective	Increased heart rate, arrhythmias, ↑ myocardial oxygen demand
Epinephrine	<10 μg/kg/min: β_1 >10 μg/kg/min: α	Vasoconstriction, tachycardia, arrhythmias, tissue ischemia, cerebral hemorrhage, ↑ myocardial oxygen demand Extravasation causes necrosis
Isoproterenol	β: nonselective ($\beta_1 > \beta_2$)	Tachycardia, arrhythmias, hypotension, ↑ myocardial oxygen demand
Norepinephrine	α and β_1 (α > β_1)	Potent vasoconstriction, arrhythmias, tissue ischemia Extravasation causes necrosis
Phenylephrine	α	Systemic vasoconstriction, hypertension, bradycardia
Vasopressin	V1 vascular receptor	Potent vasoconstriction, tissue ischemia

From Goembiewski JA: Vasopressors used in the crtical care setting, *J Peri Anesth Nurs* 18:414-416, 2003; and Vetter VL, editor: *Pediatric cardiology: the requisites in pediatrics,* Philadelphia, 2006, Mosby Elsevier.

using dexmedetomidine, it is important to monitor patients for hypotension, arrhythmias, and bradycardia.[66a]

As noted above, ECG changes can be the side effect of many medications through various mechanisms of action and may lead to dangerous arrhythmias Ventricular arrhythmias in infants and children, unlike adults, are relatively uncommon. The most commonly reported arrhythmias in pediatric patients include conduction disturbances or supraventricular tachyarrhythmias (e.g., atrial tachycardia and junctional tachycardia). A common class of agents whose cardiovascular toxicities stem from its effect on cardiac rhythms are the cardiac glycosides. Digoxin can produce a large array of dysrhythmias; the most common in adults includes unifocal or multifocal ventricular premature complexes and nonparoxysmal atrioventricular junctional tachycardia.[71] Sinus bradycardia and a sick sinus syndrome-like effect have been reported as digoxin-induced adverse effects.[72] The narrow therapeutic index of this drug class is of special concern in the pediatric population. Another class of medications that requires close ECG monitoring is the antiarrhythmic medications. These medications have mechanisms of action that manipulate cardiac action potential and therefore have the ability to produce dysrhythmias.[73,75] The most common types of dysrhythmias associated with the antiarrhythmic medications in all classes are bradyarrhythmias, torsades des pointes, and reentry rhythms.[75] An increased incidence of such problems in patients treated for attention deficit and hyperactivity disorder also warrants heightened surveillance for adverse cardiac effects in this population. The central nervous stimulants used to treat this condition can lead to tachyarrhythmias and have been associated with sudden cardiac death.[76]

Although ventricular arrhythmias are uncommon in pediatric patients, the risk of torsades de pointes is still of concern in this population. Torsades de pointes is a life-threatening subset of arrhythmias and is characterized on electrocardiogram by lengthening of the QT interval and waxing/waning QRS amplitude. Certain medications can increase the risk for this arrhythmia by blocking potassium conductance on the rapid (Ikr) and slow (Iks) receptors within potassium ion channels. This creates a delayed ventricular repolarization and can lead to multiple ventricular reentrant loops. Risk factors for drug-induced torsades de pointes include high doses of associated medications (Box 118-2); underlying structural

Box 118–2 Drugs Commonly Associated with QT Interval Prolongation

Antiarrhythmics
Amiodarone*
Dofetilide*
Flecainide
Ibutilide*
Procainamide*
Propafenone†
Quinidine*
Sotalol*

Antidepressants
Amitriptyline†
Citalopram
Desipramine*
Nortriptyline

Antiinfectives
Clarithromycin†
Erythromycin†
Fluconazole
Gatifloxacin
Grepafloxacin‡
Halofantrine†
Levofloxacin
Moxifloxacin
Pentamidine†
Quinidine†
Quinine†
Sparfloxacin‡
Trimethoprim-sulfamethoxazole

Antipsychotics
Chlorpromazine
Clozapine
Haloperidol†
Pimozide
Quetiapine
Risperidone
Thioridazine†
Ziprasidone

Cardiovascular Agents
Isradipine
Nicardipine
Verpamil

Gastrointestinal Agents
Cisapride§
Droperidol†
Dolasetron
Ondansetron

Miscellaneous
Amantidine
Arsenic trioxide
Methadone
Tacrolimus
Sumatriptan
Zolmitriptan

All unmarked medications are considered low risk; however, they have a documented or theoretical association with QT prolongation. For a complete list see www.qtdrugs.com.
*High risk.
†Medium risk.
‡Medication removed from U.S. market.
§Cisapride, though removed from the U.S. market, has been approved for limited compassionate use in some pediatric disease states.
Modified from Crouch MA, Lymon L, Cassano AT: Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy* 23(7):881-908, 2003.

heart disease; prolonged QT interval at baseline; prolonged QT noted immediately after giving associated medication; and concurrent hypokalemia or hypomagnesemia.[78] A notable exception to these risk factors would be the medication quinidine. Torsades de pointes is typically noted at lower medication concentrations and can be observed later in therapy. Most commonly, the antiarrhythmics, tricyclic antidepressants, and fluoroquinolones are general classes of agents that demonstrate the potential to prolong the QT interval.[79,80] Another concern when administering these medications is pharmacokinetic drug-drug interactions or pathophysiologic alterations in elimination. Any biochemical mechanism that increases the concentration by inhibition of cytochrome isoenzymes or decreased clearance of the associated medication has the ability to potentiate this type of arrhythmia.[81] Recently, several medications have been removed from the market due to fatal arrhythmias secondary to torsades de pointes. The FDA now requires all medications to be screened for their affinities to Ikr/Iks receptors to determine the potential for torsades de pointes. Current practice guidelines recommend avoiding high-risk medications if the patient has a baseline QTc greater than 450 msec and to discontinue or reduce the dose of the medication if the QTc increases to 560 msec or greater after initial medication administration.[78]

Anthracycline antineoplastic agents illustrate a specific pattern of direct toxicity to myocardial tissue. Drugs in this class include doxorubicin, epirubicin, and idarubicin. Acute cardiotoxicity may be manifested as arrhythmias, whereas long-term adverse effects are generally related to the magnitude of cumulative drug exposure, with cardiomyopathy being most common. There may also be the delayed development of cardiotoxicity, as children who have endured anthracycline therapy may exhibit signs of abnormal cardiac function anywhere between 4 and 20 years after exposure.[82] These defects include abnormal right ventricular wall motion, impaired myocardial growth and contractility, conduction abnormalities such as QT prolongation, and congestive heart failure.[82] Severe anthracycline toxicity cannot be reversed, and such a diagnosis leads to a poor prognosis and high mortality. Heart transplantation may be the only option in such cases.[82] Due to the severity of anthracycline cardiac toxicity and the clear association with total cumulative dose received, anthracycline lifetime dosage should be documented for each patient so that cumulative dose thresholds are not exceeded.

Central Nervous System

Prescription medications are the most common cause of iatrogenic seizures.[83] Drug-related factors that may contribute to seizures include the intrinsic epileptogenicity of the agent, factors that influence serum levels (dose, schedule, route), and factors that affect central nervous system (CNS) drug levels (lipid solubility, molecular weight, ionization of the drug, protein binding, transport by endogenous systems).[84] Patient-related factors may influence the risk for drug-induced seizures, such as preexisting epilepsy, neurologic abnormality, decreased drug elimination capacity (renal, hepatic), and conditions that disrupt the blood-brain barrier.[84] There are several medications used within the intensive care unit setting that have been implicated to cause seizures. Due to the complexity of care for many intensive care patients, increasing practitioner awareness of the medications that can induce seizures, as well as their mechanisms, should allow practitioners to recognize and diagnosis patients more effectively (Table 118-3).

Phenothiazine tricyclic antidepressants (chlorpromazine, thioridazine) may cause seizures.[83] Meperidine may induce seizures because of accumulation of the normeperidine metabolite, especially in patients with renal insufficiency.[83] Rapid administration of fentanyl can cause seizures.[83] Several antiinfective and immunosuppressive medications, such as the β-lactam antibiotic, imipenem; high-dose metronidazole; isoniazid; cyclosporine; and chlorambucil induce seizures.[83] Any of the antiepileptic drugs themselves can be implicated in worsening seizure activity. This usually occurs when higher than normal concentrations are used. Seizures also may be precipitated by medication withdrawal.[84] Withdrawal of antiepileptic drugs may cause seizures because of either subtherapeutic levels or too rapid removal of the agent.

Drug-induced headache can be caused by many medications. Headaches can be acute or chronic. They may be caused by use and abuse of the agent.[85] Headache may occur during substance withdrawal. Many medications cause acute headaches, including NSAIDs (e.g., indomethacin), vasodilators (e.g., β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors), immunomodulators (e.g., cyclosporine, tacrolimus, antithymocyte globulin), cytotoxic agents (intrathecal methotrexate, interferon-α_1, interleukin-2), and antimicrobials (e.g., amphotericin-B, tetracycline, sulfonamides).[85,86] Chronic headaches may be caused by overuse and abuse of simple analgesics, narcotics, and combination analgesics with barbiturates/sedatives and ergotamine.[86]

Numerous drugs may cause sedation. Drug-induced sedation usually is an extension of the pharmacologic action of the medication. This effect frequently is transient and diminishes with continuation of therapy. Sedation can result from excessive dosage of the medication and can be managed by decreasing the dose of medication. Excessive sedation may occur with combination therapy.

Ototoxicity usually is iatrogenic.[77] The main sites of action of ototoxic drugs are the cochlea, vestibulum, and stria vascularis.[87] Several medications cause ototoxicity, with salicylates and aminoglycosides the most commonly implicated.[87,88] Other agents involved are cisplatin, loop diuretics, erythromycin, and vancomyin.[87,88] The effect is usually dose-dependent.[77,87,88] High-dose and long-term therapy are common risk factors for aminoglycoside-induced ototoxicity.[87,88] For aminoglycosides, streptomycin is mostly vestibulotoxic and neomycin is more cochleotoxic.[88] Cisplatin is the most ototoxic of the antineoplastic agents.[88] Ethacrynic acid has the greatest potential for causing ototoxicity for the loop diuretics.[88] Appropriate dosing and monitoring of agents associated with ototoxicity are important for prevention and early detection.

Hematologic

The most common and serious adverse drug reaction resulting from chemotherapy with cytotoxic agents is bone marrow suppression. The decline in hematopoiesis results from injury to rapidly dividing stem cells and can lead to secondary morbidities. For example, neutropenia predisposes a patient to opportunistic infections and sepsis. Chemotherapy-induced thrombocytopenia may render a patient vulnerable to hemorrhage in the CNS or gastrointestinal (GI) tract.

Table 118–3 Medications That Can Induce Seizures

Medication	Potential Mechanism of Action	Comments
Acyclovir[306]	Neurotoxicity	Renal impairment and parenteral administration increases the incidence
Antipsychotics[307]	Decreases seizure threshold	Increased incidence with high doses and rapid dose adjustments
Carbapenems[308]	Potentiates seizure activity through the inhibition of GABA receptor	Caution in patients with CNS disorders and renal dysfunction Imipenem has higher incidence compared with meropenem, ertapenem, doripenem
Cephalosporins[309]	Inhibition of GABA receptor	Ceftazidime > ceftriaxone > cefuroxime and cefotaxime
Cyclosporine[310]	Unknown but may involve the release of the potent vasoconstrictor endothelin from endothelial cells which induce microvascular damage and/or changes in permeability of the blood-brain barrier	More common with high doses Increased incidence with hypocholesterolemia and hypomagnesemia
Cytarabine[311]	Cerebral dysfunction	Increased incidence with intrathecal administration
Fluoroquinolones[312]	Unknown but may involve inhibition of GABA receptor	History of seizures and use of NSAIDs associated with increased risk of seizures
Flumazenil[313]	May precipitate benzodiazepine withdrawal; inhibition with seizure medications	Use in caution with patients with underlying seizure disorder
Meperidine[83,307]	CNS excitation from toxic metabolite (normeperidine); blockade of serotonin	Common reaction with renal impairment and high doses
Metronidazole[309]	Penetrates the blood-brain barrier	Cumulative high dose and prolonged use
Penicillins[314]	Irritation of nervous system	Use in caution with infants, rapid IV infusions, and renal impairment
Tacrolimus[315-317]	Neurotoxicity	May be secondary to local vasoconstriction mediated by endothelin; elevated levels and hepatic impairment may increase the risk of neurotoxicity
Theophylline[83]	CNS toxicity	Serum concentrations >25 μg/mL have been noted to induce seizures

Severe anemia may lead to dizziness, fatigue, hypotension, and myocardial infarction.[89] In addition to bone marrow suppression, some antineoplastics may produce thrombotic and hemorrhagic coagulation toxicities. For example, L-asparaginase has been reported to induce changes in the von Willebrand factor multimer in children and thereby promote platelet aggregation.[82]

Respiratory

Respiratory adverse effects are relatively uncommon but are among the most serious adverse events. Due to the seriousness of some of the drug-induced respiratory adverse events, which could be life-threatening, intensive medical interventions are often required. Numerous agents have been known to cause lung disease. In 1975, only 19 agents were implicated with pulmonary complications.[90,91] There are now over 350 agents that have been identified as having the potential to induce respiratory complications.[90,91] The number of agents known to cause pulmonary adverse reactions continues to expand each year. Recognition of drug-induced pulmonary disease may be challenging due to the presence of confounding variables often associated with these patients that may result in the underdiagnosis of both acute and chronic lung disease.[92] Some of the confounding factors in the diagnosis of drug-induced pulmonary disease include preexisting pulmonary conditions such as bronchopulmonary dysplasia and asthma,[93] the use of oxygen,[94] and concurrent medications.

Virtually any drug can cause pulmonary infiltrates as part of a general hypersensitivity reaction. Azathioprine, 6-mercaptopurine, procarbazine, penicillamine, phenytoin, carbamazepine, and sulfasalazine are medications commonly involved in hypersensitivity pulmonary reactions.

Bronchoconstriction is one of the most common drug-induced pulmonary reactions. The two main risk factors for the development of drug-induced bronchospasm include a previous history of reactive airway disease and chronic obstructive lung disease.[93,95] There are several classes of medications that are associated with this clinically significant reaction. Analgesics and NSAIDs are two of the most common medications that can precipitate bronchospasm.[95] Other agents include antimicrobials (e.g., sulfonamides), cardiovascular agents (e.g., β-adrenergic antagonists and ACEIs), and excipients (e.g., preservatives, coloring agents, antioxidants).[95,96] The extensive list of medications suspected of causing or exacerbating bronchospastic reactions demonstrates the need to be aware of drug-induced causes of acute episodes, especially in patients with a history of preexisting lung conditions.

Opiates are commonly prescribed to pediatric intensive care patients. Acute respiratory failure secondary to a noncardiogenic pulmonary has been reported with the use of opiates including methadone, morphine, and codeine.[96] Aspirin

has also been identified to cause pulmonary toxicity. High concentrations of aspirin can lead to increased vascular permeability causing pulmonary edema. A syndrome of massive fluid retention and pulmonary edema may be seen with interleukin-2 administration. All-trans-retinoic acid may cause acute lung disease secondary to massive total body fluid accumulation.

Chronic pneumonitis/fibrosis is a relatively common syndrome associated with drug-induced pulmonary reactions and is manifested by slowly progressive symptoms of cough and dyspnea.[96] Nitrofurantoin is associated with pulmonary fibrosis, most commonly in patients receiving chronic, high-dose therapy and/or patients with renal insuffiency.[97] A delayed presentation (months to years after discontinuation of or the start of therapy) is the most common form of fibrosis seen with amiodarone,[98] but it also may cause an acute fibrosis manifesting within the first few weeks of therapy.[97,98] Many cytotoxic agents have been known to cause pulmonary fibrosis including bleomycin, carmustine (BCNU), mitomycin, mitomycin/vinca alkaloid combination therapy, and cyclophosphamide. Risk factors for this reaction to cytotoxic agents are cumulative dose, age at treatment, and radiation therapy.

Endocrine and Metabolic

Due to the complexity of the biochemical processes that influence the endocrine and metabolic balance of the body, several medications have the potential to create alterations in neuroendocrine hormonal production, binding, transport, and signaling. Additionally medications may create changes in hormonal counter-regulatory efforts. The most common types of medication-induced endocrine disorders are modifications in carbohydrate metabolism, electrolyte and calcium abnormalities, drug-induced thyroid changes, and alterations in acid-base status.[99] Variations in carbohydrate metabolism are commonly seen with many medications and are clinically manifested as alterations in blood glucose. Table 118-4 lists the multitude of medications associated with hypoglycemia or hyperglycemia subdivided by neuroendocrine effect.[99-109]

Hypoglycemia occurs most commonly with overtreatment with insulin or diabetic medications, while hyperglycemia results from medications that either increase glucose production or decrease the effects of exogenous insulin.[99,110,111] Decreased insulin secretion, changes in liver glucose metabolism and production, and increased insulin resistance are the most common mechanism of drug-induced hyperglycemia.[99] Glucocorticoid usage is commonly associated with hyperglycemia and glycosuria.[112] Corticosteroids increase blood glucose via hepatic gluconeogenesis and by increasing peripheral insulin resistance.[113] This adverse drug reaction appears to be dose-dependent and usually is reversible upon discontinuation of therapy.[113] Patients on high-dose, long-term glucocorticoid therapy are at significant risk for suppression of the hypothalamic-pituitary-adrenal axis.[114,115] Symptoms of adrenal insufficiency include arthralgias, dizziness, hypotension, nausea, and weakness.[114]

Drug-induced electrolyte disturbances can occur with a variety of pharmaceutical agents. Several medications are associated with initial or worsening hypokalemia, hyperkalemia, hyponatremia, hypernatremia, and hypomagnesemia (see Table 118-4).[99,116-131] Hyponatremia and hypernatremia are often secondary to depletional or dilutional effects of medications or drug-induced changes in antidiuretic hormone.[99,118] Hypokalemia is directly affected by medications that increase potassium excretion or that increase Na-K-ATPase activity, causing potassium influx into the cells. Drug-induced hyperkalemia can develop when medications lead to decreased Na-K-ATPase activity, aldosterone deficiencies, and resistance to aldosterone.[99,116] Medications that affect the renal tubules of the kidneys, such as amphotericin B and cyclosporine, have been associated with severe hypomagnesemia.[120] Antiepileptic agents, citrated solutions, foscarnet, and intravenous diltiazem have all been associated with critical hypocalcemia due to effects on either vitamin D metabolism or calcium reuptake mechanisms.[121-127] Electrolyte disorders represent a common adverse drug reaction and can greatly complicate therapy. Accordingly, frequent monitoring of electrolytes is warranted for patients on multiple drug therapy.

Electrolyte abnormalities are noted with the use of amiodarone; however, it is most commonly known for its adverse effects on the thyroid gland. Due to the large amount of iodine in amiodarone (3 mg of iodine/100 mg of drug), it has a counterregulatory effect on the production of thyroid hormones.[99] In patients in more developed countries, where iodine-deficiency is rare, use of amiodarone is associated with hypothyroidism; however, in countries where iodine-deficiency is more common; amiodarone can cause thyrotoxicosis.[129,130] It is important to obtain baseline thyroid studies prior to starting therapy and to continually monitor them throughout treatment.

Although uncommon, prolonged use of nitroprusside can result in methemoglobinemia and cyanide or thiocyanate toxicity.[132,133] Thiocyanate or cyanide toxicity is uncommon but can occur in patients suffering from kidney or hepatic failure or in patients receiving high-dose or prolonged infusions of nitroprusside.[134] An early indicator of thiocyanate or cyanide toxicity is metabolic acidosis.[135] Other medications associated with anion gap metabolic acidosis include chloramphenicol, epinephrine, norepinephrine, papaverine, and salicylates.[136,137]

Several life-threatening adverse drug reactions with propofol use in both the pediatric and critical care setting have been reported. In 2001, the FDA communicated a warning against off-label use of propofol for sedation in pediatric intensive care.[138,139] The FDA concern came from reviewing data of a randomized, controlled clinical trial evaluating the safety and efficacy of propofol versus standard sedation regimens in pediatric intensive care patients. Approximately 10% of patients treated with propofol died compared with 4% of children receiving standard treatment. Although large case series have reported the safe use of propofol without adverse effects,[140] given the risks of mortality with propofol infusion syndrome, prolonged propofol infusions are not recommended in the pediatric ICU setting.

Dermatologic

Erythema multiforme major, Stevens-Johnson syndrome, and toxic epidermal necrolysis are severe cutaneous reactions. They are characterized by the triad of symptoms of mucous membrane erosions, target lesions, and epidermal necrosis with skin detachment.[141] Drugs are frequently cited as the cause of these reactions. The more severe the reaction, the

Table 118–4 Drugs that Cause Endocrine/Metabolic Changes

Hyperglycemia		Hypoglycemia	Hyponatremia	Hypernatremia
↓ **Insulin secretion:**	↑ **Insulin resistance:**	↑ **Insulin secretion:**	↑ **Loss of sodium:**	↓ **Aldosterone:**
Asparaginase	Amiodarone	Aspirin	Loop diuretics	Lithium
Beta blockers	Antiretrovirals/HAART	Cotrimoxasole	Thiazide diuretics	Carbamazepine
Cyclosporine	Antipsychotics	Pentamidine		
Glucocorticoids	Beta blockers	Insulin	↑ **Aldosterone:**	**Aldosterone deficiency:**
Metolazone	Phenytoin		Vasopressin	Lithium
Octreotide	Sirolimus	↑ **Insulin sensitivity:**	Desmopressin	Amphotericin B
Phenytoin	Tacrolimus	ACE inhibitors	Spironolactone	Foscarnet
Terbutaline	Thiazide diuretics	ARBs		
Thiazide diuretics		α-blockers	**SIADH effect:**	
	Miscellaneous:		Amiodarone	
Alterations in liver glucose metabolism:	Acetazolamide	**Miscellaneous:**	Antidepressants	
	Amphotericin B liposome	β-blockers	Antipsychotics	
Beta blockers	Basiliximab	ACE inhibitors	Ciprofloxacin	
Corticosteroids	Clonidine	Haloperidol (IV, IM)	Cisplatin	
Glucocorticoids	Dapsone	Indomethacin	Cytoxan	
Oral contraceptives	Dextrose	Octreotide	Ecstasy	
Somatropin	Diazoxide		Tricyclic antidepressants	
	Isonizid		Vincristine	
	Loop diuretics			
	Mycophenolate		↑ **Fluid retention:**	
	Rifampin (oral)		NSAIDS	
	Rituximab			

Hypokalemia	Hyperkalemia	Calcium/Magnesium	Thyroid
↑ **Excretion:**	↑ **Efflux (extracellular):**	**Hypomagnesemia:**	**Hypothyroidism:**
Diuretics	Arginine	Aminoglycosides	Amiodarone
Foscarnet	β-blockers	Ampotericin B	Interferon-α
Laxatives	Digoxin	Cisplatin	Lithium
	Mannitol	Cyclosporine	Methimazole
↑ **Influx (intracellular):**	Tacrolimus	Loop diuretics	
β-agonists (albuterol, dopamine, terbutaline)	Succinyl choline		**Hyperthyroidism:**
		Hypocalcemia:	Amiodarone
Dextrose	↑ **Aldosterone:**	Bisphosphonates	
Insulin	Cotrimoxazole	Citrated solutions	
Levothyroxine	Pentamidine	Diltiazem (IV)	
Theophylline	Spironolactone	Ethylene glycol poisoning	
Aldosterone Deficiency/ Resistance:	**Miscellaneous:**	Foscarnet	
	Propofol	Phenobarbital	
ACE inhibitors	Rituximab	Phenytoin	
Cyclosporine			
NSAIDs		**Hypercalcemia:**	
		Levothyroxine	
Miscellaneous:		Lithium	
Amphotericin B		Theophylline	
Caspofungin		Tretinoin	
Corticosteroids			
Itraconazole			

ACE, Angiotensin converting enzyme; *ARBs*, angiotensin II receptor blockers; *HAART*, highly active antiretroviral therapy; *NSAIDs*, nonsteroidal antiinflammatory drugs; *SIADH*, syndrome of inappropriate antidiuretic hormone.

more likely it is drug-induced.[141] Numerous medications are implicated as the cause of these reactions, such as antiepileptic agents, antibiotics (e.g., sulfonamides), allopurinol, and NSAIDs (e.g., piroxicam).[141,142] For most agents, the pathogenesis is unknown. However, with sulfonamides and antiepileptics, the cause can be linked to a toxic metabolite that, in predisposed patients with a genetic defect, can bind covalently to proteins and elicit an immune response that causes a cutaneous reaction.[141]

Hypersensitivity syndrome reaction is a multisystem idiosyncratic reaction that manifests as fever, rash, and symptomatic or asymptomatic involvement of internal organ systems (liver, kidney, lungs, spleen, muscles, pancreas, lymph nodes, and blood).[142,143] Reactions usually occur with first exposure to medication, with initial symptoms occurring 1 to 6 weeks after exposure.[141] Aromatic antiepileptic agents (carbamazepine, phenobarbital, phenytoin, primidone) form a toxic metabolite that causes a secondary immune or hypersensitivity reaction.[143,144] Lamotrigine, valproic acid, and ethosuximide are other antiepileptics that may cause reactions. Sulfa drugs (dapsone, sulfasalazine, sulfonamide), allopurinol, and diltiazem also are implicated in hypersensitivity reactions.[143]

Drug rashes are the cutaneous manifestation of drug hypersensitivity. "Red neck" or "red man" syndrome, which is associated with the rapid infusion of vancomycin, is a histamine reaction and not a true allergic reaction. Prolongation of the administration prevents this reaction. β-Lactams and sulfamethoxazole are other common agents that cause rash.[97]

β-lactam antibiotics (most commonly) and sulfamethoxazole are medications known to cause anaphylaxis. The signs and symptoms of this immunoglobulin E–mediated allergic reaction are pruritus, urticaria, cutaneous flushing, hives, angioedema, bronchospasm, nausea, vomiting, diarrhea, nasal congestion, rhinorrhea, laryngeal edema, and hypotension. Several medications are associated with a drug-induced lupus-like reaction. Procainamide, hydralazine, isoniazid, nitrofurantoin, and griseofulvin are some of the agents involved.[97,141] Determination of the reaction is based on symptom resolution with drug discontinuation, absence of idiopathic lupus, development of antibodies, and one clinical symptom of lupus.[141]

Drug-Drug Interactions

The pediatric intensive care physician is confronted daily with potentially hazardous drug-drug interactions in the critical care setting. A potential drug-drug interaction can be defined as "the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone."[145] The ability to recognize every potential drug interaction in the pediatric critical care setting is nearly impossible. Given the extent of polypharmacy that occurs, the potential risk is significant. Of the thousands of documented drug-drug interactions, only a small fraction are clinically significant.[146] The ability to differentiate between clinically significant and insignificant interactions requires an understanding of their mechanisms. In most cases, drug-drug interactions are predictable and preventable with appropriate dosage modifications or avoidance of combinations.

The magnitude of drug-drug interactions is measured by the intensity of the response. Drugs with narrow therapeutic indexes are especially susceptible to drug-drug interactions, because small alterations in exposure can lead to large changes in response. Typically, drugs with large therapeutic indexes are at minimal risk for clinically significant drug-drug interactions.

Drug-drug interactions can occur by three different mechanisms of action: pharmacokinetic, pharmacodynamic, and pharmaceutical. Pharmacokinetic drug-drug interactions can be defined as "interactions which affect a target drug through alterations in their absorption, distribution, metabolism, or excretion; the result may be an increase or decrease in the concentration of drug at the site of action."[145] Pharmacodynamic interactions are defined as interactions at a common receptor site or that have additive or inhibitory effects as a result of actions at different sites.[145] Pharmaceutical interactions or incompatibilities "occur when drugs interact in vitro so that one or both are inactivated."[147]

The ability to distinguish significant drug-drug interactions in the critical care setting is vital to patient care. The following discussion emphasizes the mechanism underlying various drug-drug interactions and identifies clinically significant interactions among therapeutic classes.

Pharmacokinetic Drug-Drug Interactions

The most common and well-studied etiology of drug-drug interactions occurs through pharmacokinetic interactions. Pharmacokinetic interactions can occur throughout the entire pharmacologic spectrum and can potentially affect the absorption, distribution, metabolism, or elimination of the compound of interest. However, drug-drug interactions are only important when they impact the resulting drug exposure to such an extent that the patient experiences an alteration in the expected drug effect, either through diminution of drug effect (when drug exposure is decreased) or through predisposition to adverse effects (when drug exposure is increased). It is important to recognize that the dearth of pharmacokinetic information available for most drugs in children often makes recognition of drug-drug interactions difficult. However, a thorough understanding of the mechanisms behind these interactions can create an index of suspicion that is necessary to identify potential interactions clinically.

Interactions Affecting Drug Absorption (Enteral Absorption)

Several factors determine the rate and extent of oral absorption of drug products. Drug-drug interactions affecting enteral absorption occur through several mechanisms with a common end result: alteration of availability of the drug at its primary site of absorption. The most common mechanisms include adsorption or complexation of the target drug by other drugs or by food, alterations in the ionization of the drug through pH changes, and perturbation of normal GI function (e.g., motility, bacterial colonization, mesenteric blood flow). In the critical care setting, adsorption and complex formation are the most likely causes of decreased enteral drug absorption. Commonly prescribed drugs (e.g., sucralfate and kaolin pectin) are implicated in causing decreased absorption of other drugs by adsorbing target drugs and rendering them unavailable for absorption across the GI barrier.[147a,148,149] Food, especially enteral feeding products, is capable of causing adsorption of drugs. Considerable controversy surrounds the potential for this interaction in the case of phenytoin; the clinical importance of this interaction is still debatable.[150] Although less commonly prescribed in the pediatric setting, tetracyclines and quinolone antibiotics have long been known to cause drug complexes with metallic cations such as iron and calcium, resulting in a decreased effect of both the supplement and the antibiotic.[151,152]

Because only un-ionized drug is available for absorption through the intestinal (or gastric) mucosa, the pH at the site of GI absorption must be considered. In theory, absorption of weakly basic drugs such as penicillins or sulfonamides would be enhanced when given in the presence of concomitant H_2-antagonists or proton pump inhibitors for GI prophylaxis. However, most clinical investigations show this interaction is insignificant.[153-155] Logically, weakly acidic drugs such as phenobarbital would be expected to have reduced enteral absorption under the same circumstances; however, this has not been confirmed clinically.

Alterations in the structure or function of the GI tract are not often the cause for drug-drug interactions but nonetheless are important to consider. Drugs that affect gastric emptying or intestinal transit time can reduce or prolong the residence time of a drug at its site of absorption, potentially altering its systemic availability. Alterations in the normal bacterial flora of the gut can affect the absorption of drugs that are metabolized by these bacteria to active (or inactive) forms. Digoxin is the most common example of a drug whose absorption can be affected through

this mechanism.[156-158] Alterations in mesenteric blood flow potentially could impact the absorption of any drug administered enterally, but this has never been shown clinically. Although controversial, the ability of indomethacin to affect mesenteric blood flow has been cited as a theoretical reason to withhold feeds and enteral drugs in children being treated for patent ductus arteriosus.[159,160]

Interactions Affecting Drug Absorption (Alternative Sites of Absorption)

Drug-drug interactions can occur when drugs are administered by nonenteral routes. A common concern in the intensive care unit setting is "compatibility" of drugs given by the IV route, whether the drugs are to be coadministered in the same IV bag or through common IV access lines. This concept is covered in greater detail in the section on pharmaceutical drug-drug interactions. Theoretically, intramuscular or subcutaneous absorption could be reduced when patients are receiving doses of vasopressor agents necessary to maintain blood pressure, secondary to reduced peripheral blood flow. Finally, it is common practice to instruct patients on combination therapy for asthma to administer β-adrenergic agonists prior to controller medications (inhaled steroids, mast cell stabilizers) because their bronchodilatory effects may help to maximize absorption of the controller medication in the distal bronchial tree. However, an improvement in patient outcome secondary to this approach has never been proven.

Interactions Affecting Drug Distribution (Protein or Tissue Binding)

Because the majority of drugs are bound to plasma proteins or tissue binding sites, the most commonly cited mechanisms for drug-drug interactions affecting distribution are those that involve protein or tissue binding. Several examples exist in which one drug displaces an object drug through competitive inhibition at a protein or tissue binding site. However, in most cases, the impact of the drug-drug interaction is minimal. The amount of free (active) drug may increase temporarily, but the free level falls back to its previous equilibrium as the clearance of drug subsequently increases. Most cases of increased free drug concentrations secondary to protein binding displacement occur when the displacing drug also inhibits the metabolism or excretion of the displaced drug. For example, probenecid not only displaces bound ceftriaxone from albumin binding sites but also inhibits the active secretion of the drug in the kidney, resulting in increased ceftriaxone concentrations.[161] The clinical implications of this interaction are minimal because of the wide therapeutic index for ceftriaxone.

Alterations in Total Body Water

An important mechanism for drug-drug interactions affecting drug distribution that often is overlooked is alteration of body fluid composition. Severe dehydration can be caused iatrogenically, either through fluid restriction or overzealous diuretic use. In these cases, drug concentrations can be increased several-fold, resulting in untoward effects. Conversely, the volume of distribution of drugs can be increased significantly by increasing total body water. This can have the effect of decreasing drug concentrations to subtherapeutic levels. Drugs that distribute primarily in total body water, such as aminoglycosides, are particularly susceptible to these types of effects.[162]

Interactions Affecting Drug Metabolism

The majority of clinically relevant drug-drug interactions can be linked to an alteration in drug metabolism. The two major pathways for drug metabolism in humans are the phase I oxidative pathway and the phase II conjugation reactions. Inhibition or induction of the phase I pathway is the most studied mechanism of drug-drug interactions, especially in relation to the cytochrome P450 system of enzymes. Table 118-5 lists the drugs that affect cytochrome P450 enzymes and those metabolized by the various clinically relevant isoforms. Evaluation of a drug's potential to affect the P450 system is now an integral part of new drug development, and many of the older drugs have been studied extensively, such that these interactions often are predictable in adults. In fact, drug-drug interactions now are exploited clinically in human immunodeficiency virus (HIV) therapy through the use of low-dose ritonavir.[163-165] However, the relative lack of formal pediatric studies makes predicting the impact of a particular interaction difficult in a given child. Factors that must be considered include the state of maturation of the particular isoform and the presence of compensatory pathways. In general, it is reasonable to assume that a reaction that occurs in adults will also occur in children; proper action should be taken as necessary.

One important consideration is timing of drug-drug interactions secondary to P450 enzyme inhibition and/or induction. In general, enzyme inhibition results from competitive inhibition at the enzyme binding site and, therefore, becomes clinically relevant as soon as the offending drug reaches sufficient concentrations in the liver. Consequently, upon discontinuation of the offending drug, enzyme inhibition abates as the drug concentrations fall. Drugs with short half-lives have a relatively short offset of effect, whereas those with longer half-lives can cause significant effects for prolonged periods after discontinuation. In contrast, enzyme induction results from an increase in the amount of enzyme synthesized by hepatic cells. Thus, there is a lag between the time an inducer is introduced and the onset of induction effect. As expected, the offset of effect also is somewhat prolonged.

Because phase II reactions rarely are rate-limiting, their potential to be the cause of clinically significant drug-drug interactions is low. However, the potential does exist for drugs to inhibit conjugation, thus impeding the conversion of object drugs to their inactive metabolites. A classic example is the interaction between high-dose ascorbic acid and acetaminophen. Ascorbic acid competitively inhibits the sulfation of acetaminophen, resulting in accumulation of the glucuronide metabolite.[166]

Interactions Affecting Drug Excretion

The primary means for elimination of drugs or their metabolites is through renal excretion. The process of renal excretion involves three mechanisms: glomerular filtration (GFR), active tubular secretion, and tubular reabsorption. All three mechanisms can be affected by drug-drug interactions.

Alterations in GFR secondary to drug-drug interactions most often result from alterations in renal blood flow. Drugs that act to reduce renal blood flow, such as cyclosporine or NSAIDs, can reduce GFR and thereby increase the blood concentration of drugs eliminated by this route.[35,167-170]

Table 118–5 P-Glycoprotein and Cytochrome P450 Substrates, Inhibitors, and Inducers

	Substrates		Inhibitors		Inducers	
Pgp*	Amiodarone Cimetidine Ciprofloxacin Cortisol Cyclosporine Dexamethasone Digoxin Diltiazem Erythromycin Fentanyl Hydrocortisone Itraconazole Ketoconazole	Levofloxacin Lidocaine Methylprednisolone Morphine Nadolol Octreotide Ondansetron Phenytoin Ranitidine Sirolimus Verapamil	Amiodarone Carvedilol Chlorpromazine Clarithromycin Cortisol Cyclosporine Desipramine Diltiazem Erythromycin Haloperidol Imipramine Midazolam	Nicardipine Nifedipine Ofloxacin Prochlorperazine Propranolol Quinidine Quinine Sirolimus Spironolactone Tacrolimus Verapamil	Amiodarone Cyclosporine Dexamethasone Diltiazem Erythromycin Insulin Midazolam Morphine	Nicardipine Nifedipine Phenobarbital Phenytoin Probenecid Rifampin Tacrolimus Verapamil
CYP1A2	Acetaminophen Caffeine Carvedilol Cisapride Diazepam Haloperidol Levofloxacin Lidocaine	Naproxen Nicardipine Ondansetron Ranitidine R-warfarin Theophylline Verapamil	Caffeine Cimetidine Ciprofloxacin Clarithromycin Diltiazem Erythromycin Grapefruit juice Ketoconazole	Lidocaine Nifedipine Omeprazole Ondansetron Propofol Propranolol Ranitidine Theophylline	Carbamazepine Pantoprazole Insulin Lansoprazole Nafcillin Omeprazole	Phenobarbital Phenytoin Rifampin
CYP1E2	Acetaminophen Enflurane Halothane	Isoflurane Methoxyflurane Sevoflurane		Isoniazid		
CYP2C9	Caffeine Carvedilol Cisapride Dextromethorphan Diazepam Diltiazem Fluconazole Indomethacin Lansoprazole Montelukast Naproxen Nicotine	Ondansetron Pantoprazole Phenobarbital Phenytoin Propofol Quinidine S-warfarin Theophylline Valproic acid Verapamil Voriconazole Zafirlukast Omeprazole	Chloramphenicol Cimetidine Diltiazem Fluconazole Ibuprofen Indomethacin Itraconazole Ketoconazole Lansoprazole Metronidazole Nifedipine	Omeprazole Phenobarbital Phenytoin Probenecid Propofol Propranolol Sulfonamides Trimethoprim Verapamil Voriconazole	Carbamazepine Phenobarbital Phenytoin Rifampin	
CYP2C19	Cisapride Diazepam Fluconazole Ibuprofen Indomethacin Lansoprazole Metoprolol Omeprazole Pantoprazole	Phenobarbital Phenytoin Propofol Propranolol Ranitidine R-warfarin Verapamil Voriconazole	Cimetidine Diazepam Felbamate Fluconazole Indomethacin Ketoconazole	Lansoprazole Omeprazole Voriconazole	Carbamazepine Phenobarbital Phenytoin Prednisone Rifampin	
CYP2D6	Acetaminophen Amphetamine Caffeine Captopril Carvedilol Chlorpheniramine Codeine Dextromethorphan Diltiazem Fentanyl Hydrocodone Lidocaine Loratadine Meperidine	Methadone Methamphetamine Metoprolol Morphine Nelfinavir Nevirapine Omeprazole Ondansetron Oxycodone Propofol Propranolol Ranitidine Theophylline	Amiodarone Chlorpheniramine Cimetidine Cisapride Codeine Dextromethorphan Diltiazem Haloperidol Ketoconazole Lansoprazole Lidocaine Methamphetamine	Methylphenidate Metoprolol Nicardipine Omeprazole Ondansetron Oxybutynin Propofol Propranolol Quinidine Ranitidine Verapamil	Carbamazepine Dexamethasone Ethanol Phenobarbital	Phenytoin Rifampin

Continued

Table 118–5 P-Glycoprotein and Cytochrome P450 Substrates, Inhibitors, and Inducers—Cont'd

	Substrates		Inhibitors		Inducers	
CYP3A4	Alfentanil Alprazolam Amiodarone Amlodipine Atorvastatin Carbamazepine Clarithromycin Cisapride Citalopram Cyclophosphamide Cyclosporine Dapsone Dexamethasone Diazepam Diltiazem Dofetilide Doxorubicin Erythromycin Ethinyl estradiol Etoposide Felodipine Fentanyl Fluconazole Imatinib Ifosfamide Itraconazole Ketoconazole Lidocaine Loratadine	Losartan Methadone Methylprednisolone Miconazole Midazolam Montelukast Nefazodone Nimodipine Nisoldipine Pioglitazone Prednisolone Quetiapine Rifabutin Sertraline Sildenafil Simvastatin Sirolimus Tacrolimus Testosterone Theophylline Triazolam Verapamil Vinblastine Vincristine Voriconazole R-warfarin Zolpidem	Clarithromycin Cyclosporine Diltiazem Erythromycin Ethinyl estradiol Fluvoxamine Grapefruit juice Isoniazid Itraconazole	Ketoconazole Methylprednisolone Metronidazole Nefazodone Norethindrone Prednisone Verapamil Voriconazole	Barbiturates Carbamazepine Dexamethasone Griseofulvin	Phenytoin Primidone Rifabutin Rifampin

*Several drugs are listed as both P-glycoprotein (Pgp) inhibitors and inducers because their effects on Pgp expression can be concentration or duration related.

Conversely, drugs that improve renal blood flow could increase GFR and decrease plasma concentrations of drugs eliminated through the kidneys. As its name implies, active tubular secretion is an active process whereby drugs bind to receptors and are transported across the tubular cells to be excreted. Drugs that compete for these binding sites may inhibit the secretion of other drugs, causing increased concentrations. The two most commonly cited inhibitors of active tubular secretion are probenecid (inhibits the site for weak acids such as penicillin) and cimetidine (inhibits the site for weak bases such as procainamide). These reactions are rarely of clinical significance, although the probenecid–penicillin interaction has been used therapeutically to increase penicillin serum concentrations.[171-174] Tubular reabsorption is a passive process whereby drugs are reabsorbed into the systemic circulation from the lumen of the distal tubules. As with enteral absorption, only un-ionized molecules are available for reabsorption. Therefore drugs that alter the pH of the urine have the potential to alter tubular reabsorption of other drugs. A common example is phenobarbital, a weakly acidic drug. In overdose situations, sodium bicarbonate is administered to alkalinize the urine in the hopes that phenobarbital will become more ionized in urine, resulting in reduced tubular reabsorption and more rapid excretion. However, the effectiveness of this practice is not clear.[175]

Interactions Affecting P-Glycoprotein Receptors

Research in the oncology field has led to the identification of an important drug transporter that is ubiquitous throughout the human body, namely, P-glycoprotein (Pgp). Pgp can be found in renal tubule cells, hepatic cells, in the blood-brain barrier, and in mucosal cells of the intestines, the pancreas, and adrenal glands. Table 118-5 lists drugs that are inhibitors and/or substrates for Pgp. In general, Pgp is believed to serve a protective function by transporting molecules out of the body or, in the case of the blood-brain barrier, out of the CNS. This is manifested in the gut by Pgp-mediated secretion of molecules back into the intestinal lumen after absorption, in the kidney by active tubular secretion, in the liver by active secretion into the bile, and in the CNS by active removal of molecules out of the CNS. Those drugs that inhibit Pgp are expected to increase the concentrations of substrates (either in plasma or the CNS). To date, few clinically relevant interactions have been identified because of the relatively low inhibitory activity of most known drugs. However, because of their ability to aid in the treatment of multiply drug-resistant carcinomas, potent Pgp inhibitors are being developed and will be used therapeutically in the near future.[176,177]

Pharmacodynamic Drug-Drug Interactions

A pharmacodynamic drug-drug interaction can be defined as the combination of two or more drugs with additive, synergistic, or antagonistic pharmacodynamic effects. Additive pharmacodynamic interactions occur routinely when two or more drugs of the same class are given in combination, as in the case of antihypertensive medication or anticonvulsants. A synergistic interaction occurs when the combination of two drugs has an effect greater than the sum of their individual effects. One example of a clinically relevant synergistic interaction is the

use of aminoglycosides in combination with β-lactam antibiotics. In theory, combining a cell-wall active agent (β-lactam antibioitic) with an agent that inhibits bacterial protein synthesis (aminoglycoside) can achieve a greater antibiotic effect than the sum of the two individual effects. Although difficult to prove clinically, in vitro and animal studies have validated this theory.[178-180] Most antagonistic drug-drug interactions are more appropriately defined as pharmacokinetic interactions because they result from some alteration in drug concentrations, either in plasma or at the effect site. Antagonistic interactions that are truly pharmacodynamic in nature most often result from competitive inhibition at the receptor site for drug activity. Use of flumazenil to reverse benzodiazepine-induced sedation is an example of an antagonistic pharmacodynamic drug-drug interaction used clinically.[181,182,183]

Drug-Drug Interactions in Intravenous Admixtures

Parenteral administration of drug therapy poses a potential source of drug-drug interactions in the pediatric/neonatal intensive care unit. In this scenario, polypharmacy arising from an extensive problem list and limited IV access conspire to force the mixing of various drug solutions. However, disparate physicochemical properties and varying administration times preclude the indiscriminate admixing of numerous drugs into a single parenteral aliquot. In practice, both intermittently scheduled drugs and continuous infusions are often given concurrently at the Y-site of intravenous tubing, via different lumens in the same IV line, or through a different IV access altogether. This drug delivery strategy helps to reduce the contact time among different drug, electrolyte, and/or nutrient solutions. The majority of infusions require 15 to 60 minutes, a time frame in which most drugs will remain stable when they are infused with other drugs. Infusion of drugs with known incompatibilities could have serious consequences when administered to the patient. Introduction of a precipitate to venous circulation could produce adverse effects such as phlebitis and pulmonary embolism.[184] Admixing of IV drug solutions may lead to incompatibilities that could have serious consequences when administered to the patient. Factors influencing the coadministration of drugs include a limited number of IV access sites, an extensive drug therapy regimen, time constraints, and the need to administer other lengthy infusions (e.g., blood products).

Incompatibilities result from chemical reactions that may or may not be visible. Physical incompatibilities are easily identifiable because they illustrate any one of the following visual phenomena: precipitation, complexation, turbidity, color change, evolution of gas, or separation of the solution into distinct immiscible layers.[185] On the other hand, instability occurs when a mixture of drug solutions chemically reacts to yield a different species or degradation product, either of which could be pharmacologically inactive or even toxic. The rate at which these reactions occur adds another variable in determining whether or not two drug solutions can be infused together and for what duration. Generally, incompatibility is defined as a 10% decomposition of one or more components in an admixture in less than 24 hours.[185] Drug solutions typically are pH-buffered to optimize the solubility of the drug. Admixing solutions may alter the pH of the chemical environment and result in inactivation or visually ascertained incompatibilities such as precipitation. Reduction-oxidation reactions among incompatible drugs may lead to activation or generation of a toxic molecule. Salting out of drugs occurs when nonelectrolytes and weakly hydrated ions are exposed to strong electrolyte solutions. Chelation of drugs in incompatible admixtures can lead to inactivation or formation of insoluble complexes.

Drug-Drug Interactions by Therapeutic Class

As opposed to many other classes of drugs, the most common mechanism of cardiovascular drug-drug interactions results through alterations in pharmacodynamics. The potential for two drugs to act upon the same receptor subtype sets the stage for pharmacodynamic interactions, which can be antagonistic, additive, or synergistic in nature.

Cardiovascular Agents

Sympathomimetic amines (epinephrine, norepinephrine, phenylephrine, dopamine, dobutamine, ephedrine, and isoproterenol) are particularly susceptible to pharmacodynamic drug-drug interactions. The extent and significance of these interactions depend upon the selectivity of both the object drug and precipitant drug for adrenergic receptor types. β-adrenergic antagonists generally antagonize the cardiac and bronchodilating effects of the sympathomimetics.[70] However, propranolol and other nonspecific β-adrenergic antagonists (Table 118-6) may enhance the vasoconstriction produced with epinephrine. As a result, the patient may experience hypertension and bradycardia.[79,80] Labetalol possesses both α_1-adrenergic and nonspecific β-adrenergic antagonistic activity, which produces an increase in diastolic blood pressure and a decrease in heart rate when given during an epinephrine infusion.[79,80] Metoprolol and possibly other β_1-cardioselective antagonists have minimal effects on the pressor response when given concomitantly with epinephrine.[79,80] Other classes of drugs can interact with the sympathomimetics. α-adrenergic antagonists (e.g., phentolamine), when added to a regimen containing a sympathomimetic, reduce vasoconstriction and attenuate the increase in blood pressure.[70] Tricyclic antidepressants (e.g., imipramine) tend to increase the vasopressor response to sympathomimetics such as epinephrine and norepinephrine and catecholamines such as phenylephrine. The effect has been shown to produce severe and persistent hypertension in patients receiving phenylephrine.[70,79,80] Ergot alkaloids may potentiate the

Table 118–6 β-Blocker Receptor Selectivity

β-Blocker	Selectivity
Atenolol	β_1
Esmolol	β_1
Labetalol	None
Metoprolol	β_1
Nadolol	None
Pindolol	None
Propranolol	None
Sotalol	None
Timolol	None

Modified from Hoffman BB: Adrenoreceptor-activating and other sympathomimetic drugs. In Katzung BG, editor: *Basic and clinical pharmacology,* Stamford, CT, 1998, Appleton & Lange.

vasopressor effects of sympathomimetics with pronounced α-adrenergic activity (e.g., epinephrine, norepinephrine, phenylephrine).[70,79,80] Antihistamines (diphenhydramine) and tricyclic antidepressants tend to inhibit tissue uptake of epinephrine and norepinephrine. They also can increase adrenoreceptor sensitivity to epinephrine.[70]

General anesthetics (e.g., sevoflurane) and halogenated hydrocarbons (e.g., halothane) tend to increase cardiac irritability and sensitize the myocardium to the arrhythmogenic effects of sympathomimetics. Tachycardia and arrhythmias (ventricular premature contractions and fibrillation) are reported with concurrent administrations.[70] Atropine also tends to block the reflex bradycardia produced by epinephrine, norepinephrine, and phenylephrine. This effect in turn augments the pressor response.[70] Finally, concurrent administration of dopamine and intravenous phenytoin (fosphenytoin) produces hypotension and bradycardia in case reports and animal studies. Cardiovascular status should be monitored closely when these medications are given concomitantly.[79,80]

The pharmacologic effect of vasodilators, such as sodium nitroprusside, minoxidil, hydralazine, and diazoxide, are augmented by both β-adrenergic antagonists and diuretics. The decreased systemic vascular resistance and resultant reduction in mean arterial pressure provide stimuli for a compensatory increase in sympathetic nervous system activity. Normalization of blood pressure to the set point then is mediated by an increase in cardiac contractility, increased heart rate, and stimulation of the renin-angiotensin-aldosterone (RAA) pathway. β-Adrenergic antagonists prevent this sympathetic outflow and thereby enhance the vasodilator and hypotensive response. Diuretics also block the compensatory sodium retention from the RAA pathway and thereby reduce the increase in mean arterial pressure that would have been produced from plasma volume expansion.[186] Caffeine, on the other hand, increases renin secretion.[187] Caffeine may attenuate the hypotensive response to vasodilators. The combination of sodium nitroprusside and sildenafil may produce additive hypotensive effects. Studies have shown sildenafil to be effective in treatment of pulmonary hypertension and chronic lung disease in pediatric and neonatal critical care.[138,188] The increased use of this medication, especially in cardiac patients, has necessitated heightened surveillance of potential interactions. Contact between sodium nitroprusside molecules and erythrocytes or the vascular wall results in generation of nitric oxide. Nitric oxide subsequently stimulates the cyclic guanosine monophosphate (cGMP) second messenger system in vascular smooth muscle upon activation of soluble guanylyl cyclase. The molecular process of increasing intracellular concentrations of cGMP translates to vasodilation and the resultant physiologic effect of reduced blood pressure. Sildenafil augments the response to cGMP through selective inhibition of type 5 phosphodiesterase, the enzyme that catalyzes degradation of cGMP. Therefore sildenafil can react similarly with other drugs (nitroglycerin, hydralazine) that promote the generation of a nitric oxide species. However, preliminary animal studies suggest that concomitant administration of sildenafil with nitroglycerin does not result in a dose-reducing effect for nitroglycerin. Sildenafil is metobolized by the cytochrome P450 3A4 enzymes which causes significant interaction potential with CYP3A4 inhibitors. Concentrations of sildenafil have been increased by as much as 182% when combined with erythromycin.[189] It is recommended to monitor patients closely for increased hypotensive effects of sildenafil if concomitant administration of CYP3A4 inhibitors, such as macrolides, cimetidine, or azole antifungals, cannot be avoided. Although the mechanism of action is unclear, concomitant administration of indomethacin with hydralazine may reduce the hypotensive effect of hydralazine.[190]

The antiarrhythmic drugs amiodarone, disopyramide, and quinidine are substrates for the CYP3A4 isoform of the P450 enzyme system. Plasma levels of these antiarrhythmics may increase and produce adverse effects when combined with CYP3A4 inhibitors such as the macrolide antibiotics (clarithromycin, erythromycin, azithromycin), the azole antifungals (fluconazole, itraconazole, ketoconazole, voriconazole), and other miscellaneous inhibitors such as cyclosporine, the calcium channel blockers (diltiazem and verapamil), and grapefruit juice. Conversely, plasma levels decrease when therapy is combined with drugs that are known enzyme inducers, including phenobarbital, carbamazepine, phenytoin, oxcarbazepine, primidone, and rifampin. The antiarrhythmic drugs flecainide, mexiletine, and propafenone are substrates for CYP2D6. Concomitant therapy with enzyme inhibitors of CYP2D6, including amiodarone, cimetidine, diphenhydramine, fluoxetine, paroxetine, haloperidol, propafenone, and quinidine, could result in toxicity.[79,80]

As a substrate for Pgp, digoxin exhibits reduced renal and nonrenal clearance when a Pgp inhibitor is added to the drug regimen. The plasma levels of digoxin may double or quadruple, demanding close monitoring for digoxin toxicity. Pgp inhibitors include amiodarone, clarithromycin, cyclosporine, diltiazem, erythromycin, ketoconazole, itraconazole, propafenone, quinidine, and verapamil.[79,80]

Pharmacodynamic interactions with drugs that modulate atrioventricular (AV) nodal conduction may produce clinically significant adverse effects, which include heart block, bradycardia, and other arrhythmias. Concurrent therapies with the antiarrhythmic agents, calcium channel antagonists, and β-adrenergic antagonists should be monitored closely or even reevaluated.[191] Patients with severe electrolyte imbalances may be susceptible to digoxin toxicities. Hypokalemia, hypomagnesemia, and hypercalcemia are all conditions that may be drug-induced. Therefore, drugs may interact with digoxin in an indirect manner through alteration of electrolyte homeostasis. The loop diuretics, thiazide diuretics, amphotericin B, corticosteroids, laxatives, and sodium polystyrene sulfonate may contribute to digoxin toxicity.[70]

Calcium channel antagonists have been implicated in several common pharmacokinetic drug-drug interactions involving the CYP3A substrates. In addition, inhibitors of CYP3A can cause significant interactions with calcium channel antagonists. These interactions can lead to lower diastolic blood pressure, higher heart rates, and other vasodilation-related side effects.[192-196] Inducers of CYP3A4 are implicated in the reduced efficacy of calcium antagonists.[191] Droperidol affects cardiac repolarization, prolongs the QT/QTc interval, and, when concurrently administered with calcium channel antagonists, increases the risk of QT/QTc prolongation, torsades de pointes, and cardiac arrest.[197] Concomitant administration of fentanyl and nicardipine can result in severe hypotension.[198] Awareness of potential drug-drug interactions is necessary when administering calcium channel antagonists.

β-Adrenergic antagonists are associated with a variety of pharmacodynamic and pharmacokinetic drug-drug

interactions. Concomitant use of a β-adrenergic antagonist and verapamil or diltiazem can result in additive negative inotropic effects and can potentiate conduction abnormalities.[199,200] Abrupt withdrawal of clonidine when concomitantly used with an β-adrenergic antagonist can exaggerate rebound hypertension symptoms associated with clonidine withdrawal.[201-203] The probable mechanism of this interaction is unopposed α-adrenergic agonism. Use of amiodarone with β-adrenergic antagonists potentates bradycardia, sinus arrest, and AV block.[198] Fentanyl anesthesia in combination with β-adrenergic antagonists and calcium channel antagonists has been noted to cause hypotension.[198a]

Angiotensin-converting enzyme inhibitors have been implicated in a variety of drug-drug interactions. Electrolyte disturbances are a major source of complications with these drug-drug interactions. Potassium-sparing diuretics (spironolactone) in combination with ACEIs cause increases in serum potassium levels.[204] Nesiritide, a medication often used to treat decompensated heart failure, can suppress the renin-angiotensin-aldosterone system; therefore, it is important to monitor patients for severe hypotension when concurrently administering this medication with ACEIs.[205]

Loop diuretics induce hypokalemia and hypomagnesemia and, when administered concomitantly with droperidol, may precipitate QT prolongation.[197] In addition, furosemide may produce digitalis toxicity when administered concurrently with digitalis therapy through this same mechanism.[141,207] There is increased risk for nephrotoxicity and ototoxicity when furosemide and aminoglycosides are administered concurrently.[208]

Anticonvulsant Medications

The antiepileptics constitute a drug class that has the potential to be involved in a large array of drug-drug interactions. These interactions are mainly pharmacokinetic in nature and usually involve induction, inhibition, or competition among substrates for various isoforms of the cytochrome P450 enzyme system. Fortunately, these drugs typically are monitored using blood concentrations. Appropriate therapeutic drug monitoring can aid in the avoidance of adverse events secondary to drug-drug interactions. Table 118-5 lists the isoforms for which the various antiepileptics are substrates, inducers, or inhibitors.

In the intensive care unit setting, phenytoin is generally administered intravenously in the form of the water-soluble prodrug, fosphenytoin. Phosphatases in red blood cells and the liver catalyze the conversion of fosphenytoin to its active form phenytoin. Fosphenytoin generally has a serum half-life of 8 to 15 minutes.[209] Once fosphenytoin is converted to phenytoin, it is susceptible to all of the potential drug-drug interactions that affect orally administered phenytoin. Approximately 95% of phenytoin is metabolized in the liver by the CYP2C9/10 and CYP2C19 isoforms of the cytochrome P450 enzyme system to produce the inactive hydroxylated metabolite parahydroxyphenylhydantoin.[209] The CYP2C9/10 isoform is the main pathway of metabolism for this drug. Phenytoin metabolism is reduced and plasma levels increased via competition with other drugs that are substrates for CYP2C9 and CYP2C19, such as amiodarone, fluconazole, valproic acid, omeprazole, and fluoxetine. Conversely, phenytoin may competitively inhibit the metabolism of these drugs. Drugs that inhibit CYP2C9 reduce clearance of phenytoin and consequently increase plasma concentrations.[210] Examples include fluconazole, ketoconazole, cotrimoxazole, amiodarone, and valproate. Omeprazole, cimetidine, and fluoxetine are inhibitors of CYP2C19 and thus can increase phenytoin plasma concentrations.[210] In addition to serving as a substrate to CYP2C9/10 and CYP2C19, phenytoin can induce their activity. Moreover, phenytoin induces CYP3A4 and uridine diphosphate glucuronosyl transferase (UGT) activity.[209] It may take 1 to 2 weeks for maximum induction of these enzymes when phenytoin therapy is started and, conversely, the same amount of time for deinduction once the drug is discontinued.[210] Phenytoin exhibits a high degree of protein binding (≥90%) to serum proteins, mainly albumin, so displacement from its binding sites may produce clinically significant changes in free phenytoin concentration.[209] The free fraction is the pharmacologically active portion of the total phenytoin concentration in plasma. Populations in whom increased proportion of free drug may be found include neonates, patients with uremia, hyperbilirubinemia, or hypoalbuminemia, and/or patients taking concurrent anionic drugs and metabolites.[209,211,212] During the hospital course of critically ill children who experienced traumatic head injuries, protein binding and phenytoin metabolism are altered.[213] The free fraction of phenytoin may increase over time in patients with acute head injury.[214] Such a clinical condition makes this particular population of patients especially susceptible to potential protein displacement interactions with other highly protein-bound drugs, such as valproic acid. The potential clinical significance of this interaction is an increased risk for phenytoin toxicity.

Phenobarbital is a substrate for CYP2C9, CYP2C19, and CYP2E1. The CYP2C19 isoform serves as the primary pathway for metabolism.[209] Phenobarbital is converted to 5-p-hydroxyphenyl-5-ethyl-barbituric acid, an inactive species, and further conjugated with glucuronic acid or sulfuric acid for excretion in urine.[209] Phenobarbital has the potential to induce CYP2C9 and CYP3A4 enzymes.[215] The time frame for induction and deinduction of the P450 enzyme system depends upon phenobarbital's half-life, with induction beginning 1 week after initiating phenobarbital therapy and deinduction beginning 1 week after phenobarbital is discontinued. Maximum induction occurs in approximately 2 to 3 weeks. Phenobarbital also induces UGT.[210] Addition of phenobarbital or phenytoin to a regimen of methadone, which may be used in the intensive care unit for the purpose of weaning from long-term opiate sedation, may present a potential for significant drug-drug interaction. Induction of CYP2C9 and CYP3A4 leads to increased clearance of methadone. The reduced plasma concentration of methadone could result in signs of methadone withdrawal. In transplant patients, phenobarbital may reduce cyclosporine concentrations, which may lead to concerns regarding adequate immunosuppression. Another significant drug interaction involves the abrupt withdrawal of phenobarbital in a patient maintained on both phenobarbital and warfarin. In such a scenario, blood levels of warfarin may increase and lead to increased risk of bleeding. During maintenance of such a regimen, phenobarbital induces the same enzymes responsible for warfarin metabolism. As a result, warfarin dosing is adjusted based upon phenobarbital-mediated inhibition of the hypoprothrombinemia response.

The main pathway for metabolism of carbamazepine is through the CYP3A4 isoform. CYP1A2 and CYP2C8 also are sites for metabolism but are considered to play lesser roles. It is believed that carbamazepine may also be a substrate for

CYP2C19.[210] Carbamazepine is metabolized to a 10,11-epoxide, which also possesses pharmacologic activity. Carbamazepine may undergo inactivation by hydroxylation and conjugation along another pathway. The 10,11-epoxide is further metabolized to inactive compounds for elimination. Carbamazepine induces CYP1A2, CYP2C9, CYP3A4, and UGT; therefore carbamazepine may reduce the plasma concentrations of drugs that are substrates for these isoforms. Carbamazepine illustrates autoinduction, the induction of its own metabolism through CYP3A4. Autoinduction is apparent in the initial weeks of carbamazepine therapy and doubles its rate of clearance within this time frame. Induction begins within the first week of therapy and maximizes at approximately 3 weeks.[210]

Concomitant therapy with drugs that are substrates, inducers, or inhibitors of the same isoforms involved in carbamazepine clearance changes its plasma concentration. Macrolide antibiotics (e.g., erythromycin, clarithromycin, troleandomycin) inhibit the CYP3A4 enzymes, which results in elevated carbamazepine plasma levels and a consequent decrease in 10,11-epoxide.[210] Calcium channel blockers (especially verapamil and diltiazem) also inhibit CYP3A4 and have similar effects on carbamazepine plasma levels.

Oxcarbazepine undergoes extensive metabolism through the liver to an active metabolite, 10-monohydroxy (MHD). The main pharmacological properties of oxcarbazepine are due to its active metabolite MHD. This antiepileptic medication, oxacarbazepine, is a weak inhibitor of CYP2C19 and strong inducer of CYP3A4/5 isoforms. When oral contraceptives, dihydropyridine calcium antagonists, and cyclosporine are each given concomitantly with oxcarbazepine, decreased drug levels were shown, due to the induction of CYP3A4/5 isoforms.[216]

The isoforms of the P450 enzyme system that metabolize valproic acid include CYP2C9 and CYP2C19, both of which represent minor pathways. The main route of metabolism for valproic acid involves glucuronidation by UGT and β-oxidation.[209] Valproate inhibits drugs that are metabolized by CYP2C9, such as phenytoin and phenobarbital. In addition to being a substrate for UGT, valproic acid inhibits drugs that are metabolized by this enzyme, such as lorazepam and lamotrigine. Felbamate, on the other hand, inhibits β-oxidation, resulting in reduced clearance of valproic acid.[210] Valproic acid also exhibits a high degree of protein binding to plasma albumin (90%), making protein displacement interactions likely with other highly protein-bound drugs.[209]

The main pathway for metabolism of lamotrigine is UGT-mediated glucuronidation. Lamotrigine is capable of inducing its own metabolism, with maximum autoinduction observed within 2 weeks. Autoinduction typically results in a 17% reduction in plasma blood levels.[217] Through their action on UGT, carbamazepine, phenytoin, and phenobarbital reduce plasma concentrations of lamotrigine when given concomitantly. Lamotrigine, on the other hand, reduces valproic acid plasma levels when added to a regimen containing valproic acid. Concentrations may be reduced by as much as 25% in the course of a few weeks.[209] When added to carbamazepine therapy, lamotrigine promotes increases in plasma levels of the 10,11-epoxide active metabolite of carbamazepine.[210]

Antiinfective and Antimicrobial Agents

Antimicrobial agents are commonly used in the intensive care unit to treat patients with serious infections. Some drug-drug interactions involve antimicrobial agents, but most are not clinically significant.[97] Some interactions involve complexation of the antimicrobial, such as quinolones (ciprofloxacin, levofloxacin) binding to multivalent cations (aluminum, calcium, magnesium, iron).[218,219] This interaction can be avoided by administering the drugs at separate times. Ciprofloxacin may interact with theophylline and caffeine, inhibiting their metabolism by the cytochrome P450 system. This interaction does not occur with third generation (levofloxacin) and fourth generation (gatifloxacin, moxifloxacin) quinolones.[219] Cyclosporine levels may be increased with concurrent use of ciprofloxacin. Monitoring of cyclosporine levels or changing to another antibiotic to which the pathogen is susceptible are ways to manage this interaction.

Many drug-drug interactions occur with macrolide antibiotics. Erythromycin may cause interactions through inhibition of the cytochrome P450 enzymes (1A, 3A). Erythromycin may increase serum levels of theophylline, warfarin, carbamazepine, cyclosporine, midazolam, tacrolimus, and hydroxymethylglutaryl coenzyme A reductase inhibitors (e.g., lovastatin, simvastatin, atorvastatin).[135,220,221] Clarithromycin also inhibits cytochrome P450 enzymes and may increase the serum levels of carbamazepine, theophylline, caffeine, cyclosporine, warfarin, valproate, and midazolam.[220,221] Azithromycin is an azalide (macrolide subclass) that does not demonstrate cytochrome P450 complexation, so it has less drug interaction potential. No major drug-drug interactions have been shown with azithromycin and carbamazepine, theophylline, or midazolam.[220] Interactions with cyclosporine and warfarin are limited to case reports, so monitoring of serum levels and international normalized ratio (INR), respectively, is prudent when using this combination.[222]

Rifampin is a cytochrome P450 enzyme inducer that is involved in many drug-drug interactions. Rifampin may decrease serum concentrations of chloramphenicol, isoniazid, amiodarone, cyclosporine, prednisolone, and warfarin.[223,224] These interactions often complicate multidrug regimens for treatment of active tuberculosis.

Antifungal agents are used in the critical care setting for treatment and prophylaxis of systemic mycoses. The majority of drug-drug interactions with antifungals occur within the azole derivatives via inhibition of biotransformation. Azole derivatives inhibit sterol 14-α-demethylase, which is a hepatic microsomal cytochrome P450-dependent system. Unfortunately, this mechanism results in significant drug-drug interactions. Azole antifungals are known inhibitors of cytochrome P450 isoenzymes, although the specific CYP isoforms and potency of inhibition vary among agents.[106,225] Table 118-5 provides a description of cytochrome P450 isoforms inhibited by the azole antifungals. Clinically significant interactions with azoles occur most frequently with agents that have narrow therapeutic windows and are metabolized by cytochrome P450 enzymes. Clinically significant interactions can occur when azole derivatives are administered with CYP3A substrates such as midazolam,[194,225] tacrolimus,[226] sirolimus,[227] cyclosporine,[228] nifedipine,[192] felodipine,[192,229] diltiazem,[227] and alfentanil.[230] Benzodiazepines that rely on the CYP3A4 enzyme for biotransformation are predisposed to drug-drug interactions with CYP3A inhibitors. The benzodiazepines most prone are alprazolam, diazepam, midazolam, and triazolam.[195,231,232] Ketoconazole, a potent inhibitor of CYP3A, increases the area under the concentration–time curve (AUC) of oral midazolam by 16-fold.[195,229,233-236]

Whenever ketoconazole, itraconazole, voriconazole, or fluconazole is administered with midazolam, patients must be monitored for increased response to midazolam and altering the dosage or discontinuing therapy considered. Diazepam metabolism is mediated by CYP3A and CYP2C19 and is also prone to interactions with azole derivatives.[237] Fluconazole and voriconazole have the potential to cause clinically significant drug-drug interactions with compounds that are metabolized via CYP3A, CYP2C9, and CYP2C19; therefore caution should be exercised when administering fluconazole or voriconazole with diazepam. Warfarin is a racemic mixture compound for which most pharmacodynamic activity occurs with the S-isomer, whose metabolism is dependent on CYP2C9, which is inhibited by fluconazole and voriconazole.[227,238] This interaction is significant, and appropriate dosage modifications or alteration of therapeutic agents must be considered. The calcium channel antagonist class is metabolized by CYP3A isoenzymes and has the potential for interactions with azole derivatives.[229] Concomitant use of fluconazole and rifabutin has resulted in rifabutin toxicities from increased serum concentrations because of inhibition of cytochrome P450 isoenzymes.[8] Similar interactions are expected with voriconazole and itraconazole. Azole derivatives increase serum concentration of both phenytoin (after administration of fosphenytoin) and carbamazepine.[238a,239] There is the potential for decreased efficacy of azole derivatives used in combination with rifampin, an inducer of the cytochrome P450 isoenzyme system.[240]

In addition to being CYP3A inhibitors, ketoconazole and itraconazole are substrates and inhibitors of Pgp.[196,241] Drug-drug interactions mediated via Pgp typically are important determinants of bioavailability, liver metabolism, and kidney excretion.[242,243] Thus ketoconazole and itraconazole with dual CYP3A and Pgp inhibition could greatly impact the bioavailability of dual substrate drugs.[196,244] Diltiazem, verapamil, saquinavir, cyclosporine, and tacrolimus are dual CYP3A and Pgp substrates.[59,245] Clearance of digoxin, a Pgp substrate, is decreased with coadministration of itraconazole.[246] An increase in digoxin trough concentration is likely the result of impaired renal tubular secretion via inhibition of Pgp.[246]

Concomitant administration of amphotericin B with cyclosporine, tacrolimus, or aminoglycosides results in increased nephrotoxicity.[247,248] Concomitant use of digoxin and amphotericin B products results in digitalis toxicities attributed to potassium depletion mediated by amphotericin B.[249] Antifungal therapy is associated with a variety of potentially significant drug-drug interactions. Therapeutic drug monitoring is necessary in the critical care setting, but additional awareness is warranted when antifungal agents are being used.

Anesthetic Agents and Sedatives

Several agents are used for anesthesia and sedation in the pediatric critical care setting. Many of these drugs have clinically significant drug-drug interactions. The ability to recognize potential drug-drug interactions related to the use of anesthetic agents or sedatives in the pediatric critical care setting requires a fundamental understanding of the agent's clinical pharmacology. Benzodiazepines are a class of sedatives that are particularly susceptible to drug-drug interactions because of their route of biotrans-formation.[193,194,250] CYP3A4 plays a major role in the metabolism of midazolam, triazolam, and alprazolam, and caution should be exercised when combining these agents with CYP3A modulators.[251-253] As mentioned previously, concomitant use of systemic antifungals and benzodiazepines results in a known clinically significant drug-drug interaction, caused by azole antifungals inhibiting the CYP3A isoenzyme.[193-195,250] Midazolam, a short-acting benzodiazepine used in the pediatric critical care setting, is almost exclusively metabolized via the CYP3A pathway. Interactions are most prominent with oral midazolam therapy because of the role of intestinal metabolism.[193-195] However, significantly increased plasma levels have been observed when intravenous midazolam is administered with fluconazole.[193-195] Additionally, clarithromycin and erythromycin have been proven to significantly decrease systemic clearance of intravenous and oral midazolam.[195,254,255] Azithromycin, another macrolide, does not appear to increase plasma concentrations of oral midazolam.[235] Propofol has been shown to decrease the clearance of midazolam by 37%, possibly by competitive inhibition of CYP3A4.[256] Concomitant administration of verapamil or diltiazem with oral midazolam is associated with dramatic increases in AUC and the maximum concentration (C_{max}).[234] Inducers of CYP3A can drastically decrease plasma concentrations of midazolam. Rifampin, a potent inducer of CYP3A and Pgp expression in the gut mucosa, can cause dramatic decreases in plasma concentrations of oral midazolam.[234,255] Other inducers of CYP3A enzymes implicated in significant interactions with midazolam are carbamazepine and phenytoin.[252] Diazepam, a benzodiazepine with long-acting metabolites, is prone to drug-drug interactions with inhibitors or inducers of CYP2C19 or 3A4. Because the primary route of metabolism for lorazepam is through glucuronidation, this agent is associated with fewer potential pharmacokinetic drug-drug interactions.[231]

The potential for pharmacodynamic drug-drug interactions also exists with the sedative agents. Concomitant use of barbiturates and benzodiazepines causes additive respiratory and CNS depression. This additive mechanism is mediated via allosteric conformational changes at the γ-aminobutyric acid (GABA) site, which regulates the opening of chloride channels, causing the neurons to become hyperpolarized and resistant to excitation.[257] The dosage of midazolam and other benzodiazepines often is reduced by 30% to 50% when they are administered concomitantly with opioid analgesics.[258] Flumazenil competitively inhibits the activity of benzodiazepines at its recognition site on the GABA-benzodiazepine receptor complex.[259] It does not reverse the CNS effects of GABA-mimetic agents such as barbiturates, propofol, and other general anesthetics.[259]

Clonidine, an α_2-adrenergic agonist agent with sedating properties, when used concomitantly with propofol, reduces the induction concentrations required for loss of consciousness.[260] Propofol can inhibit the clearance of alfentanil and act synergistically with opioids.[261,262] Caution should be exercised when using propofol in combination with drugs that lower seizure threshold, such as meperidine and enflurane.[263]

Neuromuscular blocking agents have some significant drug-drug interactions.[264] Concomitant use of intravenous antibiotics such as aminoglycosides or clindamycin has the potential to intensify the neuromuscular blockade produced by neuromuscular blocking agents.[264] Phenytoin has been shown to increase pancuronium requirements. Additionally,

inhalation anesthetic agents can potentiate neuromuscular blockade.[264]

Analgesic Agents

A variety of agents are used for analgesia in the pediatric critical care setting. Patients receiving opioid analgesia are particularly susceptible to drug-drug interactions. Whenever an opiate agonist is administered with an agent that has CNS depressant effects, augmented effects or toxicity are possible. Therefore vigilance in monitoring for drug-drug interactions is necessary when administering these agents to help ensure that safe and effective analgesia is achieved. Analgesic pharmacokinetic drug-drug interactions can mediate clinically relevant effects. CYP3A is involved in the metabolism of methadone and alfentanil.[255] Methadone metabolism is induced by rifampin and results in enhanced clearance of methadone.[266,267] One study of adults demonstrated an approximately fourfold increase in methadone clearance, with methadone clearance ranging from 0.538 L/h/kg when administered with rifampin to 0.126 L/h/kg when methadone was administered alone.[268] This effect could provoke withdrawal symptoms in patients receiving methadone.[266] In addition, phenobarbital, phenytoin, carbamazepine, nevirapine, and efavirenz have the potential to decrease methadone blood concentrations.[269,270] Rifampin significantly lowers alfentanil plasma concentrations by the same mechanism.[255] Inhibition of CYP3A can result in increased plasma levels of methadone.[267] For example, fluconazole inhibits metabolism of methadone[267] and alfentanil.[230] Fluconazole decreased the clearance of alfentanil approximately 58% following intravenous fluconazole administration in healthy adults.[230]

Pharmacodynamic drug-drug interactions can result in synergic effects or antagonism. When a pure opiate agonist and a partial agonist/antagonist are used in combination, there is a risk for decreased clinical effects. For example, morphine (pure μ agonist) and nalbuphine (partial agonist/antagonist) used in combination can result in decreased opiate effect. This can have profound effects on analgesia and result in withdrawal symptoms for patients on long-term analgesia therapy.[271,272] Analgesic opioid therapy is associated with several side effects that can be heightened by drug-drug interactions, such as respiratory depression, hypotension, decreased GI motility, nausea, and vomiting. Use of a pure opioid antagonist, such as naloxone, is needed for reversal of undesirable effects. Most clinically significant drug-drug interactions associated with analgesics are pharmacodynamic in origin.

Anticoagulants

Warfarin is involved in a multitude of drug-drug interactions, including alterations in protein binding, in hepatic metabolism by the cytochrome P450 system, in bacterial flora of the GI tract, and of the clotting cascade (Table 118-7). Aspirin, chloral hydrate, ibuprofen, and sulfamethoxazole can displace warfarin from protein binding sites, making more free fraction of warfarin available and hence augmenting anticoagulation. Warfarin metabolism may be inhibited by amiodarone,

Table 118–7 Medication Interactions that Modify the Anticoagulant Effect of Warfarin

Increased INR	Decreased INR	Increased Risk of Bleeding	Increased Risk of Thrombosis
CYP450 inhibition via 2C9: (unless otherwise noted)	**CYP450 induction via 2C9:** (unless otherwise noted)	**Alterations in platelet function:**	**Alterations in warfarin metabolism or absorption:**
Antidepressants:	Carbamazepine	*Antiplatelet agents:*	Cholestyramine
Fluvoxamine	Phenytoin	Aspirin	Griseofulvin
Sertraline	Phenobarbital	Clopidrogrel	Nafcillin
Antiinfectives:	Rifampin	Ticlodipine	Ribavirin
Azole Antifungals (2C9/3A4)		Cimetidine	Sucralfate
Cotrimoxazole		Fish oil	
Fluoroquinolones (1A2/3A4)		*Antifibrinolytics:*	**Prothrombotic**:
Isoniazid		Alteplase	Estrogens
Macrolides		Streptokinase	OCPs
Metronidazole		Urokinase	Phytonadione
Miconazole		*NSAIDs:*	Total parenteral nutrition
Cardiovascular drugs:		Aspirin	
Amiodarone		Ibuprofen	
Fluvastatin		Indomethacin	
Gemfibrozil		Ketorolac	
Lovastatin		*SSRIs:*	
Simvastatin		Citalopram	
		Sertraline	
		Reduced vitamin K production:	
		Antiinfectives (oral)	
		Omeprazole	
		Miscellaneous:	
		Corticosteroids	
		Levothyroxine	
		Propranolol	

NSAIDs, Nonsteroidal antiinflammatory drugs; *OCP*, oral contraceptive pills; *SSRI*, selective serontonin reuptake inhibitor.

Modified from Hansten PD: Oral anticoagulants and drugs which alter thyroid function, *Drug Intell Clin Pharm* 14:331–334, 1980; Liu A, Stumpo C: Warfarin drug interactions among older adults, *Geriatrics Aging* 10(10):643–646, 2007; and Holbrook AM, Pereira JA, Labris R et al: Systemic overview of warfarin and its drug and food interactions, *Arch Intern Med* 165(10):1095–1106, 2005.

sulfamethoxazole, metronidazole, azole antifungals, macrolide and quinolone antibiotics, and isoniazid, resulting in decreased effect.[272] Phenobarbital, rifampin, and phenytoin can induce the metabolism of warfarin and decrease its effect. Most antibiotics have the potential to decrease synthesis of vitamin K-dependent clotting factors and potentiate warfarin's effect.[272,273] Other medications including NSAIDs and antiplatelet medications can exacerbate the adverse effects of warfarin by directly affecting the clotting cascade. Phytonadione (vitamin K) antagonizes the anticoagulation effect of warfarin.[215] Careful monitoring of bleeding and coagulation parameters (prothrombin time and INR) can help prevent serious adverse drug reactions. Many drug-drug interactions can occur when initiating warfarin therapy or when adding other medications to existing warfarin therapy. Clinically, it is recommended to use adjusted starting doses of warfarin when initiating therapy while patients are receiving medications with the potential for interaction.

Heparin has the potential to interact with other agents that increase the risk of bleeding or thrombosis. Common interactions include oral anticoagulants (warfarin) and platelet inhibitors (e.g., aspirin, dextran, ibuprofen, and other agents that interfere with platelet aggregation). Concurrent administration of heparin and nitroglycerin has been associated with lower aPTT values.[274] More recently, antifibrinolytic agents, which can enhance the anticoagulant effects of heparin, have become one of the primary treatments of larger arterial or intra-atrial clots. Heparin effectiveness can also be altered by the administration of additional clotting factors found in fresh frozen plasma and antithrombin III. Though concomitant anticoagulation with heparin is often indicated with antifibrinolytic agents and blood products, it is important to adjust heparin infusion rates and monitor the patient's response when combining these medications. Agents that may enhance the risk of hemorrhage with enoxaparin include anticoagulants and platelet inhibitors.[275,276] Additionally, medications that adversely affect renal clearance can prolong the elimination half-life of enoxaparin and increase the risk of adverse effects.[277]

Immunosuppressive Agents

Therapeutic agents that modulate the immune system are frequently involved in drug-drug interactions. Most immunosuppressive agents possess narrow therapeutic indexes and therefore require therapeutic drug monitoring.[278] As a result, a sophisticated knowledge of clinical pharmacology is required to evaluate the clinical relevance of potential drug-drug interactions involving these drugs. Drug-drug interactions most commonly encountered with immunosuppressive drug therapy revolve around the inhibition or induction of the CYP3A enzymes. Cyclosporine, tacrolimus, prednisone, and sirolimus, all CYP3A substrates, are most prone to these types of pharmacokinetic drug-drug interactions.[279,280] Cyclosporine is extensively metabolized in the liver and GI tract, which explains its low bioavailability. Known CYP3A inhibitors have been used intentionally to maintain therapeutic levels in patients with high presystemic metabolism of cyclosporine.[281] Medications that inhibit CYP3A metabolism should be used with caution in patients taking cyclosporine, tacrolimus, or sirolimus because of the narrow therapeutic index of these agents; dosing adjustments of immunosuppressive therapy may be required. Erythromycin, clarithromycin, voriconazole, fluconazole, posaconazole, itraconazole, ketoconazole, diltiazem, verapamil, indinavir, and ritonavir inhibit CYP3A metabolism.[191,196,282,283] Concomitant administration of sirolimus and cyclosporine increases sirolimus exposure, likely due to shared CYP3A and Pgp metabolic pathways.[284] Several drugs can induce the metabolism of cyclosporine, tacrolimus, sirolimus, and prednisone. Rifampin causes induction of CYP3A and Pgp,[285] leading to clinically significant decreases in cyclosporine and tacrolimus plasma concentrations.[285,286] Although not considered to be a narrow therapeutic index medication, mycophenolate serum concentrations are affected by concurrent administration with cyclosporine. Cyclosporine decreases enterohepatic recirculation of mycophenolic acid neccesitating higher mycophenolate doses to achieve serum concentrations equivalent to that of the drug given alone or with tacrolimus.[287]

Pulmonary and Respiratory Medications

β_2-Adrenergic agonists (e.g., albuterol, levalbuterol, terbutaline) are useful agents for treatment of asthma. Drug-drug interactions can occur when β_2-adrenergic agonists are used in combination with β_1-adrenergic antagonists, especially the nonselective antagonists. A possible decreased β_2 effect could precipitate asthma symptoms. The nonselective antagonists include propranolol, nadolol, and labetalol (see Table 118-6). Agents such as atenolol, esmolol, and metoprolol are relatively selective for β_1 receptors at usual therapeutic doses and therefore are potentially safer to use in combination with β_2-adrenergic agonists. However, these agents may lose their selectivity at higher doses. One potential side effect of the β_2-adrenergic agonists is hypokalemia, which can be enhanced with concurrent use of loop and thiazide diuretics. Monitoring of potassium levels is recommended when these agents are used concurrently.[215]

Antineoplastic Agents

Administration of a live vaccine (e.g., oral polio virus and measles, mumps, and rubella) should be avoided in patients receiving chemotherapeutic agents. Immunosuppression from chemotherapeutic regimens predisposes a patient to active infection when inoculated with a live vaccine. Severe and fatal infections from the combination are reported.[288] Administration of a live vaccine should not be attempted for at least 3 months after all chemotherapeutic agents are discontinued and the patient is in remission.[289]

Potential drug-drug interactions involving the cytochrome P450 enzyme system can be identified by pinpointing the substrates for the various isoenzymes of the mixed function oxidases among the antineoplastic agents. For example, the vinca alkaloids vincristine, vinorelbine, and vinblastine are substrates for CYP3A4. Known inhibitors and inducers of CYP3A4 increase and decrease plasma levels, respectively. Toxicities are more likely when vinca alkaloids are administered with classic CYP3A4 inhibitors such as the azole antifungals, macrolide antibiotics, calcium channel blockers (e.g., diltiazem and verapamil), quinupristin/dalfopristin, and cyclosporine. The azole antifungals modulate the metabolism of cyclophosphamide, increasing overall parent drug and metabolite exposure. Fluconazole increases the cyclophosphamide AUC by inhibiting CYP2C9 metabolism that leads to formation of the toxic metabolite acrolein, in effect reducing potential adverse drug effects.[290] However, the inhibition of the CYP3A4 metabolic pathway by itraconazole increases

formation of the precursor to the acrolein metabolite, increasing toxicity risk.[291] Antiepileptic drugs that are known inducers of the cytochrome P450 enzyme system may contribute to therapeutic failure with chemotherapeutic agents. In one study of pediatric patients with high-grade glioma, the presence of enzyme-inducing anticonvulsants increased irinotecan clearance.[292]

Multiple drug resistance in cancer cells has been attributed to the expression of a Pgp efflux transmembrane transport protein.[177] This protein offers a potential target for future directed therapies in cancer treatment. Agents that modulate the activity of Pgp currently are under development and may provide a drug interaction that favorably increases the efficacy of antineoplastic agents.[293] Coadministration of etoposide and cyclosporine, for example, results in elevation of the mean AUC of etoposide. Etoposide is a CYP3A4 substrate, whereas cyclosporine is both a CYP3A4 and Pgp inhibitor.[294] Inhibitors of the efflux pump, Pgp, increase the cytotoxicity of the vinca alkaloids, anthracyclines, epipodophyllotoxins, and taxanes.[295] Itraconazole, clarithromycin, verapamil, and cyclosporine are known to inhibit Pgp.[79,80] Currently, attempts to obviate the increased toxicity associated with greater drug exposure due to Pgp inhibition have limited clinical application of these therapies.[79,80,293]

Colony-stimulating factors are often used to treat the ensuing neutropenia that accompanies cancer chemotherapy. Patients with lymphomas undergoing their first cycle of vincristine and receiving treatment with filgrastim or sargramostim are at risk for developing a severe atypical neuropathy. The neuropathy has been described as a severe, sharp, burning pain in the feet and appears to occur more commonly in lymphoma patients receiving this combination than in patients receiving vincristine alone.[296] The mechanism of action of this interaction is unclear.

Methotrexate elimination is governed by the kidneys by both filtration and active secretion. The process of tubular secretion requires both a carrier and energy, finite resources that create a saturable process. Competition among other drugs for secretion may lead to reduced clearance of methotrexate with consequent manifestations of toxicity. Concurrent administration of methotrexate with any of the penicillins (piperacillin, amoxicillin, etc.) has demonstrated this capacity.[46,297,298] The NSAIDs, aspirin, and other salicylates all increase the likelihood of methotrexate toxicity by this same mechanism.[33,298a,299-303] Inhibition of renal prostaglandin synthesis and the resultant reduction in renal perfusion also are suggested to contribute to renal toxicities seen with methotrexate because this drug persists in renal tissue for weeks.[70] Proton pump inhibitors may exhibit another mode of interaction on the level of renal elimination. By inhibiting the transmembrane H^+/K^+-ATPase pump, they may decrease active secretion of methotrexate.[304] The antineoplastic activity of methotrexate stems from its inhibition of dihydrofolate reductase, the enzyme that catalyzes reduction of folic acid to tetrahydrofolic acid. In turn, tetrahydrofolic acid serves as a building block for purine and DNA synthesis. The clinician should be aware of other drugs that act along this pathway (e.g., cotrimoxazole and pyrimethamine) because these agents may contribute to the toxicities associated with methotrexate therapy.[70,305]

References are available online at http://www.expertconsult.com.

VII Chapter 119

Airway Management

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PEARLS

- Safe management of the critically ill child's airway requires an understanding of the anatomic and physiologic changes that occur from birth through adolescence, recognition of congenital and acquired airway abnormalities, appreciation of the pathophysiologic consequences of airway manipulation, and preparation for airways that are potentially difficult to manage.
- Laryngoscopy and intubation are potent physiologic stimuli that are associated with severe discomfort, profound cardiovascular and cerebrovascular changes, and increased airway reactivity.
- Recognizing and preparing to manage a difficult airway are essential for the prevention of potentially lethal complications of intubation.
- The approach to intubation must be tailored to specific circumstances, such as a full stomach, elevated intracranial pressure, cervical spine injury, and upper airway obstruction.
- Alternative approaches to airway management, such as the lighted stylet, laryngeal mask airway, cricothyrotomy, retrograde intubation, and tracheostomy, may be lifesaving.

Accurate assessment and safe management of the airway of a critically ill child is the essential first step in providing effective intensive care. It requires understanding of the anatomic and physiologic changes that occur from birth through adolescence, recognition of congenital and acquired airway abnormalities, appreciation of the pathophysiologic consequences of airway manipulation, and preparation for airways that may potentially be difficult to manage.

Anatomic Considerations

The configuration of the child's airway changes dramatically from birth to adulthood (Figure 119-1). The nose is the site of nearly half of the total respiratory resistance to air flow at all ages. The infant's nose is short, soft, and flat, with small, nearly circular nares. The nasal valve, the narrowest portion of the nasal airway, approximately 1 cm proximal to the alar rim in newborns, measures only about 20 mm^2.[1,2] By 6 months, dimensions of the nares have nearly doubled, but they are still easily occluded by edema, secretions, or external pressure. Although an infant is perhaps not as much the obligate nose breather as commonly assumed, signs of airway obstruction frequently develop when the infant's nose is blocked.[3,4]

In infancy the mandible is small and the basicranium (which provides the roof of the nasopharynx) is flat, creating a small oral cavity. Over the years of its development, the jaw grows primarily down and forward, with the ramus increasing in height and width. The posterior portion of the basicranium develops a progressively more rounded configuration through childhood, which results in a larger nasal airway to meet the need for increased air flow (and provides a chamber for the resonance of adult speech).

Under normal conditions, the genioglossus muscle and other muscles of the pharynx and larynx help maintain airway patency. Both tonic and phasic inspiratory activity synchronized with phrenic contraction have been noted in animal and human studies. In particular, the genioglossus increases the dimensions of the pharyngeal airway by displacing the tongue anteriorly.[5] In the infant and young child, the tongue is large relative to the bony structures surrounding it and the cavities they form. Relatively little displacement is possible at any time, and loss of tone during sleep, sedation, or central or peripheral nervous system dysfunction is more likely than in older patients to allow the tongue to relax into the posterior pharynx and cause upper airway obstruction.

The infant larynx is high in the neck at birth, with the epiglottis at the level of the first cervical vertebra and overlapping the soft palate. This approximation of structures, in combination with the relatively large tongue and small mandible, probably contributes to the vulnerability to airway obstruction in infants and young children. By 6 months the epiglottis has moved to about the level of the third cervical vertebra and is separate from the palate. It continues to descend to its adult position at about the fifth or sixth cervical vertebra by early adolescence. The infant epiglottis is soft and omega shaped, in contrast with the more rigid, flatter adult structure, and it has greater potential to occlude the airway. The immature larynx is funnel shaped, with the subglottic portion angled posteriorly relative to the supraglottic portion rather than forming a straight vertical column, as seen in adults. The larynx tapers to the cricoid cartilage, the narrowest point in the child's extrathoracic airway.

The internal dimensions of the trachea in a newborn are approximately one third those of an adult, and absolute

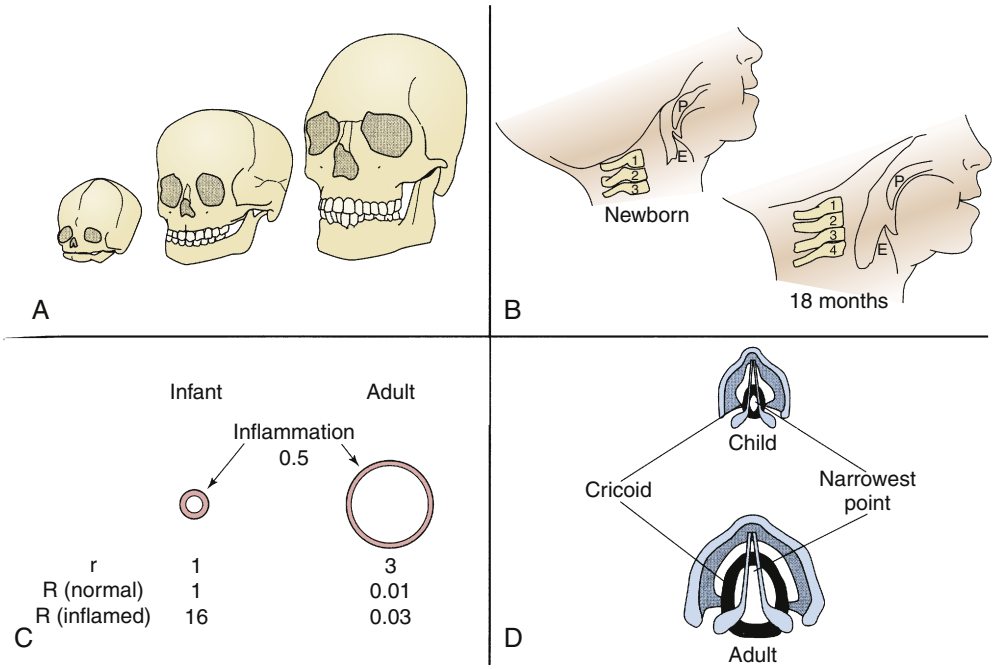

Figure 119–1. Characteristics of the pediatric airway. **A,** Changes in mandibular shape from infancy through adolescence. **B,** The epiglottis is initially cephalad in infancy, then descends throughout childhood. *E,* Epiglottis; *P,* palate. **C,** Edema has a much greater effect on airways resistance in the young child than later in life. *r,* Relative radius of the trachea; *R,* relative airways resistance. **D,** The cricoid is the narrowest portion of the airway until age 8 to 10 years.

resistance to air flow is higher in newborns than in older children and adults. Because the most important factor determining resistance (R) is the radius (r) of an airway (R proportional to 8 l/r^4), small changes in airway diameter in infants or young children as a consequence of edema or secretions have a far greater effect on resistance than similar changes in larger patients (see Figure 119-1).

Basic Airway Management

Airway management depends on a brisk assessment of the patient's breathing and knowledge of the likely progression of the airway problem, that is, deterioration versus improving function. In virtually any setting in which respiratory difficulty is suspected, oxygen should be administered until the specific abnormality can be identified and adequately treated. Although extreme hypercarbia usually is well tolerated, hypoxia is routinely catastrophic and is not necessarily obvious on initial examination. From the alveolar air equation, it is obvious that hypercarbia produces hypoxia at low fraction of inspired oxygen (Fio_2) (Table 119-1). If the patient is breathing spontaneously, attention is directed first to signs of upper airway obstruction, including absence of audible or palpable air flow, stertorous sounds, stridor, or a rocking chest and abdominal motion rather than the normal, smooth rise and fall that should occur with inspiration and expiration.

An alert child with normal neuromuscular function usually instinctively assumes a body position that minimizes upper airway obstruction. However, a child with an altered level of consciousness or severe neuromuscular weakness may be unable to maintain a patent airway because of the inability to alter his or her position or maintain adequate glossopharyngeal muscle tone.

Table 119–1 Impact of Providing Supplemental Oxygen During Hypercarbia on Alveolar Oxygen Tension

Alveolar gas equation:	$P_{AO_2} = Fio_2 (PB - P_{H_2O}) - Paco_2/0.8$
Room air, normocarbia:	$P_{AO_2} = 0.21 (760 - 47) - 40/0.8 = 99$ mm H_2O
Room air, hypercarbia:	$P_{AO_2} = 0.21 (760 - 47) - 80/0.8 = 50$ mm H_2O
Supplemental O_2, hypercarbia:	$PA_{O_2} = 0.4 (760 - 47) - 80/0.8 = 185$ mm H_2O

Fio_2, Fraction of inspired oxygen; *P_{AO_2},* partial pressure of oxygen, alveolar.

Nasopharyngeal Airway

A nasopharyngeal airway that extends through nasal passages to the posterior pharynx and beyond the base of the tongue often is adequate to relieve obstruction and is tolerated by most patients, even those who are conscious (Figure 119-2). An appropriate-size airway extends from the nares to the tragus of the ear and is of the largest diameter that passes through nasal passages without causing blanching of the skin surrounding the nares. The airway tube should be well lubricated before placement. Risks of nasopharyngeal airways include nasal ulceration, bleeding, laceration of friable lymphoid tissue, rupture of a pharyngeal abscess, laryngospasm, and potential passage through the cribriform plate in patients with basilar skull fractures. Topical vasoconstricting agents reduce but do not eliminate the risk of bleeding. Like other nasal tubes, use of nasal airways increases the risk of sinusitis;

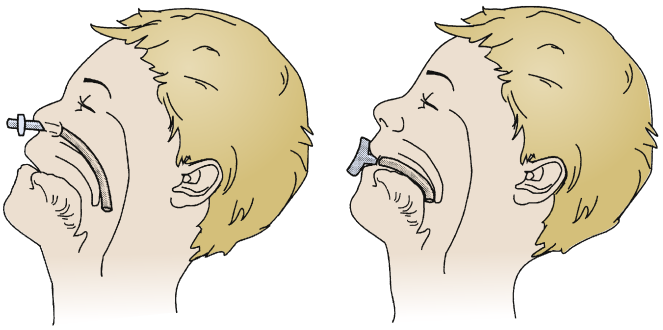

Figure 119–2. Nasopharyngeal and oropharyngeal airways in good position.

therefore, contraindications to their use include severe coagulopathy, cerebrospinal fluid (CSF) leaks, and basilar skull fractures.

Oropharyngeal Airways

Oropharyngeal airways displace the base of the tongue from the posterior pharyngeal wall and break contact between the tongue and palate (see Figure 119-2). Size selection is important. An excessively long airway may encroach upon the larynx and cause laryngospasm. An airway that is too short may actually push the tongue posteriorly and exacerbate obstruction. If the airway is held at the side of the face with the flange just anterior to the incisors, the tip should be at or near the angle of the mandible. The airway should be positioned following the curve of the tongue while the tongue is held down and forward with a tongue depressor. Inserting the airway with its concave side facing the palate and then rotating it may traumatize the oral mucosa or damage teeth. Oral airways are poorly tolerated in any patient with a functional gag reflex and may induce vomiting. As a consequence, they are of little more than temporary value in the critically ill child. They may support a patent airway for bag-valve-mask ventilation in preparation for intubation.

Oxygen Delivery Devices

Nasal Cannulas

Nasal cannulas consist of two hollow prongs projecting from a hollow face piece. Humidified oxygen (100%) flows from a standard source, effectively delivering a pharyngeal concentration of 25% to 40% after mixing with variable amounts of room air. The cannulas are easy to use, often readily tolerated, lightweight, economical, and disposable and take advantage of the humidifying properties of the nasopharynx. Flow typically is limited to only 3 to 5 L/min because of the extent to which relatively dry gas flow cools and dries the nasal airway. The use of nasal cannulas is limited by the relatively low oxygen concentration that can be delivered. High-flow nasal cannulas can deliver up to 40 L/min of warmed, humidified gas and are generally very well tolerated, although the noise level for the patient can be high. The oxygen concentration delivered is higher than with simple nasal cannulas. High-flow nasal cannulas generate positive distending pressure similar to that provided by nasal continuous positive airway pressure. The pressure generated is dependent on the interaction among the flow rate, patient size, and anatomy of the patient's airway, but it is probably limited to 4 to 5 cm H_2O.[6,7] At least in infants, positive pressure generation requires a closed mouth.[8]

Oxygen Hoods

Oxygen hoods are cylinders or boxes that enclose an infant's or small child's head. Oxygen enters through a gas inlet port, and exhaled gas leaves primarily through the opening for the neck. Hoods provide up to 80% to 90% oxygen, good humidification, and controlled temperature. They allow easy access to the child for other care. Tents for older children provide the same environment advantages but allow less ready access to the patient and usually provide only 21% to 50% oxygen. Both have the disadvantage of being very noisy for the patient and are much less commonly used than in the past.

Masks

A variety of masks are available for delivering oxygen. Simple masks fit loosely. The oxygen concentration delivered varies, depending on the patient's inspiratory flow rate and the oxygen flow into the system. Partial rebreathing masks incorporate some sort of reservoir, usually a bag below the chin. Provided that flow into the system exceeds the patient's minute ventilation and that the bag does not collapse on inspiration, little carbon dioxide is inhaled, and concentrations of oxygen up to about 60% can be achieved. Nonrebreathing masks must fit snugly. They incorporate a mask, reservoir, and one-way valves that vent expired gas but do not permit inspiration of room air. As a result, they can deliver close to 100% oxygen.

Noninvasive Positive Pressure Ventilation. Continuous positive airway pressure (CPAP) delivers high concentrations of oxygen and maintains positive airway pressure in the spontaneously breathing patient. CPAP is applied with an oxygen source connected to either a tight-fitting nasal or full-face mask or helmet in children or via nasal prongs in the neonate and older infant. CPAP offers the benefit of maintaining alveolar expansion and decreases work of breathing for many patients, particularly those with pulmonary parenchymal disease, as well as for some patients with airway obstruction related to poor upper airway tone or laryngeal, tracheal, or bronchomalacia.

Like CPAP, bilevel positive airway pressure (BiPAP) can be provided by mask, but it requires a ventilator to assist with flow delivery. The patient's inspiratory effort triggers the BiPAP machine to deliver decelerating flow in order to reach a preset pressure, defined as inspiratory positive airway pressure. When a patient's own inspiratory flow falls below a preset amount, ventilatory assistance ceases and maintains expiratory airway pressure at a predetermined value (typically between 5 and 10 mm Hg). Uses in the pediatric intensive care unit (PICU) include upper airway obstruction, atelectasis, exacerbations of neuromuscular disorders, support for mild to moderate respiratory failure, and as an assist in weaning patients from invasive mechanical ventilation.

Both CPAP and BiPAP offer the advantage of providing respiratory support without endotracheal intubation but require that the child tolerate a close-fitting mask. A more extensive discussion of CPAP and BiPAP is available in Chapter 49, Mechanical Ventilation and Respiratory Care.

Establishing a Functional Airway

A patient who is apneic or in very severe respiratory distress requires ventilation assisted initially with a bag and mask. Probably no skill is more important for the intensivist than the ability to provide effective manual bag-mask ventilation. It can be lifesaving while preparation for endotracheal intubation proceeds or when intubation cannot be accomplished. Effective technique requires positioning the patient adequately to open the upper airway, achieving a good mask-face seal, inserting an oral or nasal airway if needed, and generating an adequate tidal volume, coordinating manual breaths with patient efforts when they are present. Poor technique results in ineffective oxygenation and ventilation, gastric insufflation, and increased risk of aspiration.

If the child is too weak or obtunded to maintain pharyngeal tone independently, the head should be placed on a thin cushion to cause slight cervical spine flexion and gentle extension at the atlantooccipital joint. In infants, the large occipitofrontal diameter makes the cushion unnecessary, although a thin pad under the shoulders may be useful. It appears that aligning the external auditory meatus with the sternal notch is a reasonable guide to appropriate positioning. Current recommendations are to avoid overextending the baby's very flexible cervical spine, which may stretch and compress the trachea and potentiate, rather than relieve, obstruction. Studies have questioned the existence of this phenomenon but to date have included a very small number of infants, all with normal airways.[9] Appropriate head tilt separates the tongue from the posterior pharyngeal wall. If airway obstruction persists, the chin can be pulled forward by encircling the mandible behind the lower incisors between the thumb and fingers. The most effective means of relieving functional obstruction is the so-called *triple airway maneuver:* With the fingers behind the vertical ramus of the jaw, the mandible is displaced downward, forward, and finally upward again until the mandible and lower incisors are anterior to the maxilla. This action effectively pulls the tongue forward and away from the pharyngeal wall.

In some patients, establishing a functional airway is sufficient to allow resumption of effective spontaneous ventilation. In other patients, steady positive airway pressure is necessary to overcome residual obstruction. If breathing remains inadequate, manual ventilation is necessary. Effective ventilation requires a good mask fit. The mask should sit smoothly on the bridge of the nose and the bony prominence of the chin. It is important to avoid airway occlusion with the mask or hand or pressure on eyes, soft nasal structures, or branches of the trigeminal and facial nerves. A good mask fit is predictably difficult in a patient without teeth, a very flat or prominent nose, or micrognathia. Insertion of a nasal or oropharyngeal airway may help maintain an adequate airway. Once a good mask fit is ensured, ventilation may be assisted.

Two types of bags are in general use: self-inflating resuscitation bags and standard anesthesia bags. Because self-inflating bags vary substantially, specific directions for their use must be followed carefully. All bags incorporate an adapter to connect to a mask or endotracheal tube, a bag, a pressure-relief valve, and a port for fresh gas inflow. Most bags designed for children have pressure-relief valves designed to pop off at 35 to 45 cm H_2O pressure to prevent excessive volume delivery and subsequent barotrauma. In patients with very poor compliance or increased airway resistance, it may be necessary to bypass this valve temporarily to provide effective ventilation. Most systems incorporate valves that prevent rebreathing. Fresh gas flows through the valve on spontaneous inspiration (negative pressure) or on creation of positive pressure by squeezing the bag (Figure 119-3). Exhaled gas is vented to

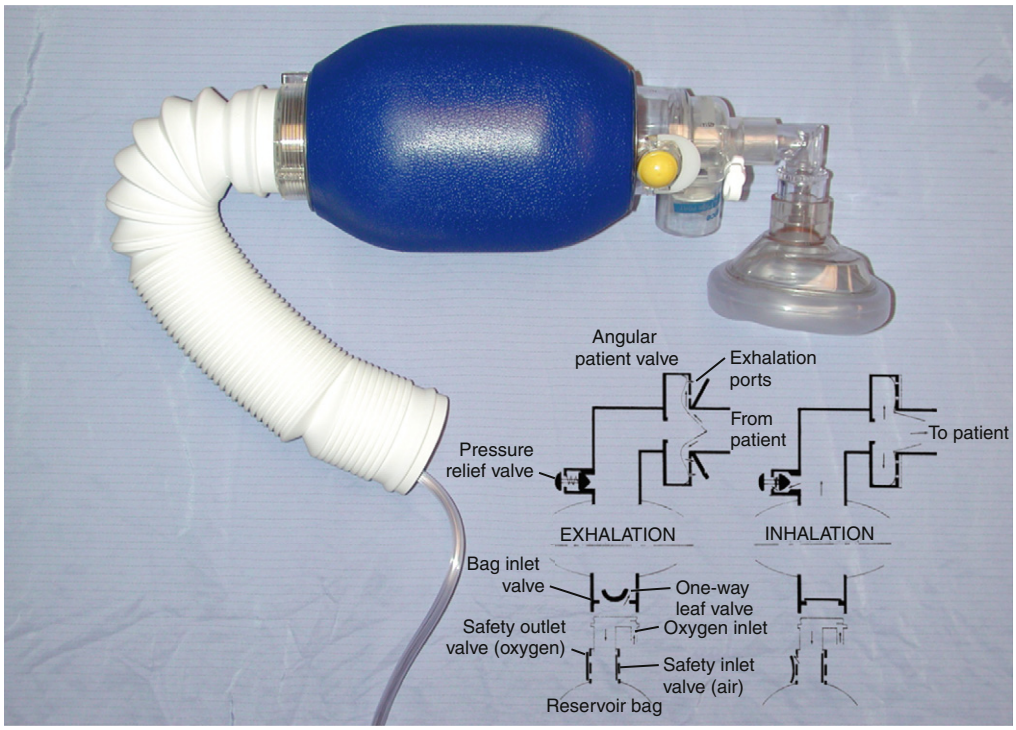

Figure 119–3. Self-inflating manual ventilation bag with tubing as a reservoir. **Inset** shows function of one type of valve, permitting manual positive pressure breathing, or spontaneous breathing, but requiring generation of negative pressure by the patient to open the valve. Simply holding the mask over the patient's face does not provide supplemental oxygen.

the atmosphere. Not all systems allow spontaneous breathing; those that do demand that the patient generate at least a little negative pressure, so a good mask fit is necessary. Holding the mask above the patient's face provides no supplemental oxygen. The percentage of oxygen delivered depends on the percentage of oxygen from the source, the fresh gas flow rate, and the respiratory rate, which determines the time available for the bag to refill. Most systems require some sort of reservoir assembly in addition to the self-inflating bag to prevent entrainment of room air. With a reservoir, 100% oxygen may be delivered; without a reservoir, most deliver less than 50%.

Anesthesia bags require flow from a source of gas under pressure in order to expand. Many variations have been reviewed extensively in the anesthesia literature. These circuits depend on the location of the fresh gas inflow and overflow valves, the rate of fresh gas flow, the respiratory rate, tidal volume, carbon dioxide production, and whether ventilation is spontaneous or controlled. Many ICUs use the Mapleson D configuration, with the fresh gas source attached just distal to the patient connection. The overflow valve is proximal to the reservoir bag. During expiration, the patient's exhaled tidal volume mixes with fresh gas flowing into the system and accumulates in the tubing and bag. With sufficiently high fresh gas flow, alveolar gas is washed to the overflow valve and eliminated from the circuit. The system requires higher fresh gas flow to avoid rebreathing during spontaneous ventilation than during controlled breathing, but a safe rule of thumb recommends fresh gas flow two to three times the minute ventilation. During controlled ventilation, a minimum of 100 mL/kg/min ensures that carbon dioxide elimination is proportional to minute ventilation.[10,11] At flows less than 90 mL/kg/min, increasing ventilation may only increase CO_2 rebreathing.

Endotracheal Intubation

The pediatric intensivist is frequently called upon to intubate critically ill patients when brief periods of ventilation with a bag and mask are inadequate to reverse the underlying disorder. Few of these intubations are performed under the optimal conditions commonly attainable in the operating room, that is, relatively healthy children with empty stomachs who have previously been sedated and are intubated in a controlled environment with all members of the team experienced in and prepared for airway management. Instead, patients are often critically unstable and require intubation suddenly, often in settings where the procedure is not routine. Intubation often is viewed only as a means to an end, namely, mechanical ventilation. However, it is associated with profound physiologic effects that may dramatically affect the patient. The intensivist's appreciation of these factors and ability to minimize the adverse physiologic consequence of airway manipulation may as decisively determine patient outcome as his or her skill in providing the intensive care that follows.

Indications

Respiratory Failure

Respiratory failure may result from dysfunction at any point along the ventilatory pathway. To provide appropriate support and to avoid hazards specific to the individual disorder, airway intervention must be tailored to the underlying cause. Outside the operating room, the need for intubation is most commonly associated with respiratory failure resulting from upper or lower airway or pulmonary parenchymal disorders that require mechanical ventilation. Respiratory failure is defined in terms of excessive work of breathing or inadequate oxygenation (in the absence of cyanotic congenital heart disease) or carbon dioxide elimination. Box 119-1 contains one set of criteria for intubation.

Hemodynamic Instability

Patients with hemodynamic instability often benefit from assisted ventilation. The need for controlled ventilation as a component of cardiopulmonary resuscitation is obvious. In addition, early intubation in anticipation of impending cardiovascular collapse may prevent catastrophic tissue hypoxia. Redistribution of blood flow away from respiratory muscles, especially the diaphragm, in patients with marginal cardiac output may improve perfusion of other vital organs, including the heart, and help prevent cardiac arrest.[12-16]

Neuromuscular Dysfunction

For additional information on neuromuscular dysfunction, see Chapter 58.

Neuromuscular dysfunction or severe chest wall instability (or deformity) may cause failure of the bellows apparatus for breathing.[17] Initially, tidal volume remains normal or at least sufficient to maintain normal blood gas tensions, but vital capacity and maximal inspiratory and expiratory pressures decrease. Inability to take a deep breath or cough forcefully risks progressive segmental or lobar atelectasis, inability to clear secretions, bronchial obstruction, and possible major airway obstruction with sudden severe hypoxia or carbon dioxide retention. Increasing weakness results in progressively smaller tidal volumes, loss of upper airway tone, and, ultimately, inadequate minute ventilation. Bulbar dysfunction may lead to aspiration as a result of impaired swallowing and inadequate cough.

Measurement of ventilatory reserve provides a better assessment of the patient's need for ventilatory assistance than does arterial blood gas tensions alone. Maximum negative inspiratory pressure and vital capacity are two simple, commonly

Box 119–1 Indications for Intubation

1. Pa_{O_2} <60 mm Hg with fraction of inspired oxygen ≥0.6 (in absence of cyanotic congenital heart disease)
2. Pa_{CO_2} >50 mm Hg (acute and unresponsive to other intervention)
3. Upper airway obstruction, actual or impending
4. Neuromuscular weakness
   - Maximum negative inspiratory pressure ≥20 cm H_2O
   - Vital capacity <12–15 mL/kg
5. Absent protective airway reflexes (cough, gag)
6. Hemodynamic instability (cardiopulmonary resuscitation, shock)
7. Controlled therapeutic (hyper)ventilation
   - Intracranial hypertension
   - Pulmonary hypertension
   - Metabolic acidosis
8. Pulmonary toilet
9. Emergency drug administration

used tests for this purpose. A variety of other measures also help assess respiratory "strength," but most are difficult to perform in sick, uncooperative infants and children. Patients with diffuse neuromuscular weakness of any cause, spinal cord dysfunction above the level of T6, or loss of phrenic nerve or diaphragm function are particularly prone to respiratory failure.[18] Because of the extreme compliance of their chest walls and relative ineffectiveness of intercostal muscles, infants younger than approximately 6 months tolerate diaphragmatic paralysis poorly.[19-23]

Many patients with neuromuscular weakness respond well to noninvasive forms of ventilatory support.[17,24] Decisions about the best approach to airway management should be based on the nature and likely progression of the illness, the child's maturity and level of consciousness, and the timing of the onset of respiratory insufficiency. In an emergency, endotracheal intubation is likely to be safest, with transition to noninvasive support when careful planning allows.[24]

Failure of Central Nervous System Regulation of Ventilatory Drive

Failure of central nervous system regulation of ventilatory drive may prompt intubation (see Chapters 54 and 57). Centrally mediated hypoventilation is manifest as CO_2 retention, usually in the absence of increased work of breathing. On occasion the decision to support ventilation may be based on observing abnormal ventilatory patterns in anticipation of neurologic deterioration. Loss of protective airway reflexes, including the cough and gag reflexes, can result from central nervous system depression, cranial nerve abnormalities, or severe motor weakness. In such patients, intubation is indicated to prevent aspiration. Intubation may be appropriate in anticipation of the need to protect the airway and support ventilation during deep sedation for procedures or diagnostic studies.

Other Indications

Intubation is indicated as a step toward therapeutic controlled (hyper)ventilation (e.g., in patients with increased intracranial pressure [ICP] or pulmonary hypertension) or to support spontaneous hyperpnea in patients with metabolic acidosis and other conditions. Patients with profuse, thick, or tenacious secretions (e.g., as a result of bacterial pneumonitis or smoke inhalation) may benefit from an artificial airway as a means of providing effective suction. Impaired mucociliary clearance occurs in patients exposed to high oxygen concentrations or other airway irritants (including particulate and gaseous components of smoke), those experiencing severe hypoxia or hypercarbia, and, paradoxically, those who have airway trauma induced by endotracheal intubation and suctioning. Endotracheal intubation also provides an effective means of delivering drugs during cardiopulmonary resuscitation when venous or intraosseous access is not available (see Chapter 34).

Physiologic Effects of Intubation

Laryngoscopy is a potent physiologic stimulus (Box 119-2).[25,26] At the very least, laryngoscopy is uncomfortable, causing significant pain and severe anxiety, especially in children who cannot understand or accept the need for it. Laryngoscopy causes an increase in systemic blood pressure and heart rate initiated by pressure on the back of the tongue or lifting the epiglottis.[27] This effect is augmented by endotracheal intubation and suction.[28] Nodal or ventricular dysrhythmias may occur. Sensory impulses triggering this reflex probably are carried along the vagus nerve supplying the base of the tongue, epiglottis, and trachea. The efferent limb is less well defined but most likely is the product of enhanced sympathetic activity. Infants respond more variably than do older patients. Hypertension develops in most patients, but a few become hypotensive, especially if they are hypoxic.[29] They may demonstrate moderate-to-severe bradycardia rather than tachycardia, perhaps as a consequence of their greater parasympathetic tone. Sedation and light anesthesia decrease but do not obliterate the hypertension and tachycardia; surface anesthesia and deeper general anesthesia are more effective.[30] Children with previous hypertension display an exaggerated vasopressor response. Sedation and neuromuscular blockade during airway manipulation in infants minimizes the associated bradycardia and systemic hypertension.[31-35] The impact of positive pressure ventilation on cardiac performance depends on the underlying disorder (discussed in Chapter 26) but should be carefully considered in preparation for intubation.

Box 119–2 Potential Physiologic Effects of Laryngoscopy and Intubation

Pain
Tachycardia
Anxiety
Bradycardia
Hypoxia
Systemic hypertension
Hypercarbia
Decreased systemic venous return
Increased intraocular
Decreased jugular venous pressure return
Increased intragastric pressure
Increased intracranial pressure
Laryngospasm
Bronchoconstriction
Pulmonary hypertension

Laryngoscopy and intubation are potent stimulators of laryngospasm and may cause bronchoconstriction, especially in patients with a history of reactive airway disease. Increased airway resistance probably results from parasympathetic stimulation, with release of acetylcholine and stimulation of muscarinic receptors on airway smooth muscle, especially large central airways.

During intubation, oxygen delivery to the patient is commonly interrupted. Ineffective breathing or apnea increases the likelihood of hypoxia, especially in children, with their relatively low functional residual volume and higher basal metabolic rate. Patients with severe pulmonary disease and abnormally low functional reserve capacity are at particular risk.[31,34] During apnea, carbon dioxide tension increases at a rate of 3 to 4 mm Hg/min in healthy, sedated adults and probably more rapidly in children, particularly those with severe cardiopulmonary disease or increased metabolic rate resulting from fever, sepsis, or pain.[36,37]

ICP rises immediately during laryngoscopy even in patients without intracranial pathology before changes in blood gas

Box 119–3 Recognizing the Difficult Airway

History

Difficult intubation
Upper airway obstruction, current or past, including snoring and sleep apnea

Anatomic features

Gross macrocephaly
Severe obesity
Facial asymmetry
Facial trauma
Midface hypoplasia
Airway bleeding
Small mouth
Oropharyngeal mass
Glossoptosis
Abnormal soft tissue infiltration
Midline clefts or high arched palate
Limited temporomandibular joint mobility
Micrognathia
Nasal obstruction
Limited neck mobility
Laryngotracheal abnormalities (congenital or acquired)

tensions occur.[30,32,38,39] Cerebral metabolic rate and blood flow increase. Hypoxia, hypercarbia, and diminished jugular venous drainage, particularly in struggling patients, contribute further to increases in cerebral blood volume and increased intracranial pressure. Although normally very transient, such intracranial hypertension may predispose patients with coagulopathies or vascular malformations to intracranial hemorrhage. Systemic hypertension in patients with impaired autoregulation of the cerebral circulation (e.g., sick infants or patients with a variety of intracranial disorders) and impedance to jugular venous return by jugular compression, pneumothorax, or coughing and struggling stress both the arterial and venous sides of the cerebral circulation. In patients with poor intracranial compliance, this effect is exaggerated and prolonged. In infants without primary central nervous system disease, muscle paralysis (even without sedation or analgesia) effectively blocks the rise in ICP associated with intubation.[34] The systemic hypertensive response is generally unaffected by neuromuscular blocking agents but can be modified by analgesia and sedation or intravenous anesthesia.

Patients with severe pulmonary hypertension are at high risk for adverse effects of laryngoscopy. Decreased oxygenation and progressive hypercarbia lead to elevated pulmonary artery pressure. The noxious stimulus of visualizing the airway in itself may precipitate life-threatening hypertension.

Recognition of a Difficult Airway

Recognition of a difficult airway is important if potentially lethal surprises in airway management are to be minimized (Box 119-3). Although the intensivist is usually focused on the immediate physiologic disturbances affecting the patient, careful preparation and as thorough an evaluation of each individual patient as is possible is critical. Key components of the history and physical examination, as well as the clinical scenario, can provide insight into potential problem airways. A history of difficult intubations in the past or episodes of upper airway obstruction (including snoring or sleep apnea) suggest structural abnormalities that may or may not be evident at the moment. Recent tonsillectomy and adenoidectomy, cleft palate repair, or any prolonged surgical procedure resulting in oral edema or bleeding increase the likelihood of difficulty. Examining facial structure is essential, and inspecting the child's profile is particularly important because significant abnormalities may not be fully apparent on frontal view alone (Figure 119-4). Certain genetic syndromes are associated with craniofacial anomalies, midline defects, or neuromuscular disorders that may make successful intubation via standard techniques exceptionally difficult. Treacher Collins syndrome (mandibulofacial dysostosis), Goldenhar syndrome (oculoauriculovertebral dysplasia), Down syndrome, Pierre Robin syndrome, and the mucopolysaccharidoses, such as Hurler syndrome and Hunter syndrome, are a few of the syndromes that have characteristic features that suggest the high probability of facing a challenging airway. Isolated micrognathia, macroglossia (glossoptosis), facial clefts, midface hypoplasia, prominent upper incisors or maxillary protrusion, facial asymmetry, a high arched narrow palate, a small mouth, and a short, muscular neck or morbid obesity are features that can interfere with effective bag-mask ventilation or visualization of the larynx. Limited temporomandibular joint or cervical spine mobility may make laryngoscopy and tube placement very difficult. Midface instability or upper airway bleeding, edema, airway or neck masses, and foreign bodies are additional reasons for concern.[40]

Several classification systems assist with recognition and classification of the adult patient with a difficult airway. Although never validated in pediatrics, they provide a useful framework for assessing infants and children. The Mallampati classification (Figure 119-5) assesses visualization of upper airway structures prior to intubation— particularly the uvula, soft palate, and faucial pillars—as a guide to the likely ease of intubation. Mallampati class 1 allows visualization of the uvula, soft palate, and faucial pillars; in class 2, faucial pillars and soft palate are visualized but the uvula is obstructed by the base of the tongue; in class 3 only the soft palate is visualized; and in class 4 the soft palate is not seen. Difficult intubation is more likely associated with classes 3 and 4. This scale can be used with cooperative children, and an approximate evaluation may be obtained by observing many crying infants and young children.

The Cormack laryngeal view grade score is shown in Figure 119-5, *B*. Because the Cormack system requires an attempt to visualize the larynx, it is more valuable as a tool for describing difficulty once it has been encountered than for predicting it. The Cormack score is grade 1, full view of vocal cords and glottis; grade 2, partial view of vocal cords and glottis; grade 3, only the epiglottis is seen; and grade 4, the glottis and epiglottis are not visualized. Grades 3 and 4 predict difficult direct laryngoscopy.[41] Although these classification systems are helpful in a controlled environment, particularly the preoperative area of a hospital, they are recognized as having limited utility in the emergent situations often encountered in the ICU, and their ability to predict the degree of difficulty with intubation in children is not well established.[42]

Ability to visualize the faucial pillars, soft palate, and uvula usually predicts an uncomplicated intubation, but this may be difficult to assess in a sick, uncooperative child.[43] Children with severe hypoxia, severe hypovolemia, or other causes of hemodynamic instability, such as intracranial hypertension, a

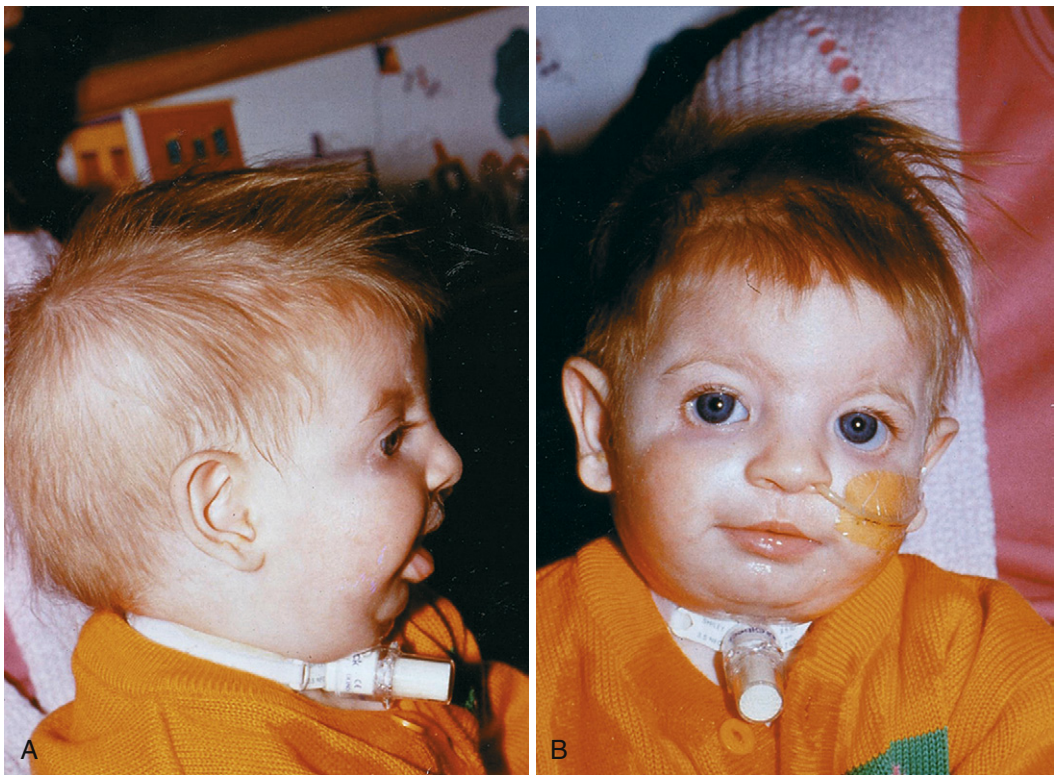

Figure 119–4. Importance of inspecting the patient's profile. Child with significant micrognathia, not immediately apparent on frontal view. *(From Lipton JM, Ellis SR: Diamond-Blackfan anemia: diagnosis, treatment, and molecular pathogenesis,* Hematol Oncol Clin North Am *23[2]:261–282, 2009.)*

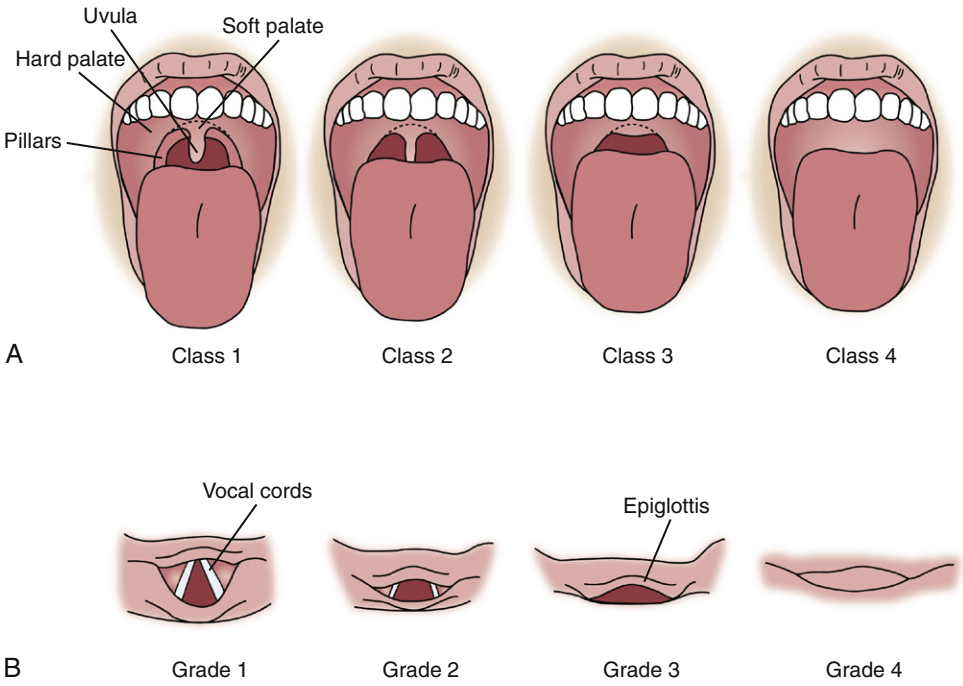

Figure 119–5. **A,** Modified Mallampati classification. Class 1: Visualization of the faucial pillars, uvula, soft and hard palate. Class 2: Visualization of complete uvula and palate. Class 3: Visualization of only the base of the uvula and palate. Class 4: Visualization of only the hard palate. **B,** Cormack and Lehane classification of the laryngeal exposure. Grade 1: Most of the glottis is visible. Grade 2: Only the posterior portion of the glottis visible. Grade III: Only the epiglottis is visible. Grade IV: Not even the epiglottis is visible. *(From Amantéa SL, Piva JP, Zanella MI, et al: Rapid airway access,* J Pediatr [Rio J] *79[suppl 2]:S127–S138, 2003.)*

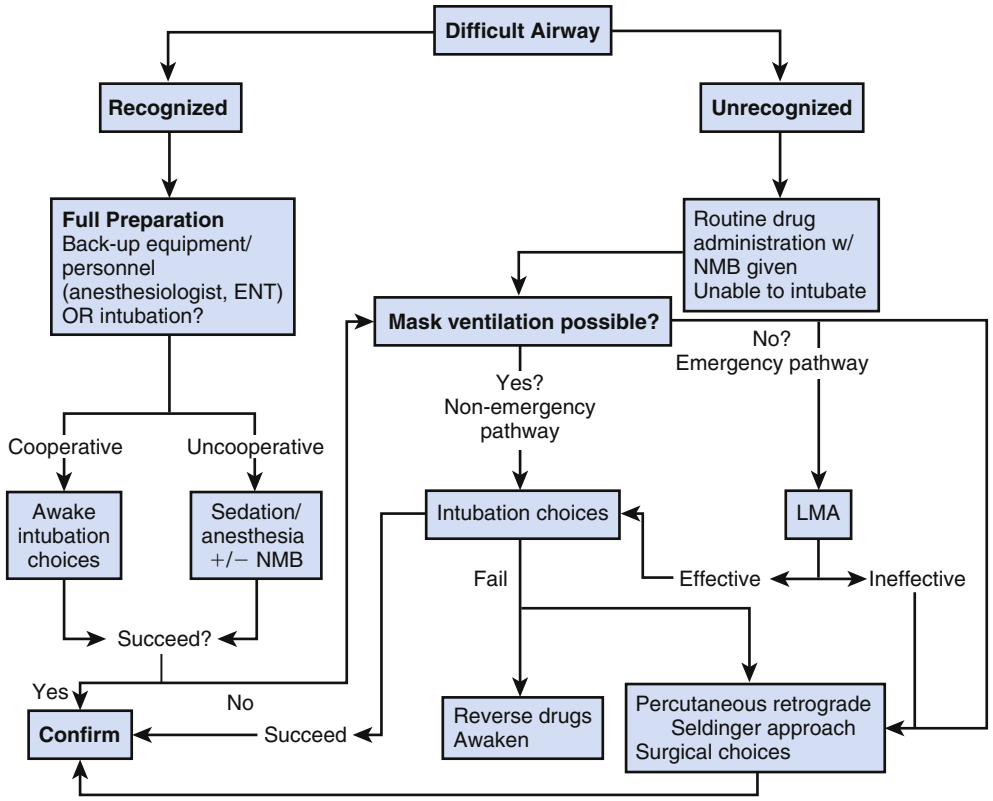

Figure 119–6. Modification of the American Society of Anesthesiologist's difficult airway algorithm. *(From Practice guidelines for the management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway,* Anesthesiology *98:1269, 2003.)*

full stomach, or some combination of these conditions, present added difficulties that must be considered.

When airway problems are anticipated, the intensivist should approach intubation with a plan specific to the difficulty noted and with a backup strategy in mind.[44,45] Extra equipment should be on hand, including a variety of laryngoscope blades, forceps, tubes, bronchoscopes, tracheostomy or cricothyrotomy trays, and additional skilled personnel as needed.[46] If sedation is required, agents that can be reversed pharmacologically are desirable and should be titrated slowly to the desired effect. Figure 119-6 shows a modification of the American Society of Anesthesiologist's difficult airway algorithm and provides an approach to managing the difficult airway.[47] A similar plan is necessary at the time of extubation, with serious consideration given to extubation in the operating room or with an airway exchange catheter left in place to facilitate reintubation if necessary.

Process of Intubation

All equipment for intubation must be available prior to the procedure (Figure 119-7). A source of suction and appropriate catheters, oxygen and necessary tubing, ventilation bag, mask, laryngoscope and proper-sized blade with a well-functioning light, endotracheal tubes of the expected size and larger and smaller sizes, airway forceps, stylet, and a means of securing the endotracheal tube should be present at the head of the bed so that the intubator does not need to look away from the patient. A functioning intravenous catheter for drug infusion is essential in all but the most extreme emergencies.

Laryngoscope handles are available in standard adult and pediatric sizes. The smaller diameter of the pediatric handle makes it easier to manipulate, particularly when intubating infants and very young children. Blades of many descriptions are available. The most important characteristic is length. Inexperienced operators often select a blade that is too short, making visualization of the larynx difficult. Excessively long blades make it difficult to avoid pressure on the upper lip and teeth. Straight blades provide good exposure in infants and young children. The slightly curved tip of the Miller blade makes visualization of the larynx possible without actually lifting the epiglottis. The broader blade and bore of the Wis-Hipple blade helps displace soft tissues in the young infant's oropharynx. The Miller No. 2 blade is especially versatile in a broad age group (i.e., children about 3 to 10 years of age). In older children, use of a curved blade is often works best. If a cuffed endotracheal tube is to be used, a curved Macintosh No. 2 or 3 blade is effective in the majority of patients and may provide more room to manipulate a cuff in the oropharynx.

Selecting the proper tube size (diameter) is important, both to achieve effective mechanical ventilation and to prevent tracheal injury. A variety of formulas are in use, with the most common being that of Cole: Tube size (inner diameter) = (Age [years]/4) + 4. For infants, no formula is very accurate. Table 119-2 gives reasonable guidelines. Individual differences require that the tube size be modified for each child so that the tube passes easily and allows gas to leak around it at roughly 15 to 30 cm H_2O pressure but fits snugly enough to allow delivery of adequate mechanical breaths at a given chest compliance.

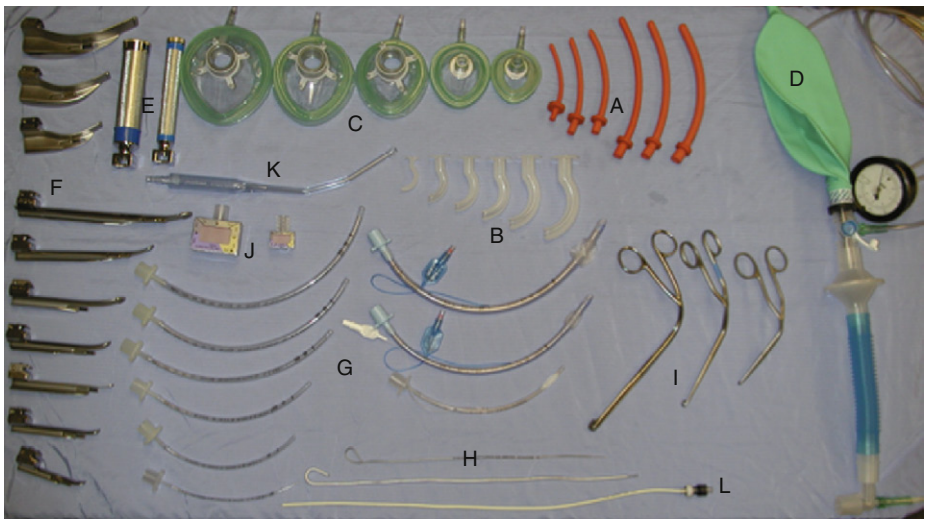

Figure 119–7. Equipment for intubation, showing a variety of sizes available for pediatric patients. *A,* Nasopharyngeal airways. *B,* Oral airways. *C,* Masks. *D,* Anesthesia (Mapleson) bag. *E,* Laryngoscope handles. *F,* MacIntosh (curved) and Miller (straight) laryngoscope blades. *G,* Uncuffed and cuffed endotracheal tubes. *H,* Endotracheal tube stylets. *I,* Magill forceps. *J,* End-tidal CO_2 detectors. *K,* Yankauer suction. *L,* Tube changer.

Table 119–2 Guidelines for Endotracheal Tube Diameter in Infants and Children

Age	Internal Diameter	Orotracheal Length (cm)	Nasotracheal Length (cm)
Premature	2.0–3.0	6–8	7–9
Newborn	3.0–3.5	9–10	10–11
3–9 mo	3.5–4.0	11–12	11–13
9–18 mo	4.0–4.5	12–13	14–15
1.5–3 y	4.5–5.0	12–4	16–17
4–5 y	5.0–5.5	14–16	18–19
6–7 y	5.5–6.0	16–18	19–20
8–10 y	6.0–6.5*	17–19	21–23
11–13 y	6.0–7.0*	18–21	22–25
14–16 y	7.0–7.5*	20–22	24–25

Ideal tube size varies according to age, height, weight, specific airway anatomy, and ventilatory requirements of a child. In general, an air leak around the tube at 15 to 30 cm H_2O pressure is desirable.
*Cuffed tube.

Traditional teaching has held that use of cuffed endotracheal tubes is not necessary or appropriate in young pediatric patients (younger than 8 years) because the narrow diameter of the trachea at the cricoid ring allows a fairly snug fit without a cuff, and a cuff may make tracheal injury at that level more likely. In addition, the bulk of the cuff usually requires using a tube of 0.5 mm smaller diameter, with the associated increased resistance to gas flow and greater risk of occlusion. Cuffed tubes are routinely recommended for children older than 8 to 10 years because the cricoid ring has been replaced by the triangular opening of the vocal cords as the narrowest point in the airway (see Figure 119-1). In addition, the greater elastic recoil of the lungs and chest wall of older patients may demand higher airway pressures for effective ventilation.

However, cuffed tubes of all sizes are available and may be useful in patients in whom consistent minute ventilation is essential (e.g., in the presence of severely elevated ICP or very reactive pulmonary vasculature) or those requiring relatively high airway pressures. Although data are limited, evidence is growing that cuffed tubes can be used in young children without higher incidence of airway complications.[48-52] The modern low-pressure, high-volume cuff requires a much lower pressure to obtain a seal than did the endotracheal tube cuffs of the past. When a cuffed tube is used, great care should be taken to inflate it with the "minimum occlusive volume," the minimum volume required to "just seal" the gas leak around the tube during mechanical inspiration and prevent mucosal ischemia and subsequent tracheal damage. Potential advantages of cuffed tubes include decreased likelihood of multiple intubations to identify the correct size and avoidance of changing the endotracheal tube of a critically unstable patient if lung disease worsens. In addition, absence of a significant leak around the endotracheal tube (ETT) may decrease the likelihood of flow-triggered ventilator autocycling. The ability to occlude the leak also facilitates pulmonary function testing and indirect calorimetry.

Pharmacologic Agents Facilitating Intubation

Although intubation often is possible without use of drugs, the physiologic and psychological benefits of their use usually outweigh the disadvantages.[53,54] Analysis of data in the pediatric National Emergency Airway Registry shows that intubation success rate is higher when both sedation and neuromuscular blockade are used.[55] This finding is equally true in neonates, in whom sedation and neuromuscular blockade are still commonly not used, with no evidence they are harmful.[56] In neonates the predominance of evidence indicates that use of neuromuscular blockade is associated with a lower risk of intracranial hemorrhage and pulmonary airleak.[57] Excellent technical airway skills are an absolute prerequisite, however, because loss of control of the airway invites catastrophe. Drugs facilitating intubation are listed in Table 119-3.

Table 119–3 Drugs Facilitating Intubation

Drugs	Dose	Duration	Comments
INTRAVENOUS ANESTHETICS			
Thiopental	4–7 mg/kg IV	5–10 min	Anesthesia, apnea, myocardial depression, decreased venous tone, ↓ $CMRO_2$, ↓ CBF, ↓ ICP, ↓ IOP
Etomidate	0.3 mg/kg IV	3–5 min	Anesthesia, adrenal suppression (↑mortality in sepsis?), minimal CV effect, apnea, ↓ $CMRO_2$, ↓ CBF, ↓ ICP
Ketamine*	1–2 mg/kg IV; 4–6 mg/kg IM	10–15 min	Anesthesia, ↑ systemic arterial pressure, ↑ HR, ↑ ICP, ↑ IOP, hallucinations, laryngospasm, bronchodilation
Propofol	1–3.5 mg/kg IV, then 0.05–0.3 mg/kg/min	10–15 min	↓ Systemic arterial pressure, ↓ $CMRO_2$, ↓ CBF, ↓ ICP, metabolic acidosis
SEDATIVES/ANALGESICS			
Fentanyl*	2–5 μg/kg IV	30–90 min	Analgesia, respiratory depression, cardiovascular stability, occasional bradycardia, or chest wall rigidity
Remifentanil	1–3 μg/kg, then 0.25–1 μg/kg/min		Analgesia, respiratory depression, cardiovascular stability
Morphine*	0.1–0.2 mg/kg IV	2–4 h	Analgesia, respiratory depression, ↓ systemic arterial and venous tone, ↓ systemic blood pressure
Midazolam*	0.1–0.3 mg/kg IV	1–2 h	Amnesia, sedation or euphoria, ± cardiovascular stability, occasional respiratory depression
Lorazepam	0.1–0.3 mg/kg IV	2–4 h	Sedation, anxiolysis, minimal cardiovascular effect
NEUROMUSCULAR BLOCKING AGENTS			
Rocuronium*	0.6–1.2 mg/kg IV	15–45 min	Minimal cardiovascular effect, prolonged duration in liver failure
Vecuronium*	0.1–0.3 mg/kg IV	30–75 min	Minimal cardiovascular effect, prolonged effect in hepatic failure
Cis-atracurium	0.1 mg/kg, then 1–5 mg/kg/min	20–35 min	Metabolized by plasma hydrolysis, mild histamine release
Atracurium	0.5 mg/kg	30–40 min	Metabolized by plasma hydrolysis, mild histamine release
Succinylcholine*	1–4 mg/kg IV	5–10 min	↓ HR, K^+ release in neuromuscular disease, trauma or burns, masseter spasm, malignant hyperthermia, myoglobinuria

Duration of effect is only approximate and varies with age and physiologic state of the patient.
*Agents may be given intramuscularly but will have slower onset and more variable duration of effect.
CBF, Cerebral blood flow; *$CMRO_2$,* cerebral metabolic oxygen requirement; *CV,* cardiovascular; *HR*, heart rate; *ICP*, intracranial pressure; *IM,* intramuscular; *IOP*, intraocular pressure; *IV*, intravenous.

Anticholinergic Agents

Anticholinergic agents decrease oral secretions and prevent bradycardia, particularly in young infants, although their use is not universally recommended. Atropine (0.02 mg/kg) and glycopyrrolate (0.01 mg/kg intravenously) are both effective. Scopolamine provides amnesia, decreases secretions, and prevents bradycardia. The drying effect commonly requires approximately 15 to 30 minutes and is rarely achieved in emergency intubation.

Sedative and Analgesic Agents

Most patients benefit from some degree of sedation. Drugs commonly used include intravenous anesthetic agents, anxiolytic agents, and narcotic analgesics. The appropriate choice in a particular patient depends on the child's hemodynamic status, level of anxiety, and underlying disease process.

Thiopental is a short-acting barbiturate that can provide deep anesthesia, obliterating awareness of the intubation process. It decreases cerebral oxygen consumption and thereby sharply lowers cerebral blood flow (CBF) and ICP. However, it is also a potent myocardial depressant; it decreases peripheral vascular resistance and may precipitate cardiovascular collapse in patients with myocardial dysfunction or hypovolemia. At anesthetic doses (4 to 7 mg/kg), it reliably causes apnea.

Etomidate is another short-acting intravenous anesthetic that causes rapid loss of consciousness (at 0.3 mg/kg) and respiratory depression, although it is less potent than thiopental. It also decreases cerebral oxygen consumption, CBF, and ICP, but without significant detrimental effects on cardiovascular function and with less respiratory depression than thiopental. These characteristics have led to its increased use for emergency intubation.[58,59] It has no analgesic properties and may be best combined with a narcotic analgesic. Adverse effects include vomiting, myoclonus, and lowering of the seizure threshold. With continuous infusion for sedation, it can cause adrenal insufficiency, making it inappropriate for long-term use in the ICU.[60] Growing evidence suggests it may suppress adrenal function even after a single dose, particularly in patients with sepsis and shock, raising questions about its use in these settings.[61-70]

Ketamine is another potent nonnarcotic analgesic and anesthetic that has been used safely in children in the critical care setting.[71,72] It increases heart rate, systemic blood pressure, and cardiac output and is a fairly potent bronchodilator. However, myocardial depression may be apparent after

administration to patients with catecholamine depletion. It may be of particular value in patients with status asthmaticus or other reasons for bronchospasm and may have a beneficial effect in sepsis. Spontaneous ventilation is preserved in most patients, but laryngospasm may occur.[73] Although in the past it has been considered inappropriate for patients with intracranial hypertension because of evidence that it increases cerebral metabolic rate, blood flow, and ICP, more recent studies indicate that it may be used safely in these patients, although no clear consensus has emerged.[74] Emergence delirium and hallucinations occur frequently and may be prolonged and recurrent, particularly in adolescents and young adults. Use of ketamine for a variety of procedures in children has been successful, with little reported difficulty with neuropsychiatric complications, but follow-up in most studies has been short and superficial.[75-80] Whereas the majority of patients do not suffer severe disturbances, those who do may have severe and prolonged distress. Benzodiazepines or barbiturates may decrease the incidence and severity of such adverse effects and the incidence of vomiting, although the data in children are limited and conflicting.[75,81,82]

Propofol is an ultra-short-acting agent with rapid onset and offset unless given by continuous infusion. It causes respiratory depression, desaturation, and systemic hypotension secondary to its negative inotropic effects and peripheral venous and arterial vasodilation. Its role in airway management of critically ill children is limited because of these effects. It has gained widespread acceptance as an anesthetic agent in children, however, and has been used extensively for procedural sedation.[83,84] Use in the ICU for more than approximately 6 hours is not recommended because of its still unexplained association with metabolic acidosis, cardiovascular collapse and death, propofol syndrome, among pediatric ICU patients.[85-87] Current labeling warns against its use for prolonged sedation in children.

The benzodiazepines, including diazepam and midazolam, relieve anxiety, produce sedation in most children, and provide amnesia for noxious procedures. They do not relieve pain. They have relatively little hemodynamic effect in most patients and rarely interfere with spontaneous breathing at therapeutic doses. Although they decrease cerebral oxygen consumption, their effect on cerebral metabolism is much less pronounced than that of thiopental. They are best combined with a narcotic analgesic when used for intubation in order to decrease the discomfort and pain associated with laryngoscopy and passage of the tube.

Narcotics commonly used for intensive care include morphine, fentanyl, and some of the ultra-short-acting agents such as remifentanil. They cause respiratory depression in a dose-dependent fashion and increase intracranial blood flow in proportion to the increase in $Paco_2$. If hypercarbia is prevented, they decrease cerebral metabolic rate and blood flow. In the setting of altered cerebral autoregulation, they may not protect the patient from alterations of CBF.[88,89] Morphine causes histamine release and peripheral vasodilation and may precipitate systemic hypotension. Fentanyl is approximately 100 times more potent than morphine but does not release histamine and has little hemodynamic effect, even at anesthetic doses. Large doses given rapidly can cause bradycardia or chest wall rigidity. Remifentanil is a rapid-onset, ultra-short-acting opiate that is even more potent than fentanyl and may have potential benefit in intubation for procedures.

Neuromuscular Blocking Agents

Neuromuscular blocking agents cause reversible paralysis, facilitating visualization of the airway and insertion of the endotracheal tube in an atraumatic fashion. Most drugs in use are nondepolarizing relaxants with very similar action. Differences are primarily in their hemodynamic effects, metabolism, and excretion.[90,91] Vecuronium and rocuronium are the agents most commonly used. Both are amino-steroid agents. Vecuronium has virtually no hemodynamic effect. Its duration of action varies depending on the patient's age, approximately 70 minutes in infants and 35 minutes in older children. It is metabolized exclusively by the liver. Rocuronium provides good intubating conditions nearly as rapidly as succinylcholine (in about 45 to 90 seconds)[92-94] without the adverse effects. Its duration is longer at 15 to 45 minutes (and longer in infants).[95-97] Like vecuronium, it has minimal hemodynamic effect, is metabolized by the liver, and largely is excreted in bile (with a small amount excreted by the kidneys). Atracurium and cis-atracurium, both benzylquinolinium agents, also have minimal hemodynamic effects in most patients but may cause histamine release and hypotension in some persons. Metabolism occurs by spontaneous plasma hydrolysis; thus neither renal nor hepatic function is necessary for elimination. Its duration of action is short at about 15 to 20 minutes.

The only depolarizing relaxant in clinical use is succinylcholine. Its only advantage is its rapid onset of action (45 to 60 seconds) and brief duration of action (5 to 10 minutes). Muscle fasciculations occur at the onset of action in patients older than 4 years and may increase intracranial, intraocular, and intragastric pressure. Defasciculating doses of a nondepolarizing neuromuscular blocker prior to succinylcholine administration minimize such effects. Massive hyperkalemia may occur following its use in patients with spinal cord injury, severe burns, crush injuries, or neuromuscular disease. More recently, the spread of acetylcholine receptors outside of the neuromuscular junction, the mechanism presumed to underlie the massive hyperkalemic response previously noted, has been recognized to occur in many forms of critical illness associated with immobility, placing many critically ill patients at risk.[98] It is a known trigger for malignant hyperthermia and frequently causes myoglobinuria in otherwise healthy children. The U.S. Food and Drug Administration has issued a warning against its use for routine intubation in children because of these complications. Although it is frequently used for emergency intubations and is widely recommended,[54,99,100] the difference in time to conditions for intubation between succinylcholine and rocuronium is small (~30 seconds), very rarely of clinical significance, and inadequate to justify the added risk in the vast majority of cases. Moreover, the time to critical hemoglobin desaturation in the case of a failed airway is shorter than its duration of action, especially in children, so its shorter duration of action does not provide a meaningful advantage over nondepolarizing blockers.[101]

A more extensive discussion of anesthetic agents and their use is given in Chapters 122, 123, and 124.

Orotracheal Intubation

When all equipment is ready, an assistant is assigned to monitor the child's color, heart rate, blood pressure, and oxygen saturation and to administer drugs when ordered. The child

is placed supine with the head in the "sniffing" position. The infant's large occipitofrontal diameter naturally results in good position most of the time, but a small pad under the shoulders may be helpful. In older children, a thin pad under the occiput helps establish slight neck flexion (Figure 119-8). The head is extended to align the oral, pharyngeal, and laryngeal axes as much as possible. Spontaneous or manual ventilation with supplemental oxygen is maintained as drugs to facilitate intubation are given. Many patients requiring emergency intubation have severely impaired gas exchange and may require several minutes of breathing 100% oxygen, often with positive inspiratory and end expiratory pressure.[102] Applying cricoid pressure during manual ventilation helps minimize gastric distension by air (Figure 119-9).[103] After the drugs take effect, the pharynx is suctioned and stomach contents are aspirated. The patient is again briefly oxygenated, and the mask is removed. In a fully relaxed patient in good position, the mouth falls open. It can be opened more widely with caudad pressure on the chin by the intubator's left fifth finger as the laryngoscope is introduced into the right-hand corner of the mouth. In an unsedated patient or when the mouth opens abnormally, it may be necessary to open the jaw with the often recommended scissorlike use of the right thumb and forefinger, but this action places the intubator at risk of both trauma and infection and should be avoided when possible.

The laryngoscope is gently advanced into the pharynx and leftward, sweeping the tongue out of the way. Holding the handle at a 45-degree angle to the bed and lifting along the line of the handle to avoid pressure on the lips, teeth, or alveolar ridge, the intubator displaces the mandible until the vocal cords are in view (Figure 119-10). Application of gentle cricoid pressure by an assistant may be helpful. Once the larynx is clearly visualized, the tube is advanced from the right corner of the mouth into the larynx (not through or along the blade itself). The nearly universal tendency to plumb the depths of the child's airway with extra centimeters of tube results in main stem intubation. Unfortunately, the recommendation to use three times the ETT size for appropriate depth of tube placement for a child results in malposition in 15% to 25% of patients.[104] Placement is likely to be better if the intubator is careful to place the appropriate markings near the tip of the endotracheal tube at the level of the cords. If such markings are absent, careful attention to advancing the tip of the tube only a few centimeters (2 to 4 cm) beyond the cords prevents main stem intubation.

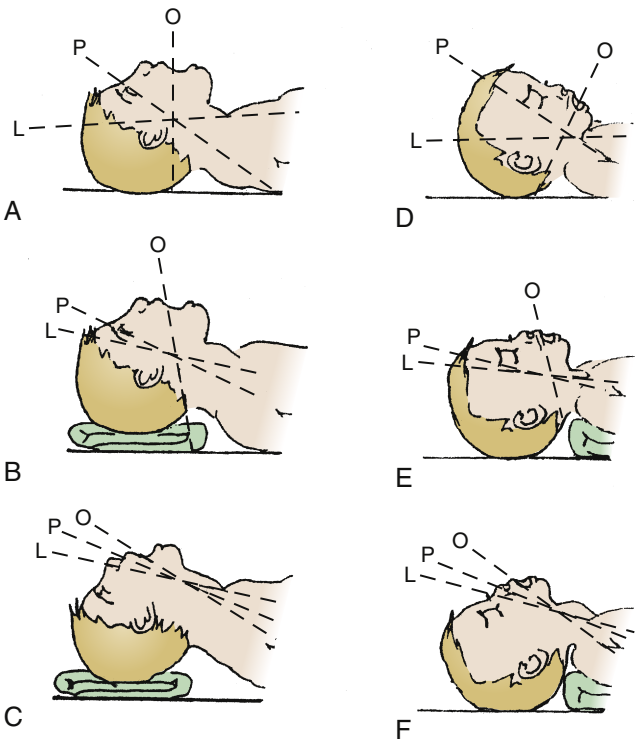

Figure 119–8. **A,** Positioning of the young child and infant for laryngoscopy and tracheal intubation. **B,** Placing the child's head on a thin pad flexes the neck slightly and helps align the pharyngeal and laryngeal axes. **C,** Extension of the atlantooccipital joint (into the sniffing position) further aligns the oral axis with the pharyngeal and laryngeal axes. **D,** Before the age of approximately 3 years, the child's large frontal occipital diameter makes the pad beneath the head unnecessary, but a small pad under the shoulders (**E**) may improve alignment of the pharyngeal and laryngeal axes. **F,** As with the older child, head extension improves alignment of the oral, pharyngeal, and laryngeal axes. *(From McAllister JD, Gnauck KA: Rapid sequence intubation of the padiatric patient. Fundamentals of practice,* Emerg Med *46:1249–1284, 1999.)*

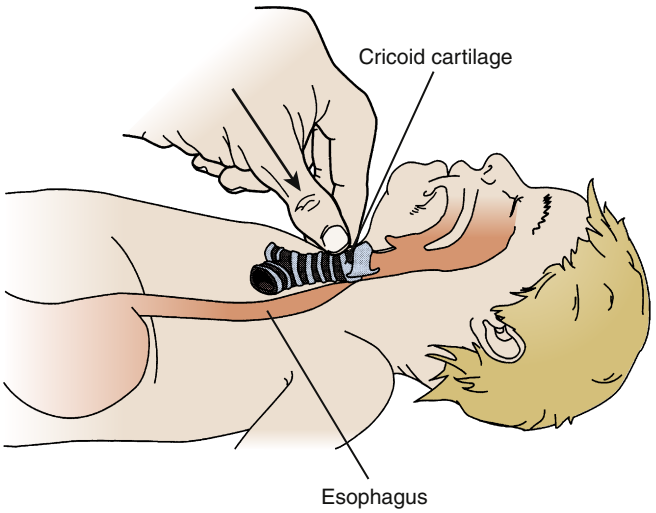

Figure 119–9. Sellick maneuver. Pressure on the cricoid cartilage occludes the esophagus or hypopharynx.

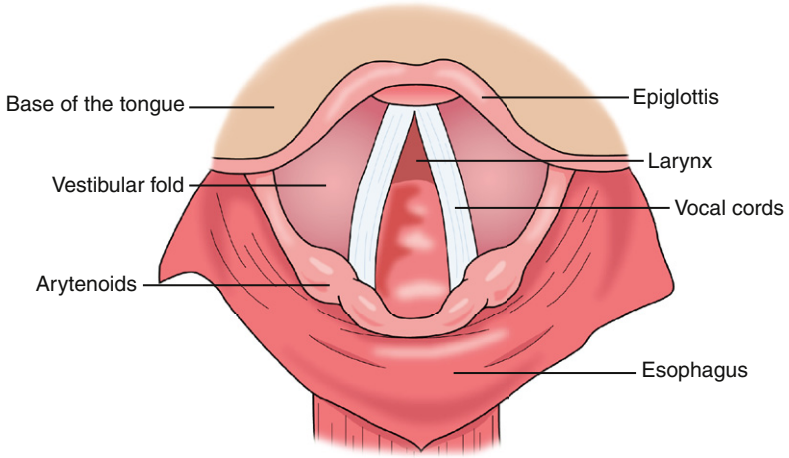

Figure 119–10. Glottic area view via laryngoscopy.

With the tube in place, the child again receives manual ventilation with oxygen, and the presence of an appropriate leak is documented. Correct tracheal placement of the tube is suggested by observation of moisture condensing in the tube, good chest excursion, symmetrical breath sounds, and effective oxygenation. The most reliable means of ensuring proper placement, following clear visualization of the tube passing between the vocal cords, is documentation of carbon dioxide in expired gas (by capnometry or a disposable CO_2 detector). Only in the settings of full cardiac arrest or extremely low pulmonary blood flow can the endotracheal tube be in the airway without detection of expired carbon dioxide. Under other conditions, malposition of the tube, most commonly in the esophagus, must be assumed. It is important to remember that capnometry does not ensure correct positioning within the airway: carbon dioxide will be detected with the tube anywhere from a bronchus to above the vocal cords. Documenting location of the tip of the tube between the thoracic inlet and T4 on chest radiograph, with the head in a neutral position, is important. (The tip will descend deeper into the trachea with neck flexion and move upward with neck extension.[105,106] With the endotracheal tube in good position an inflated cuff often can be palpated at the sternal notch when quick pressure is applied to the sentinel balloon. The tube is secured, avoiding pressure on the lips, particularly at the angle of the mouth, and keeping the vermilion border of the lip free of tape.

Nasotracheal Intubation

If nasotracheal intubation is preferred, it should generally follow orotracheal intubation so that an assistant can ventilate the child while the somewhat more difficult intubation is accomplished. A topical vasoconstricting agent such as phenylephrine 0.25% or oxymetazoline 0.05%, sprayed into the nasal fossa, minimizes the risk of bleeding. In most children a tube of the same diameter as the oral tube can be gently advanced along the floor of the nasal cavity, essentially directly posteriorly, into the nasopharynx with firm, but not brutal, pressure. With the oral tube in the left corner of the mouth, the laryngoscope is again advanced into the pharynx until the oral tube is visualized passing through the cords and the tip of the nasal tube is seen in the nasopharynx. The nasal tube is advanced until it lies directly above the cords, anterior to the oral tube. Use of Magill forceps may facilitate this maneuver. When the nasal tube is in good position to enter the larynx, the assistant removes the oral tube and helps advance the nasal tube. Difficulty advancing the tube after it has passed the vocal cords may be overcome by rotating the tube or flexing the neck. The tube then is secured; pressure on the septum or anterior rim of the nares should be avoided.

Although an orotracheal tube usually is placed more rapidly in emergencies, it often stimulates gagging, makes mouth care difficult, and it is more easily kinked or bitten. Anchoring the tube often is difficult because of saliva, and tongue movement may contribute to palatal or tracheal erosion and increase the likelihood of accidental extubation. Trauma to lips, teeth, tongue, and other oropharyngeal structures may occur. Nasotracheal intubation is more comfortable for most conscious patients, causes less stimulation of the gag reflex, is more easily secured, and prevents the problem of biting in patients with seizures, decerebrate rigidity, or extreme agitation. However, bleeding, adenoid injury, sinusitis, and trauma to the nasal turbinates, septum, or nares may occur with nasotracheal intubation, and the risk of sinusitis is greater than with orotracheal tubes.[107,108] Contraindications to nasotracheal intubation include coagulopathy, maxillofacial trauma, CSF leak, and basilar skull fracture.

Videolaryngoscopy

Videolaryngoscopy allows visualization of the larynx without requiring a direct line of sight aligning the oral, pharyngeal, and tracheal axes. In the setting of a difficult airway, video assistance improves visualization and more rapid intubation in adults. Visualization in children is also improved, but experience published to date suggests that the first-pass success rate is lower and time to intubation is longer than with direct laryngoscopy, at least in patients in whom airway visualization is only moderately difficult.[109,110] On the other hand, studies of simulated difficult airway management in infants have shown improved intubation rates without a longer time to intubation.[111] At present, it appears that these devices may be most valuable in very difficult situations, including cervical spine instability and craniofacial abnormalities, rather than as an advance in routine laryngoscopy.[112]

The videolaryngoscope also provides a useful opportunity for teaching airway skills. A duplicate video image allows an instructor to view the attempted intubation in real time and provide immediate guidance and evaluation.

Flexible Fiberoptic Bronchoscopy

Flexible fiberoptic bronchoscopy is an effective means of securing a difficult airway, especially in patients with cervical spine instability or those in whom limited jaw mobility or oropharyngeal lesions prevent good visualization of the larynx.[40,45,113] Assuming the operator's clinical proficiency, the procedure almost always is successful, with little or no trauma to the patient. The nasal route is routinely chosen because it is easier to use, better tolerated, and safer for the instrument than other routes. A topical vasoconstrictive agent and local anesthetic are applied to the nasal mucosa. The endotracheal tube is advanced through the nose into the nasopharynx, and the flexible scope is threaded through it. The scope is advanced through the vocal cords, and the tube is passed over it into the trachea. (Alternatively, the tube with its connector removed may be threaded retrograde over the scope. The scope is advanced through the nose, to the nasopharynx, and through the larynx into the trachea. The endotracheal tube is advanced over the bronchoscope into good position.) The bronchoscopist then visualizes and secures the position of the tube in the trachea and carefully withdraws the scope.

Extubation

Extubation is appropriate when the conditions for intubation are no longer present. In general, this means that the work of breathing has decreased to a level manageable by the patient. In most cases, this situation occurs when oxygenation is adequate with the administration of 40% oxygen or less; spontaneous tidal volume is greater than 3.5 mL/kg; the patient can sustain a normal $Paco_2$ without mechanical breaths with a near normal respiratory rate for age and without the use of accessory muscles; secretions are manageable; upper airway reflexes are intact; and neuromuscular function is sufficiently good to achieve an adequate vital capacity and maximum inspiratory pressure (Table 119-4).[114] Although standard teaching holds that extubation is most likely to be successful when there is an air leak around the ETT at less than 30 cm H_2O, recent study indicates that the presence or absence of a leak is a poor predictor of the success of extubation.[115] If intubation was for relief of upper airway obstruction, direct inspection revealing more normal anatomy is of particular value, and the significance of a leak may be greater. In patients with a previously difficult to manage airway, extubation over a tube changer or in the operating room, with surgical support available, should be considered.[116]

Before extubation, the child is given nothing by mouth for 4 to 6 hours. The tube and pharynx are suctioned thoroughly, and the child is ventilated with 100% oxygen to provide a reservoir of oxygen as a buffer against laryngospasm at extubation. With the lungs fully inflated, the endotracheal tube is removed, and the child is provided with humidified oxygen and observed closely.

Postextubation stridor is common and may range from mild to life-threatening. Children younger than 4 years are most frequently affected by postextubation stridor. Factors contributing to airway edema include a tight endotracheal tube or cuff, traumatic or repeated intubations, excessive movement of the tube (or patient), preexistent airway abnormalities, and airway infection.[117] Cool mist or humidified oxygen is sufficient treatment for children with mild symptoms. Nebulized racemic epinephrine (0.5 mL of a 2.25% solution in 2.5 mL of saline solution delivered intermittently or continuously) effectively relieves more severe upper airway obstruction in most children, probably by local vasoconstriction. Only the l-isomer in the racemic formulation is biologically active. Epinephrine available for cardiovascular use is as safe, effective, and less expensive if half the racemic dose is used. Following its use, edema may recur, so close observation must continue. The value of corticosteroids is more controversial, in part because most studies do not differentiate multiple causes of croup.[118-120] Patients at high risk for post-extubation stridor (e.g., those with multiple intubation attempts) appear most likely to benefit.[121-123] Dexamethasone (0.3 to 0.5 mg/kg every 6 hours for 1 or 2 days) is recommended in selected cases.

The work of breathing through a narrowed upper airway can be decreased by inhalation of a low-density gas mixture. Oxygen in helium is less dense than air or pure oxygen and permits higher inspiratory flow at lower resistance. Helium-oxygen mixtures are commercially available, usually providing 20% oxygen in 80% helium. More oxygen can be added to the mix as needed. Although traditional teaching holds that at least 70% helium is necessary to decrease airway resistance enough to make a clinical difference in the work of breathing, experience demonstrates value at considerably lower concentrations.

If pharmacologic treatment is ineffective, noninvasive ventilatory support may be useful in preventing the need for reintubation, but meticulous attention to the patient's work of breathing is critical to recognize potential catastrophic airway obstruction. Reintubation with a smaller tube for 12 to 24 hours may be necessary, and continued dexamethasone treatment and sedation to minimize agitation and further trauma to the airway may permit resolution of symptoms. Persistent symptoms are an indication for diagnostic laryngotracheobronchoscopy.

Table 119–4 Threshold Values for Low (≤10%) and High (≥25%) Risk of Extubation Failure

Variable	Low-Risk Value (≤10%)	High-Risk Value (≥25%)
V_{tspon} (mL/kg)	≥6.5	≤3.5
Fio_2	≤0.30	>0.40
Paw (cm H_2O)	<5	>8.5
OI	≤1.4	>4.5
FrVe (%)	≤20	≥30
PIP (cm H_2O)	≤25	≥30
C_{dyn} (mL/kg/cm H_2O)	≥0.9	<0.4
V_t/T_i (mL/kg/sec)	≥14	≤8

C_{dyn}, Dynamic compliance; *Fio_2*, fraction of inspired oxygen; *FrVe*, fraction of total minute ventilation provided by the ventilator; *OI*, oxygenation index; *PIP*, peak ventilatory inspiratory pressure; *V_{tspont}*, spontaneous tidal volume indexed to body weight; *V_t/T_i*, mean inspiratory flow.

From Venkataraman ST, Khan N, Brown A: Validation of predictors of extubation success and failure in mechanically ventilated infants and children, *Crit Care Med* 282:991, 2000.

Complications of Endotracheal Intubation

Complications of intubation can be divided into those related to placement of the artificial airway, those that occur while the endotracheal tube is in place, and those related to extubation or appearing late (Table 119-5). Immediate complications usually are related to the underlying disease process, the physiologic effects of laryngoscopy and intubation, or direct trauma to airway structures. The child's general condition, tube size, cuff pressure, movement, airway infection, systemic perfusion, duration of intubation, and attention to meticulous airway care are factors influencing the development of problems during maintenance of the airway.[124] Laryngospasm, aspiration, and failure (or inability) to deflate a cuff cause complications at extubation. Although laryngeal or tracheal injury may be obvious at the time of intubation, symptoms may be delayed 2 to 6 weeks.

Prolonged Intubation

The safe duration of endotracheal intubation in infants and children is not clear. Since the 1950s, the accepted period has increased from less than 12 hours to an undefined much longer period. Subglottic stenosis is reported to occur in 1% to 8% of infants after prolonged intubation, but a similar incidence has been noted after intubation for less than 1 week.[125] In older infants, children, and adults, it is becoming clear that there is no clear "safe" period. Complications can occur immediately at intubation or may not be seen after many weeks or even months with an endotracheal tube in place.[126] The decision to switch to tracheostomy should not be based on an arbitrary time limit but rather on the relative advantages and disadvantages of one artificial airway over another in each individual patient.

Special Circumstances

Full Stomach

Patients with a full stomach are at high risk for aspiration of gastric contents during airway manipulation, particularly if protective airway reflexes are impaired. Much of the morbidity associated with aspiration can be attributed to the effects of acid aspiration. Aspiration of fluid with a pH below 1.8 is associated with a very high incidence of severe pulmonary dysfunction and death. Aspiration of fluid with a pH between 1.8 and 2.5 produces symptoms of moderate severity. When fluid with a pH above 2.5 is aspirated, sequelae are less a consequence of the acid than of other characteristics of the material

Table 119–5 Complications of Endotracheal Intubation

Immediate	Maintenance	Extubation/Late
PHYSIOLOGIC		
Hemodynamic instability	Obstruction	Laryngospasm
Dysrhythmias	Sinusitis	Gagging, vomiting
Apnea	Otitis (similar to immediate)	Aspiration
↓ P_{AO_2}		Sore throat
↑ P_{aCO_2}		Dysphonia, aphonia
Coughing		
Laryngospasm		
Gagging, vomiting, regurgitation, aspiration		
↑ Intracranial pressure		
↑ Intraocular pressure		
TRAUMATIC		
Nasal septum laceration, perforation	Lip, tongue ulceration	Laryngeal or tracheal granuloma
Nasal turbinate injury	Nares ulceration	Vocal cord paralysis
Tooth loss or injury	Palatal erosion, cleft formation	Subglottic stenosis
Lip, tongue, palate laceration, hematoma	Vocal cord edema, ulceration	
Tonsillar or adenoid avulsion, laceration, hematoma	Laryngeal and tracheal mucosal ischemia, ulceration, necrosis	
Laryngeal strictures	Recurrent laryngeal nerve damage	
Cervical spine subluxation	Subglottic edema, ulceration	
ESOPHAGEAL POSITION		
Malposition		
Esophageal	Mainstem intubation	
Mainstem bronchus	Inadvertent extubation	
Intracranial	Atelectasis	
Soft tissue		

aspirated.[127] Other risk factors include the volume aspirated, the presence and nature of particulate food particles, contamination by bacterial pathogens, underlying pulmonary or systemic disease, and immunosuppression.[128]

Food particles may physically obstruct small or even large central airways, with the expected alterations in lung volume in segments distal to the obstruction. In addition, certain foods may cause severe local inflammatory changes. Bacterial contamination of the upper gastrointestinal tract secondary to bowel obstruction or even antacid administration greatly increases the risks of respiratory infection following aspiration.

Patients who have eaten shortly before intubation (<6 hours) should be assumed to have a full stomach. In addition, those with bowel obstruction, pharyngeal or upper gastrointestinal bleeding, trauma, or acute onset of illness within 6 hours of eating and those who are pregnant or who have ileus or tense abdominal distension from any cause should be considered to have a full stomach.

Although delaying airway manipulation might be the measure most certain to prevent aspiration, such an approach is not a realistic option in most situations confronting the intensivist. In a conscious child, the volume of gastric contents can be minimized by suction through a relatively large-gauge nasogastric tube, but complete emptying of the stomach, particularly of large food particles and blood clots, is rarely possible. Although H2 antagonists such as famotidine or ranitidine effectively decrease both the volume and acid content of gastric secretions, an adequate effect requires 60 to 90 minutes following administration of these agents. Neither antacid nor H2 blockers decrease the volume of gastric contents already present in the stomach. Anticholinergic agents such as atropine or glycopyrrolate also reduce gastric acidity but slowly and less effectively than the H2 antagonists. In addition, they may decrease gastroesophageal sphincter tone and appear to have no value in preventing the acid aspiration syndrome.

Antacids can effectively neutralize gastric pH. However, when aspirated, particulate antacids (aluminum and magnesium hydroxides) produce inflammatory changes as severe as gastric acid and food particles. Clear antacids, such as sodium citrate or Alka-Seltzer, appear to provide true protection. They effectively increase gastric pH and, when aspirated, appear to produce damage no more severe than that caused by normal saline solution. However, their use has not become common clinical practice.

Intubation is at once protective of the patient vulnerable to gastric aspiration and itself a risk to the patient. In an alert child with intact protective airway reflexes, it may be appropriate to pass a nasogastric tube to decrease the volume of gastric contents. A clear antacid (e.g., sodium citrate, 10 to 30 mL) can be administered orally or through the tube, which then is removed. In a child with impaired reflexes, no effort to pass a nasogastric tube should be made because of the risk of inducing vomiting or regurgitation with subsequent aspiration.

The intensivist should examine the patient's airway to be as certain as possible that intubation will not be difficult, as discussed previously. If intubation likely will be straightforward, a rapid-sequence intubation is indicated (Box 119-4). The goal of this method of intubation is to minimize the likelihood of vomiting or regurgitation and the time between loss of protective reflexes and correct positioning of the endotracheal tube. The sequence consists of preoxygenation, administration of an intravenous sedative or anesthetic with immediate cricoid pressure, pharmacologic paralysis, and endotracheal intubation. Properly applied, cricoid pressure probably decreases the likelihood of insufflation of gas into the stomach or regurgitation of gastric contents into the trachea and may improve visualization of the larynx (see Figure 119-9).[103,129-131] On the other hand, excessive pressure may actually increase the likelihood of vomiting, occlude the trachea, or make visualization more difficult.

The patient spontaneously breathes 100% oxygen by mask for 3 to 5 minutes before further manipulation. If the child can cooperate and has relatively normal gas exchange, four deep breaths provides a reasonable pulmonary reservoir of oxygen. However, in patients with severe pulmonary parenchymal disease, improvement in oxygenation may be limited and require a longer period of oxygenation.[132] If other factors in the child's condition permit, next steps in the rapid sequence intubation should be delayed until hemoglobin saturation reaches 100% or oxygenation reaches a plateau. Once preoxygenation is complete, the anesthetic or sedative is administered by rapid intravenous infusion, cricoid pressure is applied immediately by an assistant, and, as consciousness is lost, a muscle relaxant is given. The mask supplying oxygen is kept in place until the patient becomes apneic, but no effort to assist ventilation is made in order to avoid gastric distension and regurgitation. Once the patient is flaccid and apneic, the intensivist performs laryngoscopy and intubates the patient. Using a stylet in the endotracheal tube facilitates rapid intubation. Only after correct tube position is verified and the tube cuff, if present, is inflated should cricoid pressure be relieved and manual ventilation begun. In the case of unexpected difficulty intubating the patient and evidence of progressive hypoxemia, manual ventilation between attempts may be necessary but should be done with continued cricoid pressure.

Box 119–4 Rapid-Sequence Intubation for Full Stomach

Indications

Food intake <4–6 hours before intubation
Pharyngeal or upper gastrointestinal bleeding
Intestinal obstruction or ileus (includes acute onset of illness)
Tense abdominal distension
Pregnancy

Relative contraindications

"Difficult" airway
Profuse hemorrhage obscuring visualization
Upper airway obstruction
Increased intracranial pressure

Procedure

Prepare *all* necessary equipment, including suction devices
Allow patient to breathe 100% oxygen for 3 minutes
Direct assistant to apply cricoid pressure
Rapid intravenous infusion of anesthetic or sedative/analgesic and neuromuscular blocking agents
Allow patient to continue to breathe oxygen until apneic
Avoid manual ventilation to minimize gastric distension
Perform laryngoscopy and orotracheal intubation with stylet in endotracheal tube
Confirm endotracheal tube placement
Release cricoid pressure

The "classic" combination of drugs used for rapid sequence induction/intubation is sodium thiopental (4 to 6 mg/kg) and succinylcholine (1 to 4 mg/kg) with a prior defasciculating dose of a nondepolarizing muscle relaxant such as vecuronium. In hemodynamically unstable patients, alternative drugs include ketamine or a benzodiazepine alone or in combination with a short-acting narcotic. As previously discussed, etomidate has been a popular agent, but growing evidence suggests its use is inappropriate in patients with shock, especially with presumed sepsis. Succinylcholine has multiple undesirable adverse effects (as noted previously) that may include increased intragastric pressure. Most of the nondepolarizing relaxants, when given in amounts two to three times the usual intubating dose, produce good conditions for intubation nearly as quickly as does succinylcholine (60 to 90 seconds) and without adverse effects but lasting longer. Rocuronium is the current best alternative, with its rapid onset and short duration of action. Table 119-3 lists suggested drugs and doses.

Increased Intracranial Pressure and Neurologic Dysfunction

The intensivist is frequently called upon to intubate children with severe central nervous system dysfunction resulting from infection, hemorrhage, trauma, hydrocephalus, or mass lesions, any of which may be associated with actual or imminent intracranial hypertension and herniation. The pathophysiology of such disorders is discussed in depth in Section IV.

In most circumstances the intensivist can observe signs of elevated ICP or recognize settings where the likelihood is high, but there is no clinical measure of its severity. Current guidelines recommend intubation for patients with a Glasgow Coma Scale score of 8 or less.[133] Intubation under these conditions should be undertaken with the recognition that it is a likely stimulus for further and potentially lethal intracranial hypertension. The most immediate means of lowering ICP involves decreasing CBF (volume) through hyperventilation. Unfortunately, the process of intubation likely will decrease minute ventilation and increase cerebral blood volume for this and other reasons, as previously discussed.

Under normal circumstances, CBF is closely coupled to the cerebral metabolic oxygen requirement ($CMRo_2$). Cerebral oxygen consumption and blood flow increase with increasing body temperature, motor activity, pain or other noxious stimuli, and seizure activity. Blood flow also increases rapidly when Pao_2 falls below 50 to 60 mm Hg and linearly as $Paco_2$ increases over a wide range. With intact autoregulation, blood flow is independent of systemic blood pressure except at very high or low levels, but when autoregulation is impaired, mean arterial pressure may affect CBF over a much broader range. Elevated intrathoracic pressure during struggling, coughing, or Valsalva maneuvers may impede jugular venous drainage and result in intracranial venous congestion.

Laryngoscopy and intubation are powerful noxious stimuli. In the awake unsedated child and even in the severely obtunded patient, laryngoscopy and intubation likely will precipitate vigorous struggle, coughing, pain (anxiety), and marked evidence of autonomic stimulation.[25,38,39,134] In most patients, sympathetic discharge predominates with tachycardia, hypertension, and diaphoresis. In the infant, vagal stimulation often predominates with resulting bradycardia.

Even in the lightly anesthetized patient, laryngoscopy itself and then intubation are associated with hypertension, tachycardia, and increased ICP. As might be predicted, massive surges in ICP are more likely to occur in patients suspected of having borderline or high baseline ICP before intubation than in those with intracranial pathology with well-compensated or previously controlled pressure. Arterial hypertension may precipitate further hemorrhage in the child with a vascular malformation, coagulopathy, or bleeding into a tumor. ICP waves may reduce cerebral perfusion pressure to ischemic levels or cause frank herniation.

Given the risk of life-threatening systemic and intracranial hypertension in these patients, it is clear that laryngoscopy and intubation should be undertaken with every effort to minimize stimulation and associated struggle.[89,135-137] In general, this implies ensuring excellent oxygenation, ventilation, and intubation under protection of profound sedation or anesthesia, with the assistance of neuromuscular blockade (Box 119-5). Neurologists and neurosurgeons are frequently loathe to relinquish the opportunity to examine the patient following intubation, but the risk of life-threatening intracranial hypertension justifies temporarily obscuring the neurologic examination. In most cases, adequate assessment is possible before intubation, and diagnostic studies require deep sedation for a period afterward.

The patient is provided 100% oxygen by bag and mask. An anesthetic or sedative agent in combination with a neuromuscular blocking agent is given, and manual ventilation is initiated to lower ICP as much as possible before airway manipulation. Although extreme hyperventilation may decrease CBF to ischemic levels, current guidelines support ventilation to a $Paco_2$ of approximately 30 to 35 mm Hg for patients with intracranial hypertension.[138]

In the hemodynamically stable patient, thiopental provides relatively deep anesthesia associated with a rapid decline in $CMRo_2$, CBF, and ICP.[135,137] Alternative agents include

Box 119–5 Intubation for Increased Intracranial Pressure

- Prepare equipment
- Monitor heart rate, blood pressure, and arterial oxygen saturation
- Provide 100% oxygen and assisted ventilation as tolerated by patient
- Consider possible difficult airway
- If no airway contraindications, administer anesthetic and neuromuscular blocking agents:
  - Associated cardiovascular compromise or hypovolemia:
    - Midazolam (0.2–0.3 mg/kg IV) and fentanyl (5–10 μg/kg IV) plus lidocaine (1.0–1.5 mg/kg IV) and rocuronium (0.6–1.2 mg/kg IV) or other relaxant; consider etomidate (0.3 mg/kg IV)
  - No associated cardiovascular compromise or hypovolemia:
    - Thiopental (4–6 mg/kg IV) plus lidocaine (1.0 mg/kg IV), plus rocuronium (0.6–1.2 mg/kg IV) or other relaxant
- Ventilate patient until drug effect achieved (consider short-term hyperventilation in patients with signs of critically elevated intracranial pressure)
- Perform laryngoscopy and orotracheal intubation

IV, Intravenous.

narcotic analgesics alone or in combination with a benzodiazepine, which has less hemodynamic effect but also less effect on $CMRo_2$ unless given in anesthetic doses.

Etomidate is widely used in patients with suspected intracranial hypertension. Its ability to decrease CBF without apparent detrimental effect on systemic hemodynamic stability makes it a useful agent, although concerns about its effect on adrenal function, perhaps even following a single dose, require caution in the patient with sepsis or shock. Because it lacks analgesic properties, combining it with an intravenous narcotic agent should be considered.

Lidocaine, 1 to 1.5 mg/kg, decreases $CMRo_2$ and modestly decreases the systemic and intracranial hypertensive response and the cough reflex, as long as a dose below the seizure-producing threshold is used. Effective serum concentrations are obtained more quickly and at lower doses by the intravenous route than when the agent is administered endotracheally. The available literature addresses patients fully premedicated and monitored undergoing neurosurgical procedures or patients already intubated, ventilated, and monitored in the ICU. Studies addressing intubation in the acute setting are lacking and unlikely to be accomplished.[138-142]

Although the classic recommendation has been to avoid ketamine in patients with elevated ICP because of its potential to further increase pressure, newer studies suggest that ketamine may be safe in this population. It does, however, increase systemic blood pressure and CBF and most likely should be avoided in patients at risk of failed autoregulation until further evidence is available.[74,143-145] In addition, evidence that ketamine is associated with neuronal injury in immature animal models supports continued caution with respect to its use in patients with elevated intracranial pressure.

In nearly all patients, orotracheal intubation is preferred because it is accomplished quickly and easily with less risk of prolonged manipulation and interrupted ventilation. Nasotracheal intubation is contraindicated in patients with basilar skull fractures and CSF leaks as a potential source of infection or even perforation of the cribriform plate and intracranial tube placement.

Cervical Spine Instability

Flexion and extension of the head on the neck occur between the atlas (C1) and the basiocciput. Rotation occurs between the atlas and axis (C2), as the thin arch of the atlas pivots around the odontoid process. Below the axis, the cervical vertebrae articulate with each other anteriorly at the intervertebral disks and posteriorly at the facet joints. Further neck flexion and extension occur at these joints. Anterior and posterior ligaments complete the stable spine.

Spinal cord injury generally occurs as a result of bony fracture, compression, or disruption of cervical ligaments. In young children, actual ligamentous disruption or bony fracture is not necessary for severe cord injury, even transection, to occur; extreme stretching, as may occur in acceleration or deceleration injury, is sufficient.[146-148] Instability results from disruption of both the anterior and posterior columns. Congenital or degenerative anatomic abnormalities, penetrating wounds, or expanding mass lesions in the spinal canal may compromise cord integrity.

During routine intubation, the intensivist flexes the neck and extends the head. In children with known or suspected cervical spine injury or instability resulting from other causes (e.g., Down syndrome or rheumatoid arthritis), manipulating the head and neck for intubation risks extending the existing condition or injury and may precipitate new problems. Cervical spine films and knowledge about the nature of the traumatic event help define the precise injury and predict maneuvers most likely to do harm, but such information rarely is complete and may be falsely reassuring.

The ideal approach to intubation in this setting is controversial.[149-152] Although evidence in cadavers, in addition to common sense, indicates that typical airway maneuvers can cause anterior or posterior subluxation or widening of the disk space, evidence in patients is lacking.[153] Axial traction increases distraction and even subluxation in some patients[154]; in others traction is helpful. However, information about the appropriate amount of force or the correct plane in which it should be applied is rarely sufficient to make a timely informed decision. Therefore immobilization of the head and neck in the midline without traction is recommended.

Current advanced trauma life support guidelines no longer recommend blind nasotracheal intubation.[155,156] Orotracheal intubation is more reliably accomplished and less time-consuming than blind nasotracheal intubation and is associated with far fewer complications, including tube malposition and bleeding, even in adults.[157] The high anterior location of the pediatric larynx makes nasotracheal intubation even more difficult in young children. As a result, it is rarely a necessary or desirable choice for emergency airway stabilization in children.

Just as manipulation of the airway for intubation may risk additional cord injury, patient movement can cause additional damage. Few children of any age will tolerate awake intubation by any route without violent struggle. Even heavily sedated patients likely will cough upon stimulation of the airway.

Patients with spinal cord injuries are at risk for extreme hyperkalemia and resulting dysrhythmias or cardiac arrest following administration of succinylcholine. This response occurs from approximately 48 hours to 6 to 9 months after injury. Cervical injury often also disrupts sympathetic nervous system outflow and results in unopposed vagal tone and severe bradycardia. For these reasons, in most instances intubation is best accomplished in these patients via the orotracheal route, using an intravenous anesthetic or combination of sedative and analgesic agents, atropine, and a nondepolarizing neuromuscular blocking agent with an assistant immobilizing the head and neck in neutral position with one hand over the ear on each side of the head. If time, equipment, and available expertise permit, fiberoptic bronchoscopy may assist visualization of the larynx and intubation with minimal head or neck movement.[158]

If orotracheal or nasotracheal intubation cannot be accomplished because of associated facial or airway injuries or other technical obstacles, cricothyrotomy or primary tracheotomy may be indicated. However, no data support either the necessity or safety of routinely using a surgical approach before attempting orotracheal intubation.

Upper Airway Obstruction

Upper airway obstruction may result from many disorders (see Chapter 39). When symptoms are related to loss of oropharyngeal muscle tone, changing the patient's position,

reversing the effects of a drug, or placing a nasal airway may be sufficient, if the duration of the underlying process likely will be brief. However, when airway structures likely are severely or progressively distorted by edema, inflammation, trauma, or another space-occupying process, achieving an endotracheal airway is necessary.

Patients should be allowed to assume whatever position is most comfortable. Supplemental oxygen is provided at the maximum concentration possible, but a young child's anxiety should not be heightened with an overly aggressive approach with a mask. Contrary to popular belief, breathing can be assisted in nearly all cases by application of positive pressure, initially with continuous positive airway pressure and then gradually with assisted breaths.

In general, no action should be taken that compromises the child's ability to breathe spontaneously until the capacity to control ventilation is certain. In particular, use of neuromuscular blocking agents is dangerous and inappropriate until after the airway is controlled. Distortion of the airway may be so extreme that recognition of landmarks for intubation is impossible, and loss of pharyngeal tone in such patients may remove the last barrier to complete airway occlusion. However, reducing a child's anxiety with cautious sedation (with a reversible agent) may decrease peak inspiratory flow rate and symptoms of obstruction and make it easier to assist breathing and establish an artificial airway. When possible the child is gently lowered to a supine position (or to 30 degrees) and intubated by the orotracheal route. When time and available expertise permit, intubation in the operating room using an inhalational anesthetic in a high oxygen concentration allows spontaneous breathing until the patient is deeply anesthetized and untroubled by airway manipulation. This method may be especially helpful in cases of supraglottitis. In most cases, the proper tube size is 0.5 to 1.0 mm smaller in diameter than predicted for age because of airway inflammation and edema, and no leak will be present.

Extubation usually is well tolerated when a leak has developed.

Facial and Laryngotracheal Injury

Children with facial injuries present airway problems nearly as varied as the injuries themselves. Appropriate management depends primarily on accurate assessment of airway patency at presentation, the rate of bleeding (if any) into the airway, and the amount of additional swelling and distortion likely to occur later. Evaluation of possible ocular and intracranial injury must proceed simultaneously.

Profuse bleeding, unstable facial fractures, or aspiration of blood, gastric contents, or teeth causes early respiratory distress. Maxillary fractures may result in a free-floating maxilla with occlusion of the nasopharynx and pressure on the tongue. Isolated mandibular fractures often cause trismus but rarely cause airway obstruction or interfere with visualization of the larynx.

Airway management begins with suctioning blood and debris from the mouth and pharynx. If permitted by other injuries, the child is placed with the head down and turned to the side. The tongue and maxilla are pulled forward manually if necessary. A spontaneously breathing patient receives oxygen by mask and may not require further intervention before surgery. Patients with persistent obstruction may require an immediate artificial airway.

In most cases, orotracheal intubation is accomplished first. If ventilation can be assisted with bag and mask and bleeding is controlled, the patient may be sedated, paralyzed, and intubated with full stomach precautions. If bag-mask ventilation exacerbates airway obstruction, awake intubation may be necessary. Uncontrollable bleeding, inability to visualize the larynx, or violent struggle in a child with cervical spine instability or evidence of increased ICP may make a primary tracheostomy desirable. Nasotracheal and nasogastric tubes are avoided until the possibility of a basilar skull fracture and CSF leak is eliminated.

Laryngotracheal injuries may be subtle or dramatic. They should be suspected in children with a history of anterior neck trauma and often cause hoarseness, stridor, subcutaneous emphysema, pneumothorax, or pneumomediastinum. Aerosolized epinephrine may temporarily decrease swelling and provide a little extra time to evaluate the airway and plan intervention. Awake intubation with cautious sedation and topical anesthesia that is conducted under direct vision by laryngoscopy or fiberoptic bronchoscopy minimizes the risk of sudden, complete obstruction or creation of a false passage adjacent to the airway.

Open Globe Injury

Children with penetrating eye injuries may require emergency intubation for respiratory failure resulting from associated injuries or other underlying problems. Management in these cases seeks to prevent increased intraocular pressure with subsequent extrusion of the vitreous and permanent blindness. Intraocular pressure can be increased by struggling, crying, coughing, straining, or rubbing the eye. Hypoxia and hypercarbia can increase intraocular pressure. In general, central nervous system depressants lower intraocular pressure, with the possible exception of ketamine. Intubation should be performed smoothly under full muscle relaxation if possible, taking into consideration associated injuries and the risk of a full stomach.

The child should be preoxygenated with 100% oxygen, taking care not to apply pressure to the eye with the mask. Efforts to empty the stomach are delayed until the patient is fully relaxed and intubated. In hemodynamically stable patients, thiopental or other rapidly acting sedatives/anesthetics are administered, followed by a nondepolarizing neuromuscular blocking agent if other airway anatomy permits. Succinylcholine, a depolarizing relaxant, has been associated with increased intraocular pressure, even in the absence of fasciculations. As in patients with head trauma, a combination of sedative and analgesic agents may replace thiopental if hemodynamic stability is uncertain. Lidocaine supplements the effect of other agents in blunting the rise in intraocular pressure that may occur even during a smooth intubation. Heavy sedation or paralysis should be maintained following intubation until after repair.

Alternative Approaches to the Airway

Lighted Intubation Stylet (Light Wand)–Assisted Intubation

A number of lighted intubation stylets have become available in the past decade. Each uses transillumination of the neck to guide placement of an endotracheal tube. The devices consist

of a handle containing the power source and a malleable wand (stylet) with a light at the tip. Pediatric versions accommodate tubes as small as 3.5 mm.

Use of the lighted stylet for intubation is a technique recommended for use in patients with airways that are difficult to manage. Reported experience in children is limited, but the technique has been successful in the hands of both highly skilled and novice operators.[159-163] The equipment is fairly simple to use and easy to learn. It does not require visualization of the airway, is less stimulating than laryngoscopy, allows nasal or oral intubation, and is portable and relatively inexpensive. Reported series indicate that mucosal and dental injuries are uncommon, and sore throat is less of a problem than following standard laryngoscopy.[164] Because intubation may be accomplished from the patient's side, it may be useful in awkward settings such as emergency transport vehicles.

Potential disadvantages include trauma to the upper airway and larynx. Anything that obscures transmission of light through the anterior neck interferes with its use, including scarring, massive edema, subcutaneous emphysema, or mass lesions. Profuse bleeding or thick airway secretions that obscure the bulb also interfere with effective use.

A lubricated lighted stylet is inserted through an endotracheal tube of desired size until the light is just short of the end of the tube, and the tube is firmly attached. The tube and stylet are bent to approximately 90 degrees, just proximal to the cuff if present. Dimming the room lights improves appreciation of the transillumination. The intubator may stand at the head of the bed or to the side of the patient. The head is extended. A shoulder roll may be useful. The mandible and tongue are pulled forward and upward by the intubator, and the styletted tube is introduced into the patient's mouth in the midline. It is advanced into the pharynx, while the operator observes transillumination of the soft tissues of the neck. Entry into the airway typically is recognized by the presence of a focused glow of light in the midline below the thyroid prominence; more diffuse light suggests esophageal placement. The tube is advanced until the light is at the level of the sternal notch. The lighted stylet is withdrawn and placement is confirmed with capnography.

Nasal intubation is possible with the light wand. In this case, the trocar is removed to increase the flexibility of the device. When a glow is noted above the thyroid prominence, the tube is likely in the vallecula. The epiglottis can be moved out of the way with a jaw thrust, allowing further advancement of the tube into the trachea. An alternative is to flex the patient's neck, as is sometimes necessary with visualized nasotracheal intubation.

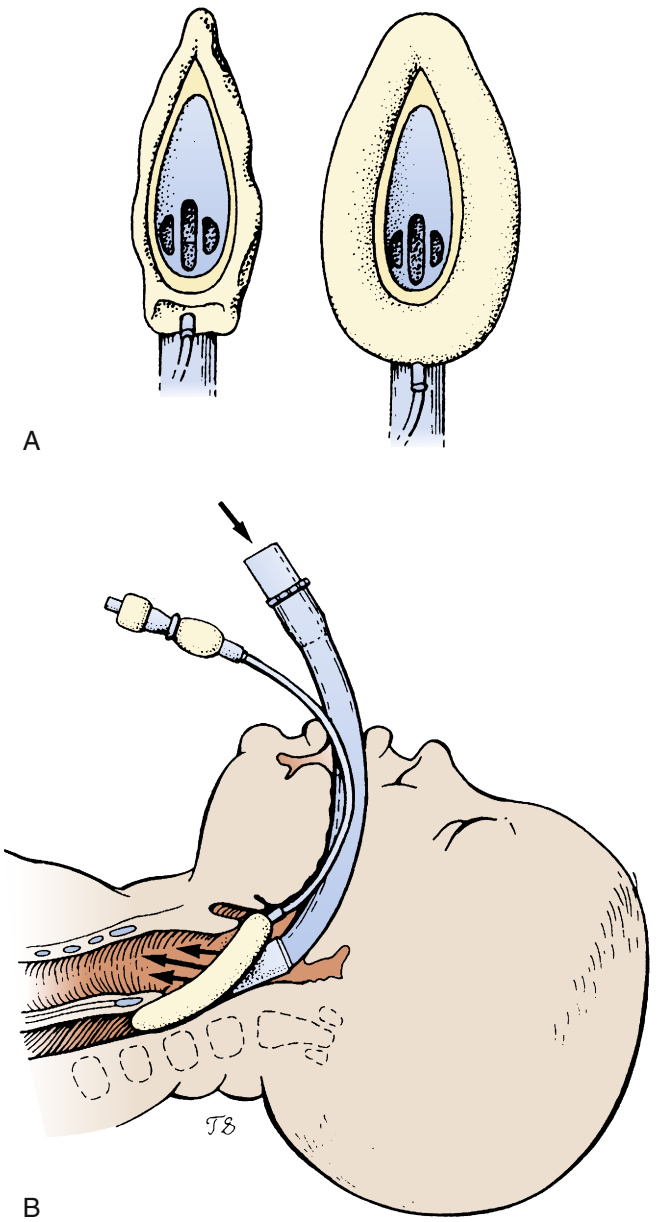

Figure 119–11. LMA. **A,** Mask portion of the airway with the rim deflated for insertion (*left*) and inflated (*right*). **B,** LMA in position, with the rim inflated around the laryngeal inlet. *(From Efrat R, Kadari A, Katz S: The laryngeal mask airway in pediatric anesthesia: experience with 120 patients undergoing elective groin surgery,* J Pediatr Surg *29:206, 1994.)*

Laryngeal Mask Airway

The laryngeal mask airway (LMA) is a relatively new and fairly safe means of securing a difficult to manage airway in an infant or child.[165-167] It was designed to provide a supraglottic airway device that would offer the benefit of noninvasive ventilation. Its use rapidly gained acceptance in anesthesiology and has been incorporated into the American Academy of Anesthesiology difficult airway algorithm.[46] It consists of a small mask with an inflatable rim and a tube with a "universal adaptor," which permits attachment to a resuscitation or anesthesia bag or ventilator (Figure 119-11). The original LMA consists of a wide-bore tube designed to sit in the hypopharynx and is attached to an inflatable bowl-shaped base that bypasses the tongue, sits around the epiglottis, conforms to the shape of the larynx, and provides a low-pressure seal around the supraglottic area.[168] The LMA is available in a wide range of sizes, allowing use in very small infants to very large adolescents and adults. Choice of LMA size is based on weight: size 1 for patients weighing 2.5 to 6.0 kg, size 2 for patients weighing 6.0 to 30 kg, and size 3 for patients weighing more than 30 kg.[169,170] Since the initial development of the LMA, several other types have been designed, including the flexible LMA, intubating LMA, disposable LMA, and ProSeal LMA, not all of which are available in pediatric sizes.[171]

The insertion technique can be learned quickly by physicians and other providers, including emergency transport personnel, often more quickly than endotracheal intubation. Experience with a mannequin appears to be effective training. Once in place, the LMA can serve as a means of ventilating the patient until the desired definitive airway can be established. It can facilitate subsequent tracheal intubation, if desired, either with blind technique or via fiberoptic bronchoscopy.

Insertion of the LMA does not require muscle relaxation or the use of a laryngoscope and is therefore considered a "blind" technique. Topical anesthesia, with lidocaine spray or lidocaine jelly applied to the inflatable rim, is helpful in patients with intact protective airway reflexes who are awake. With the rim deflated or partially inflated, the LMA is advanced along the posterior pharyngeal wall with the dorsum of the mask facing the palate until resistance of the upper esophageal sphincter is encountered. The cuff is then inflated, forming a seal around the laryngeal outlet, and the attached tube is connected to a source of oxygen and positive pressure (Figure 119-12).

Proper placement is essential but is most uncertain in infants requiring the LMA size 1, most likely because the margin of error for placement in the small pharynx is so small. In general, the risk of downfolding the epiglottis, thus occluding the trachea, is greater in children than in adults. Successful placement depends on the shape and tone of the pharynx, adequate matching of the cuff, the palatopharyngeal curve and shape of the posterior pharynx, the extent to which anterior structures (such as tonsils) obliterate the curve, the position of the head and neck, efficacy of digital manipulation, and the depth of anesthesia/sedation, muscle relaxation, or loss of airway reflexes.[166] Tissue trauma is uncommon, and the need to manipulate the cervical spine during placement is minimal. In most patients the autonomic response to placement is less pronounced than with laryngoscopy and intubation. On the other hand, the device does not fully protect against aspiration in the setting of a full stomach. In addition, it may not be effective in patients with glottic or subglottic pathology.

Although its primary use is in the operating room, growing experience demonstrates that the LMA can be lifesaving in a variety of other settings when no other nonsurgical means of maintaining an airway is successful, particularly in patients with anatomically abnormal airways.[172] Success with airway management in the operating room with children with airways that are anticipated to be difficult to manage, including patients with Pierre Robin, Treacher Collins, and Goldenare syndromes, suggests that the LMA would be valuable for managing such patients in emergency settings such as the emergency department or ICU. The ease and rapidity of insertion and decreased gastric air insufflation during resuscitation make it a valuable tool when intubation fails during adult resuscitation.[173] The current Pediatric Advanced Life Support

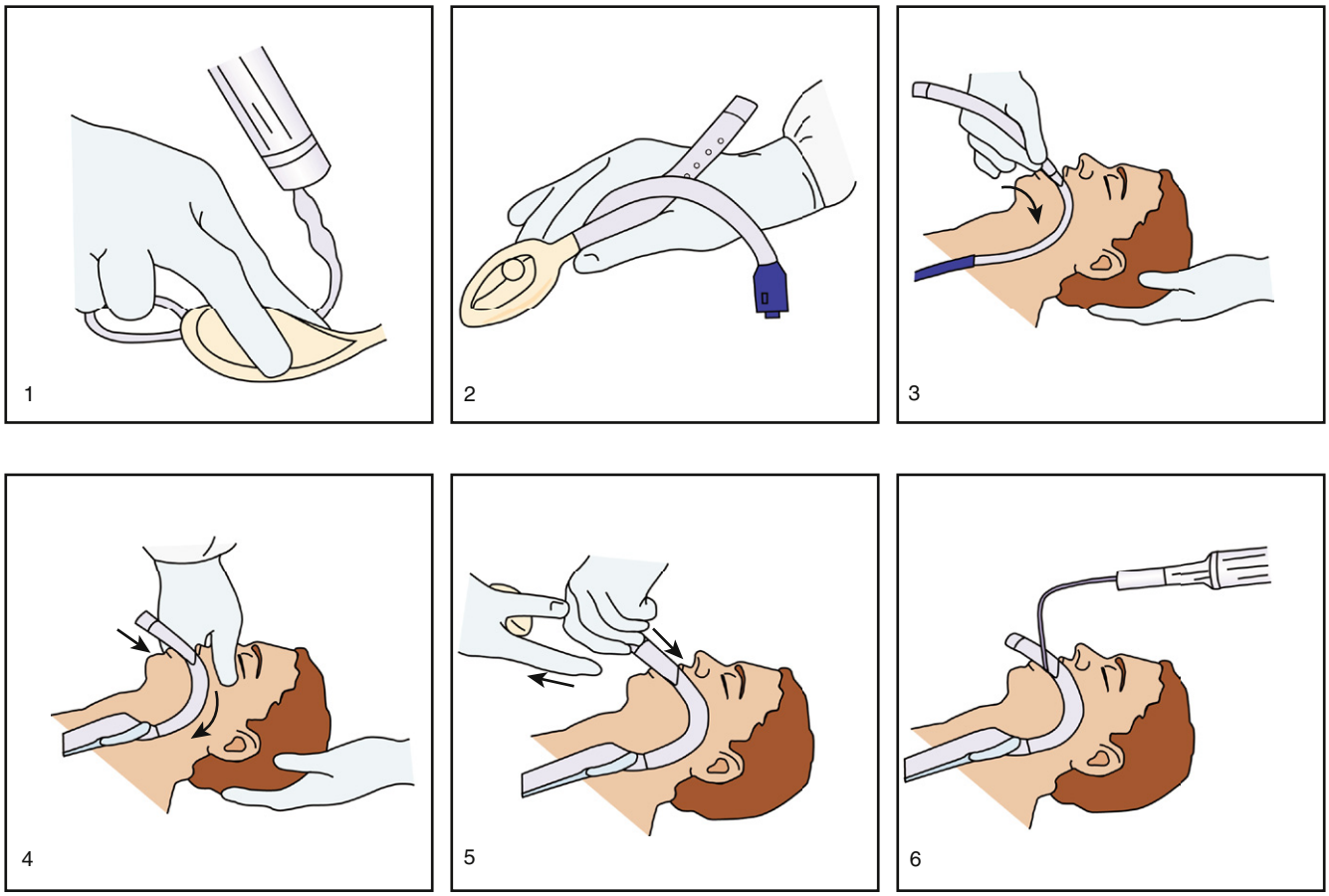

Figure 119–12. Inserting the LMA. Preoxygenate the patient as necessary. *1,* Deflate the cuff against a flat surface with index finger and middle finger on either side of the bowl. *2,* Hold the LMA like a pen, with the index finger at the junction of the tube and mask. *3 and 4,* Insert the LMA into the mouth and advance, following the palate and posterior pharyngeal wall until resistance is met. *5,* Let go of the mask and tube. *6,* Inflate the cuff, allowing the device to move into correct position. *(Modified from* Ambulance technician study, *http://www.ambulancetechnicianstudy.co.uk/.)*

textbook supports the LMA as an effective alternative to intubation during resuscitation when inserted by trained providers.[174] In neonatal resuscitation, when face mask ventilation or intubation is not successful, the LMA provides a means of rapidly improving oxygenation and heart rate. It is not, however, effective for aspirating meconium and may be inadequate for infants with severely noncompliant lungs. Use by prehospital personnel has been effective for critically ill adults, but experience in children in the field has not been reported.[175,176]

The LMA is poorly tolerated by patients with intact protective reflexes, so its use is largely limited to those with severely depressed levels of consciousness or heavy sedation or anesthesia. Lidocaine jelly on the inflatable rim or lidocaine pharyngeal spray may promote tolerance in patients with active airway reflexes. A disadvantage with use of the LMA is the inability to use airway pressures greater than approximately 20 mm Hg to prevent air leaking around the mask and to avoid gastric distention, and therefore it is not an optimal airway device in patients with severe subglottic airway obstruction, parenchymal disease requiring high ventilatory pressures, or in obese persons.[177] It also is not the ideal technique to use in a patient with a full stomach because its design does not prohibit aspiration of gastric contents. However, in an emergency situation the benefit of providing oxygenation and ventilation via an LMA outweighs the risk of an aspiration event. Other scenarios that may limit placement of the LMA include excessive neck extension, limited mouth opening, or excessive application of cricoid pressure.[177]

Although the seal is somewhat protective, patients with a full stomach remain at risk for aspiration. Positive airway pressure should be minimized as much as possible and a nasogastric tube passed to decrease gastric distension. Cricoid pressure may further decrease the risk of aspiration but also may interfere with proper LMA placement. If desired, an endotracheal tube can be inserted through the mask, either blindly or with fiberoptic bronchoscopy.[178]

Tracheostomy

Indications for tracheostomy include structural abnormalities of the upper airway requiring surgery, laryngeal trauma or complex craniofacial injury, severe facial burns, congenital anomalies lacking surgical treatment, vocal cord paralysis, and iatrogenic injury to the upper airway. Severe chronic neurologic dysfunction with impaired protective reflexes is an additional indication. Even in the absence of evidence of upper airway damage, tracheostomy may be performed to provide a more comfortable airway, which simultaneously allows airway protection, respiratory support, and greater patient mobility so that nutritional, developmental, and psychosocial needs may be met, especially, but not only, in patients undergoing chronic ventilation.[179-182]

Tracheostomy spares laryngeal and subglottic structures from the trauma of an artificial airway, particularly in active or thrashing patients. Tracheostomy tubes are less likely to be inadvertently dislodged or to become obstructed, but if either problem occurs early following tracheostomy, it is more likely to be catastrophic. Because the tube is inserted below the cricoid ring, it often is possible to use a larger tracheostomy tube than endotracheal tube. Nevertheless, a larger leak around the tube may interfere markedly with effective ventilation in patients requiring high airway pressures.

Complications in the early postoperative period include bleeding, subcutaneous air dissection, pneumothorax, pneumomediastinum, injury to the recurrent laryngeal nerve, and death, usually as a consequence of loss of control of the airway intraoperatively or an unrecognized complication from the preceding list. Nearly all pediatric patients can and should be intubated before tracheostomy. Prior intubation decreases the incidence of most technical problems. Exceptions include patients with complex facial or airway injuries or deformities and those in whom no other means of establishing an airway have been successful. Wound colonization occurs rapidly. Bacterial infection may occur, rarely involving major cervical and mediastinal structures. Swallowing difficulty is common and may result from the tube and fixation tapes limiting excursion of the larynx. Aspiration may result from alteration of the laryngeal closure reflex.

Tracheostomy tube obstruction or accidental dislodgment is suspected when the patient becomes agitated and shows signs of increased respiratory distress, a suction catheter no longer passes freely, manual ventilation is ineffective, or, in case of dislodgment, the child is suddenly able to vocalize. In such cases the tube should be removed and replaced with a new one. The child is placed supine with the head and neck extended. Oxygen is delivered to the nose, mouth, and tracheal stoma. If manual ventilation is necessary, the stoma can be occluded to allow bag-mask ventilation as previously described. A fresh tracheostomy tube is inserted, initially directly posteriorly and then caudad. Replacement with a smaller tube or endotracheal tube may be necessary if resistance is encountered. Resistance to passage of a suction catheter or ineffective ventilation following replacement of a tracheostomy tube, particularly in the first 7 to 10 days postoperatively, is highly suggestive of creation of a "false passage" in a tissue plane outside the tracheal lumen. Reestablishing tracheal cannulation may require surgical intervention. Life-threatening pneumothorax or pneumomediastinum occurs frequently in such patients.

Late complications include granuloma or stricture formation at the stoma or where the tip of the tube meets the tracheal wall. Persistent posterior wall pressure may cause tracheoesophageal fistula formation. Erosion into the innominate artery is another rare occurrence, usually when the tracheostomy incision is below the third tracheal ring. The importance of an experienced, well-trained staff immediately available to address problems is supported by data demonstrating that mortality related to tracheostomy is significantly lower when performed in a children's hospital and decreases with increasing volume.[183]

Decannulation occurs when the indications for tracheostomy are no longer present. Diagnostic laryngotracheobronchoscopy before a planned decannulation permits identification of problems likely to interfere with effective breathing, including granulation tissue, severely stenotic areas, or vocal cord abnormalities. If none is present, the indwelling tube is replaced with successively smaller tubes until the smallest available is in place and the child is breathing well. If no distress occurs, the tube is removed and the stoma is covered.

Cricothyrotomy and Retrograde Intubation

Although airway management by endotracheal intubation is possible and endotracheal intubation is the appropriate first choice in the vast majority of pediatric patients, intubation is

not possible or should not be done on certain occasions. Such situations include massive facial trauma, oropharyngeal hemorrhage or presence of a foreign body, or severe upper airway obstruction.[184] Cricothyrotomy is an alternative to tracheostomy for rapidly establishing an airway in apneic or severely distressed patients.

The child's head and neck are extended with a roll under the shoulders. The cricothyroid membrane is palpated between the inferior margin of the thyroid cartilage and the superior edge of the cricoid cartilage. With one hand (or an assistant) stabilizing the larynx and trachea, the membrane is punctured in the midline with a large angiocatheter, the stylet is withdrawn, and the catheter is connected to a source of oxygen using the connector to a size 3 endotracheal tube. Kits are available that facilitate cricothyrotomy using the Seldinger technique. Oxygenation is rapidly improved in spontaneously breathing patients, but carbon dioxide elimination is minimal. Transtracheal jet ventilation is effective through such catheters, provided that the upper airway permits passive exhalation; otherwise, severe hyperinflation and life-threatening barotrauma are certain.

Retrograde intubation can be accomplished by this approach. Once the cricothyroid membrane has been punctured and the catheter has been placed in the tracheal lumen, a long wire from a vascular access kit is advanced cephalad into the mouth. With the wire firmly secure, an ETT may be advanced into the trachea. Once the tube is in the tracheal lumen, the wire is withdrawn and the tube is further advanced into the desired position. If the wire is insufficiently stiff to permit passage of the tube into the trachea, an ETT exchanger can be advanced over the wire first, followed by the ETT.

In adults and adolescents, a small horizontal incision over the cricothyroid membrane is an alternative approach. Once the membrane is incised, it is spread vertically, and a standard tracheostomy or ETT is inserted into the tracheal lumen. This approach is not recommended in infants and young children except in highly skilled hands because of the potential for grave injury to a small, soft trachea or nearby neurovascular structures.

Complications are similar to those of tracheostomy. Complication rates of 10% to 40% are reported in adults.[184] Few experiences have been reported in pediatric patients, particularly in younger children.

References are available online at http://www.expertconsult.com.

VII Chapter 120

Organ System Considerations that Affect Anesthetic Management

Antonio Cassara and Peter J. Davis

PEARLS

- The anesthetic care of intensive care unit patients involves the extension of principles of medical management used in the operating room.
- The anesthesiologist caring for a critically ill child must have an understanding of the desired therapeutic endpoints and a knowledge of the patient's preexisting condition.
- For the intensive care physician, a patient returning to the intensive care unit after surgery frequently requires an altered management plan. The physiologic perturbations of surgery and anesthesia frequently change the focus and direction of medical management. The intensive care physician must understand not only the events that occur in the operating room but also the rationale for using anesthetic agents and anesthetic techniques.
- Prompt recognition of the propofol infusion syndrome and discontinuation of the infusion is key to increased survival. Early administration of hemodialysis and perhaps even extracorporeal support improves survival.
- Thromboelastography is a point-of-care test that provides a global dynamic assessment of hemostasis within 60 minutes. It is used successfully for the guidance of blood component therapy in liver transplantation.
- Recombinant activated factor seven (rFVIIa, NovoSeven) has been used to control life-threatening hemorrhage in nonhemophiliac patients. Rapid reconstitution and low volume make it easy to infuse; however its shorter half-life in children necessitates higher doses to achieve the same plasma levels as in adults.

Cardiovascular Performance

For the anesthesiologist, knowledge of the hemodynamic characteristics that have ensured adequate organ perfusion in the pediatric intensive care unit (PICU) and the interventions that the intensive care physician has used to optimize the patient's cardiovascular function is essential to choosing the appropriate anesthetic.

Changes with Development

Cardiac assessment of the PICU patient requires a knowledge of normal cardiovascular growth and development and an understanding of the influence of disease and the effects of anesthesia on cardiovascular function. The myocardium of the neonate is less compliant than that of the adult and the neonate's cardiac output depends primarily on the heart rate. Cardiac output increases substantially with age, whereas cardiac index (cardiac output divided by body surface area) ranges from 2.5 to 4.2 L/min/m^2 throughout life. Sympathetic innervation of the neonatal heart is not fully developed, and myocardial catecholamine stores are limited.[1] The response of the neonatal heart to vasoactive drugs is attenuated and the capacity for peripheral vasoconstriction during hypovolemia is reduced, probably because of the immature baroreceptor and α-adrenergic receptor systems.[2] Systemic vascular resistance is normally 800 to 1200 dynes • sec/cm^{-5} at birth and reaches the adult value of 1600 by 1 to 2 years of age. Systolic and diastolic blood pressures increase nonlinearly with age.

Pulmonary vascular resistance decreases dramatically after birth as hypoxemia-induced vasoconstriction is attenuated. During the first weeks of life, pulmonary vascular resistance continues to decrease, and by 6 to 8 weeks of age pulmonary artery pressure and resistance have reached adult values. Mean right atrial (central venous) pressure normally is 1 to 5 mm Hg. Mean left atrial pressure is 2 mm Hg greater than mean right atrial pressure throughout life. Heart rate decreases markedly during the first few months of life and then decreases gradually until adulthood. Oxygen consumption (VO_2) increases from approximately 4.6 mL/kg/min in the term newborn infant to 7 mL/kg/min by 10 days of age and 8 mL/kg/min by 4 weeks of age. Oxygen consumption gradually decreases with age, reaching an adult value of 234 mL/min/1.7 m^2 (140 mL/min/m^2 or 3.3 mL/kg/min).

Effects of Disease

Disease states can affect cardiovascular performance by their effects on the pulmonary and peripheral vasculatures and by their direct effects on the myocardium. Changes in myocardial compliance and filling pressures can profoundly influence myocardial performance. In addition, factors associated with disease states such as hypoxia, hypercarbia, acidosis, and hypothermia can affect pulmonary and systemic vascular resistances and thereby further modify myocardial function. The effects of changes in preload (i.e., the effects of fluid challenges) on the patient's blood pressure, cardiac output, and stroke volume and the clinical effects of changes in afterload

on heart rate and myocardial contractility all influence the anesthesiologist's care of critically ill children.

Effects of Anesthetic Agents

Anesthetic agents affect myocardial performance. During induction of anesthesia, potent inhaled agents such as halothane and isoflurane are associated with higher incidences of bradycardia, hypotension, and cardiac arrest in infants and children than in adults.[3] These cardiovascular depressant effects appear to be more pronounced in infants than in older children. Diaz and Lockard[4] found that more than 70% of healthy newborns had greater than 30% decrease in systolic blood pressure during induction with halothane, whereas Friesen and Lichtor[3] noted that infants 1 to 6 months of age had a 40% decrease in mean atrial pressure and a 30% decrease in heart rate when they received a halothane and nitrous oxide anesthetic. In a study of healthy children, 1.5 to 12 years of age, undergoing halothane anesthesia, Barash et al.[5] noted that systolic blood pressure and heart rate decreased in a dose-dependent manner. Similar hemodynamic effects are noted in infants anesthetized with isoflurane.[6]

Because it can be problematic to insert invasive monitors in unsedated, awake children, much of the information about the potent inhaled anesthetic agents and their effects on the determinants of cardiac output is derived from animal studies. In a neonatal piglet model, Boudreaux et al.[7] noted that the major adverse effect of halothane was its negative inotropic effect and not its negative chronotropic or unloading activity. In similarly designed studies, Schieber et al.[8] observed that, although isoflurane reduced contractility and decreased blood pressure and systemic vascular resistance more than did equipotent concentrations of halothane, cardiac index was better preserved in the isoflurane-anesthetized animals. Thus when compared with halothane, the direct myocardial depressant effect of isoflurane is offset by its effect on the peripheral vasculature, which results in afterload reduction.

Desflurane and sevoflurane are two new potent inhalational anesthetic agents. Because of their low blood solubility, they afford patients rapid induction and rapid awakening.[9-14] Desflurane has a blood gas solubility coefficient (0.42) that is similar to nitrous oxide in children. However, desflurane's pungent airway properties result in a high incidence of laryngospasm, coughing, and hypoxemia that limit its utility as an induction agent in nonintubated children.[14] The cardiovascular profile of desflurane is age dependent.[12] Compared with awake values, arterial blood pressure decreased in children anesthetized with 1 minimal alveolar concentration (MAC) of desflurane by approximately 30%, whereas the heart rate decreased or remained the same. Thus at 1 MAC, desflurane, like isoflurane and halothane, appears to attenuate the baroresponse in children. Weiskopf et al.[15] demonstrated that rapid increases in desflurane from 0.55 to 1.66 MAC in adults can transiently increase arterial blood pressure and heart rate. This cardiovascular excitation is associated with an increase in sympathetic and renin-angiotensin system activity.

Information on the hemodynamics of sevoflurane in children suggests that sevoflurane (blood gas coefficient of 0.68) appears to produce the same hemodynamic effects as isoflurane.[10] In adults anesthetized with sevoflurane or isoflurane, administration of exogenous epinephrine had similar dysrhythmogenic properties.[16] In a study of children, using echocardiograms, in which sevoflurane and halothane were compared at equal MAC, Holzman et al.[17] noted sevoflurane had fewer myocardial depressant effects than sevoflurane.

The synthetic opioids may offer more hemodynamic stability than the inhaled anesthetic agents.[18-20] Robinson and Gregory[21] were the first to report the safety and efficacy of high-dose fentanyl anesthesia in children, in a study of premature infants undergoing patent ductus arteriosus ligation. In subsequent reports on pediatric patients, Hickey and Hansen[22] documented the safety of opioid anesthesia in children with complex congenital heart disease. Although these investigators noted that high doses of fentanyl (50 and 75 μg/kg) decreased heart rate and mean arterial pressure (MAP) by 7% and 9%, respectively, in patients with bidirectional shunts, opioids had a salutary effect on pulmonary vascular resistance, increasing transcutaneous oxygenation by 45%.

Because of the prolonged respiratory and sedative effect associated with moderate- and high-dose administration of fentanyl and its congeners, shorter-acting opioids may offer the advantage of more predictable control with a similar cardiovascular profile than the longer-acting opioids. Remifentanil, a new synthetic opioid agonist with an ultrashort half-life, has been introduced into clinical practice. Remifentanil is metabolized by plasma and tissue esterases. It is independent of organ elimination. Consequently, its kinetic parameters do not change with the duration of infusion. This flat, context-sensitive half-time coupled with its ultrashort half-life (7 to 10 minutes) allow better drug effect predictability. Pharmacokinetic studies in children demonstrate faster clearances and larger volumes of distribution in neonates compared with older infants and children. In vitro studies by Olgatree et al.[23] have demonstrated that remifentanil has no significant direct negative inotropic effects on the myocardium and that β-adrenergic stimulation of the heart remains intact. Comparative studies of remifentanil to inhaled anesthetic agents in children undergoing pyloromyotomy surgery suggest that the short half-life of remifentanil may be beneficial with regard to postoperative respiratory changes.[24,25] Because of remifentanil's ultrashort half-life and its nonaccumulation with prolonged infusion, it may be a beneficial agent for the short-term (less than 12 hours) sedation of infants and children in the PICU setting. However, the rapid development of tolerance and cost issues will likely preclude its use for longer periods of time.

Dexmedetomidine, a sedative analgesic that has become increasingly popular, like clonidine is an α_2-adrenergic agonist and is highly selective with a α_2/α_1 ratio of 1600:1. Stimulation of these receptors in the central nervous system (CNS) and the spinal cord produces sedation, anxiolysis, analgesia, deceased MAC of inhalational anesthetic agents (increased sensitivity), decreased renin and vasopressin levels with increased diuresis, decreased sympathetic tone with decreased heart rate and blood pressure.[26] Dexmedetomidine has a rapid distribution phase (6 minutes) and an elimination half life of 2 hours.[27] Petroz et al.[28] demonstrated that children, 2 to 12 years of age, have similar pharmacokinetics to adults. Rodarte et al.[29] studied the pharmacokinetics in infants 1 to 24 months of age. He concluded that infants have a faster clearance of dexmedetomidine than adults (27 mL/kg/min versus 13 mL/kg/min). A loading dose of 1 μg/kg and continuous infusions of 0.2 to 0.7 μg/kg/hr have been used in various clinical scenarios to produce sedation-analgesia. The most common

adverse events are hypotension and bradycardia, whichare enhanced in the presence of cardiac comorbidities or when dexmedetomidine is used with other medications that have negative chronotropic effects (propofol, succinylcholine, digoxin, pyridostigmine).[30-32] When a loading dose of dexmedetomidine is administered, there is a biphasic response. The initial response is an increase in blood pressure with a decrease in heart rate, followed by a decrease in blood pressure and a further decrease in heart rate.[33] This biphasic effect is thought to be due to dexmedetomidine's initial ability to stimulate peripheral postsynaptic α_{2b}-adrenergic receptors resulting in vasoconstriction, followed by the more intense central CNS effects on α_{2a}-adrenergic receptors causing sympatholysis. Bloor et al.[33] administered boluses of 0.25, 0.5, 1.0, and 2.0 μg/kg to healthy volunteers and noted a decrease in mean arterial blood pressure (MAP) respectively of 14%, 16%, 23%, and 27%. Cardiac output decreased 20% following a loading dose of 1 μg/kg in the first minute and returned to 90% of baseline after 60 minutes. When a loading dose of 2 μg/kg was administered, cardiac output decreased by 60% and returned to 85% of baseline after 1 hour. Venn et al.[34] studied the effects of dexmedetomidine in 66 patients with comorbidities who were in the ICU, mechanically ventilated, and who received a loading dose of 1 μg/kg followed by a continuous infusion of 0.2 to 0.7 μg/kg/hr. Hypotension and bradycardia (≥30% decrease from baseline) was observed in 18 of the 66 patients. Reports of bradycardia and sinus arrest have also been noted by Ingersoll-Weng.[31] Khan et al.[35] reported similar effects of dexmedetomidine during anesthesia with isoflurane. The majority of the effects occurred with end-tidal isoflurane levels greater than or equal to 1%. Animal studies and studies on isolated human papillary muscle have demonstrated no direct negative inotropic effects on myocardial contractility.[36] The sympatholytic effects of dexmedetomidine on pediatric patients have been evidenced by Muktar et al.[37] Thirty infants and children undergoing CPB were randomized to receive dexmedetomidine (1 μg/kg load followed by a continuous infusion of 0.5 μg/kg/hr) or placebo. Plasma cortisol norepinephrine, epinephrine, and glucose levels were significantly less in the dexmedetomidine group.

Propofol is a sedative hypnotic that is widely used as an induction agent in anesthesia. It is also used as a continuous infusion for prolonged sedation in the ICU. Its popularity in the ICU setting comes from its rapid clearance that allows quick awakening for rapid weaning or neurologic evaluation. Propofol is suspended in a lipid emulsion, which when administered by a continuous infusion results in a significant lipid load. Induction doses for anesthesia vary from 2 to 3 mg/kg, while ICU sedation doses vary from 50 to 250 μg/kg/min. Induction doses of propofol can cause a 10% to 15% decrease of MAP as well as bradycardia, especially when coadministered with other vagotonic drugs. Propofol has a modest negative inotropic effect, due to antagonism of β-adrenergic receptors and calcium channels.[38] Since 1992, there have been increasing reports of a fatal adverse reaction that has been termed the Propofol Infusion Syndrome (PRIS).[39] To date, 61 cases (32 pediatric and 29 adult) have been reported, and there have been 20 pediatric and 18 adult deaths.[40] PRIS is characterized by severe intractable bradycardia that leads to cardiac failure, severe metabolic acidosis, hyperlipidemia, rhabdomyolysis with consequent hyperkalemia, and renal failure.[41] Prolonged propofol infusions (more than 48 hours) and infusion rates greater than 4 mg/kg/hr have been linked to PRIS. Priming factors such as critical illness (respiratory failure and traumatic brain injury) and triggering factors such as catecholamine and steroid infusion are associated with the syndrome.[44] The underlying mechanism of PRIS is not well understood. It is speculated that high doses of propofol inhibit the mitochondrial respiratory chain. As a result, there is a decreased ATP production and a decreased mitochondrial lipid metabolism, with an accumulation of toxic long fatty acid chains that are arrhythmogenic.[45-47] Management of PRIS is very difficult and consists of prompt recognition and interruption of the infusion. Aggressive cardiac resuscitation must be initiated early on with high dose inotropes, fluid administration, and the use of pacing devices. The early administration of hemodialysis and hemofiltration together with ECMO has improved survival.[48-50]

Anemia and Transfusion

Concerns about transfusion-related disease transmission have forced clinicians to reassess transfusion criteria. Rothstein[51] previously recommended that in patients younger than 3 months of age, hemoglobin concentration should be greater than 10 g/dL, whereas in children older than 3 months, a hemoglobin concentration of 9 g/dL was adequate. Slogoff[52] concluded that in normovolemic adults, a hematocrit of 20% (hemoglobin 7 g/dL) is adequate. Carson et al.[53] retrospectively reviewed mortality in 125 adult surgical patients who refused blood transfusion for religious reasons. Mortality correlated inversely with preoperative hemoglobin level and directly with operative blood loss. No operative deaths occurred among patients with a preoperative hemoglobin level above 8 g/dl and an operative blood loss of less than 500 mL.

Transfusion guidelines should anticipate age-related changes in the oxygen dissociation curve. P_{50} (partial pressure of oxygen at which hemoglobin is 50% saturated with oxygen) is lower in newborns than in adults. In a child 1 year of age, the P_{50} is higher than in normal adults. By 9 to 12 years of age, the P_{50} has decreased to adult values. These age-related changes in hemoglobin's affinity for oxygen alter oxygen unloading to the peripheral tissues.

Minimum acceptable hemoglobin (and approximate hematocrit) levels can be inferred from anticipated tissue oxygen delivery (Table 120-1). A hemoglobin concentration of 7 to 8 g/dL (hematocrit 21% to 24%) is reasonable for adults and children based on the previous discussion. Minimum values chosen for infants should be more conservative (i.e., ensure greater oxygen delivery to tissues) than those for older patients. This takes into consideration the higher oxygen consumption of infants and provides them with a larger margin of safety against hypoxic injury. Infants younger than 2 months probably require a hemoglobin level of 13 g/dL (hematocrit of 40%); infants older than 3 months require a hemoglobin level of 7 g/dL (hematocrit of 21%). Infants aged 2 to 3 months are in a transitional phase, and minimum hemoglobin levels are more difficult to predict. These values are intended as guidelines only; each patient must be considered individually.

Patients with chronic anemia increase oxygen delivery by increasing cardiac output. Although the potent inhaled anesthetic agents decrease myocardial function and cardiac output and thereby decrease oxygen delivery, these side effects

Table 120–1 Hemoglobin Requirement for Equivalent Tissue Oxygen Delivery

	P_{50} (mm Hg)	Hb for Equivalent O_2 Delivery (g/dL)						
Adult	27	7	8	9	10	11	12	13
Infant >3 mo	30	5.7	6.5	7.3	8.2	9.0	9.8	10.6
Neonate <2 mo	24	10.3	11.7	13.2	14.7	16.1	17.6	19.1

Data from Motoyama EK, Zigas CJ, Troll G: Am Soc Anesthesiol (abstract), 1974.

are offset by the decrease in oxygen consumption that occurs in anesthetized patients. The need to transfuse blood in the perioperative period frequently is determined by the patient's underlying hemodynamic stability, the type of surgery anticipated, and the known risks of administering blood products. In general, unless the procedure is minor, blood should be available for all ICU patients. Because ICU patients frequently are monitored with invasive catheters, serial measurements of hematocrit or hemoglobin usually can be obtained during the operative procedure to determine whether transfusion is warranted.

Respiratory Failure

When respiratory failure is present, the anesthesiologist must be aware of its precipitating factors. Acute respiratory distress syndrome (ARDS) is a clinical syndrome of respiratory distress, poor pulmonary compliance, and hypoxemia that usually occurs after a nonpulmonary condition such as shock, trauma, sepsis, or an unexplained condition leading to pulmonary parenchymal disease and respiratory failure. Direct mortality from respiratory failure is approximately 10% to 20%; overall mortality may be as high as 65%. ARDS was first described as a clinical entity occurring in pediatric patients in 1980.[54] Recognized factors predisposing pediatric patients to the development of ARDS include severe infection, cardiac arrest, shock, and aspiration. Although the cause of this condition is uncertain, the fundamental defect in the lung is injury to the pulmonary capillary endothelial cells, leading to interstitial and, ultimately, alveolar pulmonary edema. This pulmonary vascular leakage results in hypoxemia, decreased pulmonary compliance, increased pulmonary vascular resistance, and venoarterial shunting.

The mainstays of treatment are endotracheal intubation, continuous positive-pressure ventilation with positive end-expiratory pressure (PEEP), and supplemental oxygen. Invasive monitoring by arterial, central venous, and pulmonary arterial cannulation may be necessary to optimize preload and cardiac output in the presence of high PEEP and high transpulmonary pressures. The patient's requirements for oxygen, PEEP, and pulmonary toilet must be understood preoperatively. Patients with poor pulmonary compliance challenge the ability to maintain adequate intraoperative ventilation. Preoperative knowledge of the interaction of PEEP with the adequacy of ventilation and cardiovascular function is an important concern of the anesthesiologist. Anesthetic agents can modify not only cardiovascular function, but also respiratory function, by their effect on hypoxic pulmonary vasoconstriction. Patients with ARDS may rely in part on regional hypoxic pulmonary vasoconstriction to minimize intrapulmonary shunting. Shifting of pulmonary blood flow away from atelectatic lung regions has been well described. The administration of vasoactive drugs and potent inhaled anesthetic agents inhibits hypoxic pulmonary vasoconstriction and therefore may exacerbate hypoxemia by increasing intrapulmonary shunting.[55,56]

Table 120–2 Signs of Intracranial Hypertension in Infants and Children

Infants	Children	Infants and Children
Irritability	Headache	Decreased consciousness
Full fontanelle	Diplopia	Cranial nerve (III and VI) palsies
Widely separated cranial sutures	Papilledema	Loss of upward gaze (setting sun sign)
Cranial enlargement	Vomiting	Signs of herniation, Cushing triad, pupillary changes

Neurologic Injury

The leading form of pediatric trauma is traumatic brain injury (TBI), which accounts for 36% of traumatic deaths in the USA.[57,58] Eighty percent of trauma patients have central nervous system injury, and in 60% of these patients, the CNS injury is the most severe. It is estimated that 185 of every 100,000 children experience head trauma requiring hospitalization.[58,59] Poor outcomes have been associated with early hypotension, low Glasgow Coma Scale score, altered cerebral blood flow (CBF), hyperglycemia, and deranged autoregulation.[59] Neurologic injury may be the primary insult resulting from trauma. However, secondary cerebral injury may result from the development of intracranial hypertension and resultant cerebral ischemia. Recognition and control of elevated intracranial pressure (ICP) are key elements to preventing neurologic deterioration and patient morbidity. Secondary traumatic brain injury can be characterized by an array of biochemical, cellular, and molecular events that are associated with ischemia, excitotoxicity, energy failure, and cell death cascades, all of which result in cerebral swelling, axonal injury, inflammation, and regeneration.[60]

Intracranial Pressure

The signs of intracranial hypertension in infants and children are listed in Table 120-2. The presence of these signs and symptoms, in conjunction with the baseline findings on neurologic examination, may dramatically alter the patient's anesthetic care. The anesthesiologist must be aware of ongoing interventions to control ICP. Control of cerebral

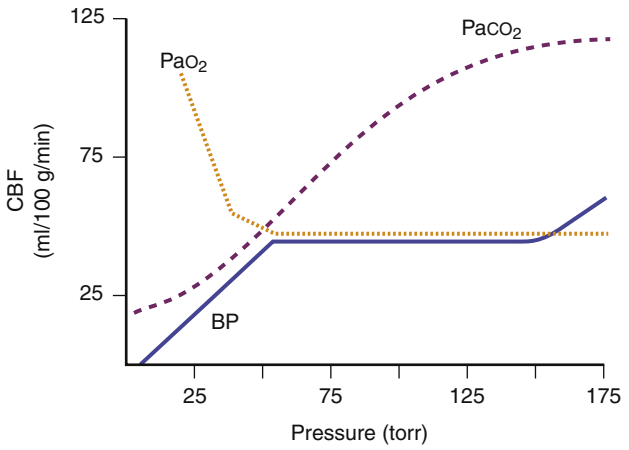

Figure 120–1. Cerebral blood flow *(CBF)* changes resulting from alterations in $Paco_2$, Pao_2, and blood pressure. The other two variables remain stable at normal values when the remaining variable is altered. *(Modified from Shapiro HM: Intracranial hypertension: therapeutic and anesthetic considerations,* Anesthesiology *43:445, 1975.)*

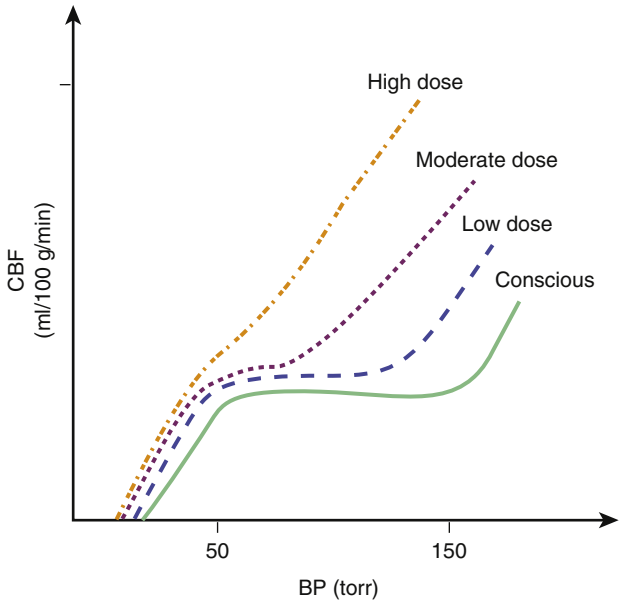

Figure 120–2. Volatile anesthetics and autoregulation. Schematic representation of the effect of a progressively increased dose of a typical volatile anesthetic agent on cerebral blood flow *(CBF)* autoregulation. Both upper and lower thresholds are shifted to the left. *(Modified from Drummond K, Shapiro HM: Cerebral physiology. In Miller R, editor:* Anesthesia, vol 2, *ed 3, New York, 1990, Churchill Livingstone.)*

perfusion pressure is essential for maintaining neurologic function in pathologic states. Cerebral perfusion pressure is expressed as the difference between MAP and the highest value obtained out of the following: central venous pressure, intrathoracic pressure, or ICP. Thus in the presence of intracranial hypertension (ICP ≥15 to 20 mm Hg), higher systemic blood pressures must be achieved to prevent cerebral ischemia. Intracranial compliance depends on the volumes of the intracranial contents, cerebral tissue, blood, and extracellular fluid. The most dynamic of these is the blood compartment. Changes in cerebral blood volume are mediated primarily through changes in cerebral vascular resistance. Cerebral vascular resistance is affected by both intracranial and extracerebral factors.

Regulation of Cerebral Blood Flow

The normal brain receives 15% of cardiac output. Kennedy and Sokoloff[61] determined that healthy children have a high CBF (100 mL/100 gm/min), this value decreases to adult values of 50 mL/100 gm/min during the teenage years. Cerebral blood flow regulation depends primarily on the local chemical and metabolic milieu, particularly the concentrations of hydrogen ion, adenosine, and prostanoids. Production of these compounds correlates with normal cerebral activity and metabolic rate. Neurogenic and myogenic components also have minor roles in regulating cerebral vascular resistance.

Extracerebral factors that can change cerebral vascular resistance and CBF include the arterial partial pressures of carbon dioxide ($Paco_2$) and oxygen (Pao_2), MAP, and various drugs (Figure 120-1). Cerebral circulation is very sensitive to variations of $Paco_2$, and has been studied using transcranial Doppler ultrasound.[62] CBF varies linearly by 2% to 4% for every variation of 1 mm Hg of $Paco_2$. Data from anesthetized children show that CO_2 vasoreactivity is higher than in adults (13.8% vs. 10.3% change).[63] Low blood pressure decreases cerebral vascular vasoreactivity.[63] As $Paco_2$ is rapidly lowered toward 20 mm Hg, there is marked cerebral vasoconstriction and reduction in both CBF and ICP. Theoretically, an acute decrease in $Paco_2$ below 20 mm Hg may be detrimental by reducing CBF enough to cause cerebral ischemia. The salutary effects of acute hyperventilation on ICP are diminished over time because acute changes in cerebrospinal fluid pH are normalized in approximately 6 hours. Arterial oxygenation within the normal clinical range has little effect on cerebral vascular resistance. However, Pao_2 less than 50 mm Hg results in cerebral vasodilation and increased CBF. Hyperoxia in excess of 300 mm Hg may produce cerebral vasoconstriction.

Cerebral autoregulation is a homeostatic process by which the brain maintains a constant CBF over a MAP range from 60 to 150 mm Hg in adults. At an MAP less than 60 mm Hg, symptoms of cerebral ischemia may appear. If the upper limit of MAP for autoregulation is exceeded, the resultant increase in CBF may cause cerebral edema. The autoregulatory curve may shift in the presence of chronic hypertension, intracranial tumors, head trauma, or shock states. This renders the brain more susceptible to ischemic effects.[63] The range of MAP over which autoregulation of CBF occurs in infants and children likely shifts in tandem with age-related changes in normal systemic blood pressures and cerebral perfusion pressures. Raju et al.[64] suggest that an infant's mean cerebral perfusion pressure is approximately equal to its gestational age in weeks and that this estimate holds true for growing preterm infants up to 5 weeks after birth.

Effects of Anesthetics on Cerebral Blood Flow

In general, the potent inhaled anesthetic agents impair autoregulation and may cause hypotension and increased CBF (Figure 120-2). Consequently, they must be used cautiously, if at all, in patients with evidence of traumatic brain injury.

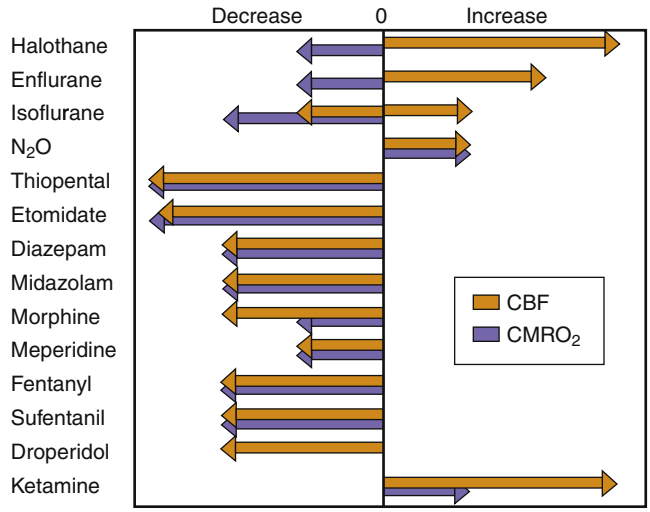

Figure 120–3. Effects of anesthetic agents on cerebral blood flow *(CBF)* and cerebral metabolic rate of oxygen ($CMRo_2$). *(Modified from Cucchiara RF, Block S, Steinkeler JA: The effects of anesthetic agents on cerebral blood flow and cerebral metabolism: anesthesia for intracranial procedures. In Barash PG, Cullen BF, Stoelters SK, editors:* Clinical anesthesia, *Philadelphia, 1989, JB Lippincott.)*

Halothane and enflurane at 1 MAC abolish cerebral autoregulation. Isoflurane impairs autoregulation less than halothane.[65] The effects of anesthetic agents on CBF and cerebral metabolism are summarized in Figure 120-3. In general, the perfect agent would decrease both CBF and cerebral metabolic rate of oxygen ($CMRo_2$). The potent inhaled agents (halothane, enflurane, and isoflurane) "uncouple" the normal relationship between CBF and metabolism and cause marked cerebral vasodilation. Isoflurane is the only inhaled anesthetic agent with which CBF actually may decrease when concomitant hyperventilation to $Paco_2$ of 20 to 25 mm Hg is used.[66] Whereas nitrous oxide alone is known to cause mild cerebral vasodilation and to increase $CMRo_2$ (probably related to inadequate anesthetic depth), these effects are easily countered by the addition of intravenous sedatives, hypnotics, and narcotics. There are limited data regarding the effects of the two newest inhaled agents, sevoflurane and desflurane, on intracranial dynamics. Although the effects of desflurane on CBF have been studied, there is relatively little information regarding the effects of sevoflurane on CNS physiology in human subjects. Artru et al.[67] noted that desflurane increases CSF pressure in animals. Ornstein et al.[68] showed that in patients with intracranial mass lesions, desflurane and isoflurane have similar effects on CBF. The electroencephalographic effects of desflurane are similar to those of isoflurane, with prominent burst suppression occurring at 1.24 MAC.[69]

In volunteers using transcranial Doppler, Bedforth et al.[70] noted that at 1 MAC of desflurane, cerebral autoregulation was impaired and that at 1.5 MAC autoregulation was abolished. In a separate study of adult non-neurosurgical patients, Bedforth et al.[71] noted that the introduction of desflurane following induction of anesthesia with propofol impaired cerebral autoregulation more than with equi-MAC doses of sevoflurane. In contrast, in studies of static and dynamic compliance of autoregulation, Strebel et al.[72] noted that, at 1.5 MAC desflurane and 1.5 MAC sevoflurane, autoregulation was impaired but propofol (200 μg/kg/min) had no effect. Muzzi et al.[73] showed that 1 MAC of desflurane in adults with supratentorial lesions increases ICP as opposed to 1 MAC of isoflurane. Desflurane may alter CSF dynamics. Desflurane does not appear to change CSF absorption but does increase CSF production.[73]

In a study of patients undergoing non-intracranial neurosurgical procedures, Summors et al.[74] noted that dynamic cerebral autoregulation using transcranial Doppler ultrasonography is better preserved during 1.5 MAC sevoflurane than 1.5 MAC isoflurane anesthesia. Others noted similar findings with sevoflurane and isoflurane. In patients studied at 0.5 and 1.5 MAC, the dose-dependent vasodilatory effect was less for sevoflurane.[75,76] Nishiyama et al.[77] assessed comparative cerebral vasodilatory responsiveness to CO_2 during either sevoflurane or isoflurane anesthesia. Nishiyama et al.[71] noted in a group of adult patients that changes in CBF caused by changes in CO_2 are greater during isoflurane anesthesia. However, attempts to decrease ICP by decreasing CO_2 were more successful with isoflurane than with sevoflurane. In addition to cerebral vascular autoregulation, sevoflurane use is associated with epileptiform activity. In pediatric patients with and without a preexisting history of epilepsy, induction by sevoflurane of tonic, clonic, and silent seizures during the induction and maintenance of anesthesia is reported.[78-80]

For the anesthesiologist, knowledge of the patient's ICP and cranial compliance and an understanding of the pathophysiology of the CNS lesion are important for planning appropriate anesthetic management.[81] In experimental animals, Statler et al.[81] demonstrated that isoflurane had more neuroprotective effect than fentanyl in rats that had undergone controlled cortical impact lesions. Hendrich et al.[82] quantified CBF using labeled magnetic resonance imaging in normal rats anesthetized with fentanyl, isoflurane, or pentobarbital. In this study, CBF values were found to be approximately 2.5 to 3 times lower in most regions analyzed during anesthesia with either fentanyl (with N_2O/O_2) or pentobarbital versus isoflurane (with N_2O/O_2). In addition, these investigators noted that CBF was heterogeneous in rats anesthetized with isoflurane (with N_2O/O_2) but relatively homogenous in rats anesthetized with either fentanyl (with N_2O/O_2) or pentobarbital. In previous human studies with opioid anesthesia, opioids maintained static cerebral autoregulation. Engelhard et al.[83] subsequently demonstrated that remifentanil, a mu-opioid agonist with unique pharmacokinetic properties, when combined with low-dose propofol maintains both static and dynamic compliance of cerebrovascular autoregulation. Propofol also has been used to alter CNS dynamics.[84] Positron emission tomography suggests that propofol produces global metabolic depression.[85,86] Like thiopental, propofol decreased $CMRo_2$, CBF, and ICP. Cerebral responsiveness to arterial CO_2 appears to be preserved during propofol anesthesia.[87,88]

Hepatic Dysfunction

An assessment of liver function is important for two aspects of anesthetic management. The liver is a major site of drug metabolism and is involved in homeostasis of the coagulation system. Anesthesia and surgery may exacerbate liver dysfunction in patients with preexisting liver disease and,

in some instances, may cause life-threatening hepatic failure. Although the cause of hepatic dysfunction in surgical patients is unknown, it may be related to decreases in hepatic blood flow. Consequently, anesthetic drugs and techniques that may decrease hepatic blood flow should be avoided if possible.

Effects of Anesthetics on Hepatic Blood Flow

Blood flow in the splanchnic circulation can be altered by numerous factors. Mechanical ventilation, by altering the normal relationship between splanchnic venous outflow and venous outflow from the kidney and lower extremities, may affect splanchnic blood flow. The changes associated with mechanical ventilation can be further exacerbated by increasing tidal volume and applying PEEP.[89] Carbon dioxide concentration also influences splanchnic blood flow.[90] Various anesthetic agents may have different effects on hepatic blood flow.[91] Gelman et al.[92] showed that hepatic oxygen supply is better maintained during isoflurane than during halothane anesthesia. In addition, in hypoxic rat models, the incidence of hepatic centrilobular necrosis was least with isoflurane compared with halothane, nitrous oxide, and fentanyl. Although anesthetic agents can decrease hepatic blood flow, Gelman et al.[92] demonstrated that the decrease in hepatic blood flow is small compared with the decrease associated with the surgical stress of a laparotomy. Surgical procedures involving traction and manipulation of the abdominal viscera are associated with the release of various vasoactive compounds that may further alter splanchnic blood flow. In sevoflurane-anesthetized dogs, Frank et al.[93] demonstrated that hepatic arterial blood flow was maintained, portal blood flow was decreased, and total hepatic blood flow was unchanged. In desflurane-anesthetized dogs, hepatic artery blood flow was maintained, portal blood flow was decreased, and total hepatic blood flow was reduced.[94]

Effects of Liver Disease on Pharmacokinetics

In addition to the effects of anesthetic agents on the liver, hepatic disease affects the pharmacology of anesthetic agents. Little is known about the pharmacologic properties of anesthetic agents in pediatric patients with liver disease.[95,96] Although the liver is the major site of drug biotransformation, the effects of hepatic dysfunction on drug elimination and disposition are inconsistent.[97] The degree of liver dysfunction and a drug's ability to bind to plasma proteins are important variables in determining drug kinetics in patients with liver disease. For drugs with a high hepatic extraction ratio, hepatic clearance is sensitive to changes in hepatic blood flow, whereas for drugs with a low hepatic extraction ratio, hepatic drug clearance is a function of intrinsic hepatic enzyme activity and protein binding.[97] Thus the reported inconsistent effect of liver disease on drug pharmacology may be a function of the heterogeneous pathophysiology of liver disease with respect to hepatocellular function, protein binding, and hepatic blood flow. Table 120-3 compares opioid pharmacokinetics in patients with and without liver disease. Note that the effects of hepatic disease are variable with respect to the pharmacokinetics of opioids. Remifentanil, a μ-opioid agonist that undergoes plasma and tissue esterase metabolism, is unaffected, with respect to its pharmacokinetic profile, by liver disease.[98,99]

The pharmacokinetics of neuromuscular blocking agents (NMBAs) in adults have been well studied. Of the nondepolarizing NMBAs, pancuronium, vecuronium, and atracurium are significantly metabolized. Of these agents, only pancuronium and vecuronium pharmacokinetic profiles are altered by liver disease. In a study of children with moderate-to-severe liver dysfunction, Brandom et al.[100] showed that liver failure has no effect on atracurium pharmacokinetics. Mivacurium is a benzylisoquinolium diester metabolized by plasma cholinesterase. It is an NMBA of short duration. Greene et al.[101] noted

Table 120–3 Pharmacokinetics of Narcotics

Drug	Disease	Vd	$t_{1/2\beta}$	Clearance
Meperidine‡	Cirrhosis	263 ± 286 L/kg	359 ± 77 min*	573 ± 158 mL/min*
	Control	232 ± 536 L/kg	213 ± 25 min	900 ± 316 mL/min
Meperidine†	Acute hepatitis	5.56 ± 1.8 L/kg	6.94 ± 2.74 h*	649 ± 228 mL/min*
	Control	5.94 ± 2.65 L/kg	3.37 ± 0.82 h	1261 ± 527 mL/min
Morphine†	Cirrhosis	2.3 ± 1.3 L/kg	2.2 ± 1.3 h	1.15 ± 0.35 L/min
	Control	2.9 ± 2.4 L/kg	2.5 ± 1.5 h	1.23 ± 0.43 L/min
Fentanyl†	Cirrhosis	4.27 ± 0.65 L/kg	304 ± 74 min	11.3 ± 1.6 mL/kg/min
	Control	3.44 ± 0.64 L/kg	263 ± 48 min	10.8 ± 1.2 mL/kg/min
Alfentanil†	Cirrhosis	351 ± 206 mL/kg	219 ± 128 min*	1.6 ± 1.0 mL/kg/min*
	Control	281 ± 97 mL/kg	90 ± 18 min	3.1 ± 1.6 mL/kg/min
Alfentanil‡	Cirrhosis§	0.46 ± 0.16 L/kg	45 ± 13 min	7.59 ± 3.6 mL/kg/min
	Control	0.40 ± 0.21 L/kg	41 ± 16 min	7.25 ± 4.3 mL/kg/min

From Davis PJ, Cook DR: Anesthesiology problems in pediatric liver transplantation, *Transplant Proc* 21:3493, 1989.
$t_{1/2\beta}$, Elimination half-life; *Vd,* volume of distribution.
*Significantly different from controls.
†Adults.
‡Children.
§Cirrhosis resulting from cholestatic liver disease.

that the severity of disease did not correlate with the duration of mivacurium blockade in pediatric patients with liver disease compared with controls. However, mivacurium's initial recovery and overall recovery from neuromuscular blockade did correlate inversely with the concentration of plasma cholinesterase.

Cisatracurium is a stereoisomer of atracurium. In patients with normal hepatic and renal function, the duration of action of cisatracurium is similar to that of atracurium. DeWolf et al.[102] noted that although the kinetic profile of cisatracurium differed in patients with liver failure compared with control patients, the duration of clinical effectiveness was similar for the two groups of patients. In patients with hepatic failure, clearance of rocuronium is reduced, and the volume of distribution is increased. Consequently, the elimination half-life is prolonged.

The Role of the Liver in Coagulation

The liver has a dual role in the coagulation system. It synthesizes proteins necessary for the coagulation cascade, and it functions as a clearing mechanism of the fibrinolytic system. Because coagulopathies are common in patients with liver disease and because hemostasis is paramount in any surgical procedure, coagulation monitoring and knowledge of the clinical effects of blood products on the coagulation system provide important information. Surgical procedures in which massive volumes of blood are transfused frequently result in dilutional thrombocytopenia. The need for platelet transfusions is a function of the amount of blood transfused and the initial platelet count. The appropriate use of blood products is discussed elsewhere in this textbook. For patients with severe hepatic dysfunction undergoing surgical procedures, as well as for patients with normal coagulation profiles who are anticipated to need transfusion of more than one blood volume, an adequate supply of blood products must be available before surgery is started.

Thromboelastography (TEG) has been in use for more than 60 years.[103] Developed during the Second World War, it has had a revival with the advent of transplantation and the ability to perform more complex surgeries. Moreover, new technology has made this point-of-care test easier to execute, more reliable, and reproducible.[104,105] TEG is a global dynamic assessment of hemostasis that can yield information on several different components of coagulation within 60 minutes. Its use for the guidance of blood component therapy in liver transplant has been demonstrated.[106,107] TEG measures the static viscoelastic properties of whole blood. As a clot begins to form in the sampling cup, the viscoelastic properties of the sample increase and an increase in amplitude is registered on the tracing. At the end of the test a characteristic trace with two arms is created.[108] Various measurements are derived from the tracing (Figure 120-4).[109] The R-time is the time in minutes from the start of the sample run until the first traces of clot mesh are detected (defined as an increase in amplitude of 2 mm). R-time generally reflects factor levels. The K-time is the time elapsed between the amplitudes of 2 and 20 mm on the TEG tracing and reflects velocity of clot formation. The α-angle is the slope drawn from r to k. The angle reflects fibrinogen activity. The maximum amplitude (MA) is the greatest vertical amplitude. It reflects clot strength and indirectly assesses platelet number and function and fibrin formation. The clot lysis index (A60) is the amplitude 60 minutes after the MA is achieved. It represents fibrinolytic activity. Alternatively, lysis 30 (Ly30) can be used, which assesses fibrinolysis at a shorter time interval.

Andrew et al.[110] demonstrated that the coagulation system of newborns is immature and undergoes a maturational process in the first year of life, during which time factor levels reach near adult levels. Clinical practice, however, shows that this does not expose neonates and infants to increased bleeding during surgery. Paradoxically, TEG tracings of healthy newborns show that neonates initiate and develop clots faster than adults.[111] R-time is significantly shorter despite a prolonged aPTT when compared to adults. MA values are also increased when compared to adults. An explanation of this can be due to the presence of adult levels of factors VIII and XIII, vonWillebrand factor, and platelets, already at birth, and lower levels of inhibitors, especially antithrombin III. This imbalance could promote faster activation and a more resistant clot.[111]

Thromboelastography has facilitated solid organ transplantation, and much of our understanding of the relation of TEG with the coagulation cascade has come from patients undergoing liver transplantation. Patients during liver transplants are frequently in a hypocoagulable state, with an increased risk for perioperative bleeding. The reasons for this hypocoagulable state included decreased synthesis of coagulation proteins, decreased platelet number and function, and increased fibrinolysis secondary to decreased hepatic clearance of TPA.[112] TEG tracings can reflect this state with prolonged r-time, decreased α-angle and decreased MA. During the anhepatic phase (when the liver is removed), fibrinolysis increases and there is further deterioration of the MA and the α-angle. The A60 is also decreased. The TEG tracing shows signs of hyperfibrinolysis. With the absence of the liver, there is no hepatic clearance of TPA and, in addition, low levels exist of the plasmin inhibitor α_2-antiplasmin.[113] When the donor liver is reperfused (reperfusion phase), a reperfusion coagulopathy can further affect hemostasis. Increased amounts of plasminogen activators released by the damaged endothelium of the donor liver and the presence of exogenous heparin in the donor liver are the cause. TEG tracings can show extreme levels of hyperfibrinolysis, and the r-time can be further prolonged. TEG analysis with heparinase sample cups demonstrates the contribution of heparin to the coagulopathy by a partial correction of the tracing when compared to the native without heparinase.[114]

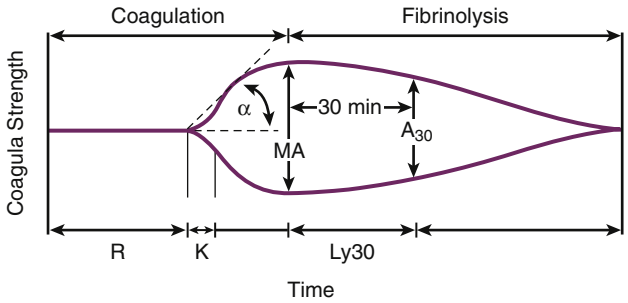

Figure 120–4. R reflects coagulation factor activites, K and α show fibrinogen and coagulation formation, MA indicates platelet function, Ly30 reflects fibrinolysis, A30 is the amplitude after MA. *(Modified from Raikvam H, et al: Thromboelastography,* Transfus Apher Sci *40:119-123, 2009.)*

In 1985, Kang et al.[107] devised a protocol for blood component therapy guided by TEG tracings. This protocol dictated that an r-time of ≥15 min needed 2 units of FFP, an MA of ≤40 mm needed 10 units of platelets, and when the α-angle was ≤45° or there was no improvement with the above blood component therapy, 6 units of cryoprecipitate was given. When blood requirements of this group were compared to a historical control group, they found that the TEG-monitored received 33% less blood. In addition, TEG can be used as an in vitro test to predetermine the effectiveness of the antifibrinolytic agents tranexamic acid and epsilon aminocaproic acid (EACA).[115,116]

Recombinant activated factor VII (rFVIIa, NovoSeven) is an analogue of the naturally occurring activated Factor VII and is a powerful hemostatic agent. It is approved by the FDA for use in patients with congenital or acquired hemophilia with inhibitors who are actively bleeding or for prophylaxis prior to invasive surgery or procedures.[117,118] rFVIIa directly enhances thrombin generation, locally at the site of endothelial damage where tissue factor is exposed, and indirectly on the activated platelet surface, creating the thrombin burst generating enormous amounts of fibrin mesh in the proximity of the damaged vasculature.[119,120] Since its marketing in the United States in 1999, there has been an exponential increase of publications regarding the off-label use for life-threatening hemorrhages of various origins in nonhemophiliac patients, giving rFVIIa a potential role as a universal hemostatic agent.[121] The lack of randomized trials for off-label use of rFVIIa in children makes it difficult to evaluate its efficacy and safety. At present, the only randomized trials are in children with hemophilia where a standardized treatment regimen of 90 μg/kg every 2 hours was administered until hemostasis was obtained.[118] Its fast reconstitution and low volume leads to rapid administration without risk of fluid overload. There is, however, intersubject variability, and its short half-life in children (1.32 hours vs. 2.72 hours in adults)[122] increases costs, because higher doses are necessary to achieve the same plasma levels as in adults.[123] There are several case series describing the use of rFVIIa in children with severe liver failure.[124-126] Varying doses from 40 to 100 μg/kg were used as a last effort to correct severe bleeding after failure of conventional blood component therapy. Pediatric liver transplants have a higher incidence of vascular graft thrombosis because of the smaller caliber of the vascular grafts, and it is feared that the administration of rFVIIa can increase the incidence of vascular graft thrombosis. Kalicinski et al.[127] reviewed 89 consecutive patients, aged 1 to 20 years, who underwent cadaveric liver transplant. Twenty-eight of these patients had a high risk of intraoperative blood loss and received rFVIIa prior to transplant. When compared to the 61 patients that had no increased intraoperative risk of blood loss, they noted no difference in blood loss, operating time, reexploration, and hospital stay. Interestingly no thromboembolic events were observed in the group that received rFVIIa, while in the 61 patients that did not receive rFVIIa, three had hepatic artery thrombosis, two had portal vein thrombosis, and one had hepatic vein thrombosis. The authors suggest that despite the use of rFVIIa, the overall hemostatic balance remains modestly hypocoagulable.[127] Currently, there are no laboratory tests that can predict the clinical response to rFVIIa. Most clinicians are using the prothrombin time to monitor its hemostatic effect, although it does not reflect in vivo responses.[128] Hendricks et al. reported monitoring the effects of rFVIIa by TEG analysis.[129] Both onset of clot formation and amplitude and clot stability improved after administration of rFVIIa.

Renal Failure

One major function of the kidneys is the regulation of fluid and electrolyte balance. Hyponatremia and hyperkalemia, the electrolyte disorders seen most often in patients with renal failure, are discussed briefly. Management of fluid and electrolyte abnormalities associated with renal failure is reviewed elsewhere in this textbook. However, some aspects of fluid and electrolyte disturbance have implications for anesthetic management.

Fluid and Electrolyte Disturbances

In clinical practice, it is desirable to maintain serum sodium concentrations greater than 125 mEq/L. At lower levels, symptoms including irritability, personality change, muscle weakness, and depressed deep tendon reflexes may occur. More severe hyponatremia (≤120 mEq/L) may cause cerebral edema and may be associated with nausea, vomiting, confusion, convulsions, hypothermia, and even death. In addition, anesthetic requirements may decrease significantly in the presence of serum and CSF hyponatremia.

Hyperkalemia may produce well-recognized electrocardiographic changes, including symmetrical peaking of the T wave, ST-segment depression, and heart block. Ventricular fibrillation or asystole may result from extreme hyperkalemia. This has been observed after the use of depolarizing NMBAs such as succinylcholine, which further increase plasma potassium concentrations by increasing muscle plasma membrane permeability.

The acidosis associated with renal failure would not be expected to interfere with reversal of neuromuscular blockade. Miller and Roderick[66] demonstrated that metabolic alkalosis, but not metabolic acidosis, may prevent neostigmine-induced antagonism of pancuronium. The mechanism proposed depends on simultaneous decreases in calcium and potassium levels. Whether the hypocalcemia associated with renal failure clinically affects reversal of NMBAs remains to be demonstrated. In the event of prolonged neuromuscular blockade, dialysis should easily remove both NMBAs and anticholinesterase agents used for reversal of blockade. Both classes of drugs are highly ionized compounds.

Perioperative dialysis may be required to control hyponatremia, fluid overload, hyperkalemia, or severe acidosis in the surgical patient with renal failure. When possible, dialysis should be accomplished shortly before surgery to optimize the patient's preoperative status. The goals of dialysis should not include dehydration. Patients who are dehydrated may become hypotensive during induction and maintenance of anesthesia. Laboratory evaluations including electrolytes may need to be evaluated following dialysis and prior to anesthetic care.

Renal Drug Metabolism

The kidneys also function in drug elimination. The effects of renal failure on drug disposition and elimination are of particular interest to the anesthesiologist. Nondepolarizing NMBAs

are the major class of anesthetic agents excreted primarily by the kidneys. Drugs that are almost exclusively eliminated by the kidney (e.g., gallamine and metocurine) should be avoided in the presence of renal failure. Pancuronium accumulates despite its partial hepatic metabolism and biliary excretion and may demonstrate as much as a fivefold increase in elimination half-life in anephric patients. The intermediate-duration NMBAs vecuronium and atracurium should be considered for use in patients with renal failure.[130,131] Although vecuronium depends primarily on hepatobiliary excretion with only 20% primarily excreted by the kidney, its active hepatic metabolites are dependent on renal excretion and may accumulate with repeated dosing in patients with renal dysfunction. Therefore it may result in prolonged blockade, depending on the degree of renal failure or insufficiency. Atracurium elimination occurs by Hoffmann elimination and ester hydrolysis in the plasma. Because these processes are independent of renal and hepatic function, the elimination half-life of atracurium is constant regardless of failure of these organs.[100,132] Atracurium metabolism produces laudanosine, which is associated with seizures in laboratory animals at high plasma concentrations.[133] Data in human subjects indicate that the risk of such seizures probably is not clinically relevant. ICU patients receiving atracurium infusions for up to 219 hours had maximum plasma concentrations well below the threshold for canine seizures and showed no evidence of cerebral excitation.[134] The effects of renal failure on this scenario are not documented. Mivacurium is a bisquarternary benzylisoquinolinium diester, nondepolarizing NMBA that is metabolized by plasma cholinesterase. It is a mixture of three optical isomers. Mivacurium at a dose of 0.15 mg/kg prolonged neuromuscular blockade by a factor of 1.5 in patients with renal disease compared to patients with normal renal function.[135]

Cisatracurium is one of the stereoisomers of atracurium and is thought to be three times more potent than atracurium but with a similar duration of action. Like atracurium, cisatracurium is metabolized by Hoffmann elimination, and the drug does not accumulate. Its duration of action is not prolonged in patients with renal failure.[136] Rocuronium is a monoquaternary steroidal NMBA of rapid-to-intermediate onset of action and intermediate duration. The clinical duration of rocuronium is similar to that of vecuronium. It has a rapid onset of action, but in patients with renal disease, the onset of action is decreased by 30% to 40% and its duration of action is prolonged and variable.[137,138]

The anticholinesterase agents used to reverse neuromuscular blockade (neostigmine, pyridostigmine, and edrophonium) are eliminated primarily by the kidney, and renal failure markedly prolongs their duration of action. In the absence of renal function, the reversal of neuromuscular blockade induced by atracurium and vecuronium should not be complicated by recurrence of blockade.

Opioids are metabolized primarily by the liver. Thus renal failure should not have a major effect on the primary clearance of opioids, although the metabolism of some opioids (meperidine and morphine) results in pharmacologically active metabolites that are water soluble and undergo renal elimination. As such, the elimination and hence the clinical effects of these agents may be prolonged, especially after repeated dosing or continuous infusions in patients with renal dysfunction. The pharmacokinetics of fentanyl, sufentanil, and alfentanil in children appear to be minimally affected by chronic renal failure.[139,140] Morphine glucuronide accumulates at higher plasma concentration in patients with chronic renal failure.[141,142] Normeperidine, the major metabolite of meperidine, may accumulate and cause prolonged respiratory depression and seizures.

Of the inhaled anesthetic agents, isoflurane is probably the safest for patients with renal failure. It is not metabolized to fluoride ion or associated with potential renal toxicity, as are enflurane and methoxyflurane. It also is not associated with bromide ion production, as is halothane. Although bromide is not a renal toxin, it may account for persistent sedation. The metabolic breakdown of desflurane is insignificant. Less than 1% of the absorbed dose is metabolized. Sevoflurane, however, undergoes metabolic breakdown into organic and inorganic compounds. Inorganic fluoride is a potential cause of nephrotoxicity with the prolonged administration of sevoflurane. Studies with methoxyflurane show that plasma inorganic fluoride levels greater than 50 μmol/L are associated with nephrotoxicity. However, plasma levels may not accurately predict nephrotoxicity. Kharasch et al.[143] demonstrated that inhalational anesthetic agents are metabolized within the kidney by the cytochrome P-450 system and that various anesthetic agents are metabolized differently within the kidney. Consequently, it appears that intrarenally produced fluoride. and not the plasma fluoride level. may explain the relationship of nephrotoxicity to anesthetic metabolism. These data suggest that agents that do not undergo primarily metabolism in the kidney (sevoflurane) are less likely to result in nephrotoxicity than older agents that were metabolized by the kidneys (methoxyflurane). The newer agents, sevoflurane and desflurane have been studied in patients with and without renal disease. Desflurane is a polyfluorinated ethyl ether that does not undergo in vivo metabolism. Studies in both animals and humans suggest that desflurane has no hepatic or renal toxic effect; however, it does interact with dry carbon dioxide absorbants and produces carbon monoxide.[144] Sevoflurane is a polyfluorinated methylisopropyl ether that undergoes in vivo degradation to difluorovinyl products and fluoride ion. In addition, sevoflurane undergoes degradation by the CO_2 absorber system to form fluoromethyl-1-1-difluoro-1-(trifluoromethyl) vinyl ether, also known as compound A. Both compound A and free fluoride ions have potential nephrotoxic effect. However, clinical studies in patients with normal renal function and those with abnormal renal function demonstrate that changes in kidney function following sevoflurane anesthesia are similar to changes that occur after desflurane, isoflurane, or enflurane anesthesia.[145-151]

Remifentanil is an opioid agonist that is metabolized by plasma and tissue esterases. The metabolic product of remifentanil metabolism has a potency of 1/3400 of its parent compound. It is independent of organ elimination, and its extremely rapid metabolism does not allow for drug accumulation. Ross et al.[152] reported the pharmacokinetic properties of remifentanil in children. Its ultrashort half-life (less than 7 minutes) allows patients a rapid recovery from anesthesia. Because it is independent of organ elimination, the pharmacokinetic profile of remifentanil is unchanged in either renal or hepatic insufficiency.[153] Remifentanil also demonstrates a flat, context-sensitive half-time. Thus the length of time remifentanil is infused does not affect the time to patient recovery when infusion is discontinued.[154,155]

In addition to the fluid and electrolyte problems and pharmacologic concerns posed by renal failure, the presence or development of renal failure per se may affect perioperative outcome. In adults, perioperative renal failure is associated with mortality rates as high as 70%. Similar data from children are lacking. However, in a study of pediatric patients undergoing liver transplantation, the 1-year survival rate in patients with renal failure was 53% compared with 81% for patients in whom renal failure did not develop.[156]

Intravenous Alimentation

ICU patients frequently receive intravenous hyperalimentation for nutritional support. Intravenous hyperalimentation regimens should be adjusted in anticipation of surgery. Surgical trauma results in accelerated protein catabolism. Administration of glucose to traumatized patients does not have the protein-sparing effect observed during starvation. The capacity of postoperative patients to handle exogenous glucose loads is impaired as a result of the neuroendocrine response to injury.[157] Hyperglycemic, hyperosmolar, nonketotic coma (HHNKC) is reported as a cause of delayed awakening after anesthesia. In two reports, the patients had diabetes mellitus, and they returned to the baseline level of consciousness within 1 to 3 postoperative days after appropriate therapy. Bedford[158] reported the fatal development of HHNKC postoperatively in a nondiabetic patient who received high-dose steroid therapy for thrombotic thrombocytopenic purpura.

Conversely, abrupt interruption of hyperalimentation containing high concentrations of dextrose may result in hypoglycemia, the signs and symptoms of which may be undetected in an anesthetized patient. Therefore optimal preoperative preparation should include weaning of glucose-containing solutions to concentrations less than or equal to 10% for a period of several hours before surgery or the decrease in the hyperalimentation to approximately 50% of its baseline rate during the surgical procedure. During this weaning period of dextrose and intraoperatively, interval monitoring of serum glucose is mandatory. Such a practice should help prevent the problems of hyperglycemia and hypoglycemia. In addition, glucose concentrations less than or equal to 10% may be administered peripherally, thus facilitating central access for administration of fluid volume, vasopressors, and/or resuscitation medications. Glucose concentrations greater than 10% should be administered only through a central cannula; when administered peripherally, these solutions may result in intense thrombophlebitis associated with venous extravasation.

Although the perioperative administration of fat emulsions used for hyperalimentation has not been shown to increase anesthetic risk, routine anesthesia practice is to discontinue their use. Potential complications of intravenous lipids include hepatobiliary injury, pancreatitis, and hypoxemia resulting from interstitial lipoid pneumonitis with alveolar capillary block.

References are available online at http://www.expertconsult.com.

Anesthesia Principles and Operating Room Anesthesia Regimens

Joseph D. Tobias

Intraoperative anesthetic can be provided by one of five techniques, which include local anesthesia (sometimes referred to as "local only," monitored anesthesia care (MAC), peripheral nerve blockade, neuraxial techniques (spinal or epidural anesthesia), and general anesthesia. Local anesthesia involves the infiltration of a surgical site with a local anesthetic agent to render the site insensitive to pain. This may be done solely by the surgeon without the involvement of an anesthesia provider. MAC involves monitoring a patient with standard monitors in accord with guidelines of the American Society of Anesthesiologists (ASA monitors, see below) and administering a sedative and/or analgesic agent intravenously to provide anxiolysis, sedation, and analgesia. MAC is frequently combined with either infiltration of the surgical site with a local anesthetic agent or a regional anesthetic technique. MAC is provided using a combination of a drug with amnestic properties (midazolam or propofol) combined with a drug to provide analgesia (an opioid such as fentanyl). During MAC, spontaneous ventilation is maintained during the procedure, thereby eliminating the need for endotracheal intubation and controlled ventilation. The depth of sedation may range from a state in which the patient is awake and relaxed with the ability to respond to verbal stimuli to a state of deep sedation where a painful stimulus is required to elicit a response. Peripheral nerve blockade and neuraxial anesthesia are frequently considered together under the title of regional anesthesia. A peripheral nerve block involves the placement of a local anesthetic agent around a nerve or group of nerves (plexus) to render specific dermatomes insensitive to pain. Examples of plexus blockade include cervical plexus blockade for superficial and deep neck surgery, brachial plexus blockade for upper extremity or shoulder procedures, or lumbar plexus blockade for hip or leg surgery.[1-3] Intravenous regional anesthesia, the Bier block, is another example of a peripheral nerve block that can be used to provide surgical anesthesia. A Bier block involves the intravenous injection of a dilute local anesthetic into a vein of an extremity after that extremity has been exsanguinated by wrapping it with a bandage and then occlusion with a tourniquet. Although the latter technique is generally successful and easy to accomplish, it may not be feasible in younger children except when combined with deep sedation. Given the use of an occlusive tourniquet, its duration is limited to 60 to 70 minutes due to tourniquet pain. The major concern with the Bier block is that the dose of local anesthetic used approaches the toxic limits and should the tourniquet fail, cardiovascular or central nervous system (CNS) consequences from the local anesthetic agent may occur. Neuraxial anesthesia involves the injection of a local anesthetic agent into either the subarachnoid or epidural space. This reasults in blockade of the spinal cord and its accompanying nerve roots to render an entire region of the body (lower abdomen, pelvis, perineum, or lower extremities) insensitive to pain. Examples of neuraxial anesthesia include spinal, epidural, and caudal anesthesia.[4,5] In infants and children, a regional anesthetic technique such as a peripheral nerve block or epidural anesthesia can be used instead of general anesthesia in patients with comorbid diseases that significantly increase the risk of anesthesia. More frequently, the regional anesthetic technique is combined with a general anesthetic as part of a balanced anesthetic technique and continued into the postoperative period by use of a continuous infusion via the catheter to provide postoperative analgesia.

When a general anesthesia is used, it should include the four requisites of amnesia, analgesia, muscle relaxation, and attenuation of the sympathetic nervous system's response to surgical trauma. The phases of general anesthesia include induction, maintenance, and emergence. The induction of anesthesia can be carried out with the intravenous administration of an anesthetic agent (thiopental, propofol, ketamine, or etomidate) or via the inhalation route with an inhalational anesthetic agent such as sevoflurane. Advantages of an intravenous induction include the rapid onset of anesthesia and avoidance of issues associated with inhalation induction including claustrophobia from anesthesia mask placement and the odor of the inhalational anesthetic agent. In pediatric patients, the inhalation induction of anesthesia is frequently chosen to avoid the need for obtaining intravenous access on an awake child. However, when inhalation induction is carried out without intravneous access, airway and cardiovascular issues may arise which may mandate immediate treatment without intravenous access. In such cases, if intravenous access cannot be rapidly obtained, it may be feasible to use the intramuscular (IM) route for a select number of medications (atropine, succinylcholine). However, more aggressive resuscitation such as the administration of

epinephrine for hemodynamic compromise may require the use of intraosseous access (IO).[6] Fortunately, the majority of problems during inhalation induction can be easily reversed with appropriate airway techniques or the administration of IM medications. Hemodynamic compromise including cardiac arrest was more common with the use of halothane, given its negative inotropic and chronotropic properties.[7] However, halothane is no longer used in the practice of anesthesia, having been replaced by sevoflurane. Even if intravenous access is present, the inhalational induction of anesthesia may be chosen as it allows the maintenance of spontaneous ventilation even during deep planes of anesthesia (deep enough to allow for direct laryngoscopy and endotracheal intubation). Such a technique may be used if there is a question regarding the ability to bag-valve-mask ventilate the patient, such as for patients with compromised airways from infection, tumor, or anatomic abnormalities. Following anesthetic induction, one progresses into the maintenance phase of general anesthesia. This can be achieved by the administration of intravenous agents, inhalational agents, or, most often, a combination of the two (balanced anesthesia). An example of a balanced technique includes some combination of inhalational (nitrous oxide and an inhalational anesthetic agent), a continuous infusion of an intravenous anesthetic (propofol), a nondepolarizing neuromuscular blocking agent (NMBA), and an opioid. In most circumstances, the choice of maintenance anesthesia is based on the presence of comorbid features and the preferences of the anesthesiologists.

Preoperative Evaluation

Regardless of the type of procedure, the patient's status, and the anesthetic technique that is planned, a preoperative evaluation should be performed. In many centers, such an evaluation is performed well in advance of the anticipated surgical procedure in a specialized clinic to allow for specific preoperative interventions or preparation that may be required to allow for the safe completion of the anesthetic care and surgical procedure. Alternatively, in low-risk patients without accompanying comorbid diseases, the preoperative evaluation can be performed the day of surgery. The latter may also be required for patients admitted to the hospital or those presenting for emergent or urgent surgical procedures.

The preoperative evaluation includes a history of present illness, past medical problems including drug allergies, a past surgical and anesthetic history, and a review of the patient's current and perhaps past medical record and medication list. For elective surgical procedures, the status of comorbid conditions should be optimized prior to the surgical procedure. The latter may not be feasible for urgent or emergent cases. The physical examination is directed primarily at the central nervous system, cardiovascular system, and respiratory system, including an examination of the airway. The preoperative evaluation can identify many of the patients with a difficult airway which may preclude successful endotracheal intubation using standard techniques of direct laryngoscopy. An airway history should be obtained seeking medical, surgical, and anesthetic factors that may indicate a difficult airway. Examination of previous anesthesia records is helpful, although a patient's airway may change with growth or the development of comorbid conditions. A physical examination of the airway is performed to detect physical characteristics associated with a difficult airway such as a large tongue, small mouth, short neck (shortened thyromental distance), recessed mandible, limited extension or flexion of the neck, limited mouth opening, and difficulty visualizing the uvula and tonsillar pillars when the patient opens their mouth. Risk of airway access is assessed using the Mallampati grading system. Visualization of the entire uvula and tonsillar pillars (Mallampati grade I) suggests that endotracheal intubation will be uncomplicated while failure to visual the tonsillar pillars and the soft palate (Mallampati grade IV) suggests that endotracheal intubation will be difficult. Based on the preoperative evaluation, an ASA Physical Status classification is assigned to the patient based on his or her comorbid features and associated medical conditions (Table 121-1).[8] The physical classification is based on the physical condition of the patient and does not include the planned surgical procedure. Laboratory tests and additional investigations are ordered based on the positive findings obtained during the history and physical examination and on the complexity of the surgical procedure.[9] The routine preoperative testing of all patients for elective surgery has been shown to be unjustified and expensive. In the absence of comorbid conditions, for surgical procedures with limited chance of significant blood loss, no laboratory or radiologic evaluation is necessary. Although commonly performed, routine testing of coagulation function has been shown to be of limited value without an antecedent history of bleeding problems.[10] The most common coagulation disorder that may cause problems intraoperatively is von Willebrand disease; however, it cannot be identified on routine coagulation screening, which is limited to a prothrombin time (PT), partial thromboplastin time (PTT), and an international normalized ratio (INR). Another area of ongoing controversy is the need for routine preoperative pregnancy testing in postmenarchal patients. Given the theoretical potential for anesthetic agents to be teratogenic and the risks of spontaneous abortion, the history should

Table 121–1 ASA Physical Status Classification

Classification	Description	Example
1	Normal healthy patient	—
2	Mild systemic disease with no functional limitation	Mild asthma, acyanotic congenital heart disease (atrial septal defect)
3	Severe systemic disease with functional limitation	Sickle cell disease, cystic fibrosis, palliated cyanotic congenital heart disease
4	Severe systemic disease that is a constant threat to life	Advanced stages of muscular dystrophy, cyanotic congenital heart disease with pulmonary hypertension
5	Moribund patient not expected to survive without operation	Perforated bowel with sepsis and shock
6	Brain-dead patient; organs are being removed for donor purposes	—
E	Emergency operation	—

include specific questioning about the potential for pregnancy including the patient's last menstrual cycle. In addition, there is increasing use of a point-of-care urine pregnancy testing in many centers. Further testing such as pulmonary function tests, electrocardiography, and echocardiography are based solely on the presence of comorbid conditions following the preoperative visit, including the history and physical examination. The planned management of anesthesia is discussed with each patient, and risks and possible complications are reviewed. Options and plans for postoperative pain management are discussed. The history and informed consent complete the preoperative evaluation.

NPO Guidelines

Although the aspiration of gastric contents is an uncommon event, the consequences may be severe, including pneumonitis, respiratory failure, or even death. Classical teaching states that the severity of the aspiration injury relates to the volume aspirated as well as its pH, with severe complications occurring with the aspiration of a volume 0.4 mL/kg or greater or a pH of 2.5 or less. Although aspiration may occur in any setting, patients at risk include parturients, obese patients, diabetics, patients who have received opioids, patients with gastrointestinal disease (reflux, obstruction), patients with altered mental status, patients with intraabdominal pathology (acute abdominal emergencies including appendicitis) and patients in whom difficult airway management is anticipated. These factors may predispose to aspiration by limiting the patient's ability to protect their own airway, decreasing the normal barrier to aspiration (lower esophageal sphincter tone), increasing gastric volume, or delaying gastric emptying.[11,12] Patients who have the highest incidence of perioperative aspiration are those with a high ASA physical status classification (III, IV, or V) and those having emergency surgery. The majority of aspirations occur during the induction of anesthesia or following tracheal extubation when the patient has lost his or her protective airway reflexes.

Classically, keeping patients *nil per os* (NPO) has been the mainstay of therapy to prevent acid aspiration. In the past, patients were fasted for 8 to 12 hours before surgery to reduce the volume of gastric contents at the time of induction of anesthesia and to decrease the risk of aspiration pneumonitis. This preoperative fast does not take into account differences in gastric emptying of clear liquids and solids. More recently, based on several investigations, there has been a significant revision in the perioperative fasting rules, especially for infants and children. It has been demonstrated that clear liquids have a gastric emptying time of 1 to 2 hours, while solids have an unpredictable gastric emptying time that may be greater than 6 hours.[13-16] The ingestion of clear liquids up to 2 hours before surgery does not increase gastric fluid volume or acidity.[13-16] As a result, the liberalization of guidelines for ingestion of clear liquids for elective surgery of otherwise healthy patients has been recommended.[17,18] A survey of anesthesiologists in the United States has shown that 69% have either changed their NPO policy or are flexible in their practice in allowing clear liquids before elective operations in children.[19] Suggested guidelines as recommended by the American Society of Anesthesiologists for patients with no known risk factors include no solid food for at least 6 hours before surgery and unrestricted clear liquids until 2 hours before surgery. Oral medications may be given 1 to 2 hours before surgery with a small sip of water.

Although on theoretical grounds, several maneuvers may be indicated in patients with risk factors for acid aspiration, there is limited if any evidence-based medicine to demonstrate their efficacy in preventing perioperative aspiration. Many centers routinely use preoperative medications to decrease the acidity of the gastric fluid (H_2-antagonists or proton pump inhibitors) and speed gastric emptying (metoclopramide). To be effective, it is recommended that these medications be administered 60 to 90 minutes prior to anesthetic induction. Alternatively, a nonparticulate antacid (sodium bicitrate) can be given immediately prior to anesthetic induction, a common practice in obstetrical anesthesia. Additionally, in patients at risk for acid aspiration, rapid sequence induction is practiced. This involves the use of a rapidly acting neuromuscular blocking agent (see below) with an anesthetic induction agent and the application of cricoid pressure. As the cricoid is the only complete ring of the trachea, it can be gently pushed posteriorly to effectively occlude the esophagus and prevent passive regurgitation of gastric contents when consciousness is lost during anesthetic induction. This practice is commonly referred to as rapid sequence induction or intubation (RSI). In its pure form, RSI involves preoxygenation, the administration of medications for neuromuscular blockade and anesthetic induction, and the performance of endotracheal intubation without bag-valve-mask ventilation, as the latter may distend the stomach and predispose to regurgitation. A modification of this technique, known as a modified RSI, uses gentle bag-valve-mask ventilation to maintain oxygenation while waiting for the anesthetic agents to take effect. The modified RSI may be used more commonly in pediatric anesthesia, as even brief periods of apnea without bag-valve-mask ventilation may result in precipitous decreases in oxygenation due to the low functional residual capacity and high metabolic rate for oxygen in young children and infants.

Preoperative Medication

There are several categories and uses of preoperative medications (Table 121-2). The most common use of a preoperative medication is to provide sedation and anxiolysis prior to transport to the operating room. Preparing the patient for surgery includes psychological preparation and, frequently, pharmacological premedication. Psychological preparation includes the preoperative visit and an interview by the anesthesiologist. Pharmacologic premedication may be given orally or, rarely, intramuscularly 1 to 2 hours before the induction of anesthesia or intravenously in the immediate preoperative period. Popular choices include benzodiazepines such as midazolam or occasionally, α_2-adrenergic agonists such as clonidine or dexmedetomidine. A frequently used agent and route of administration is the oral administration of the benzodiazepine midazolam to ease separation from parents and improve mask acceptance for inhalation induction. This is generally necessary when children are at least 9 to 18 months of age and begin to manifest stranger anxiety. Given alterations in bioavailability when administered by the oral route, doses of 0.3 to 0.5 mg/kg are required.

Additional preoperative medications may be used in patients with certain comorbid features, such as the use of H_2-antagonists, proton pump inhibitors, or motility agents to increase

Table 121–2 Types and Uses of Premedications

Type of Medication	Purpose
Benzodiazepine	Sedation, anxiolysis, amnesia—eases parental separation
α_2-Adrenergic agonists (clonidine, dexmedetomidine)	Sedation, anxiolysis—decrease intraoperative anesthetic needs
Opioids	Analgesia during invasive procedures
Anticholinergic agent (atropine, glycopyrrolate)	To prevent bradycardia, blunt airway reflexes, dry secretions
Inhaled β-adrenergic agonists (albuterol) and anticholinergic agents (ipratroprium)	Prevention or relief of bronchospasm
Inhaled lidocaine	Prevent airway reflexes during awake fiberoptic intubation, direct laryngoscopy or bronchoscopy
H_2-antagonists, proton pump inhibitors	Decrease pH of stomach contents
Promotility agents such as metoclopramide	Decrease volume of gastric secretions
Antiemetic agents (scopolamine patch, neurokinin-1 inhibitors)	Prevention of perioperative nausea and vomiting

gastric pH and decrease gastric volume in patients at risk for acid aspiration; inhaled β-adrenergic agonists (albuterol) or anticholinergic agents (ipratropium) may be administered to patients with reactive airway diseases (asthma, recent upper respiratory infection, or chronic obstructive pulmonary diseases). Anticholinergic agents may be used to dry airway secretions in patients requiring fiberoptic intubation.

Monitoring

The standards for intraoperative anesthetic monitoring have been outlined by the American Society of Anesthesiologists. Monitoring standards are the same regardless of whether the case entails a general anesthetic, regional anesthetic (peripheral nerve block, spinal or epidural), or monitored anesthesia care. The standards according to the ASA include an oxygen analyzer, noninvasive blood pressure cuff, continuous ECG, pulse oximeter, end-tidal carbon dioxide analyzer, precordial or esophageal stethoscope, temperature probe, and a ventilator disconnect alarm. Based on the medical condition of the patient and the surgical procedure, more elaborate and invasive monitoring may be added to these standard monitors, such as a urinary catheter; catheters for measuring intraarterial, central venous, and pulmonary artery pressures; and transesophageal echocardiography. Although there are no strict guidelines dictating which patients should have invasive monitors placed, there have been recommendations set forth for the adult population. These recommendations must be taken in context of the limited data available comparing outcomes, for instance, in patients managed perioperatively with or without pulmonary artery (PA) catheters.[20,21] The ASA recommends considering three variables including disease severity, magnitude of the surgical procedure, and practice setting when assessing benefit versus risk of PA catheters.[22] Additional information regarding structural and functional issues of the myocardium may be obtained by the use of transesophageal echocardiography (TEE). TEE is used with increasing frequency in the adult population. There are now specific curriculae in cardiac anesthesia fellowships to teach the skills necessary for performance of TEE. The practice has been encouraged by the American Board of Anesthesiology, which recognizes such training and provides the opportunity for credentialing through the completion of a written examination. The strongest indications for perioperative transesophageal echocardiography that are supported by evidence-based medicine include cardiac surgery procedures such as repair of valvular lesions (insufficiency or stenosis) or congenital lesions, assessments and repairs of thoracic aortic aneurysms and dissections, pericardial window procedures, and the repair of hypertrophic obstructive cardiomyopathy.[23] For noncardiac surgery, intraoperative transesophageal echocardiography is indicated to evaluate acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and which have not responded to treatment, especially when placement of a PA catheter is not feasible.

In addition to standard ASA monitors, there is growing interest in the development and potential use of "depth of anesthesia" monitors. Although controversial, the potential impact of such monitors is highlighted by the results of several trials which demonstrate that intraoperative awareness may occur in anywhere from 0.1% to 0.2% of all patients, with even higher incidences in specific procedures including trauma, cardiac, obstetrical, and emergency surgery. Several manufacturers have marketed or are developing monitors which provide the anesthesia provider with a numerical value against which anesthetic agents are titrated. There are currently five such monitors, including the Bispectral Index (BIS monitor, Aspect Medical, Newton, MA); the Narcotrend (MonitorTechnik, Bad Bramstedt, Germany), which is currently available only in Europe; Patient State Analyzer (PSA 4000, Baxter Healthcare, Deerfield, IL); SNAP (Everest Medical, Minneapolis, MN); and Auditory Evoked Potential Monitor (AEP Monitor, Danmetter Medical). To date, the one that has received the most clinical use is the BIS monitor. The BIS is a modified electroencephalographic monitor that uses a preset algorithm based on intraoperative data obtained from adults to evaluate the electroencephalogram. The BIS number is determined from three primary factors, including the frequency of the electroencephalographic waves, the synchronization of low and high frequency information, and the percentage of time in burst suppression. Part of the simplicity and attraction of the BIS monitor is that the depth of sedation/anesthesia is displayed numerically, ranging from 0 to 100, with 40 to 60 being a suitable level of anesthesia to ensure amnesia and lack of recall. With the use of BIS monitoring, a decreased incidence of awareness has been demonstrated, as well as a decrease in the total amount of anesthetic agent used.[24-26] Additional studies have suggested faster recovery times and faster discharge times from the postanesthesia care unit; all of which may translate into reduced perioperative costs.[26,27] Although not considered the standard of care as of yet for intraoperative anesthesia care, the ASA does recommend the availability of such monitors whenever general anesthesia is provided. Given the success of such monitors in

the perioperative arena, there is ongoing interest in the application of such technology in the ICU and the procedural sedation arena.[28-30]

The Pharmacology of Anesthetic Agents

Local Anesthetic Agents

The local anesthetic agents can be divided into two chemically distinct classes: esters and amides. Local anesthetic agents in the amino ester class include procaine, chloroprocaine, and tetracaine. Amino amides used clinically include lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, and ropivacaine. Several clinically important differences exist between these two classes of local anesthetic agent, including site of metabolism, plasma half-lives, adverse effect profile (CNS vs. cardiac toxicity), and allergic potential. Amino esters are metabolized by plasma cholinesterases, while amino amides undergo hepatic metabolism.

The mechanism of action for the majority of local anesthetic agents involves blockade of sodium channels in the nerve membrane, thereby preventing depolarization. The nonionized portion of the local anesthetic agent penetrates the lipid membrane, while the ionized portion reversibly blocks the inner aspect of the sodium channel. Local anesthetic agents differ in intrinsic potency, onset of action, duration of action, and their ability to produce differential sensory and motor blockade. Potency is determined primarily by lipid solubility (high lipid solubility is directly related to potency).[31] Bupivacaine and tetracaine are examples of local anesthetic agents with high lipid solubility and hence high potency. The onset of action is determined primarily by the pK_a with onset being most rapid in those agents with a pKa closest to physiologic pH.[32,33] With a pKa close to physiologic pH, the percentage of the un-ionized form is greater, thereby increasing passage through the nerve membrane. Lidocaine has a pK_a of 7.7 and at a pH of 7.4, 35% exists in the un-ionized base form yielding a relatively rapid onset of blockade. In contrast, tetracaine has a pK_a of 8.6 with only 5% in the un-ionized form at a tissue pH of 7.4, resulting in a slower onset of blockade than lidocaine. Duration of action is determined primarily by the degree of protein binding to receptors in the sodium channel.[34] Local anesthetic agents bind to protein receptors in the sodium channels. High protein binding and therefore a prolonged duration of action are characteristic of bupivacaine, levobupivacaine, tetracaine, and ropivacaine. Duration of action is also influenced by the degree of vasodilation produced by the local anesthetic.[35] Vasodilatation results in increased blood flow to the area and therefore an increased removal of the agent from the depot in the tissues. The local anesthetic agents also differ in their differential effects on sensory versus motor nerves. Bupivacaine and ropivacaine demonstrate this property, which is very beneficial for postoperative analgesia administered through an epidural catheter so that patients are able to ambulate with minimal discomfort.

When performing regional anesthesia, the goal is to place the local anesthetic agent as close as possible to the nerve or plexus that needs to be anesthetized. A recent addition to the armamentarium of the anesthesiologist has been the use of ultrasound to visualize the individual nerve roots or the plexus that is to be anesthetized.[37-40] This technology is also being used for neuraxial techniques including spinal and epidural anesthesia. The advantages of this technology are not only an increased success rate of various regional anesthetic techniques, but also the ability to provide blockade with a decreased dose of the local anesthetic agent. Additional factors that must be considered when using these agents are the maximal allowable dose of the agent, the impact when a vasoconstrictor such as epinephrine is added to the solution, and the effect of the site of administration. Increasing the dose of a local anesthetic (increased concentration or volume) yields a faster onset of effect, a longer duration of action, and a greater depth of blockade.[41] However, higher plasma concentrations of the local anesthetic agent will also be achieved, thereby increasing the risks of toxicity (discussed later).

Given the catastrophic effects of local anesthetic toxicity, mechanisms to avoid it and prevent its occurrence are mandatory during the performance of regional anesthetic techniques in infants and children. Epinephrine (5 μg/mL or a concentration of 1:200,000) is added to the local anesthetic solution during performance of a regional anesthetic technique to cause local vasoconstriction, thereby decreasing the vascular absorption of the drug and also to serve as a marker of inadvertent systemic injection.[41-43] However, the ability of epinephrine to prolong the duration of action depends on the local anesthetic used and the site of administration. More importantly, epinephrine is used as a marker for inadvertent systemic injection. Even with negative aspiration for blood, there is the potential for inadvertent intravascular administration, thereby suggesting the use of a test dose. The test dose entails the administration of 3 mL of the 5 μg/mL epinephrine solution or a total epinephrine dose of 15 μg. If this amount of epinephrine is injected intravascularly, it can generally be detected by changes in heart rate, blood pressure, or the ST-T wave segments of the electrocardiogram and will thereby alert the practitioner that inadvertent intravascular injection is occurring.[44]

The site of injection of the local anesthetic agent also has a significant impact on the clinical effects including duration of action and vascular uptake (plasma concentrations). The shortest durations of action occur with either intrathecal injection for spinal anesthesia or subcutaneous administration. The longest duration of action and onset of blockade are seen with major peripheral nerve blocks (brachial or lumbar plexus blockade).[45,46] The vascular absorption of the local anesthetic agent and its plasma concentration are also dependent on the site of administration. The highest plasma concentration occurs following an intercostal nerve block or interpleural analgesia followed in order by caudal epidural, lumbar or thoracic epidural, brachial plexus, peripheral nerve blockade, subarachnoid, and subcutaneous infiltration.[47]

During performance of regional anesthesia, the greatest risk of morbidity and mortality results from the achievement of toxic plasma concentrations of the drug. Local anesthetic-induced systemic toxicity affects the CNS and the cardiovascular (CV) system. The differential effects on these two organ systems and the plasma concentration at which toxic effects are noted vary according to the agent. With most local anesthetic agents, CNS toxicity occurs at doses and blood levels below those that produce cardiovascular toxicity. The latter provides some degree of safety, as the CNS symptoms (seizures) are generally more amenable to treatment than the cardiovascular effects (arrhythmias and conduction blockade). Death from local anesthetic toxicity is most commonly the result of the

cardiovascular effects of these agents with adverse effects on cardiac electrical and mechanical activity.[48] Bupivacaine produces cardiac arrhythmias by inhibiting the fast sodium channels and the slow calcium channels in the cardiac membrane. Hypercarbia, acidosis, and hypoxia potentiate the negative chronotropic and inotropic effects of high plasma concentrations of local anesthetic agents. These effects are so profound that resuscitative measures for ventricular tachycardia/fibrillation including standard ACLS protocols may be ineffective. Anecdotal case reports have suggested the potential role of various agents such as amiodarone for refractory ventricular arrhythmias. More recently, anecdotal human data and animal studies have suggested that intralipid solutions may be used to bind the local anesthetic agent, thereby resulting in return of spontaneous circulation. Current recommendations from the ASA include easy and ready access to 20% intralipid solutions whenever large doses of local anesthetic agents are used for regional anesthetic techniques. Given the risks of morbidity and mortality from local anesthetic toxicity, avoidance of toxicity is the goal through careful calculation of the dose, use of the lowest necessary dose (concentration and volume), use of a test dose with epinephrine to identify inadvertent intravascular injection, intermittent aspiration to identify vascular penetration, and slow incremental injection of the dose.

Intravenous Anesthetic Agents

The intravenous anesthetic agents in common clinical use include the barbiturates (thiopental, methohexital, and thiamylal), propofol, etomidate, and ketamine. These agents are used to induce (bolus administration) and/or maintain (continuous infusion) the general anesthetic state. In lower doses, agents in this class such as propofol can be used by continuous infusion to provide MAC while maintaining spontaneous ventilation. Although any of the intravenous anesthetic agents will induce anesthesia, the choice of the agent and its dose are based on the clinical scenario, the anticipated duration of the surgical procedure, and the patient's underlying hemodynamic status.

Thiopental, propofol, and etomidate mediate their anesthetic properties through interactions with the γ-aminobutyric acid $(GABA)_A$ receptor complex. These interactions lead to enhanced activity of the inhibitory neurotransmitter system (GABA).[49-52] Activation of the $GABA_A$ receptor increases the transmembrane movement of chloride, resulting in hyperpolarization of the postsynaptic cell membranes. Ketamine's analgesic and anesthetic effects are the result of its interactions with the *N*-methyl-D-aspartate (NMDA) system, which is activated by glutamate, an excitatory transmitter, as well as by other sites within the CNS, including those involved with opioid and cholinergic transmission.[53-55] The intravenous anesthetic agents result in somewhat varying end-organ effects. The barbiturates, propofol, and etomidate reduce cerebral metabolism ($CMRO_2$), cerebral blood flow (CBF), and intracranial pressure (ICP). As such, they are valuable agents in the practice of neuroanesthesia or in critically ill patients with increased ICP. When compared with propofol or the barbiturates, etomidate may be preferred in patients with abnormal cardiovascular function as it provides greater hemodynamic stability. As a result, etomidate maintains cerebral perfusion pressure (CPP = MAP – ICP), whereas propofol and thiopental may decrease MAP through their effects on systemic vascular resistance (vasodilatation) as well as direct negative inotropic properties. Thiopental, and perhaps etomidate and propofol, may possess "neuroprotective" properties secondary to reducing $CMRO_2$, which improves the ability of the brain to tolerate incomplete ischemia during procedures such as carotid endarterectomy or the temporary occlusion of cerebral arteries during an aneurysm repair.[56,57] Ketamine's direct effects on ICP remain controversial, with the older literature suggesting that ketamine may directly increase cerebral blood flow and ICP. However, recent studies suggest that ketamine has limited effects on CBF and ICP, especially when given in combination with other anesthetic agents including midazolam.[72-74]

Propofol, midazolam, and the barbiturates have similar effects on the electroencephalogram (EEG). Initial low doses with low brain concentrations result in transient high-frequency activity followed by lower-frequency, higher-amplitude waveforms at high brain concentrations, and eventually burst suppression and even electrical silence with high enough doses. These effects, which are similar to those produced by the potent inhalational anesthetic agents, have been studied in enough detail and are consistent enough that algorithms have been developed that can analyze the EEG patterns and thereby determine the depth of anesthesia. These algorithms are used by several different monitoring systems to provide modified EEG monitors, which are used clinically to evaluate the depth of anesthesia. Although controversial, it is these monitors that are purported to have efficacy in avoiding intraoperative awareness during anesthetic care.

Most intravenous anesthetics have anticonvulsant properties. Various of the barbiturates and propofol have been incorporated into algorithms for the treatment of refractory status epilepticus.[61,62] Opposite effects are generally seen with etomidate, which can produce involuntary myoclonic movements from an imbalance of inhibitory and excitatory influences in the thalamocortical tract. Etomidate also stimulates the EEG resulting in increased amplitude and frequency.[63] Myoclonic movements and opisthotonic posturing have also been reported following the administration of propofol. These movements are attributed to propofol's antagonism at glycine receptors in subcortical structures.

The intravenous anesthetic agents also have dose-dependent effects on ventilatory function. Thiopental, propofol, etomidate, and midazolam result in a decrease of tidal volume and minute ventilation as well as a rightward shift of the CO_2 response curve. As with many of the end-organ effects of the anesthetic agents, the respiratory depressant effects may be magnified in patients with comorbid conditions (chronic respiratory or cardiovascular disease) and when coadministered with other medications that are respiratory depressants (inhalational anesthetic agents, opioids, phenothiazines). Given these effects on central control of ventilation, a transient period of apnea generally occurs following an anesthetic induction dose of any of these agents. In contrast to the respiratory effects of propofol, etomidate, and the barbiturates, in the absence of comorbid diseases, ketamine can generally be expected to result in minimal respiratory depression in clinically relevant doses and may preserve airway protective reflexes.[64,65] Ketamine also stands apart from the other intravenous anesthetic agent in that the release of endogenous catecholamines following its administration results in bronchodilatation, thereby making it a suitable

induction agent in patients who are actively wheezing or at risk for reactivity during airway manipulation. Propofol has also been shown to have beneficial airway effects in patients with airway reactivity. In a prospective trial, 77 adult patients were randomized to receive one of three agents: propofol (2.5 mg/kg), etomidate (0.4 mg/kg), or thiopental (5 mg/kg) for anesthetic induction and tracheal intubation.[66] Following endotracheal intubation, respiratory resistance was lower with propofol when compared to either etomidate or thiopental. Additional evidence for the beneficial effects of propofol on airway reactivity are provided by Pizoz et al., who randomized asthmatic or nonasthmatic patients to anesthetic induction with thiopental/thiamylal (5 mg/kg), methohexital (1.5 mg/kg), or propofol (2.5 mg).[67] In asthmatic patients, the incidence of wheezing was 45% with thiopental/thiamylal, 26% with methohexital, and 0% with propofol. In nonasthmatic patients, the incidence of wheezing was 16% with thiopental/thiamylal and 3% with propofol. The potential beneficial effects of propofol on airway reactivity are further supported by animal studies.[68,69] The proposed mechanism for these effects are a decrease of intracellular inositol phosphate, resulting in a depression of intracellular calcium availability.

During anesthetic induction or maintenance, the intravenous anesthetic agents can depress the cardiovascular system resulting in hypotension by various mechanisms. These include a reduction of central and/or peripheral autonomic nervous system activity, blunting compensatory baroreceptor reflexes, decreasing preload, systemic vasodilatation, or directly depressing myocardial contractility. Hemodynamic function during the induction of anesthesia may also be affected by comorbid cardiovascular disease, intravascular volume status, resting sympathetic nervous system tone, concomitant medications (angiotensin-converting enzyme inhibitors, β-adrenergic antagonists), and the administration of other agents used for anesthetic care including opioids and benzodiazepines. An induction dose of thiopental causes a variable decrease in cardiac output, systemic vascular resistance, and arterial pressure. The decrease in cardiac output is the result of vasodilation as well as direct myocardial depression. This effect is generally well tolerated in patients with adequate cardiovascular function, but can be exaggerated with preexisting cardiovascular disease, necessitating the use of a lower dose of thiopental or, preferably, the use of alternative agents in patients with compromised cardiovascular function. Propofol demonstrates cardiovascular depressant effects similar to or greater than those of thiopental. Propofol is a direct myocardial depressant and reduces systemic vascular resistance. Significant cardiovascular responses following propofol are more common with high doses, in hypovolemic patients, in elderly patients, and in patients with significant cardiovascular disease.[71,72] The deleterious cardiovascular effects of propofol can be attenuated by the administration of calcium chloride (10 mg/kg).[73] Additional cardiovascular effects from propofol may result from its augmentation of central vagal tone leading to bradycardia, conduction disturbances, and asysole.[74,75] The negative chronotropic effects of propofol are more common when it is administered with other medications known to alter cardiac chronotropic function (fentanyl or succinylcholine). Although the relative bradycardia may be beneficial in elderly patients at risk for myocardial ischemia, it may be detrimental if cardiac output is heart rate dependent.

In contrast to the negative inotropic effects of propofol and the barbiturates, etomidate causes minimal cardiovascular depression and may be used for anesthetic induction in patients with significant cardiovascular disease.[76,77] As etomidate has little effect on systemic vascular resistance, it may be used in patients with cyanotic congenital heart disease in whom pulmonary blood flow is dependent on mean arterial pressure. Although suppression of adrenal cortical function occurs even following a single bolus dose of etomidate through inhibition of the activity of 17-α hydroxylase and 11-β hydroxylase, it remains controversial whether such effects are of clinical significance.[78,79] However, the risk: benefit ratio of this effect must be entertained when etomidate is chosen for anesthetic induction. Additionally, although still used as a single induction dose in patients with comorbid cardiovascular disease, repeated doses or continuous infusions are not recommended.[80]

The cardiovascular effects of ketamine are different from those of the other intravenous anesthetic agents. Ketamine stimulates the cardiovascular system by activation of the sympathetic nervous system and the release of endogenous catecholamines.[81] Anesthetic induction doses of ketamine (1 to 2 mg/kg) generally increase heart rate and MAP. Although the indirect effects of ketamine include the release of endogenous catecholamines and stimulation of the sympathetic nervous system, ketamine is a direct myocardial depressant. In most clinical scenarios, the indirect effects compensate for the direct negative inotropic effects. However, in critically ill patients who have depleted their endogenous catecholamines, cardiovascular collapse may occur.

The pharmacokinetic profile of the intravenous anesthetic agents is characterized by a rapid onset of CNS effects secondary to the high lipid solubility of these agents and the high percentage of cardiac output perfusing the brain. The termination of the central CNS effect results from redistribution of the drug from the central to the peripheral compartment. It is not dependent on primary metabolism and elimination of the drug from the body. Most intravenous anesthetics are metabolized in the liver and excreted in the kidney. Some metabolites are active, such as desmethyldiazepam (diazepam) and norketamine (ketamine), and may result in prolonged effects especially with repeated dosing or the use of continuous infusions. There is a wide variation in the elimination half-lives of intravenous anesthetic agents because of differences in clearance. Drugs with short elimination half-lives include propofol, etomidate, ketamine, and midazolam, whereas thiopental has a long elimination half-life. Propofol is widely used, especially in ambulatory surgery centers, because of its short duration of action, fast recovery time, and early discharge potential.[82,83] This rapid recovery results in less "hangover" effect or residual drowsiness following outpatient surgical procedures, thereby facilitating return to work and resumption of activities of daily life.

Opioids

There are various roles for the opioids in the perioperative and anesthetic management of patients. The commonly used opioids are pure agonists that are selective for μ (mu) opioid receptors located at discrete sites throughout the spinal cord and the CNS.[84] However, they are generally combined with either an inhalational anesthetic agent or an intravenous

anesthetic agent (total intravenous anesthesia or TIVA). This combination is necessary as even when administered in doses sufficient to produce profound analgesia and apnea, the opioids do not consistently produce amnesia in healthy patients.[85] Therefore other agents are required to ensure amnesia during the intraoperative care of patients. Intraoperatively, the opioids are used to blunt the sympathetic stress response to surgical trauma, decrease the requirements for inhalational or intravenous anesthetic agents, and provide postoperative analgesia.

Although discrete differences in the chemical structure exist in the intravenous opioid agents, when used clinically, the clinically relevant differences include their potency, onset of action, duration of action, lipid solubility, hemodynamic effects, and metabolic fate (Table 121-3).[86,87] During the conduct of general anesthesia, the synthetic agents including fentanyl and its derivatives are frequently chosen, given their brief duration of action, ability to effectively blunt the hemodynamic changes related to the surgical stress response, and limited cardiovascular effects. However, other opioids including morphine may be chosen, given their longer duration of action with the ability to provide postoperative analgesia during the transition from general anesthesia to the awake state (emergence). Morphine is the least lipophilic of the commonly used opioids and therefore it has a slower onset of action than the more lipophilic synthetic opioids such as fentanyl. Morphine, like all of the opioids except for remifentanil, undergoes hepatic metabolism. In part, morphine is converted to morphine-6-glucuronide (M6G), a water-soluble metabolite with a potency far greater than that of the parent compound. However, given that it is water soluble, M6G does not rapidly pass through the blood-brain barrier into the CNS and therefore has limited clinical effects. In patients with renal insufficiency or failure, a significant amount of M6G can accumulate and result in respiratory depression.

Meperidine has a potency that is approximately 10% that of morphine with a similar half-life of 2 to 3 hours. Hepatic metabolism produces normeperidine, a metabolite that may accumulate in renal insufficiency. High plasma concentrations of normeperidine may cause seizures. Given these concerns and the higher incidence of psychomimetic effects with meperidine, our current clinical practice does not include its use except in low doses (10 mg) to treat postanesthesia shivering. Hydromorphone has a potency that is 6 to 8 times that of morphine with a half-life of 2 to 3 hours. As there are no active metabolites of hydromorphone, it may be an effective alternative to morphine in patients with renal insufficiency. When compared with morphine, hydromorphone causes less histamine release and may be an effective alternate agent when pruritus occurs with morphine use.

The synthetic opioids, including fentanyl, sufentanil, and alfentanil, are very potent, highly lipid-soluble drugs with rapid onsets of action and short durations of action. Hepatic metabolism does not result in active metabolites. Fentanyl is 100 times as potent as morphine, while sufentanil has 10 times the potency of fentanyl. The pharmacokinetics of fentanyl and sufentanil are similar, with both drugs being short-acting at low doses and longer-acting at higher doses. Alfentanil is less potent than sufentanil and fentanyl and has a very rapid onset of action and short duration of action. Because its elimination half-life is substantially less than that of sufentanil and fentanyl, it is suitable for multiple dosing and continuous infusions and is popular for ambulatory surgery in many centers. Remifentanil is the newest of the synthetic opioids. It is the first true ultrashort-acting opioid.[88] It has a rapid onset of activity and undergoes ester metabolism, which results in a short, predictable duration of action. Its elimination half-life is 8 to 10 minutes and its potency is comparable to fentanyl. It is administered as a continuous infusion and remains short-acting regardless of the duration of the infusion. Unlike the other opioids, which have longer half-lives and a variable duration of effect in neonates and infants, the duration of action and half-life of remifentanil is constant across all age ranges, thereby making it a suitable agent in neonatal anesthesia.

The opioids play a key role in anesthesia practice. Fentanyl, sufentanil, and alfentanil are common components of various anesthetic techniques. They have replaced their predecessors (morphine and meperidine) because of their faster onsets of action, shorter and more predictable duration of action, and minimal hemodynamic side effects. For general anesthesia, they reduce the surgical stress response and the associated cardiovascular responses to endotracheal intubation and surgical stimulation. They potentiate the hypnotic effects of barbiturates and benzodiazepines. They produce a dose-related decrease in the need for the potent inhalational anesthetic agents, thereby facilitating recovery from prolonged anesthetic cases. High-dose opioid techniques are commonly used in cardiac surgery because the synthetic opioids produce a smooth induction process, provide hemodynamic stability, suppress the hemodynamic responses to various surgical stimulations, reduce the production of stress hormones, and provide a smooth transition to mechanical ventilation at the end of the case.

As with all medications used in the practice of anesthesia, there are several adverse effects related to opioid administration. Opioids produce a dose-related depression of the ventilatory response to CO_2 and blunt the response to hypoxia through a direct effect on the medullary respiratory centers.[89] Increasing plasma concentrations result in a slowing of the respiratory rate that is initially offset by an increase in tidal volume. Equianalgesic doses of all opioids (fentanyl, morphine, meperidine, etc.) produce equivalent degrees of respiratory depression. Opioid-induced respiratory depression is antagonized by pain, movement, and opioid antagonists such as naloxone. When postoperative respiratory depression related to opioids occurs, small incremental doses of naloxone

Table 121–3 Potency and Half-Life of Opioids

Agent	Potency	Half-Life	Active Metabolites
Morphine	1	2–3 hours	Yes
Meperidine	0.1	2–3 hours	Yes
Hydromorphone	5	2–4 hours	No
Oxymorphone	10	2–4 hours	No
Methadone	1	12–24 hours	No
Fentanyl	100	20–30 minutes	No
Sufentanil	1000	20–30 minutes	No
Alfentanil	20	10–15 minutes	No
Reminfentanil	100	5–8 minutes	No

(1 μg/kg every 2 to 3 minutes) may be used to reverse opioid-induced respiratory depression without reversing analgesia. Given that the clinical half-life of naloxone is 20 to 30 minutes, repeated doses or a continuous infusion may be needed if longer acting opioids (morphine, meperidine, or hydromorphone) have been administered. Longer acting opioid antagonists (nalmefene) are now clinically available; however, there is limited clinical experience with their use in the pediatric population. Opioid reversal using naloxone can result in undesirable or dangerous hemodynamic responses such as hypertension, tachycardia, and myocardial infarction. The potential for such effects must be weighed against the anticipated benefits of opioid reversal.

Opioids generally produce minimal cardiovascular effects at usual analgesic doses. With higher doses, when combined with other anesthetic drugs, or in patients with comorbid features, opioids may produce bradycardia and a decrease in SVR, resulting in hypotension. The synthetic opioids may result in bradycardia from stimulation of the central nuclei of the vagus nerve, leading to prolonged AV conduction and direct depression of the SA node, while peripheral vasodilation results from depression of the vasomotor centers in the medulla.[90,91] Patients with elevated levels of sympathetic tone (hypovolemia, CHF) are more likely to become hypotensive after opioids. Although anesthetic techniques using high doses of the synthetic opioids may result in bradycardia and peripheral vasodilation, given that there is no direct negative inotropic effect, these techniques are effective for patients with myocardial pathology including patients undergoing cardiovascular surgery for whom high-dose fentanyl (25 to 75 μg/kg) is a frequently chosen anesthetic technique. Decreases in blood pressure with such techniques result from a decrease in SVR and are usually easily treated with a direct acting α-adrenergic agonist such as phenylephrine. Morphine may result in more profound venodilatation, leading to decreased venous return, decreased cardiac output, and hypotension. Meperidine, given its structural similarity to atropine, may result in a mild tachycardia.

Inhalational Anesthetic Agents

A unique aspect of intraoperative anesthetic care is the administration of inhalational anesthetic agents, including nitrous oxide (N_2O), halothane, enflurane, isoflurane, sevoflurane, and desflurane. Although their anesthetic properties are similar, the potent inhalational anesthetic agents can be divided into two chemically distinct classes (alkanes and ethers). Halothane is an alkane (a two-carbon chain) while the other four agents (enflurane, isoflurane, desflurane, and sevoflurane) are ethers. The potent inhalational anesthetic agents are volatile liquids and are administered to the patient via a vaporizer on the anesthesia machine. Nitrous oxide is administered either from a central hospital source or from E cylinders on the anesthesia machine. Flows of nitrous oxide and oxygen are mixed in varying concentrations and then directed through the vaporizer to pick up the desired concentration of the potent inhalational anesthetic agent.

The potency of inhalational anesthetic agents is measured by MAC (minimum alveolar concentration). MAC is defined as the percent of the inhalational anesthetic agent that is required to prevent 50% of patients from moving in response to a surgical stimulus. The lower the MAC, the more potent the inhalational agent. Halothane is the most potent inhalational anesthetic agent, followed in order by isoflurane, enflurane, sevoflurane, and desflurane. Nitrous oxide has a very low potency (MAC of 110%) and must be combined with other intravenous sedatives/analgesics/anesthetics or a potent inhalational anesthetic agent to fulfill the prerequisites (unconsciousness, analgesia, muscle relaxation, decrease in sympathetic nervous system activity) of a general anesthetic. As 1.5 to 2.5 MAC of an agent is required to maintain anesthesia solely with a potent inhalational anesthetic agent, in most clinical scenarios, 1.0 to 1.5 MAC of an inhalational anesthetic agent is combined with N_2O, opioids, or intravenous anesthetic agents to provide maintenance anesthesia during a surgical procedure.

Nitrous oxide (N_2O) was the first of the inhalational anesthetic agents to be discovered. Although there has been a decline in its use with the introduction of newer inhalational anesthetic agents with low blood-gas solubility partition coefficients (desflurane, sevoflurane), it remains a common component of intraoperative anesthetic regimens and is also used in some centers for procedural sedation. Depending on the concentration administered, N_2O can provide sedation and analgesia or a weak anesthetic level. In concentrations of 70%, N_2O will render the majority of patients amnestic and provide moderate to significant analgesia. However, only minor surgical procedures can be performed with N_2O and O_2 alone and its amnestic properties are not a given, thereby necessitating its combination with other agents. When used as the sole agent, N_2O causes minimal respiratory and cardiac depression.[92] Recovery from N_2O sedation is rapid given its low blood-gas solubility coefficient. During recovery, high concentrations of O_2 are needed to avoid diffusion hypoxia.[93] As N_2O diffuses from the blood into the alveoli, its alveolar concentration rises, thereby decreasing the effective concentration of oxygen, which can lead to "diffusion hypoxia." N_2O diffuses into and expands gas-containing closed spaces in the body (obstructed bowel, pneumothorax, middle ear, pneumocephalus, pulmonary artery catheter balloons, and air emboli).[96]

When used for procedural sedation on repeated occasions, N_2O can lead to inactivation of methionine synthetase, an enzyme necessary for vitamin B_{12} metabolism, leading to bone marrow impairment with megaloblastic anemia and deterioration of the posterior columns of the spinal cord and neurologic impairment.[94,95] These effects may occur not only in patients, but also in health care workers with chronic exposure, thereby mandating effective scavenging of exhaled gases to avoid environmental pollution whenever N_2O is administered.

When administered in appropriate inspired concentrations, all of the potent inhalational anesthetic agents (halothane, isoflurane, enflurane, desflurane, and sevoflurane) provide the basic components of a general anesthetic including amnesia, analgesia, skeletal muscle relaxation, and control of the sympathetic nervous system. Despite their use for over 150 years in clinical anesthetic care, the exact site and mechanism of action of these agents remains elusive. Recent work suggests that they stabilize critical proteins, possibly the receptors of neurotransmitters.[97] Although these agents all provide general anesthesia, their end-organ effects can be quite varied, thereby dictating their use in various clinical scenarios. In infants and children, given the potential stress that may be inflicted by placement of an intravenous cannula, anesthetic induction

may be carried out by the inhalation route with placement of the intravenous cannula after the patient is anesthetized. As halothane and sevoflurane are less pungent to the airway than the other agents, they are the only agents used for the inhalation induction of anesthesia. Although halothane had been the time-honored agent for inhalation induction of anesthesia in infants and children, it has recently been removed from the market and replaced by sevoflurane due to sevoflurane's significantly lower incidence of bradycardia, myocardial depression, and cardiac arrest. In fact, surveys evaluating the etiology of cardiac arrest during general anesthesia in infants and children have implicated halothane as the primary factor responsible for many of these events.

All of the potent inhalation anesthetic agents cause a dose-related depression of cardiovascular and respiratory function. With increasing anesthetic depth, there is a rightward shift of the CO_2 response curve with a progressive decrease in alveolar ventilation, characterized by a reduction in tidal volume in spontaneously breathing patients and an increase in $PaCO_2$. Beneficial effects on the airways include a direct effect on bronchial smooth muscle with bronchodilatation making them effective agents both intraoperatively and outside of the operating room for the treatment of patients with refractory status asthmaticus.[98]

The potent inhalational anesthetic agents decrease mean arterial pressure, myocardial contractility, and myocardial oxygen consumption. The exact changes in cardiac output, systemic vascular resistance, and heart rate vary from agent to agent and with the inspired concentration of the agent that is administered. Isoflurane and desflurane result primarily in vasodilatation and a decrease in SVR with reflex tachycardia. Direct negative chronotropic effects predominate with sevoflurane and halothane, leading to a lowering of heart rate. As mentioned previously, this effect is less with sevoflurane than with halothane. Because of its alkane structure, halothane sensitizes the myocardium to catecholamines and can cause dysrhythmias, especially when there is associated hypercarbia or high circulating catecholamines. The latter is of clinical significance when epinephrine-containing local anesthetic agents are administered to patients anesthetized with halothane.

The potent inhalational anesthetic agents cause a dose-dependent decrease in CNS activity, depressing EEG activity and reducing cerebral metabolic oxygen consumption. Enflurane and sevoflurane can activate the EEG and produce clinical and EEG evidence of seizure activity at high concentrations. Such problems are exacerbated by the hypocarbia that may occur if there is hyperventilation during anesthetic induction. CBF increases via a reduction in cerebral vascular resistance, which can lead to an elevation of ICP in patients with compromised intracranial compliance. The effect on ICP is least with isoflurane and can be blunted by hyperventilation and hypocarbia. These effects make isoflurane a common choice for neurosurgical anesthesia. These agents also have peripheral neuromuscular effects; they potentiate the effects of the neuromuscular blocking agents, and along with succinylcholine are triggering agents for malignant hyperthermia.

In addition to the parent compound, metabolic products may be responsible for the toxicity of the potent inhalational anesthetic agents. For halothane, 15% to 20% of halothane is metabolized, compared to 5% to 10% for sevoflurane, 2% to 3% for enflurane, 0.2% for isoflurane, and less than 0.1% for desflurane. In the early days of inhalational anesthesia, hepatic toxicity was a significant concern and existed into the modern era with halothane. Hepatotoxicity occurs from an immune-mediated reaction following exposure to halothane, enflurane, isoflurane, or desflurane.[99-102] However, given the limited metabolism of enflurane, isoflurane, and desflurane, the risk of hepatotoxicity is extremely low. The mechanism of hepatotoxicity relates to the metabolic product, TFA or trifluroacetic acid, acting as a hapten. It binds to hepatocytes and induces an immune-mediated hepatitis. The metabolic pathway of sevoflurane is different and does not result in the production of TFA. Risk factors for halothane hepatitis include prior anesthetic exposure, female gender, age 35 years or more, and obesity.[103,104] Albeit rare, specific issues related to renal function must be considered during anesthetic care. Most importantly, alterations related to cardiac output due to the inhalational anesthetic agents may secondarily decrease renal blood flow and result in renal damage. As with other end organs, the kidneys may be damaged by the agent itself or by its metabolites. Additionally, both enflurane and sevoflurane contain fluoride around their carbon atoms, which can be released during metabolism.[105] Fluoride concentrations in excess of 50 μmol/L can result in decreased glomerular filtration rate and renal tubular resistance to vasopressin, with nephrogenic diabetes insipidus. Although high levels of serum fluoride may occur following the prolonged administration of sevoflurane, clinical signs of nephrotoxicity are extremely rare. This is postulated to be the result of the low blood: gas partition coefficient of sevoflurane and its rapid elimination from the body or the fact that sevoflurane, unlike older agents such as methoxyflurane, does not undergo metabolism in the kidney, but only in the liver. Therefore, unlike methoxyflurane, there is no local renal release of fluoride, thereby limiting the risk of toxicity. Although high serum fluoride concentrations have been documented with prolonged enflurane administration, this agent is no longer commonly used in clinical anesthesia practice. An additional concern regarding the potential nephrotoxicity of the potent inhalational agents is unique to sevoflurane, in particular a unique metabolite, a vinyl ether also known as compound A. Compound A is produced during the metabolism of sevoflurane and its reaction with the soda lime in the carbon dioxide absorber of the anesthesia machine.[106-108] Compound A concentrations are increased by several factors including a high inspired concentration of sevoflurane, low fresh gas flows through the system (<2 L/min), increasing temperatures of the soda lime canister, decreased water content of the CO_2 absorbent, and high concentrations of potassium or sodium hydroxides in the CO_2 absorbent. Although of potential concern when studied in laboratory animals, there are no clinical data to suggest the nephrotoxic potential of compound A, which suggests that such concerns should not limit the use of sevoflurane, even in patients with preexisting renal dysfunction.

Neuromuscular Blocking Agents

The reader is referred to Chapter 122 for a complete review of the use of neuromuscular blocking agents (NMBAs). The following section will deal briefly with those aspects of NMBA administration that relate specifically to perioperative anesthetic care. Intraoperatively, skeletal muscle relaxation may be required for the successful completion of a surgical procedure (exploratory laparotomy), may be required briefly for

endotracheal intubation, or may be used to ensure patient immobility in situations where inadvertent movement may be detrimental (craniotomy). Although frequently administered during the perioperative period, many surgical procedures can be performed without the administration of NMBAs. NMBAs have no effect on the level of consciousness, provide neither amnesia nor analgesia, and do not alter the dose of other medications required to induce and maintain general anesthesia. When NMBAs are used, the patient requires an adequate level of general anesthesia and in the intensive care unit an adequate level of sedation. This is especially important since clinical signs of inadequate anesthesia (movement) are abolished. It is also important to recognize that the airway must be controlled when NMBAs are used These agents are contraindicated if there is any concern regarding one's ability to control ventilation. One additional caveat regarding the administration of NMBAs is that although problems are rare, NMBAs are high on the list of agents responsible for intraoperative anaphylactic reactions (along with antibiotics and latex).

Neuromuscular blockade may be used only to facilitate endotracheal intubation or may be continued throughout the surgical procedure to provide surgical relaxation. When ongoing neuromuscular blockade is required, incremental doses which are approximately one fourth to one fifth of the initial intubating dose are administered based on the response obtained using neuromuscular blockade monitoring. Alternatively, a continuous infusion of short or intermediate acting agents is occasionally used.

Given that repetitive doses or an infusion may result in excessive levels of neuromuscular blockade, monitoring of neuromuscular transmission is used to predict optimal conditions for endotracheal intubation, adequacy of surgical muscle relaxation, effectiveness of reversal of neuromuscular blockade, and to guide dosing of NMBAs during intraoperative care. The goal of such monitoring is to allow incremental titration of NMBAs to maintain the desired level of blockade while maintaining sufficient neuromuscular function to allow reversal of residual neuromuscular blockade at the completion of the surgical procedure.

To accomplish monitoring of neuromuscular blockade, a supramaximal electrical stimulation from a peripheral nerve stimulator is delivered to electrodes placed over the distribution of a peripheral nerve. This can be accomplished using the ulnar nerve at the wrist or elbow, the common peroneal nerve as it passes over the head of the fibula, or the facial nerve. As any of these involve electrical stimulation, they are painful and should only be performed in an appropriately anesthetized patient. Although various patterns of electrical stimulation of the peripheral nerve (single twitch, train-of-four [TOF], double-burst suppression, tetanus, and posttetanic stimulation) have been advocated in the literature, TOF monitoring remains the technique used most commonly in clinical anesthesia practice. Two electrical stimuli are delivered each second for 2 seconds to give four twitches or a TOF. Despite its acceptance and use in everyday anesthesia practice, TOF monitoring is relatively nonspecific in that up to 70% to 80% of the acetylcholine receptors must be blocked in order to achieve any visible decrement in the TOF. The goal of monitoring is to ensure that some residual neuromuscular function is present at the completion of the surgical procedure so that the effects can be reversed. The goal of reversal is for the patient to sustain minute ventilation and maintain a patent airway to allow for tracheal extubation.[109,110] In most clinical circumstances, one or two twitches of the TOF must be present to allow for effective pharmacologic reversal. A TOF of 0.7 or greater, where the fourth twitch is 70% or more of the height of the first twitch, is evidence of adequate reversal. Other tests of adequacy of reversal include a sustained response to tetanus, a sustained head lift for 5 to 10 seconds, and strong grip strength. In infants, sustained hip flexion is a useful clinical sign. Patients demonstrating profound blockade (no response to electrical stimulation) should not be reversed until some evidence of return of neuromuscular function has occurred. Despite adequate reversal, recurrence of partial paralysis resulting in respiratory insufficiency or upper airway obstruction may occur during the postoperative period. Reversal of residual neuromuscular blockade is accomplished using drugs that inhibit acetylcholinesterase (edrophonium, neostigmine, or pyridostigmine). By inhibiting acetylcholinesterase, these medications result in the accumulation of acetylcholine at the nicotinic (neuromuscular junction) and muscarinic sites, thereby increasing the competition between acetylcholine and the NMBA for the α subunits of the nicotinic cholinergic receptor. As these medications also inhibit acetylcholinesterase at muscarinic sites, they must be coadministered with an anticholinergic agent such as atropine or glycopyrrolate to prevent bradycardia or asystole. An inadequate response to the anticholinesterase medication with residual weakness may be secondary to excessive blockade at the time of reversal, allowing inadequate time since the administration of the reversal drug, an altered acid-base or electrolyte status, hypothermia, effects of other medications, or impaired clearance of NMBAs from the plasma secondary to renal or hepatic dysfunction.

Intraoperative Anesthetic Care

Maintenance Anesthesia

The current chapter has discussed the perioperative care of a surgical patient from the preoperative evaluation through premedication, monitoring, and the induction of general anesthesia. Once the airway has been secured and ventilation/oxygenation established, maintenance anesthesia is provided for the duration of the surgical procedure. Given the variety of inhalational anesthetic agents, intravenous anesthetic agents, opioids, and NMBAs available, there are several combinations of agents that can be used to provide the prerequisites of general anesthesia. The choice of agent varies widely and is determined by personal preferences and experiences of the anesthesia provider, the patient's comorbid features such as underlying cardiovascular function, the anticipated duration of the surgical procedure, the postoperative requirements (will the patient's trachea be extubated at the completion of the procedure; is ongoing postoperative analgesia required?), and the operative setting (is rapid turnover of cases desirable and are rapid awakening and hospital discharge needed?).

In most scenarios, the baseline level of anesthesia is provided by either a potent inhalational anesthetic agent or propofol and supplemented with intermittent dosing or a continuous infusion of an opioid. If ongoing neuromuscular blockade is required, a continuous infusion of a short-acting agent or intermittent dosing of an intermediate- to long-acting agent can be used. Although controlled ventilation is most commonly practiced, there are many surgical procedures for which spontaneous ventilation is acceptable. The use of

spontaneous ventilation is more common in the outpatient setting where endotracheal intubation is less common and general anesthesia is provided using a mask or an laryngeal mask airway. In addition to commonly monitored hemodynamic parameters, spontaneous ventilation provides a very effective means of assessing the depth of anesthesia by respiratory rate and provides the optimal parameter for dosing of opioids. When spontaneous ventilation is used, opioids can be dosed based on the patient's respiratory rate to ensure that an appropriate amount is administered to provide postoperative analgesia while avoiding overdosing and postoperative respiratory depression.

Intraoperative Fluid Management

In addition to monitoring hemodynamic and respiratory function, the anesthesiologist must also maintain fluid, electrolyte, and glucose homeostasis during anesthetic care. Intraoperative fluid management uses isotonic crystalloid solutions such as lactated Ringer solution (LR), normal saline (NS), or Plasmalyte to provide ongoing maintenance fluids and replace preoperative deficits, intraoperative third-space losses, and blood losses when blood therapy is not necessary. Third-space losses may be relatively trivial during superficial procedures (2 to 3 mL/kg/hr) or significant (10 to 15 mL/kg/hr) for intraabdominal procedures. Although generally considered an isotonic fluid, LR has only 130 mEq of sodium per liter and therefore is relatively contraindicated in patients at risk for cerebral edema, including the multiple trauma patient. Large volumes of NS, although effective in supporting the serum sodium, can result in a dilutional acidosis. These issues have led to the consideration of using a combination of NS and LR or the use of a more balanced solution such as Plasmalyte, which contains 140 mEq/L of sodium, physiologic amounts of chloride, and gluconate/acetate as buffers. Given their distribution between the intravascular and extravascular space, if blood therapy is not administered, blood loss is routinely replaced as 3 mL of crystalloid for each 1 mL of blood loss. Alternatives to isotonic crystalloid solutions include synthetic and natural colloids such as hydroxyethyl starch, albumin, or gelatins (these are not currently available in the United States). As with resuscitation in other areas, there are currently no studies demonstrating the superiority of any of these solutions over standard isotonic crystalloids and it is likely that the crystalloid-colloid debate will continue for many years. Potential drawbacks to the use of hydroxyethyl starch solutions including hetastarch solutions (Hespan or Hexted) includes the potential for platelet dysfunction when amounts greater than 15 to 20 mL/kg are administered. This reversible platelet dysfunction results from alterations in the potency of von Willebrand factor caused by the hydroxyethyl starch solutions.

During the postoperative period, especially in pediatric patients, given the potential for the development of postoperative hyponatremia, fluids more hypotonic than half-normal saline are rarely indicated. For short surgical procedures when a Foley catheter is not inserted, aggressive fluid therapy with replacement of the preoperative deficit is not necessarily required since bladder distention during emergence from anesthesia may be quite uncomfortable for the patient. Additionally, specific surgical procedures such as intracranial neurosurgical procedures and thoracic procedures or underlying cardiovascular dysfunction may mandate that the patient "be kept dry" to improve the intraoperative and postoperative course. However, in many other surgical procedures, especially intraabdominal cases, burn debridement, or other cases with significant third-space losses, the administration of significant amounts of isotonic crystalloids may be required to maintain intravascular volume status. Except for the neonatal population or patients chronically receiving parenteral nutrition fluids, dextrose-containing fluids are rarely administered. In high-risk patients, those receiving glucose-containing fluids, and diabetics, intermittent monitoring of blood glucose may be indicated. Although a review of the perioperative care of the diabetic patient is beyond the scope of this chapter, recent evidence has demonstrated that the postoperative outcome of such patients may be improved by tight perioperative glucose control. With the availability of rapid bedside testing, the rapid and intermittent determination of blood glucose concentrations is feasible.

Postoperative Care

Postoperative Analgesia

Various factors may interfere with the delivery of effective postoperative analgesia. Inadequate pain relief following surgery generally results from inappropriate methods of administration rather than ineffective analgesic agents. Although frequently used in the past for the delivery of opioids in the delivery of postoperative analgesia, the intramuscular route should be abandoned, as several factors result in inadequate analgesia including variable absorption and unpredictable plasma opioid concentrations, in addition to the child's reluctance to ask for pain medications due to the pain associated with IM injections.[111] Fortunately, the area of acute and postoperative analgesia has been an area of intense research that has resulted in the development of new techniques and refinement of treatment strategies.[112] Current modalities to provide better postoperative analgesia include intravenous patient-controlled analgesia (PCA) and the use of epidural and spinal local anesthetics and/or opioids. Although introduced into the adult population, these techniques are now widely applied across all age ranges in pediatric patients. PCA involves the self-administration of small doses of opioids to obtain and maintain analgesia. Analgesia occurs when the plasma opioid concentration reaches the minimum effective analgesic concentration (MEAC). With PCA, patients titrate the opioid to their own MEAC and can thereby maintain consistent analgesia.[113-115] Numerous studies have demonstrated improved analgesia, fewer adverse effects, and decreased opioid consumption with the use of PCA. Prior to the initiation of PCA, the patient receives a loading dose of the opioid administered either intraoperatively or postoperatively as multiple small doses of an opioid to achieve the MEAC. Once this is accomplished, the PCA is started and a dose of opioid is self-administered at a specific interval or lockout period (generally 5 to 10 minutes) as needed by the patient. Additionally, a continuous infusion can be added to the PCA regimen, although it has been suggested that this negates the safety feature of PCA in which no opioid is delivered if the patient is too sleepy to push the button. With the continuous infusion, opioid is infused regardless of the patient's demand, which may increase the incidence of adverse effects including respiratory depression.

In addition to the use of opioids, acetaminophen and nonsteroidal antiinflammatory agents (NSAIDs) play a significant

role in the control of postoperative pain. NSAIDs, acetaminophen, and salicylates act through the inhibition of the enzyme cyclooxygenase, thereby blocking the synthesis of prostaglandins. In distinction to opioids, these agents demonstrate a ceiling effect so that once a specific plasma concentration is achieved, no further analgesia is provided by increasing the dose. These agents are classified according to their chemical structure as (1) para-amino phenol derivatives (acetaminophen), (2) NSAIDs (ibuprofen), and (3) salicylates (acetylsalicylic acid, choline magnesium trisalicylate).[116] When considering the para-aminol phenol derivatives, acetaminophen has a significant role in the management of acute pain, while phenacetin is no longer used, given its potential toxicity profile (renal papillary necrosis). Although currently available only as an oral or rectal medication in the United States, the prodrug (propacetamol) is available in Europe and elsewhere throughout the world for intravenous administration. FDA approval is anticipated soon for the use of intravenous acetaminophen in the United States. Commonly used NSAIDs include either ibuprofen for oral administration or ketorolac for intravenous administration. An intravenous preparation of ibuprofen has recently received FDA approval for the treatment of pain and the control of fever in adults. The reader is referred to reference 116 for a more in-depth discussion of the prostaglandin synthesis inhibitors.

The prostaglandin synthesis inhibitors are used alone for minor pain, combined with weak opioids (codeine or oxycodone) for oral administration to control moderate pain, or added to parenteral opioids and regional anesthetic techniques for severe pain. In the last scenario, their use does not replace opioids or neuraxial techniques, but rather provides adjunctive analgesia, thereby lowering the total amount of opioid required. As the majority of opioid-related adverse effects are dose-related, modalities that decrease total opioid consumption play a significant role in decreasing or preventing opioid-associated adverse effects. When used for this purpose, the prostaglandin synthesis inhibitor is administered around-the-clock and not on an as-needed basis.

Regional anesthetic techniques including either neuraxial blockade (epidural or spinal analgesia) or peripheral nerve blockade can be continued into the postoperative period to provide effective analgesia, while avoiding the potential adverse effects associated with parenteral opioid therapy. Epidural and spinal local anesthetics provide profound analgesia; however, undesirable side effects of the use of high concentrations of local anesthetics include blockade of the sympathetic nervous system with hypotension, urinary retention, blockade of motor function, and risks of local anesthetic toxicity from systemic absorption. Epidural and spinal opioids can provide intense, segmental, localized analgesia without sensory, motor, or sympathetic nervous system effects, although their adverse effects profile may include respiratory depression, nausea, pruritus, sedation, and urinary retention. As a result, a combination of low-dose epidural local anesthetics and opioids are commonly used to take advantage of their synergistic effects and limit the side effects of each. Fentanyl and morphine are commonly used opioids, and bupivacaine is the usual local anesthetic of choice. The lipid solubility of the opioid predicts its clinical behavior. Fentanyl is very lipid soluble, penetrating the dura and rapidly binding to spinal cord opioid receptors, which produces a fast onset of action but a short duration of action. Significant vascular absorption of fentanyl also occurs, decreasing its epidural effect and reducing its advantage over parenteral administration. Morphine is lipid-insoluble and has a slower onset of action, but a much longer duration of action. However, given its hydrophilic nature, morphine remains in the cerebrospinal fluid for a longer period of time with cephalad spread and the risks of delayed respiratory depression for up to 24 hours after neuraxial administration, thereby mandating ongoing monitoring of respiratory function during this time. Other methods of postoperative analgesia include the use of long-acting local anesthetic agents for either wound infiltration or peripheral nerve blockade. Examples of peripheral nerve blockade include brachial plexus blocks for upper extremity pain, femoral nerve blocks for femur and knee surgeries, sciatic nerve blocks for analgesia below the knee, and intercostal nerve blocks for thoracic and abdominal surgeries. Options include the placement of a catheter to allow for a continuous infusion during the postoperative period and provide long-term analgesia for up to 3 to 5 days.

Conclusions

The perioperative care of pediatric patients begins with the preparation of the operating room site as well as the preoperative evaluation of the patient. The complexity of the latter varies tremendously based on the presence of comorbid conditions. These coexisting conditions as well as the requirements of the surgical procedure influence the techniques used for intraoperative monitoring. In its simplest form, a general anesthesia includes amnesia, analgesia, muscle relaxation, and attenuation of the sympathetic nervous system's response to surgical trauma. The phases of general anesthesia include induction, maintenance, and emergence. The induction of anesthesia can be carried out with the intravenous administration of an anesthetic agent or via the inhalation route, with an inhalational anesthetic agent such as sevoflurane. In pediatric patients, the inhalation induction of anesthesia is frequently chosen to avoid the need for obtaining intravenous access on an awake child. Following anesthetic induction, one progresses into the maintenance phase of general anesthesia. This may include the administration of intravenous agents, inhalational agents, or, most likely, the a combination of the two. Following the successful completion of the surgical procedure, a plan is determined for the postoperative delivery of analgesia, including some combination of intravenous opioids, agents to inhibit prostaglandin formation, or a regional anesthetic technique. For complex surgical procedures, tracheal intubation and mechanical ventilation may be continued into the postoperative period, while tracheal extubation and resumption of spontaneous ventilation is the general rule for the majority of surgical procedures. Regardless of the type of anesthesia administered, close monitoring of hemodynamic and respiratory function is continued into the postoperative period either in the ICU or a specialized postanesthesia care unit.

References are available online at http://www.expertconsult.com.

VII Chapter 122

Neuromuscular Blocking Agents

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PEARLS

- As neuromuscular blocking agents (NMBAs) result in blockade of skeletal muscle function, these agents cause cessation of ventilatory function, mandating airway control and the institution of mechanical ventilation. Inability to manage the airway via the provision of bag-mask ventilation and endotracheal intubation will result in hypoxia and death. These agents should not be used if there is any question as to the normalcy of the airway and the ability to successfully accomplish bag-mask ventilation and endotracheal intubation.
- We would recommend the use of the term neuromuscular blocking agent rather than muscle relaxant as the latter seems to imply some implicit type of sedative property, which of course these agents do not have. Rather, it seems appropriate to use the term "NMBA," thereby identifying in their name their mechanism of action and further emphasizing that they are devoid of sedative and analgesic properties.
- NMBAs can broadly be divided into two separate classes based on their mechanism of action. Depolarizing agents such as succinylcholine mimic the action of acetylcholine at the neuromuscular junction and activate or depolarize the muscle, whereas nondepolarizing agents such as pancuronium or rocuronium block the effects of acetylcholine at the neuromuscular junction, acting as competitive antagonists.

In the pediatric intensive care unit (PICU) setting, there may be circumstances in which total prevention of movement is necessary, thereby mandating the use of neuromuscular blocking agents (NMBAs) (Box 122-1).[1] Although these agents can be used as a single dose to facilitate endotracheal intubation, more prolonged administration may be needed in specific circumstances. A survey from the PICU setting suggests that the prolonged administration of these agents is used most commonly as an adjunct in the control of intracranial pressure (ICP).[2] With an improved understanding of the techniques for providing sedation and analgesia in the PICU setting and data demonstrating not only their adverse effect profile, but also their lack of efficacy in specific clinical scenarios, there has been a decrease in the prolonged administration of NMBAs.

Given their potential for adverse effects, it is recognized that NMBAs should be used only when absolutely indicated, only after appropriate training in their pharmacology, and only after obtaining the knowledge and skills needed to treat adverse effects related to their use. Furthermore, it may be appropriate to avoid the use of the term *muscle relaxant,* which seems to imply some implicit type of sedative property that, of course, these agents do not have. Rather, these agents should be thought of as NMBAs, thereby identifying in their name their mechanism of action and further emphasizing that they are devoid of sedative and analgesic properties. Given their action (blockade of skeletal muscle function), these agents will cause cessation of ventilatory function, mandating airway control and the institution of mechanical ventilation. Inability to manage the airway via the provision of bag-mask ventilation and endotracheal intubation may result in hypoxia and death. These agents should not be used if there is any question as to the normalcy of the airway and the ability to successfully accomplish bag-mask ventilation and endotracheal intubation. In the absence of comorbid disease processes that alter the sensorium, patients receiving NMBAs are unable to move and yet totally aware. These agents provide no amnestic, analgesic, or sedative properties, and should not be used without the coadministration of an amnestic agent (i.e., benzodiazepine or barbiturate).

The Neuromuscular Junction

Normal neuromuscular transmission results from the release of acetylcholine from the nerve terminal, its movement across the synaptic cleft, and subsequent binding to the postsynaptic nicotinic receptor on the sarcolemma of the skeletal muscle (Figure 122-1). Acetylcholine is synthesized in the cytoplasm from acetyl coenzyme A and choline and stored in synaptic vesicles in the axonal terminals of the presynaptic membrane. Depolarization of the axonal membrane results in the opening of calcium channels (P channel) and the movement of calcium through channels in the presynaptic membrane, resulting in the fusion of the synaptic vesicles with the axonal membrane and the release of acetylcholine into the synaptic cleft. The P channel is blocked by cations such as magnesium and lithium, but not by calcium channel antagonists. As such, the concurrent administration of magnesium or lithium will potentiate the effect of NMBAs, and the excessive administration of either cation can have significant effects on normal neuromuscular function. After its release from the synaptic vesicles, acetylcholine diffuses across the synaptic cleft and binds to acetylcholine receptors on the postsynaptic membrane (sarcolemma). The acetylcholine receptor (nicotinic receptor on the sarcolemma) is a pentameric protein

composed of five subunits. There are five classes of subunits (alpha, beta, gamma, delta, and epsilon) each of which is coded for by a different gene. During various stages of development or in pathologic disease states, the composition of the acetylcholine receptor may change. The normal variant of the acetylcholine receptors found in adults includes two alpha subunits combined with one each of the beta, delta, and epsilon subunits. Binding of an acetylcholine molecule to each of the two alpha subunits is necessary for opening of the channel and depolarization of the sarcolemma. Immature and denervated acetylcholine receptors have a gamma subunit instead of the epsilon while a demyelinated neuromuscular junction contains acetylcholine receptors composed of a pentamer of alpha$_7$ subunits. The importance of these variants is that their response (opening of the ion channel) is dramatically different from the normal adult variant of the acetylcholine receptor. These differences can result in devastating consequences following the administration of succinylcholine (see below). The acetylcholine receptor occupies the space from the outside of the muscle through the cell membrane to the inside and thereby regulates the transmembrane movement of ions. It converts the chemical stimulus (acetylcholine) into an electrical impulse (depolarization of the sarcolemma). Stimulation of the acetylcholine receptors opens ion channels allowing the movement of small, positively charged cations such as sodium, potassium, and calcium. The sodium influx depolarizes the muscle membrane leading to excitation-contraction coupling, with the release of calcium from the sarcoplasmic reticulum and muscle contraction. Cessation of muscle contraction and repolarization occurs when acetylcholine is metabolized by a specific enzyme, acetylcholinesterase, which is present in the synaptic cleft. This repolarization sets the muscle for the next round of depolarization and excitation-contraction coupling.

Box 122–1 Reported Indications for Neuromuscular Blockade in the PICU

Facilitation of procedures or diagnostic studies:
- Endotracheal intubation
- Central line placement
- Radiological imaging (MRI, CT scanning)

Immobilization during interhospital or intrahospital transport

Intensive care indications:
- Facilitate mechanical ventilation
- Control increased intracranial pressure
- Eliminate shivering (especially during therapeutic hypothermia)
- Decrease peripheral oxygen utilization
- Control severe agitation unresponsive to adequate sedation
- Maintain immobilization after surgical procedures
- Decrease the risk of pulmonary vasospasm in patients with pulmonary hypertension
- Manage patients with tetanus

Neuromuscular Blocking Agents: Depolarizing Agents

The two general classes of NMBAs (depolarizing and nondepolarizing agents) differ in their basic mechanism of action. Depolarizing agents such as succinylcholine (suxamethonium in Europe and the United Kingdom) mimic acetylcholine, binding to the acetylcholine receptor at the neuromuscular junction, and activating it. As succinylcholine is resistant to degradation by acetylcholinesterase, there is sustained occupation of the receptor and thereby failure of repolarization,

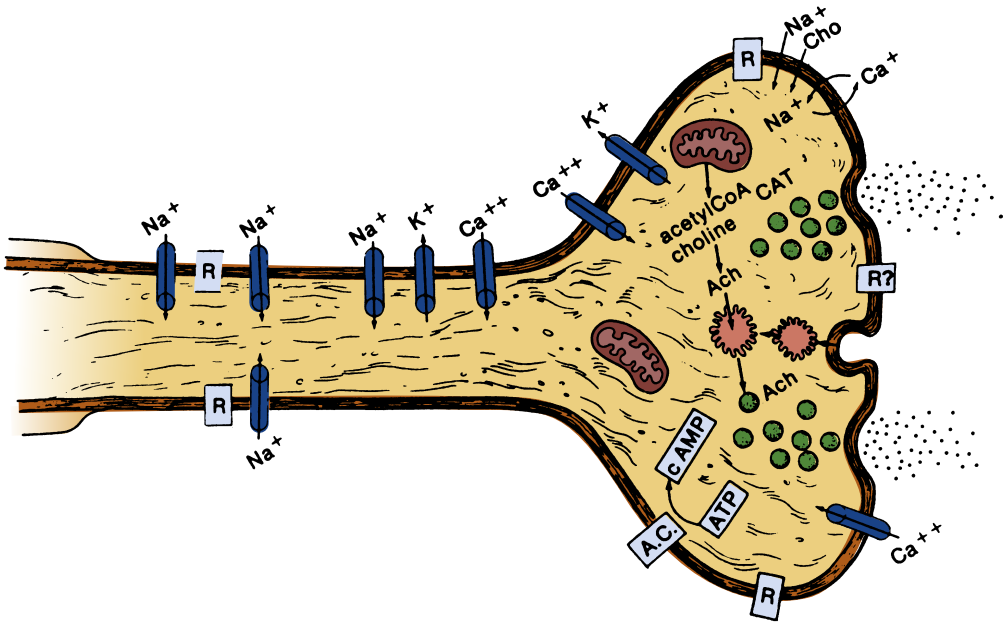

Figure 122–1. Scheme of a motor nerve terminal. The proximal zone, immediately next to the last segment of myelin, is shown as rich in sodium channels (*Na⁺*) that may be activated by cholinergic receptors (*R*). A midzone contains enzyme systems related to metabolism and transmission (*CAT*, choline acetyl transferase; *A.C.*, adenylate cyclase). Some of these are dependent on the entry of sodium and choline (*Cho*), processes that are linked and may be modulated by a cholinergic receptor. Between the proximal and midzone, the terminal is shown as having a variety of ion channels, but as being rich in potassium channels. The final zone, that of release, is sketched as having calcium channels and perhaps having muscarinic or nicotinic receptors (*R?*) that can modulate the release of transmitter (*Ach*).

resulting in a more prolonged duration of neuromuscular blockade. This action of succinylcholine accounts for the clinical effects that are seen, which include the initial muscle fasciculations followed by flaccid paralysis that generally lasts 5 to 10 minutes, the time necessary for the degradation of succinylcholine by pseudocholinesterase. The onset of action of succinylcholine is more rapid than any of the nondepolarizing agents, with neuromuscular blockade occurring in 30 to 45 seconds, thereby allowing for rapid control of the airway by endotracheal intubation. Succinylcholine undergoes rapid redistribution and metabolism by the plasma enzyme pseudocholinesterase (plasma cholinesterase), which limits its clinical duration to 5 to 10 minutes.

In isolated cases, a congenital or acquired deficiency of pseudocholinesterase can lead to a prolonged duration of action. In general, there may be issues with the total amount of the enzyme (quantitative defect) or the efficacy of the enzyme (qualitative defect).[3] Quantitative problems are generally acquired while qualitative issues are inherited. The inherited form of pseudocholinesterase deficiency results in a qualitative defect in the enzyme. It is an autosomal recessive trait with an incidence of 1 in 2500 to 3500. Only homozygotes have a clinically significant prolongation of the effect of succinylcholine, with neuromuscular blockade lasting up to 4 to 8 hours following a single normal intubating dose of succinylcholine (1 to 2 mg/kg). Disease states that lead to a quantitative decrease in pseudocholinesterase levels include severe liver disease, myxedema, pregnancy, protein-calorie malnutrition, and certain malignancies. Drugs and medications can also affect pseudocholinesterase levels, including chemotherapeutic agents such as cyclophosphamide and echothiopate ophthalmic drops. Deficiency can also result from recent plasmapheresis as the enzyme is removed with the plasma. Treatment is aimed at prompt identification by noting failure of the return of the train-of-four (TOF) with peripheral nerve stimulation (see below). The possibility of such an occurrence stresses the need to ensure return of neuromuscular function following the administration of succinylcholine prior to the administration of a nondepolarizing agent. If such a problem is suspected, primary therapy includes continuation of ventilatory support until the patient's muscle strength returns and the provision of amnesia with a benzodiazepine or some other anesthetic agent. Although the patient cannot move, he or she will be aware and awake once the effects of the anesthetic induction agents have diminished. The enzyme plasma cholinesterase is contained in fresh frozen plasma (FFP); however, due to the infectious disease risk with the use of blood products, reversal through the administration of FFP cannot be recommended.[4-6] More recently, purified human plasma cholinesterase has also been used in such circumstances; however, such a practice is expensive and not available in most centers.

Despite its rapid onset and cessation of effect, the potential adverse effects associated with succinylcholine can be devastating and even fatal (Box 122-2). Direct effects on cardiac rhythm have been described following the administration of succinylcholine, including bradycardia, tachycardia, and atrial or ventricular ectopy.[7] Succinylcholine has a chemical structure similar to two molecules of acetylcholine and may result in bradycardia from activation of cardiac muscarinic receptors. This effect is especially common in infants and children, in patients who are anesthetized with halothane (given its negative chronotropic effects), in the presence of hypoxemia, with intravenous as compared to intramuscular administration, when succinylcholine is given concurrently with other medications that have negative chronotropic effects (propofol, fentanyl), and with repeated doses. Therefore, in these scenarios, succinylcholine should always be preceded by an anticholinergic agent such as atropine. The bradycardic effects of succinylcholine may also be accentuated by hypothermia and by elevated ICP. Arrhythmias may also be seen. Although common, occurring in up to 50% of patients, they are generally short-lived and of no clinical significance. The use of an anticholinergic agent will decrease, but not eliminate the incidence of arrhythmias. As with the potential for bradycardia, arrhythmias tend to be more common with repeated doses of succinylcholine.

As succinylcholine activates the acetylcholine receptor prior to producing neuromuscular blockade, depolarization of the muscle end plate occurs, with contraction of the muscle fascicles or fasciculations. These fasciculations are responsible for the myalgias that may occur following succinylcholine administration.[8] Although not a significant issue when succinylcholine is used to emergently secure the airway, these fasciculations can result in severe muscle pain; therefore many advise against the use of succinylcholine for outpatient surgery when such issues may interfere with activities of daily living and return to work. The severity of the fasciculations can be diminished by the administration of a small dose of a nondepolarizing agent (curare 0.03 to 0.05 mg/kg, rocuronium 0.05 mg/kg, or pancuronium 0.01 mg/kg) prior to succinylcholine. The dose of the nondepolarizing agent is generally one tenth of the recommended dose for endotracheal intubation.[9] This is referred to as a *defasciculating dose*. The technique is commonly used in the operating room when succinylcholine is administered to adults, as a means of preventing or attenuating the postoperative myalgias that may occur with succinylcholine. One advantage of fasciculations is that their cessation signals that neuromuscular blockade is complete and the patient's trachea can be intubated.

Defasciculation is not commonly used in the pediatric population for several reasons: (1) children less than 6 years of age do not fasciculate; (2) the use of the defasciculating dose delays the onset of paralysis and increases the succinylcholine dose requirement; (3) in patients with severe respiratory or hemodynamic compromise, the defasciculating dose can cause a significant degree of neuromuscular blockade leading to respiratory insufficiency or laryngeal incompetency with

Box 122–2 Adverse Effects of Succinylcholine

Arrhythmias
- Bradycardia
- Tachycardia
- Asystole
- Atrial and ventricular ectopy

Hypertension
Increased intraocular pressure
Increased intragastric pressure
Increased intracranial pressure
Diffuse myalgias
Myoglobinuria
Malignant hyperthermia
Prolonged paralysis with pseudocholinesterase deficiency
Hyperkalemia (see Box 122-3)

the risk of aspiration; and (4) full efficacy may require up to 2 to 3 minutes, thereby making the technique less optimal when emergent securing of the airway is necessary. If a defasciculating dose is used in patients who are awake and coherent, they should be warned that they may feel effects of the medication, such as diplopia from effects of the drug on the extraocular muscles. Additionally, some patients may feel effects on the muscles of ventilation and complain of shortness of breath.

In addition to myalgias, the fasciculations caused by succinylcholine may result in a transient increase in plasma creatinine phosphokinase (CPK) and myoglobin level. Myoglobinemia occurs most commonly (in up to 40% of patients) when there is concomitant administration of general anesthesia with halothane. In these patients, levels high enough to result in myoglobinuria have been reported in 8% of patients.[10] The rise in plasma CPK and myoglobin levels does not occur with intramuscular administration and may be attenuated by the administration of a defasciculating dose of a nondepolarizing agent (see above). These effects should be differentiated from the potentially lethal complication of rhabdomyolysis, which may occur in patients with specific disorders of the neuromuscular junction and in malignant hyperthermia (see later discussion). These latter disorders absolutely contraindicate the use of succinylcholine. Fasciculations may also increase intragastric (IGP) and intraocular pressure (IOP). The transient and minimal rise in intragastric pressure is generally of limited clinical significance and does not increase the risk of vomiting or passive regurgitation during endotracheal intubation. In the emergency setting, when succinylcholine is chosen for endotracheal intubation, rapid sequence intubation will be used, with the application of cricoid pressure to protect against acid aspiration. The contraction of extraocular muscles leads to an increase in intraocular pressure following the administration of succinylcholine. The increase is transient, with a return of the IOP to baseline within 5 to 8 minutes. Given this effect, administration to patients with an open globe injury is generally contraindicated due to the theoretical risk of causing extrusion of the intraocular contents. Although succinylcholine has been safely administered to such patients,[11] standard practice generally considers the presence of an open globe injury a contraindication to its use.

The effects of succinylcholine on intracranial pressure and its use in patients with altered intracranial compliance remain controversial. Succinylcholine increases ICP not only through the production of muscle fasciculations and increased venous tone, but also via a direct cholinergic mechanism due to activation of muscle spindles in the peripheral skeletal musculature.[12] The effects on ICP are generally mild and transient. Given its rapid onset (30 to 45 seconds), succinylcholine allows for rapid endotracheal intubation and control of arterial oxygenation and ventilation. As the latter are primary determinants of ICP, any mild increase due to the direct effects of succinylcholine are rapidly controlled. Succinylcholine's effects on muscle spindles have also been postulated as an explanation of the CNS activation and dreaming that has been reported during general anesthesia in patients who received succinycholine.[13] The dreaming has not been associated with awareness or recall.

Succinylcholine has also been shown to occasionally result in a transient increase in the tone of the masseter muscles. This effect may be seen in all of the peripheral skeletal musculature, but may be accentuated in the masseter muscles, resulting in what is clinically known as masseter spasm. The effect is generally mild and can be overcome by manual opening of the mouth.[14] A defasciculating dose of a nondepolarizing agent may abolish this phenomenon. In rare circumstances, the masseter spasm may be severe, preventing mouth opening and precluding standard oral endotracheal intubation. It has been suggested that patients who manifest masseter spasm to this degree are at risk for malignant hyperthermia (MH), a rare inherited disorder of muscle metabolism which, if untreated, is generally fatal (see below). The data regarding the relationship between masseter spasm and MH are conflicting. In a prospective evaluation with monitoring of masseter muscle tone, patients who developed significant increases in masseter muscle tone did not proceed to develop MH.[15] However, retrospective series have suggested that the development of masseter spasm may be a prelude to MH, thereby clouding the issue as to how to deal with such patients.[16] In the emergency situation, should patients develop masseter spasm following the administration of succinylcholine, patients should be monitored for signs of MH including hypercarbia, hyperthermia, tachycardia, and rhabdomyolysis with myoglobinuria. Treatment with dantrolene is suggested should there be a concern regarding the development of MH (see below).

The major concerns with succinylcholine are its potential to trigger malignant hyperthermia and its ability to cause massive hyperkalemia if administered to patients with various comorbid disease processes. MH is an inherited (autosomal dominant) disorder of muscle metabolism with abnormalities of the ryanodine receptor (the calcium release channel of the sarcoplasmic reticulum of skeletal muscle). The point mutation of the ryanodine receptor leads to ongoing release of calcium and therefore sustained muscle contraction following exposure to succinylcholine or a potent inhalational anesthetic agent. During MH, ongoing muscle contraction and metabolism leads to hyperthermia, acidosis, tachycardia, hypercarbia, and rhabdomyolysis with secondary hyperkalemia. Treatment includes discontinuation of the triggering agent, treatment of hyperthermia and the biochemical derangements including acidosis and hyperkalemia, and administration of dantrolene, which blocks ongoing calcium release from the sarcoplasmic reticulum. Therefore, in clinical scenarios where succinylcholine may be administered, ready access to dantrolene is recommended.

The other major concern with succinylcholine is the occurrence of lethal hyperkalemia in patients with certain underlying disorders or comorbid diseases (Box 122-3).[17] The reader is referred to reference 17 for a full discussion of the hyperkalemic response following succinylcholine. While many of the disorders listed in Box 122-3 are readily apparent, such as the muscular dystrophies, the occurrence of cardiac arrest following succinylcholine administration to apparently healthy children has led to a restructuring of the recommendations for the use of succinylcholine. The problem is that some children with muscular dystrophy may not manifest symptoms until they are 4 to 6 years of age. If succinylcholine is administered to these children during perioperative care or other clinical scenarios, lethal hyperkalemia can occur. Because of such problems, the current recommendations are that succinylcholine should only be used for emergency airway management when rapid endotracheal intubation is necessary, when there is a concern about the ability to provide endotracheal intubation (potentially or documented difficult airway), or when

intramuscular administration is needed because an appropriate intravenous access cannot be secured. Also of concern in the pediatric population are patients with relatively rare genetic, chromosomal, or metabolic defects in whom the effects of succinylcholine have not been evaluated. In such settings, the risk/benefit ratio of succinylcholine must be fully examined. In many of these patients, the use of a rapidly acting, nondepolarizing agent may be the best option. However, succinylcholine is generally an acceptable option in patients with cerebral palsy and related problems. Regardless of the clinical scenario, if problems occur following the administration of succinylcholine, hyperkalemia should be suspected and the resuscitation tailored to treat it.

In emergency situations when intravenous access cannot be readily obtained, succinylcholine can be administered intramuscularly in a dose of 4 to 5 mg/kg. Intramuscular administration will result in neuromuscular blockade sufficient to allow for endotracheal intubation in 2 to 3 minutes and will rapidly (less than 30 seconds) treat laryngospasm occurring during anesthetic induction when intravenous access is not available, thereby allowing for effective bag-valve-mask ventilation. In this scenario, it is generally recommended that succinylcholine be administered into the deltoid muscle as the onset times are more rapid than with administration into the quadriceps. Alternatively, administration into the tongue or the submental space has been suggested as blood flow to this area is generally well-maintained even when peripheral vasoconstriction has occurred. Unlike intravenous administration, there is limited risk of bradycardia with IM administration.[18] However, the IM route is not recommended in patients with conditions that decrease cardiac output or blood flow to the muscles such as shock or bradycardia. In the latter situation, the onset of action will be significantly delayed. Given these concerns, IM administration is generally not recommended in critically ill children and intraosseous administration (1 to 2 mg/kg) should be considered when IV access is not available.[19]

Currently, the package insert and good clinical practice allow for the administration of succinylcholine when there may be a potentially difficult airway, in the emergency situation when rapid securing of the airway is necessary (full stomach when a rapid sequence intubation is performed), and when there is no intravenous access (IM administration), provided that there is no contraindication to its use (see Box 122-3 and reference 17). When dealing with the potentially difficult airway or unrecognized difficult airway, the major advantage of succinylcholine is that there should be return of normal neuromuscular function within 10 minutes as opposed to 60 minutes following a 1 mg/kg intubating dose of rocuronium (see later discussion). Dosing recommendations for succinylcholine vary from 1 to 2 mg/kg.[20] Larger doses are not likely to improve intubating conditions, and they slightly prolong the duration of action.

Box 122–3 Conditions Associated with Hyperkalemia After Succinylcholine Administration

Preexisting hyperkalemia
Muscular dystrophy
Burns
Metabolic acidosis
Paraplegia/quadriplegia
Denervation injury
Metastatic rhabdomyosarcoma
Parkinson disease
Disuse atrophy/prolonged bedrest
Polyneuropathy
Degenerative CNS disorders
Purpura fulminans
Tetanus
Guillain-Barré syndrome
Myotonia dystrophy
Prolonged administration of nondepolarizing NMBA

Neuromuscular Blocking Agents: Nondepolarizing Agents

The nondepolarizing NMBAs act as competitive antagonists at the neuromuscular junction, and block the effects of acetylcholine at the receptor. Unlike succinylcholine, these agents do not activate the acetylcholine receptor and therefore do not result in fasciculations. Nondepolarizing NMBAs are commonly used in the operating room to facilitate endotracheal intubation and to provide ongoing muscle relaxation for specific surgical procedures such as exploratory laparotomy. When used to provide ongoing neuromuscular blockade in the operating room or the intensive care unit, these agents can be administered by intermittent bolus dosing or by continuous infusion. There are two basic chemical structures of the nondepolarizing NMBAs available for clinical use: aminosteroid and benzylisoquinolinium compounds (Box 122-4). The difference in their chemical structure has limited clinical significance. Of more importance are differences regarding onset, duration of action, cardiovascular effects, metabolism, metabolic products, and cost. These principles will be reviewed in the remainder of this chapter.

The first nondepolarizing NMBAs (curare, gallamine, metocurine), which were introduced into clinical practice in the 1940s, are rarely, if ever, used in today's clinical practice. The past 20 years have seen a rapid growth in the development and introduction of nondepolarizing NMBAs for clinical use. As these agents have more favorable profiles (onset times, recovery times, metabolic fate), they have displaced the original group introduced in the 1940s. However, with the introduction of new agents comes the potential for unrecognized morbidity and even mortality related to adverse physiologic

Box 122–4 Classification of Nondepolarizing NMBAs

Aminosteroid Compounds

Pancuronium
Rocuronium
Vecuronium
Pipecuronium
Rapacuronium (no longer available)

Benzylisoquinolinium Compounds

Mivacurium
Atracurium
Cis-atracurium
Doxacurium

effects. This potential is illustrated by the introduction and subsequent withdrawal of rapacuronium (see below). Given the potential for problems with succinylcholine, the search continues for a nondepolarizing NMBA with similar onset and cessation of action.

Pancuronium

Pancuronium is an aminosteroid compound. It is generally available in a solution containing 1 mg/mL of pancuronium, although other concentrations are available, depending on the manufacturer. The common clinical dose, 0.1 to 0.15 mg/kg, provides adequate conditions for endotracheal intubation in approximately 90 to 120 seconds. Although the higher end of the dosing range may speed the onset time to acceptable conditions for endotracheal intubation, the clinical duration is prolonged from 40 to 60 minutes to 70 to 80 minutes. Given its duration of action, pancuronium is considered a long-acting NMBA (Box 122-5). The effective dose in 95% of children (ED_{95}) is 52 μg/kg during halothane anesthesia and 81 to 93 μg/kg during opioid-based anesthesia. The latter is more applicable to the PICU setting.[21] Further study has shown that the ED_{95} in children is slightly higher than that of adolescents (77 μg/kg).[22] Following a dose of 70 μg/kg, the onset of neuromuscular blockade occurs more quickly in children when compared to adults, with 90% twitch ablation occurring at an average of 2.4 minutes in children and 4.3 minutes in adults.[23] The time to return of the twitch height to 10% of baseline was 25 minutes in children and 46 minutes in adults.

Vagal blockade and release of norepinephrine from adrenergic nerve endings results in an increase in heart rate and blood pressure. Intraoperatively, this effect can be used to balance the negative chronotropic effects of certain anesthetic agents such as fentanyl and halothane. However, there may be a slight proarrhythmogenic effect for atrial tachyarrhythmia in patients with comorbid diseases or when used with other agents that increase heart rate. Elimination is primarily renal (80%), resulting in a significantly prolonged effect in patients with renal insufficiency or failure. Hepatic metabolism is primarily hydroxylation, with production of an active 3-OH metabolite that retains approximately half of the neuromuscular blocking effects of the parent compound. The 3-OH metabolite is also dependent on renal excretion, thereby further prolonging the effect in the setting of renal insufficiency or failure.

Given its long half-life, pancuronium is generally administered intermittently to provide ongoing neuromuscular blockade in the PICU setting. One prospective study has evaluated dosing requirements in the PICU population.[24] The study cohort included 25 patients, ranging in age from 3 months to 17 years and in weight from 3.2 to 68 kilograms. Pancuronium was administered as an initial bolus dose of 0.1 mg/kg, followed by an infusion starting at 0.05 mg/kg/hr. The infusion was titrated up and down to maintain one to two twitches on TOF testing (see below). Pancuronium infusion requirement averaged 0.07 ± 0.03 mg/kg/hr for the 1798 hours of the infusion. Approximately 70% of the time, the infusion requirements were within the range of 0.05 to 0.08 mg/kg/hr. Seven patients were receiving anticonvulsant agents, including pentobarbital, carbamazepine, felbamate, valproic acid, phenytoin, and phenobarbital. Increased pancuronium infusion requirements were noted in these patients (0.14 ± 0.06 vs. 0.056 ± 0.03 mg/kg/hr) and in patients that received pancuronium for more than 5 days. The requirements on day 1 were 0.059 mg/kg/hr versus 0.083 mg/kg/hr on day 5. Upon discontinuation of the infusion, time to spontaneous recovery of neuromuscular function (return of the TOF to baseline and sustained tetanus to 50 Hz) varied from 35 to 75 minutes. No adverse effects directly related to pancuronium were noted. The authors concluded that pancuronium could be effectively administered by continuous infusion to provide neuromuscular blockade in the PICU setting and that it provided a cost-effective alternative to other available agents.

Box 122–5 Duration of Action of NMBAs

Short-Acting (10 Minutes)
Succinylcholine
Mivacurium
Rapacurium

Intermediate-Acting (20–40 Minutes)
Atracurium
Vecuronium
Cis-atracurium
Rocuronium

Long-Acting (60–90 Minutes)
Pancuronium
Pipecuronium
Doxacurium

Vecuronium

Like pancuronium, vecuronium is an aminosteroid compound. It was released for clinical use in the 1980s. Despite minor differences in pharmacologic structure from pancuronium, its plasma clearance is two to three times as rapid. Vecuronium is available as a powder (10 mg), which in common clinical practice is diluted to a concentration of 1 mg/mL. Given the added step of mixing the solution and thereby introducing another step during which a mistake may occur, some practitioners have voiced preference for other agents which are premixed.

At doses of 0.1 to 0.15 mg/kg, acceptable intubating conditions are provided in 90 seconds, with a clinical duration of action of 30 to 40 minutes, making it an intermediate-acting agent.[25] Increasing the dose to 0.3 mg/kg speeds the onset time to acceptable conditions for endotracheal intubation to 60 to 75 seconds, but also prolongs the duration of neuromuscular blockade to 60 to 90 minutes. Even with higher doses, vecuronium is devoid of cardiovascular effects. Metabolism is primarily hepatic (70% to 80%); however, hepatic metabolism results in the production of pharmacologically active metabolites, which are water soluble and therefore dependent on renal excretion. These metabolites possess roughly half of the neuromuscular blocking effects of the parent compound. This combined with the 20% to 30% renal excretion of the parent compound results in a prolonged clinical duration in patients with renal insufficiency. Given its 70% to 80% dependency on hepatic metabolism, the duration of action is also prolonged with hepatic insufficiency. Additionally, due to immaturity of the hepatic microsomal enzymes, a prolonged duration can be expected in neonates. Vecuronium in doses of 0.1 and

0.15 mg/kg maintained neuromuscular blockade at greater than or equal to 90% of baseline for 59 and 110 minutes in neonates and infants, 18 and 38 minutes in children, and 37 and 68 minutes respectively in adolescents.[26] The opposite effect occurs with the chronic administration of anticonvulsant agents, with resistance to the neuromuscular blocking effects and increased dose requirements in patients receiving phenytoin.[27] A similar effect has been reported with other anticonvulsant agents and NMBAs of the aminosteroid group. Given its lack of hemodynamic effects and its current availability in generic form, thereby providing a cost-effective agent for neuromuscular blockade, vecuronium remains a commonly used agent when administered by continuous infusion for ongoing neuromuscular blockade in the pediatric ICU setting.

Rocuronium

Rocuronium is one of the newer aminosteroid NMBAs, having been released for clinical use in the early to mid 1990s. It is available in a solution containing 10 mg/mL of rocuronium in 5 or 10 mL vials. The usual dose for endotracheal intubation (0.6 mg/kg), has a duration of action of 20 to 40 minutes, making it an intermediate-acting agent; however, larger doses (1 to 1.2 mg/kg) are frequently used during rapid sequence intubation, as the onset time at that dose has been shown to approximate that of succinylcholine (see below). As with other agents, the duration of action increases when larger doses are administered, so that 60 to 90 minutes of neuromuscular blockade occurs following a dose of 1.0 mg/kg. A mild vagolytic effect, less intense than that seen with pancuronium, may increase heart rate by 10 to 20 beats per minute. Bolus dosing may also raise mean arterial pressure.

Rocuronium is primarily metabolized by the liver, without the production of active metabolites. Its clinical duration is prolonged and its clearance decreased in patients with hepatic insufficiency or failure. Despite its primary dependence on hepatic elimination, there are mixed results in both adults and children regarding the duration of its effects in patients with renal insufficiency or failure. When comparing adults with and without renal failure, Robertson et al. reported that there was prolongation of the clinical duration (time to recovery of the first twitch of the TOF to 25% of baseline) from 32 to 49 minutes following a dose of 0.6 mg/kg in patients with renal failure.[28] The same investigators reported no difference in the pharmacodynamics in adults with and without renal failure with the use of a smaller dose (0.3 mg/kg).[29] With the smaller dose of 0.3 mg/kg, the onset time was 4 minutes and neuromuscular blockade was reversible at 20 minutes. When comparing adults with renal failure and those with normal renal function, Cooper et al. reported that following rocuronium (0.6 mg/kg), onset time (65 ± 16 vs. 61 ± 25 seconds), clinical duration (55 ± 26.9 vs. 42 ± 9.3 minutes), and spontaneous recovery (time for return of the final twitch of the TOF to 70% of baseline) were all prolonged (99 ± 41 vs. 73 ± 24 minutes).[30] Following an initial dose of 0.3 mg/kg, pediatric patients with renal failure had a longer onset time (139 ± 71 vs. 87 ± 43 seconds); however, there was no difference in the clinical duration.[31] More specific pharmacokinetic data and an explanation for the apparent prolonged elimination half-life of rocuronium in renal failure patients are provided by Szenohradszky et al. in their evaluation of rocuronium in a cohort of 10 adult patients undergoing renal transplantation.[32] Following a dose of 0.6 mg/kg, although the total plasma clearance and the volume of the central compartment did not differ between renal failure and control patients, the volume of distribution at steady state was larger in patients with renal failure; this resulted in a longer elimination half-life with renal failure (97.2 ± 17.3 vs. 70.9 ± 4.7 minutes). A summary of these studies demonstrate a slightly prolonged onset time with rocuronium and a prolonged elimination half-life (and therefore a prolonged clinical effect) in the presence of renal failure. The current data suggest that these findings result from alterations in the volume of distribution rather than primary alterations in clearance due to renal effects. The prolonged duration of action may be clinically significant with doses of 0.6 mg/kg or more, and can be minimized with doses of 0.3 mg/kg. However, with the smaller doses, onset times for successful endotracheal intubation will be prolonged to 2 to 3 minutes.

Given its dependence on hepatic metabolism, alterations in clearance are likely not only in patients with primary hepatic diseases, but also in neonates and infants, due to the immaturity of the hepatic microsomal enzymes. When comparing infants (0.1 to 0.8 years) and children (2.3 to 8 years), plasma clearance is decreased (4.2 ± 0.7 vs. 6.7 ± 1.1 mL/kg/min), the volume of distribution is increased (231 ± 32 vs. 165 ± 44 mL/kg), and the mean residence time is increased (56 ± 10 vs. 26 ± 9 minutes).[33] Also of note, the plasma concentration required to exert a 50% neuromuscular blocking effect is decreased in neonates and infants compared to older children (1.2 ± 0.4 vs. 1.7 ± 0.4 mg/mL). The latter effect, which indicates that the neuromuscular junction of neonates and infants is more sensitive to the effects of NMBAs, is not specific for rocuronium and is seen with all NMBAs. Similar results were reported by Rapp et al., as they reported progressive increases in the clinical duration with a decrease from 5 to 12 months, to 2 to 4 months, to 0 to 1 months of age.[34] The effect was further magnified when increasing the dose from 0.45 to 0.6 mg/kg. The authors also reported excellent or good intubating conditions in all infants with doses of 0.45 mg/kg and ablation of the twitch response at 15 to 30 seconds in neonates, thereby demonstrating a rapid onset even with the use of lower doses (0.45 mg/kg). As with other medications that undergo primary hepatic metabolism, the clinical effects of rocuronium are prolonged in neonates and infants. Metabolism and clinical effects approach those of the adult population by 6 to 12 months of age. In the neonate or younger infant, acceptable conditions for endotracheal intubation can be achieved at 45 to 60 seconds with doses of 0.3 to 0.45 mg/kg.

Rocuronium's welcome in the clinical arena has been expedited by its major clinical advantage over other nondepolarizing NMBAs, a rapid onset. Clinical studies have demonstrated acceptable conditions for endotracheal intubation in the majority of older children and adolescents within 60 seconds following a dose of 1.0 mg/kg. Of the currently available nondepolarizing NMBAs, only rocuronium has an onset of action that approaches that of succinylcholine. The remainder of the NMBAs require 90 to 120 seconds to provide conditions acceptable for endotracheal intubation, even when larger doses are used. In both the pediatric and adult populations, various studies have demonstrated that rocuronium in a dose of 1 mg/kg provides acceptable intubating conditions within 60 seconds in the majority of patients.[35-37] Mazurek et al.[36] prospectively compared the onset times of rocuronium (1.2 mg/kg) and succinylcholine (1.5 mg/kg) in a cohort of

26 children. Anesthesia was induced with thiopental (5 mg/kg). Endotracheal intubation attempts were started 30 seconds after the administration of the agent. Time to endotracheal intubation was comparable between the two groups, being 41.8 ± 2.9 seconds (range, 36 to 45 seconds) with succinylcholine and 40.2 ± 4.0 seconds (range, 33 to 48 seconds) with rocuronium. However, the conditions for endotracheal intubation were slightly less favorable with rocuronium; seven were excellent, five were good, and one was fair versus 10 that were excellent, two that were good, and one that was fair with succinylcholine. Scheibner et al.[37] compared conditions for endotracheal intubation provided by three of the commonly used NMBAs (rocuronium 0.6 mg/kg, vecuronium 0.1 mg/kg, and atracurium 0.5 mg/kg).[37] Endotracheal intubation was attempted every 30 seconds. Conditions for all of the endotracheal intubations were graded as excellent or good, 60 seconds after rocuronium, 120 seconds after vecuronium, and 180 seconds after atracurium. Although a larger dose of rocuronium speeds the onset time to acceptable conditions for endotracheal intubation, there is also a prolonged duration of action (60 to 80 minutes) unlike that of succinylcholine (5 to 10 minutes). The longer duration of action may be problematic should difficulties arise with the performance of endotracheal intubation, resulting in a "cannot intubate/cannot ventilate" scenario. Additionally, in patients with traumatic brain injury or other conditions resulting in alteration of mental status, the neurologic examination will be lost for 60 to 80 minutes following rocuronium in doses of 1 mg/kg. Despite these issues, because of its rapid onset, rocuronium remains the drug of choice for rapid sequence intubation when there are concerns regarding the use of succinylcholine.

Various investigators have evaluated potential techniques to speed the onset of rocuronium without the need to increase the dose. Although there was no difference noted in the time to 50% blockade (42 ± 14 vs. 45 ± 10 seconds) or onset time when comparing rocuronium 0.6 mg/kg administered with either ketamine 1.5 mg/kg or thiopental 4 mg/kg in parturients, tracheal intubation at 50% blockade was easily performed in all patients in the ketamine group while it was difficult in 75% of patients who received thiopental.[38] Munoz et al. demonstrated a significant decrease in the onset time of rocuronium (0.6 mg/kg) in patients who received ephedrine (70 μg/kg), 30 seconds prior to the start of rapid-sequence induction compared to patients receiving placebo (72 ± 19 vs. 98 ± 31 seconds).[39] Ephedrine indirectly increases cardiac output through the release of endogenous catecholamines. The increase in cardiac output increases blood flow and therefore drug delivery to the skeletal muscle, thereby accelerating the onset time.

As with other NMBAs such as vecuronium, priming may accelerate the onset times of rocuronium.[40] In a cohort of 84 children randomized into one of 4 groups: saline followed by rocuronium 0.45 mg/kg, rocuronium 0.045 mg/kg followed by rocuronium 0.405 mg/kg, saline followed by rocuronium 0.6 mg/kg, or rocuronium 0.06 mg/kg followed by rocuronium 0.054 mg/kg, the median onset times and 95% confidence in the four groups were 122.5 (8 to 186), 92.5 (68 to 116), 85 (60 to 142), and 55 (48 to 72) seconds, respectively, thereby demonstrating a clinical advantage of priming regardless of whether the total dose was 0.45 or 0.6 mg/kg. However, as noted previously, there may be issues with priming, including the potential to induce upper airway or respiratory muscle weakness with the potential for aspiration, airway obstruction, or hypoventilation, especially in critically ill patients—even with the small priming dose—as well as the need to wait 60 seconds for the full effect of the priming dose.

Given its rapid onset and lack of adverse effects, most notably rhabdomyolysis and hyperkalemia with underlying neuromuscular disorders, the use of rocuronium via the IM route instead of succinylcholine in the treatment of emergencies such as laryngospasm during anesthetic induction when IV access is lacking could be clinically helpful. However, when evaluating onset and recovery times following IM rocuronium, adequate or good-excellent intubating conditions took an average of 2.5 minutes in infants following a dose of 1 mg/kg and 3 minutes in children following a dose of 1.8 mg/kg.[41] The clinical duration was 57 ±13 minutes in infants and 70 ± 23 minutes in children. The authors also demonstrated a more rapid and predictable onset with IM administration into the deltoid as compared to the quadriceps muscle, an effect similar to that noted with succinylcholine (see above). Given these onset times, the authors cautioned that IM rocuronium was not an alternative to IM succinylcholine for the emergent treatment of laryngospasm.

An additional issue with rocuronium in clinical practice is pain on injection through a peripheral IV cannula.[42] Although the issue may be of limited significance in the PICU setting given the clinical scenarios in which this agent is administered, pretreatment (defasciculation etc.) is occasionally used when rocuronium is administered. Additionally, the practitioner should be aware of this problem, as even when rocuronium is administered immediately after the induction agent for endotracheal intubation, limb withdrawal and grimacing may be seen. The incidence of pain on injection with rocuronium has been reported to be as high as 50% to 80%, with a higher incidence in women than men. As with propofol, various techniques have been suggested to prevent or lessen this problem including diluting the rocuronium solution to 0.5 mg/mL instead of the commercially available 10 mg/mL or the preadministration or coadministration of various pharmacologic agents including lidocaine, ketamine, dexmedetomidine, thiopental, magnesium, alfentanil, and ondansetron. All of these have met with varying degrees of success. When rocuronium is coadministered with thiopental into the same IV site, a precipitate may form and occlude the IV cannula or tubing. This problem can be prevented by thoroughly flushing the IV site between the thiopental and the rocuronium. As with the other aminosteroid NMBAs, chronic anticonvulsant therapy causes resistance to the neuromuscular blocking effects of rocuronium.[43]

Although used most commonly by bolus injection for rapid-sequence endotracheal intubation, there has been one publication addressing the use of rocuronium infusions in the PICU setting.[44] In a cohort of 20 PICU patients, rocuronium was administered by continuous infusion to maintain 1 to 2 twitches of the TOF. The duration of the rocuronium infusion varied from 26 to 172 hours with a total of 1492 hours of administration. Following the initial bolus dose of 0.6 mg/kg, there was an increase in heart rate of 24 beats/minute and a modest increase in blood pressure (maximum increase in systolic blood pressure of 24 mm Hg). The infusion requirements on day 1 varied from 0.3 to 0.8 mg/kg/hr (0.76 ± 0.3 mg/kg/hr). When evaluating all patient days, the infusion requirements varied from

0.3 to 2.2 mg/kg/hr (0.95 ± 0.4 mg/kg/hr). The infusion requirements were 0.5 to 0.8 mg/kg/hr in 45 of the 64 patient days (70%) and 0.3 to 1.0 mg/kg/hr in 58 of the 64 patient days (90%). As with other agents, there was an increase in infusion requirements over time. In 14 patients who received rocuronium for 3 days or more, infusion requirements increased from 0.65 mg/kg/hr on day 1 to 0.84 mg/kg/hr on day 3, and in five patients that received rocuronium for 5 days, the infusion requirements increased from 0.67 mg/kg/hr on day 1 to 1.2 mg/kg/hr on day 5. When the infusion was discontinued, spontaneous return of neuromuscular function occurred in 24 to 44 minutes (31 ± 12 minutes). No adverse effects related to the use of rocuronium were noted.

Pipecuronium

Pipecuronium is structurally related to the other aminosteroids including pancuronium and vecuronium. Like vecuronium, it is devoid of cardiovascular effects. Following the clinically recommended dose for endotracheal intubation of 0.07 mg/kg, onset times vary from 2 to 3 minutes with a longer duration of action (70 to 80 minutes) than pancuronium. Pipecuronium is eliminated primarily by the kidneys (80%), with the remainder of the elimination dependent on hepatic metabolism. Unlike the other previously mentioned aminosteroid NMBAs, there is little enthusiasm for or clinical information concerning the use of pipecuronium in the pediatric population.

Rapacuronium

As mentioned previously, there remains a clinical need for a nondepolarizing NMBA whose onset and offset parallel that of rocuronium. In an effort to meet this need, rapacuronium was introduced into the clinical arena in 1998. The initial clinical experience demonstrated a rapid onset, paralleling that of succinylcholine or larger doses of rocuronium, with a recovery time of less than 10 minutes, thereby offering a significant clinical advantage over rocuronium. Hemodynamic effects included a mild tachycardia like other aminosteroid NMBAs related to a vagolytic effect. Metabolism was hepatic, with the presence of active metabolites that were dependent on renal excretion although they did not appear to result in a clinically significant duration of action in the presence of renal failure or insufficiency.

Unfortunately, with increased clinical use came the recognition that profound and even potentially fatal bronchospasm were associated with its administration. Although initially postulated to be the result of an inadequate depth of anesthesia, subsequent studies suggested a direct effect on the cholinergic receptors of the airway. In a retrospective review of their clinical data base, Rajchert et al.[45] reported that bronchospasm occurred in 12 of 287 (4.2%) patients receiving rapacuronium. Five of the episodes with rapacuronium resulted in an inability to move the chest with no exhaled end-tidal CO_2 following endotracheal intubation. The risk of bronchospasm was 10.1 times greater with rapacuronium compared to other NMBAs. Additional clinical data demonstrating the potential for alterations in respiratory compliance and resistance were reported in a prospective trial in 20 adults randomized to receive either cis-atracurium or rapacuronium.[46] Rapacuronium was administered following endotracheal intubation and the provision of general anesthesia by the continuous infusion of propofol and remifentanil. No changes in compliance or resistance of the respiratory system were noted with cis-atracurium; however, following rapacuronium administration, peak inflating pressure increased from 22 ± 6 to 28 ± 9 cmH_2O, compliance decreased from 108 ± 43 to 77 ±41 mL/cmH_2O, peak inspiratory flow rate decreased from 0.43 ± 0.11 to 0.39 ± 0.09 L/sec, peak expiratory flow rate decreased from 0.67 ± 0.10 to 0.59 ± 0.09 L/sec, and tidal volume decreased from 744 ± 152 to 647 ± 135 mL. Proposed mechanisms for rapacuronium's effects on airways have focused on alterations in cholinergic function with antagonism of the M_2 muscarinic receptor, augmentation of acetylcholine effects at the M_3 muscarinic receptor, and potentiation of vagal nerve and acetylcholine-induced bronchoconstriction.[47-49] The M_2 muscarinic mechanism may be of particular interest, as various NMBAs have been shown to have differing degrees of activity at this receptor. These effects have been reported with pipecuronium, but not with rocuronium.[50] During normal function at the neuromuscular junction of smooth muscle including the airway, some of the acetylcholine that is released diffuses back to the prejunctional (M_2) receptor and shuts off ongoing acetylcholine release. Thus the M_2 receptor is a negative feedback receptor that regulates acetylcholine release. With blockade of the M_2 receptor, there may be exaggerated release of acetylcholine and hence exaggerated muscle contraction or bronchospasm. Although rapacuronium was removed from the market in 2001, there may be other NMBAs in the clinical development process and their potential activity at the M_2 receptor warrants investigation.

Mivacurium

Although it has currently disappeared from the US market, mivacurium may still be available outside of the United States. Mivacurium is a benzylisoquinolinium NMBA and is the shortest-acting of the nondepolarizing NMBAs. It is available in a premixed solution containing 2 mg/mL of mivacurium. Following a dose of 0.2 mg/kg, onset times vary from 2 to 3 minutes with a duration of action of approximately 10 minutes. In a cohort of 62 children anesthetized with nitrous oxide and fentanyl, mivacurium infusion rates to maintain neuromuscular blockade were 375 ± 19 $\mu g/m^2$/min with a spontaneous recovery time ($T_4/T_1 \geq 0.75$) of 9.8 ± 0.4 minutes.[51] There was no evidence of accumulation during prolonged infusions. Mivacurium is metabolized by plasma cholinesterases. Prolonged blockade can occur in the same clinical situations described with succinylcholine, including congenital and acquired deficiencies of this enzyme system.[52,53] The metabolites of mivacurium, which are renally excreted, have limited neuromuscular blocking properties. Like all of the benzylisoquinoliniums, mivacurium can produce histamine release. In children, the histamine release may be associated with flushing and erythema of the skin; however, the hemodynamic effects are generally of limited clinical significance.[54]

Mivacurium's role in clinical practice has been for brief procedures (less than 10 minutes), in either the operating room or PICU, when neuromuscular blockade is required. Mivacurium can be a useful agent to provide a brief duration of neuromuscular blockade for direct laryngoscopy in the PICU patient to follow the progression of epiglottitis or some other airway problem and then provide spontaneous return of neuromuscular function without the use of reversal

agents. In the intraoperative setting, the avoidance of the need to reverse residual neuromuscular blockade with neostigmine (see below) may be beneficial as a means of limiting postoperative nausea and vomiting.

A second potential use for mivacurium has been in combination with other nondepolarizing NMBA to provide a rapid onset of neuromuscular blockade and yet avoid the prolonged duration seen when large doses of vecuronium (0.3 mg/kg) or rocuronium (1 to 1.2 mg/kg) are administered.[55,56] Onset times to 90% neuromuscular blockade were 39 ± 2.3 seconds with 1 mg/kg succinylcholine and 48 ± 3.5 seconds with vecuronium 0.16 mg/kg and mivacurium 0.2 mg/kg.[55] Conditions for endotracheal intubation were graded as excellent in 10 of 10 patients in both groups. Despite the rapid onset, recovery times were prolonged with the combination of vecuronium and mivacurium. Similar results were reported with a combination of mivacurium 0.2 mg/kg and rocuronium 0.6 mg/kg.[56] Although onset time was comparable to that of succinylcholine, the recovery time (49.0 ± 9.6 minutes) was prolonged.

Mivacurium may also been potentially advantageous in patients with underlying neuromuscular disorders (i.e., muscular dystrophy). In such patients, prolonged neuromuscular blockade may occur following even a single dose of an intermediate-acting agent such as vecuronium, atracurium or cis-atracurium. Therefore the use of an agent with the shortest possible clinical duration may be beneficial.[57-59] When compared with healthy control subjects, although there was no difference noted in the onset times, patients with Duchenne muscular dystrophy demonstrated only a modest prolongation of the clinical effect of mivacurium.[57] The median times for recovery of the first twitch of the TOF to 10%, 25%, and 90% of baseline in controls and patients with muscular dystrophy were 8.4 versus 12.0 minutes, 10.5 versus 14.1 minutes, and 15.9 versus 26.9 minutes. Similar results were demonstrated by Tobias and Atwood in their cohort of seven children with Duchenne muscular dystrophy. Following a dose of 0.2 mg/kg, time to recovery of the first twitch varied from 12 to 18 minutes. They also noted significant interpatient variability with infusion requirements varying from 3 to 20 μg/kg/min. Five of the 7 patients required 10 μg/kg/min or less, further demonstrating increased sensitivity to this agent in patients with muscular dystrophy. Of note, there was no correlation with infusion requirements and the patient's preoperative motor function.

Atracurium

Atracurium is a nondepolarizing NMBA of the benzylisoquinolinium class that was released for clinical use in the 1980s. It is supplied in a 10 mg/mL solution. Following a dose of 0.6 mg/kg, acceptable conditions for endotracheal intubation are achieved in 2 to 3 minutes with complete twitch suppression for 15 to 20 minutes, followed by another 10 to 15 minutes with a variable degree of blockade (twitch height, 5% to 25%). Spontaneous recovery ($T_4/T_1 \geq 0.7$) occurs in 40 to 60 minutes. As with all of the NMBAs, the use of a smaller dose (0.3 to 0.4 mg/kg) is feasible, but will prolong the time to the onset of acceptable conditions for endotracheal intubation as well as shorten the recovery time. Atracurium's recovery profile makes it an intermediate-acting agent. When compared with vecuronium, approximately five times as much atracurium is required to provide the same degree of neuromuscular blockade. As with other NMBAs of the benzylisoquinolinium class, atracurium can lead to histamine release. Although facial flushing and cutaneous erythema may occur as with mivacurium, effects on heart rate and blood pressure are generally minimal following doses up to 0.6 mg/kg.[60] With larger doses, hypotension may occur. In the pediatric-aged patient, histamine release is less frequent and less profound than in adults and even when histamine release occurred, no hemodynamic changes were noted.[61] Following its introduction into clinical practice, ongoing safety surveillance demonstrated no difference in the adverse effect profile of atracurium related to histamine release when compared with other NMBAs.[62] Extremely rare anecdotal case reports exist regarding anaphylactoid reactions with severe bronchospasm temporally related to its administration; however, a true causal relationship cannot be proven as the patients also received thiopental during anesthetic induction.[63]

Atracurium undergoes spontaneous degradation via a process known as Hofmann elimination as well as ester hydrolysis. Therefore, its duration of action is unchanged by either renal or hepatic insufficiency. Because of these properties, it rapidly gained favor for providing neuromuscular blockade in intensive care unit patients. For this purpose, it is most commonly used by continuous infusion (see below). The metabolites of atracurium do not possess significant neuromuscular blocking properties. However, one of the metabolic byproducts of Hofmann degradation, laudanosine, has been shown to be epileptogenic in animals. The actual concentration required to cause seizures in humans is unknown and no formal study has ever documented problems from high laudanosine levels. Laudanosine is renally excreted and its accumulation in patients with renal insufficiency is at least a theoretical concern.

Infusion requirements to maintain clinical neuromuscular blockade, defined as a single twitch height of 1% to 10% of baseline, averaged 9 μg/kg/min during a nitrous oxide-opioid–based anesthetic.[64] Recovery remains predictable and stable regardless of the duration of the infusion. Within 30 minutes of discontinuation of the infusion, twitch height had spontaneously recovered to $T_4/T_1 \geq 0.7$.[65] Reversal with neostigmine (see below) is generally available within 10 to 15 minutes of discontinuing an infusion or following the administration of a single dose of 0.6 mg/kg. When compared to a longer-acting agent such as pancuronium, spontaneous recovery following a continuous infusion occurred at an average time of 15 minutes (range, 6 to 34 minutes) with atracurium compared to 25 minutes (range, 10.5 to 37 minutes) with pancuronium.[66] Given its intermediate duration of action and stable recovery profile,atracurium has been used safely and effectively in patients with neuromuscular disorders including myasthenia gravis, myotonic dystrophy, and muscular dystrophy[67,68]; however, prolonged neuromuscular blockade of 3 to 4 hours has also been reported following a single dose of 0.6 mg/kg. In the PICU, similar recovery profiles have been reported. In a cohort of 20 infants and children requiring neuromuscular blockade for 10 to 163 hours during mechanical ventilation, the mean dose of atracurium was 1.4 mg/kg/hr (range, 0.44 to 2.4 mg/kg/hr).[69] When no TOF could be elicited, the time required for the first twitch to become evident with discontinuation of the infusion was 13.8 minutes (range, 1 to 38 minutes). The authors reported that there was no correlation between the recovery time and the dose that was being

administered; however, they did note a faster recovery time when the infusion had been administered for more than 48 hours. Given its non-organ-dependent elimination, atracurium has also been used in pediatric patients following orthotopic liver transplantation.[70] Recovery time ($T_4/T_1 \geq 0.7$) when the infusion was discontinued averaged 23.6 minutes (range, 12 to 27 minutes) and was not prolonged compared to the general pediatric population.

As with rocuronium, administration with thiopental may result in precipitation and occlusion of the intravenous cannula, necessitating flushing the line with normal saline between these two agents. Given its dependence on Hofmann elimination, a temperature-dependent process, elimination will be prolonged during induced or inadvertent hypothermia.[71] During induced hypothermia (32° C) in a cohort of children, the atracurium infusion requirement was 784 μg/kg/hr or 56% of that in normothermic children (1411 μg/kg/hr). Recovery time was also prolonged to 2.86 times that seen in normothermic patients. A similar effect has been reported with the use of cis-atracurium during hypothermia (see following section).

Cis-atracurium

Cis-atracurium is one of the 10 stereoisomers that comprise atracurium. It is six to eight times as potent as atracurium, but devoid of clinically significant histamine release and hemodynamic effects.[72] Cis-atracurium is available as a 2 mg/mL solution. Like atracurium, cis-atracurium is an intermediate-acting neuromuscular blocking agent, with a duration of action of 20 to 30 minutes following a bolus dose of 0.2 mg/kg. Acceptable conditions for endotracheal intubation are provided in approximately 2 minutes. In a cohort of 80 adult patients, cis-atracurium in doses of 0.1, 0.15, and 0.2 mg/kg provided acceptable conditions for endotracheal intubation in 4.6, 3.4, and 2.8 minutes with a clinically effective duration of 45, 55, and 61 minutes.[73] In a cohort of 27 infants (1 to 23 months of age) and 24 children (2 to 12.5 years of age), the onset time to achieve maximal blockade following a dose of 0.15 mg/kg was more rapid in infants (2.0 ± 0.8 versus 3.0 ± 1.2 minutes, $P = .0011$).[72] The clinical duration (recovery to 25% of baseline) was longer in infants (43.3 ± 6.2 versus 36.0 ± 5.4 minutes; $P < .0001$). Once neuromuscular recovery began, the rate of recovery was similar between the two groups. However, de Ruiter et al.[74] reported no difference in the ED_{50}, ED_{95}, or the infusion rate required to maintain 90% to 99% block when comparing 32 infants (0.3 to 1 year of age) and 32 children (3.1 to 9.6 years of age). The ED_{50} in the two groups was 29 ± 3 versus 29 ± 2 μg/kg, the ED_{95} was 43 ± 9 versus 47 ± 7 μg/kg, and the infusion rate required to maintain 90% to 99% blockade in the two groups was 1.9 ± 4 versus 2.0 ± 0.5 μg/kg/min.

A prospective study evaluated cis-atracurium dosing requirements in 15 PICU patients ranging in age from 10 months to 11 years and in weight from 4 to 28 kg.[75] The cis-atracurium infusion was adjusted to maintain one twitch of the TOF. Infusion requirements varied from 2.1 to 3.8 μg/kg/min (average, 3.1 ± 0.6 μg/kg/min) on day 1, from 2.9 to 8.1 μg/kg/min (average, 4.5 ± 1.6 μg/kg/min, $P < .01$ compared to day 1) on day 3, and from 1.4 to 22.7 μg/kg/min during all patient days. The highest infusion requirements were noted following the administration of the drug for prolonged periods of time (150 and 224 hours). When the infusion was discontinued, spontaneous return of neuromuscular function was noted in 14 to 33 minutes. Effective neuromuscular blockade was provided and no adverse effects related to cis-atracurium were noted. In particular, no hemodynamic changes were noted with bolus dosing. Odetola et al.[76] evaluated the dosing requirements of cis-atracurium in a cohort of 11 PICU patients, ranging in age from 0 to 2 years. The duration of the infusions varied from 14 to 122 hours (64.5 ± 36 hours). The infusion requirements to maintain 90% to 95% neuromuscular blockade were 5.36 ± 3.0 μg/kg/min. Laudanosine concentrations during the infusion were 163.3 ± 116 ng/mL. As in the previous study, there was an increase in dose requirements over time and no hemodynamic effects were noted with cis-atracurium.

Reich et al. compared vecuronium and cis-atracurium, administered by continuous infusion, to provide neuromuscular blockade following surgery for congenital heart disease in a cohort of 19 patients less than 2 years of age.[77] The NMBA was administered to maintain one twitch of the TOF. Median infusion times were 64.5 hours for cis-atracurium and 46 hours for vecuronium (P = not significant). Median recovery time, defined as a normal TOF without fade, was shorter with cis-atracurium than with vecuronium (30 minutes versus 180 minutes, $P < .05$). Recovery time was more than 4 hours in three of nine patients who received vecuronium. Two of these patients had high vecuronium plasma concentrations, while the other had an elevated 3-OH vecuronium level. There was no difference in time to tracheal extubation, intensive care unit stay, or hospital stay.

As with other NMBAs, resistance to the effects of cis-atracurium may be seen in patients treated with anticonvulsant agents.[78] Time to recovery of T_1 to 25% of baseline was 69 ± 13 minutes in patients not receiving anticonvulsant medications, 64 ± 19 minutes in those receiving acute therapy with anticonvulsants, and 59 ± 19 minutes in those receiving chronic anticonvulsant therapy. As with atracurium, altered clearance and decreased infusion requirements occur with hypothermia.[79] During induced hypothermia (34° C) to control increased ICP, cis-atracurium infusion requirements were 1.7 μg/kg/min and increased to 3.4 μg/kg/min with return to normothermia.

Doxacurium

Doxacurium is the benzylisoquinolinium derivative with the longest duration of clinical activity. It is the most potent of the clinically available NMBAs, with approximately twice the potency of pancuronium or pipecuronium. Following a dose of 0.05 mg/kg, its duration of action is 80 to 90 minutes. The ED_{95} in children is 30 μg/kg, approximately 1.5 times that reported for the adult population.[80] Elimination is primarily renal, with a small percentage dependent on hepatic excretion. The duration of action is prolonged in patients with either hepatic or renal insufficiency. Despite it being a benzylisoquinolinium derivative, it is primarily devoid of histamine-releasing properties and cardiovascular or hemodynamic effects. To date, there has been limited use of this agent in the PICU population.

Reversal of Neuromuscular Blockade

Although neuromuscular blockade is necessary for many surgical procedures and used for various indications in the PICU setting, even a small residual amount of blockade may

compromise ventilation or upper airway patency in the critically ill patient or during the immediate postoperative period. In the operating room setting, residual neuromuscular blockade is frequently reversed at the completion of the procedure to ensure adequate strength to maintain airway patency and ventilatory function following extubation of the trachea. In the PICU setting, reversal of neuromuscular blockade is less common. In most clinical scenarios, when there is no longer a need for neuromuscular blockade, the agent is discontinued and spontaneous recovery is allowed. The latter is generally appropriate in the PICU setting, as ongoing tracheal intubation and mechanical ventilation will likely be provided for some period of time following the discontinuation of the NMBA. However, in a smaller percentage of patients, tracheal extubation coincides with discontinuation of the NMBA, thereby mandating the use of a reversal agent.[81]

Reversal of neuromuscular blockade is possible only with nondepolarizing NMBAs. Additionally, some degree of residual neuromuscular function is necessary to allow for effective reversal of neuromuscular blockade. In general clinical practice, this means that there should be 1 to 2 twitches in the TOF or that the T_1 has recovered to 25% of its baseline height. Therefore, reversal with a drug that inhibits acetylcholinesterase is not feasible immediately after the administration of an NMBA. Rather, depending on the dose, some time is necessary, which is generally 15 to 30 minutes with intermediate-acting agents.

The drugs used to reverse neuromuscular blockade inhibit the enzyme acetylcholinesterase. This, in turn, provides more acetylcholine to compete with the NMBA at the nicotinic receptor of the neuromuscular junction. The commonly used acetylcholinesterase inhibitors or "reversal agents" include neostigmine, pyridostigmine, and edrophonium. Despite a similar mechanism of action, the clinical effects (onset, duration, etc.) of these agents differ. Neostigmine and pyridostigmine are hydrolyzed by acetylcholinesterase. During this process, the enzyme is carbamylated and inactivated. Edrophonium does not breakdown the enzyme acetylcholinesterase, rather it competitively and reversibly inhibits its function. The difference in the molecular mechanism of these agents has little impact on clinical use or practice. With these three agents, the peak plasma concentration is achieved at 5 to 10 minutes following bolus administration, followed by an elimination half-life of 60 to 120 minutes. Clearance is markedly reduced in the setting of renal failure or insufficiency. There is a marked difference in the onset times of the three reversal agents. The onset of peak effect is 1 to 2 minutes with edrophonium, 7 to 11 minutes with neostigmine, and 16 minutes with pyridostigmine.[82,83] An additional difference is the efficacy of these agents when reversing intense blockade (≥90%), in that neostigmine is more effective than either edrophonium or neostigmine.

Adverse effects associated with the use of reversal agents generally relate to their inhibition of acetylcholinesterase at sites away from the neuromuscular junction. These agents should always be preceded by an anticholinergic agent such as atropine or glycopyrrolate, since the inhibition of acetylcholinesterase occurs not only at nicotinic receptors (neuromuscular junction), but also at muscarinic receptors. Therefore, unless preceded by an anticholinergic (antimuscarinic) agent, bradycardia and asystole can occur. The time course of the bradycardic effects varies based on the onset time of the agents. As such, if edrophonium is used, glycopyrrolate should be administered first and followed in 1 to 2 minutes by edrophonium, given that the onset time of glycopyrrolate is longer than that of edrophonium. The onset time of glycopyrrolate correlates well with that of neostigmine and pyridostigmine and therefore these agents may be administered at the same time. Given that the onset of atropine is rapid, it may be administered with any of the three reversal agents. Other adverse effects related to the reversal agents included augmentation of cholinergic function in the gastrointestinal tract (salivation, diarrhea, nausea, and vomiting) and the respiratory tract (bronchospasm). Although the anticholinergic agents may block salivation and alterations in airway tone, their efficacy in blocking the increased gastrointestinal motility are somewhat limited.

More recently, there has been development of a novel agent for reversal of neuromuscular blocking agents. However, this drug has not achieved approval from the United States Food and Drug Administration as of the end of 2010. The agent, suggamadex, is a cyclodextrin, and, instead of inhibiting the enzyme acetylcholinesterase, it forms a tight 1:1 complex with the steroidal neuromuscular blocking agents. It has been shown to rapidly and effectively reverse rocuronium and vecuronium and perhaps even pancuronium.[84,85] There is a limited dissociation rate so that the reversal is maintained. Unlike with acetylcholinesterase inhibitors, reversal using suggamadex is feasible even with intense blockade, thereby providing the potential for the rapid reversal of neuromuscular blockade in the "cannot intubate— cannot ventilate" scenario. Future studies are needed to fully evaluate this medication in the pediatric population.

Monitoring Neuromuscular Blockade

In the operating room, NMBAs may be used as a single dose at the start of the case to facilitate endotracheal intubation or by repeated doses or a continuous infusion to provide ongoing neuromuscular blockade. Some means of monitoring neuromuscular blockade is necessary since administration of excessive doses may mandate the use of postoperative mechanical ventilation until neuromuscular blockade has worn off or can be reversed. Additionally, given concerns regarding prolonged paralysis, monitoring neuromuscular function may also be considered in the PICU setting.

Monitoring may include some combination of visual, tactile, or electronic means of measuring the residual neuromuscular function following electrical stimulation. The technique, most commonly used by anesthesiologists in the operating room to monitor the degree of neuromuscular blockade, is peripheral nerve stimulation or TOF monitoring. TOF monitoring involves placement of standard electrocardiographic electrodes over a peripheral nerve. The nerves most commonly used are the facial, ulnar, or common peroneal, which results in corresponding movement in the muscles of the face, hand, or leg. In some circumstances, direct stimulation of the muscle may occur, giving the false impression that an appropriate amount of neuromuscular blockade has not been achieved. To avoid such problems, it may be appropriate to place the TOF monitor and assess the twitch response prior to the administration of the initial dose of the NMBA. The electrodes of the TOF monitor are connected to a hand-held peripheral

nerve stimulator that delivers two stimuli per second at 50 mA for 2 seconds. A total of four stimuli are administered over 2 seconds, hence the term *train-of-four*. As this is painful, it should only be performed in patients that are anesthetized or sedated. Depending on the number of acetylcholine receptors that are occupied by the nondepolarizing NMBA, there will be anywhere from zero to four responses or twitches. Despite the availability of other more sophisticated machines to monitor the degree of neuromuscular blockade in the operating room and ICU setting, these monitors are generally used only for clinical research purposes; in clinical practice in either the operating room or the PICU, TOF monitoring remains the technique that provides the most useful information with limited requirements for training and equipment.

In clinical practice, the TOF monitoring is combined with clinical assessment at the end of the case to ensure that the patient is strong enough for extubation. Following reversal of neuromuscular blockade, clinical assessment of strength is combined with neuromuscular monitoring. These latter measures become necessary as residual weakness may be present despite apparent reversal using TOF monitoring. Techniques of clinical assessment to evaluate the presence of residual neuromuscular blockade include measurement of negative inspiratory force (NIF) or maximum inspiratory pressure (MIP), hand grip, or head lift. Although head lift and hand grip require the ability to follow a simple command, the measurement of NIF does not. The technique involves measuring the inspiratory force that the patient can generate against an occluded airway. The test can be completed with a simple manometer attached to the 15 mm adaptor of the ETT. Initial studies suggested that a NIF of at least −20 cm H_2O indicated sufficient muscle strength to maintain an adequate minute ventilation.[86] Subsequently, a value of −25 to −30 cm H_2O became the generally accepted value for use in clinical practice. However, subsequent work suggested that although strength was adequate to maintain minute ventilation, it may not be adequate to maintain upper airway patency and therefore, the use of voluntary responses (head lift for 5 seconds or hand grip) were suggested as adjuncts to ensure adequate reversal of neuromuscular blockade.[81] In infants, reflex leg lift (both legs lifted off of the operating room table) was shown to correlate with a mean NIF or MIP of −51 cmH_2O; therefore the authors concluded that this was a sign of adequate reversal of neuromuscular blockade in infants.[87] Given the variability of these responses and their correlation with reversal of neuromuscular blockade, the best clinical approach may be the use of several clinical maneuvers if TOF monitoring is not available. The literature suggests that the ability to maintain a sustained head lift for 5 seconds is the most sensitive clinical tool.[81]

In the ICU setting, given the degree of neuromuscular blockade that is induced, voluntary measures of muscle strength are not adequate and therefore, titration of NMBAs should be guided by the use of TOF monitoring. The technique may allow the use of the lowest possible dose of agents and theoretically avoid complications such as prolonged blockade (see below). In a prospective randomized trial in 77 adults, TOF monitoring (maintaining one twitch of the TOF) was compared with clinical parameters (patient breathing over the preset ventilator rate) as a means of titrating NMBAs.[88] TOF monitoring resulted in a lower total dose and lower average infusion rate of vecuronium as well as a more rapid recovery once the infusion was discontinued. A subsequent study in adults revealed a decreased incidence of persistent neuromuscular weakness when using TOF monitoring.[89]

Although data are lacking to clearly demonstrate the superiority of TOF monitoring in the PICU setting, its use is suggested as a means of titrating the administration of NMBA agents. Of note is the significant interpatient variability that has been reported in the PICU setting and the inability, therefore, to ensure an appropriate dose without some monitoring modality. The choice of the number of twitches to maintain has not been prospectively studied. The majority of the clinical evidence suggests that maintaining one twitch of the TOF ensures an adequate degree of neuromuscular blockade while potentially limiting the incidence of persistent neuromuscular weakness. However, the least amount of blockade that can be clinically tolerated is suggested. In some patients, maintaining two twitches may be acceptable, especially with the use of an appropriate degree of sedation and analgesia.

No study has evaluated the best nerve (facial, ulnar, common peroneal) to monitor. In clinical practice, any accessible nerve can be used. However, several patient and technical factors may affect the response. As such, whenever feasible, placement of the monitor prior to the institution of neuromuscular blockade is suggested to ensure that a TOF can be obtained prior to the administration of the NMBA. If no response is obtained, the technique should be evaluated by first evaluating the monitor (faculty monitor, electrodes, or batteries). Is the electrode too far from the nerve (improper placement, edema, obesity)? If these technical problems are ruled out, the infusion can be decreased by 10% to 15% and the TOF measured again in 2 hours. When two or more twitches are noted, if the patient is stable and a more profound degree of blockade is not required, ongoing observation is suggested. If a deeper level of blockade is required, a bolus equivalent to the hourly infusion rate should be administered and the infusion increased by 10% to 15%.

Adverse Effects of Neuromuscular Blockade

As with any medication used in the PICU patient with comorbid diseases, adverse effects may occur with NMBAs. Perhaps the most devastating of these adverse effects is the inability to provide adequate ventilation following the administration of a medication that induces apnea. Therefore, these medications should never be used if there is any suspicion that the airway cannot be controlled. In rare circumstances, endotracheal intubation using direct laryngoscopy may be impossible and in even rarer circumstances, adequate bag-mask ventilation cannot be provided. In such scenarios, death or permanent CNS morbidity will result with the administration of NMBAs. Measures to avoid such problems include an assessment of the airway prior to the administration of these agents and a knowledge of the "cannot intubate— cannot ventilate" algorithm as outlined by the American Society of Anesthesiologists.

Various physical characteristics may suggest that direct laryngoscopy and intubation will be difficult, including micrognathia, a short neck, limited neck mobility (flexion/extension), limited mouth opening, a large tongue, and a small mouth. An additional tool is the Mallampati grade which describes the ability to visualize the tip of the uvula and the tonsillar pillars. If there is a suspicion that endotracheal

intubation using direct laryngoscopy will not be possible and there is time, other techniques to control the airway are suggested. Some of the more commonly used approaches to the difficult airway in infants and children have been outlined by Davidson et al.[90] More importantly, the techniques needed for the "cannot intubate— cannot ventilate" scenario should be understood and available in any situation in which NMBAs are being administered. Aside from repositioning the patient or using a direct type of laryngoscope, physicians using NMBAs should have a working knowledge of the laryngeal mask airway as it can be used to rescue patients when direct laryngoscopy, endotracheal intubation, and bag-mask ventilation fail.[91]

Other adverse effects from NMBAs relate to the elimination of routine physiologic functions. Eye care with the use of artificial tears or lacrilube at fixed intervals during the administration of NMBAs is necessary to avoid drying of or damage to the cornea. Additionally, repositioning of the patient at frequent intervals is needed to avoid pressure sores. For prolonged immobility, the use of special mattresses may be considered as an adjunct to frequent patient moving. Passive range of motion may also be indicated with splinting to prevent forearm and ankle contractures, while sequential compression devices may be indicated to prevent deep vein thrombosis. Ineffective coughing and clearance of secretions mandates the implementation of suctioning protocols to limit the risk of nosocomial pneumonias. Alterations in functional residual capacity, dead space, and ventilation-perfusion ratios may result in ventilatory issues including hypoxemia or hypercarbia and the need to adjust ventilatory parameters.

As noted previously, although NMBAs prevent movement, they provide no degree of sedation or analgesia. As such, the most important monitor of the depth of sedation, the clinical score, is eliminated. Therefore, some other measure of the depth of sedation may be required. In the majority of clinical situations, physiologic parameters such as heart rate or blood pressure are used as a means of titrating sedative and analgesic agents. However, issues arise in critically ill patients in whom alterations in heart or blood pressure may not occur in response to stress or pain. In this patient population, exogenous vasopressors may be in use and thereby eliminate the reliability of physiologic parameters. In the operating room setting, the availability of depth of anesthesia monitors is recommended and it is suggested that their use be considered in patients at high risk for awareness. Despite the rare occurrence of such events, means for their prevention of awareness during the use of neuromuscular blocking agents in the pediatric ICU appear indicated given the consequences of such problems.

In the operating room setting, depth of sedation or anesthesia monitors are available. To date, there are no data in the PICU to demonstrate their efficacy in preventing recall during the use of neuromuscular blocking agents. The bispectral index is a processed electroencephalographic parameter expressed as a numeric value ranging from 0 (isoelectric EEG) to 100 (awake, eyes open, no sedative agent). In the pediatric population, its intraoperative use has been suggested to decrease the incidence of awarness.[92] In the PICU population, the BIS value has been shown to correlate with the depth of sedation assessed using various clinical scoring systems.[93,94] BIS monitoring has been used to evaluate the depth of sedation in a cohort of 12 PICU patients receiving NMBAs.[95] BIS monitoring was used for a total of 476 hours in the patients and revealed that the desired depth of sedation (BIS number 50 to 70) was achieved 57% of the time. The BIS number demonstrated a deeper than desired depth of sedation (BIS number ≤49) 35% of the time and an inadequate depth of sedation in patients receiving neuromuscular blockade (BIS number ≥71) 8% of the time. Additional sedation was sometimes administered by the bedside nurse on the basis of clinical judgment (he or she was not allowed to view the monitor). At 64% of the times this was done, the BIS number was greater than or equal to 71; at 31% of the times, it was 50 to 70; and at 5% of the times, it was 49 or less. Although no long-term follow-up or assessment of awareness was pursued, the authors concluded that physiologic parameters are not a viable means of assessing the depth of sedation during the use of NMBAs.

The adverse effect that has received the most attention in the adult population with the administration of NMBAs is residual neuromuscular paralysis. In clinical practice, it appears that there are two distinct entities that may account for prolonged neuromuscular paralysis including (1) prolonged recovery from neuromuscular blockade related to excessive dosing or delayed clearance of the parent compound or metabolites due to renal or hepatic issues, and (2) what is now termed the acute quadriplegic myopathy syndrome (AQMS).[95,96] The former generally resolves spontaneously over time with the eventual clearance of the parent compound or its metabolites. In clinical practice, it is defined as a prolonged recovery time of more than 100% of the predicted parameter. In distinction, AQMS presents with acute paresis, myonecrosis with increased levels of plasma markers demonstrating muscle breakdown such as creatinine phosphokinase (CPK), and abnormal electromyography (EMG) with the demonstration of reduced compound motor action potential amplitude, decreased motor nerve conduction, and evidence of acute denervation. Clinical findings include flaccid paralysis, relative preservation of extraocular movements, decreased deep tendon reflexes, respiratory insufficiency, intact sensory function, and normal findings in the cerebrospinal fluid. Recovery may require weeks to months, with the need for prolonged rehabilitation care, and tracheostomy with chronic ventilatory support. Although initially reported only with aminosteroid compounds, it has also been subsequently reported with the benzylisoquinolinium derivatives. It remains to be determined whether the relative majority of reports with the use of the aminosteroid compounds relates to the current clinical practice which favors the use of these agents or to some particular vulnerability related to these agents.

Given that CPK values are elevated in up to 50% of patients with AQMS, periodic screening of patients receiving ongoing neuromuscular blockade may be indicated. Additionally, given that the syndrome is reported following the prolonged, continuous infusion of NMBAs, it has also been suggested that drug holidays or periodic interruption of the infusion be considered. However, there are no data to demonstrate that such practice will alter the incidence of AQMS, and the withdrawal of neuromuscular blockade must be considered on a risk-benefit ratio. Obviously, termination of the use of NMBAs is suggested whenever it is clinically feasible, given their adverse effect profile. Other factors and comorbid processes that may contribute to the development of AQMS include nutritional deficiencies, coadministration of other medications (cyclosporine, corticosteroids, aminoglycosides), hyperglycemia, hepatic or renal insufficiency, and electrolyte disturbances.

The association is most profound with the coadministration of NMBAs and corticosteroids, thereby suggesting a heightened awareness in such patients.[97] In addition to AQMS, other conditions to consider in the differential diagnosis of patients with prolonged weakness following the use of NMBAs include neuromuscular conditions (myasthenia gravis, Eaton-Lambert syndrome, Guillain-Barré syndrome), acquired or primary myopathic conditions (mitochondrial myopathy, steroid myopathy), central nervous system injury, spinal cord injury, critical illness polyneuropathy, disuse atrophy, and electrolyte or metabolic disturbances. Critical illness polyneuropathy may be confused with AQMS. It is a combined motor and sensory neuropathy that results from ischemia of the microvasculature of the nerves, which is seen most commonly in patients with multisystem organ failure. The EMG demonstrates a pattern different from that seen in AQMS.

Summary: Neuromuscular Blocking Agents in the PICU

In addition to their use in the operating room, specific situations may arise that mandate the use of neuromuscular blocking agents in the pediatric ICU (see Box 122-1). Although these agents are generally administered as intermittent bolus doses in the operating room, in the PICU, a more stable baseline level of neuromuscular blockade may be desired and therefore a continuous infusion may be used. When choosing an agent for use in the PICU population, the major issues include cardiovascular effects, metabolism, and cost. Since many of the patients in the PICU have some degree of hemodynamic instability, agents that cause excessive histamine release should be avoided. Additionally, the presence of hepatic or renal insufficiency may affect metabolism or elimination or the parent compound as well as its metabolites. In the absence of end-organ dysfunction, pancuronium offers an inexpensive means of achieving neuromuscular blockade. Its vagolytic effect will result in tachycardia with an increase in heart rate of 10 to 20 beats per minute above baseline. Given its duration of action, intermittent dosing is feasible. With its availability in generic form, vecuronium provides another cost-effective option in the PICU setting while eliminating the tachycardia that is seen with pancuronium. Although vecuronium and pancuronium are generally effective and inexpensive in patients without end-organ dysfunction, significant alterations in infusion requirements occur in patients with renal insufficiency/failure (pancuronium and vecuronium) or hepatic insufficiency/failure (vecuronium). Atracurium or cis-atracurium may be a more appropriate choice in patients with hepatic or renal failure since such problems do not alter dosing requirements of either agent.[99]

In the PICU setting as in the operating room, adjustment of the dose based on monitoring with a peripheral nerve stimulator is recommended. Regardless of the agent used, significant interpatient variability with up to tenfold variation in infusion requirements may be noted. The variability results not only from interpatient variability, but also from various associated conditions that may increase or decrease the sensitivity to NMBAs (Boxes 122-6 and 122-7). Based on this knowledge, the recommended doses (Table 122-1) for the various NMBAs are starting guidelines and the infusion should be increased or decreased as needed to maintain one twitch of the TOF or to provide the required depth of neuromuscular blockade. An

Box 122–6 Factors that Increase Sensitivity to NMBAs

Medications

Inhalational anesthetic agents
Local anesthetic agents
Antibiotics (aminoglycosides)
Antiarrhythmic agents (quinidine, procainamide)
Calcium channel blockers
β-Adrenergic antagonists
Chemotherapeutic agents (cyclophosphamide)
Diuretics (furosemide)
Dantrolene
Lithium, magnesium
Cyclosporine

Underlying Disorders

Electrolyte disturbances (hypokalemia, hypermagnesemia, hypocalcemia)
Hypothermia
Respiratory acidosis
Metabolic alkalosis
Myasthenia gravis
Eaton-Lambert syndrome
Muscular dystrophy
Multiple sclerosis
Amyotrophic lateral sclerosis
Poliomyelitis

Box 122–7 Factors that Decrease Sensitivity to NMBAs

Medications

Anticonvulsant agents (phenytoin, carbamazepine)
Aminophylline

Underlying Conditions

Hypercalcemia
Burns
Prolonged administration of NMBAs

Table 122–1 Suggested Starting Guidelines for the Continuous Infusion of Neuromuscular Blocking Agents

Agent	Dose	Comments
Pancuronium	0.06–0.08 mg/kg/h	Vagolytic effect, primary renal excretion
Vecuronium	0.1–0.15 mg/kg/h	No cardiovascular effects, hepatic metabolism to active metabolites that are renally excreted
Rocuronium	0.6–0.8 mg/kg/h	Mild vagolytic effect, hepatic metabolism
Atracurium	1–1.5 mg/kg/h	Mild histamine release, non-organ-dependent elimination
Cis-atracurium	0.2 mg/kg/h	No cardiovascular effects, non-organ-dependent elimination

additional problem that occurs in the ICU patient who receives NMBAs for a prolonged period of time is the development of tachyphylaxis or an increased dose requirement over time. The primary cause is an upregulation of acetylcholine receptors in patients who are chronically exposed to NMBAs. Dodson et al. demonstrated an increased density of acetylcholine receptors in muscle from patients who had received prolonged infusions of NMBAs.[100] Prolonged neuromuscular blockade, like partial or complete deafferentation, leads to proliferation of acetylcholine receptors at the neuromuscular junction. This problem requires that the dose of the NMBA be increased over time to maintain the same amount of neuromuscular blockade.

Given their adverse effect profile, it is recommended that NMBAs be administered only when aggressive attempts at sedation have failed to provide the desired level of patient immobilization. An ongoing assessment regarding the need for continuing such therapy is suggested with discontinuation of the medication as early as is feasible. Specific protocols should be in place to ensure appropriate care of the patient who is receiving neuromuscular blockade, with attention toward the provision of adequate sedation and analgesia, eye care, prevention of pressure sores, and pulmonary toilet. Given the variability in requirements that is present in the PICU setting, monitoring with the TOF is recommended.

References are available online at http://www.expertconsult.com.

Sedation and Analgesia

Christopher M.B. Heard and James E. Fletcher

PEARLS

- A wide selection of sedation and analgesia options is available in the pediatric intensive care unit.
- No ideal sedative agent exists for all patients.
- Most children do well with a combination of opiates (fentanyl) and supplementation with benzodiazepines either by infusion (midazolam) or on an as-required basis (lorazepam) to provide adjunct anxiolysis and amnesia.
- Postoperatively, patients require adequate analgesia, which may include the use of epidural anesthesia or patient-controlled analgesia.
- In circumstances in which the ability to perform a rapid neurologic examination is required, use of short-acting agents such as remifentanil, propofol, or isoflurane may be warranted.
- All sedative agents result in tolerance with prolonged use. The intensive care physician must be aware that withdrawal may occur with the prolonged use of these agents (i.e., more than 3 to 5 days).
- A proactive treatment plan with methadone at the equivalent dose can effectively and safely prevent opiate withdrawal in the patient in the pediatric intensive care unit.

Sedation is an integral part of patient management in the pediatric intensive care unit (PICU). It is necessary to minimize the perception of and response to anxiety and pain. Children who are not adequately sedated or who are experiencing pain may become tachycardic and hypertensive. They also may become agitated and as a result endotracheal tubes and central lines may become dislodged. Conversely, oversedation can cause cardiovascular depression and ileus and may interfere with a comprehensive neurologic examination. In patients who undergo prolonged sedation, tolerance and tachyphylaxis develop, which lead to increasing sedative requirements.

Patients may recall their stay in the ICU. Many patients remember having an endotracheal tube or having their lungs mechanically ventilated. Nightmares and hallucinations also have been reported.[1] Either single-drug therapy or inadequate dosing may be associated with a higher incidence of recall in the patient receiving neuromuscular blocking agents. [2] In adults, delusional memories and an underlying anxiety state were predictors of the development of a posttraumatic stress disorder after sedation in the ICU.[3] Delusional memories were reported much more frequently than factual memory, probably because most patients have difficulty correctly remembering the events that occur during their stay in the ICU. In pediatric patients, recall of the PICU experience also has been reported.[4] More than 66% of pediatric patients remembered their stay in the PICU. Eighteen percent had bad memories, 16% remembered mechanical ventilation and anxiety, and 29% remembered pain from a procedure or movement. Overall the recollections of patients in the PICU were considered negative in approximately 15% of the patients. Sleep disturbance also was a problem.

Various scoring systems are often used to guide sedation. The most widely used is the Ramsay scale.[5] The patient's level of consciousness is classified as one of six scores (Table 123-1). The nurse at the bedside assesses the patient and then changes the sedation regimen as necessary to achieve the desired level of sedation. The ideal level of sedation varies from patient to patient, but in general, most intensive care physicians seek to maintain patients in a sleepy but easily awakened state. A Ramsay score of 2 to 3 seems to be ideal as the clinical end point for sedation. Deeper sedation should be reserved for select patients who are often younger, are receiving neuromuscular blocking agents, or have a head injury. The use of a sedation scoring system to guide sedation of surgical critical care patients has been evaluated for cost-effectiveness. Use of scoring systems has proved to save costs in the ICU.[6] Because the patient can be weaned more rapidly from the ventilator through better control of the sedation level, the number of days a patient is connected to a ventilator is reduced. The COMFORT score, which is composed of eight variables (each with five categories), also has been validated for use in the PICU to assess sedation level in children. Use of this system, however, is more complicated and time consuming.[7]

Many scoring systems are subjective and are limited by interobserver variability. The more objective methods may be too cumbersome for routine use. A simple scoring system has been devised that is easy to use and minimizes subjectivity and observer variability.[8] This system is the Brussels sedation scale. It is similar to the Ramsay scale, but the Brussels scale levels that correspond to the Ramsay scale levels 4 and 5 are better differentiated (Table 123-2).

The Bispectral Index (BIS) is a processed electroencephalogram (EEG) monitor that measures the hypnotic effects of anesthetics and sedatives. The BIS is an empirical, statistically derived measurement. The BIS monitor reports a single

Table 123–1 Ramsay Scale

Level	Description
1	Patient awake, anxious, and agitated or restless or both
2	Patient awake, cooperative, oriented, and tranquil
3	Patient awake, responds to command only
4	Patient asleep, brisk response to light glabellar tap or loud auditory stimulus
5	Patient asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Patient asleep, no response to light glabellar tap or loud auditory stimulus

Table 123–2 Brussels Sedation Scale

Level	Description
1	Unable to be aroused
2	Responds to painful stimulation (trapezius muscle pinching) but not auditory stimulation
3	Responds to auditory stimulation
4	Awake and alert
5	Agitated

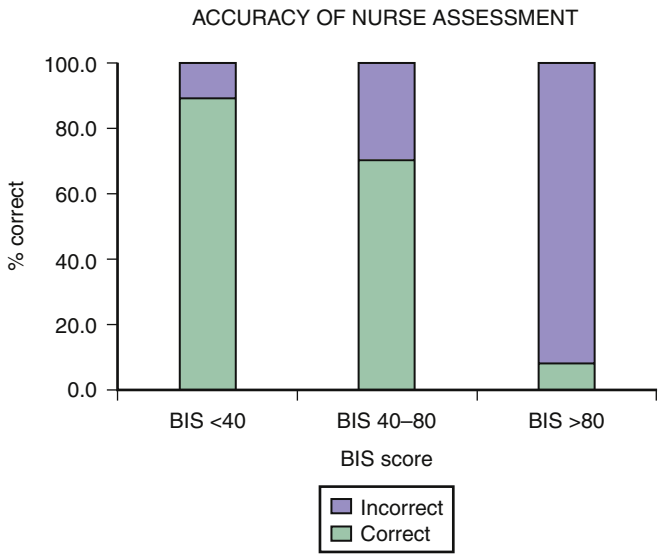

Figure 123–1. Nurse sedation assessment of the paralyzed patient. *BIS,* Bispectral index.

number from 0 to 100 that represents an integrated measure of cerebral electrical activity. The BIS has been validated as a measure of hypnosis in adults in the operating room and ICU.[9] More recently it has been validated in the PICU.[10] The BIS is an exciting new approach to EEG processing. It measures a state of the brain, representing the degree of alertness. It does not measure the concentration of a particular drug.[11] A number of 100 on the BIS score indicates that the patient is fully awake, while a number less than 40 is suggestive of a deep hypnotic effect. A BIS value of less than 60 in surgical patients was not associated with a recall of intraoperative events.[12] The use of the BIS monitor in adult surgical patients and in older pediatric patients has shown a reduction in anesthesia requirements and a shorter recovery time. The BIS monitor has been studied in several adult ICU populations. These studies have shown a correlation between the BIS score and a variety of sedation scores.[13]

One of the main difficulties with clinical sedation scoring systems is their inability to assess depth of sedation in the patient receiving neuromuscular blocking agents (NMBAs). Patients who require NMBAs in the operating room are considered to be at increased risk of awareness during anesthesia.[14] This problem also exists for the sedated patient with paralysis in the PICU. It is well known that the clinical signs of inadequate anesthesia or sedation are not reliable,[15] and many other reasons account for alterations in the heart rate, blood pressure, perfusion, and pupillary responses in the PICU patient. In a study using the BIS in pediatric patients with paralysis,[16] researchers found that in more than 8% of the sedation assessments in which patients were thought to be adequately sedated by the bedside nurse, their BIS scores were greater than 80 (Figure 123-1). This score reflected a significant risk of awareness. The BIS correlates well with the Ramsay scale in the sedated child and may be a useful monitor to prevent inadequate sedation in a child with paralysis.

Although the BIS monitor is used in many institutions, the question of whether its use can prevent awareness under anesthesia is still debated. A recent study enrolled 2000 adults whose anesthesia was either titrated to a BIS score of less than 60 or by the end-tidal inhalational concentration of the anesthetic agent to at least 0.7 minimum alveolar concentration (MAC).[17] Postoperatively all patients were interviewed to assess their intraoperative awareness. This study found two cases of awareness in each group. The MAC values in both groups were the same. The BIS was greater than 60 in one case of awareness. Although the BIS monitor was not able to reduce this low incidence of awareness, the level of anesthesia between the groups was very similar. This study was severely underpowered to show any benefit. However, the combination of end-tidal monitoring and BIS monitoring may be helpful in reducing intraoperative awareness.

Another potential concern with using the BIS monitor is its relevance or reliability for the pediatric patient. Research thus far showing correlation with the myriad of sedation scoring systems used in the PICU is limited by the limitations of these scoring systems. Furthermore, the lack of continuous sedation assessment by these scoring systems, as is possible with BIS monitoring, makes comparison difficult. Also of concern is whether the EEG analysis algorithms used in the BIS monitor are applicable to the pediatric brain. This issue needs further evaluation before the BIS monitor can be considered a "standard" in the PICU. Finally, a limitation of the BIS monitor is that it is less reliable when used with certain hypnotic agents such as ketamine, dexmedetomidine, nitrous oxide, xenon, and opiates.

Other processed EEG sedation assessment monitors are now available. The SNAP IITM monitor[18] uses a different spectrum of EEG frequency analysis. Little difference between the BIS and the SNAP IITM monitors has been shown thus far. Currently little experience has been reported with the SNAP IITM monitor in pediatric patients.

Table 123–3 Classification of Opiate Receptors and Subtypes

Subtype	Prototypic Drugs	Actions
Mu_1	Opiates and most opiate peptides	Supraspinal analgesia including periaqueductal gray matter, nucleus raphe magnus, and locus coeruleus
		Prolactin release
		Acetylcholine turnover in brain
		Catalepsy
Mu_2	Morphine	Respiratory depression
		Dopamine turnover in brain
		Gastrointestinal tract transit
		Most cardiovascular effects
Delta	Enkephalins	Spinal analgesia
		Dopamine turnover
Kappa	Dynorphin	Spinal analgesia
		Inhibition of antidiuretic hormone
		Sedation
Sigma	N-allynormetazocine	Psychotomimetic effects

Modified from Baresh PG, Cullen BF, Stoelting RK et al, editors: *Clinical anesthesia*, ed 2, Philadelphia, 1992, JB Lippincott.

Opioids and Analgesia in the Pediatric Intensive Care Unit

Sedation in the PICU is most commonly achieved with a mixture of opioids and benzodiazepines (BZDs). Although many synthetic and naturally occurring opioids exist, morphine is considered the agent against which others are compared. The primary source of morphine is opium obtained from the opium poppy (*Papaver somniferum*), which also produces alkaloids such as codeine, thebaine, papaverine, and noscapine. Opiates are substances derived from opium; the term opioid also describes substances derived from opiates (e.g., oxycodone) but also includes substances that are created synthetically but have properties that are similar to those of opiates (e.g., fentanyl and methadone) and endogenous ligands. The terms often are used interchangeably because the pharmacologic effects fall into the same category. Opioids are agonists at various opioid receptors, for which several endogenous ligands exist. There are three major classes of receptors: mu (μ), kappa (κ), and delta (δ). The opioid receptors possess the same general structure of an extracellular N-terminal region, seven transmembrane domains, and an intracellular C-terminal tail structure. Subtypes of each receptor (e.g., μ_1, μ_2) exist (Table 123-3), as do less well-characterized opioid receptors ε, λ, τ, and ξ.

Most of the therapeutic and adverse effects can be accounted for by agonist activity at the μ-receptor, which is responsible for analgesia, respiratory depression, pupillary constriction, and euphoria. At the cellular level, μ-receptor activation alters ionic permeability to K^+, causing hyperpolarization and depression of excitability in the neuronal system. Associated effects on cholinergic, adrenergic, serotonergic, and dopaminergic neurotransmitter systems are seen within the central nervous system (CNS). These receptors are found at multiple sites along pain pathways including the spinal cord, midbrain, thalamus, and the cortex. At the spinal cord level, pain reflexes (nociceptive) are depressed by receptors in the substantia gelatinosa, which are mostly presynaptic and inhibit the release of substance P from C-fiber nerve terminals and account for the effectiveness of intrathecally and epidurally administered opioids. In the midbrain the analgesic effect is mediated in the periaqueductal gray matter through ascending fibers and also descending fibers that modulate the function of the dorsal horn. Acetylcholine, γ-aminobutyric acid (GABA), norepinephrine, and serotonin also are involved in these pain-modulating pathways. Peripheral opioid receptors also have been shown and can be expressed in response to inflammation.[19] The intraarticular injection of morphine produces analgesia following arthroscopy through activation of opioid receptors located on white blood cells.[20]

The endogenous ligands for the opioid receptors are the enkephalins, endorphins, and dynorphins. They have a morphine-like effect that can be specifically antagonized by the μ-receptor antagonist naloxone. The endomorphins have potent analgesic and gastrointestinal (GI) effects. At the cellular level, they activate G proteins ([35S] GTP gamma-S binding) and inhibit calcium currents.[21] Pro-opiomelanocortin is the precursor for β-endorphin (as well as adrenocorticotropic hormone and melanocyte-stimulating hormone). β-Endorphin, itself very active, also includes the amino acid sequence for met-enkephalin, although the main precursor is proenkephalin A, which contains four copies of met-enkephalin and one copy of leu-enkephalin. The met-enkephalin sequence also gives opioid activity to a number of other larger peptides. Proenkephalin B (prodynorphin) gives rise to the dynorphin series and contains three leu-enkephalin sequences. Local application of these endogenous substances to the brain provides effects that are similar to those of opiates. They do not function as analgesics because the administration of naloxone does not cause pain in the normal state. They are released during periods of sustained pain, stress, or activity to modulate physiologic pathways, including those involved with pain. Therefore they are probably important to the physiologic condition of the patient in the ICU.

Specific Opioid Agonists

Morphine

Morphine is an opiate, and its primary therapeutic actions are sedation and analgesia; anxiolysis and euphoria also may occur. These four therapeutic effects may be exploited to the benefit of the patient. These actions are mediated through the periaqueductal gray matter, the ventromedial medulla, and the spinal cord. The reduction of nociceptive reflexes occurs all over the body, even below a completely transected spinal cord. In addition to increasing the sensory threshold for pain, morphine may decrease the hurting aspect (or unpleasantness) of pain. A patient given morphine may say something such as, "I have just as much pain, but it doesn't distress me as much." It blunts most types and intensities of pain, although some forms of neuropathic pain are relatively resistant. The resulting analgesia may be potent enough to abolish diagnostic symptoms and signs. The sedative effects reduce higher cortical function, cause difficulty in concentration, and cause

a sense of drowsiness and dream-filled sleep. Higher doses will cause a state of unconsciousness or coma. The rate of respiration is reduced with a resultant fall in minute ventilation despite an accompanying increase in depth of breathing. This effect is associated with a decreased responsiveness to carbon dioxide (CO_2) and is additive to the decreased CO_2 response seen during sleep. In some circumstances respiratory drive may be restricted to hypoxic stimulation of the carotid chemoreceptors; this is the most serious dose-related adverse effect of morphine. It can occur at doses used clinically for analgesia. In general, all opiates produce the same degree of respiratory depression when given in equipotent doses and for any given level of analgesia. Opioids do not have anticonvulsant properties, whereas meperidine (and its metabolite normeperidine) may lower the seizure threshold.

Another CNS effect of morphine is pupillary constriction due to a central effect on the oculomotor nucleus. Nausea results from stimulation of the chemotrigger zone; however, opioids also depress the vomiting center, so the final effect is unpredictable. Nausea and vomiting are much more frequent in ambulatory patients than in patients confined to a hospital bed. Stress-related endocrine responses can be modified by morphine. It decreases the release of several hormones including adrenocorticotropic hormone, antidiuretic hormone, prolactin, growth hormone, and epinephrine. The neuroendocrine stress response that is normally seen with trauma and surgery may be blunted. Itching may be caused by histamine release, but it also may be due to opiate receptor activation in the spinal cord.[22]

Morphine's effects on smooth muscle cause constipation. It reduces the intestinal propulsion activity through its central and peripheral effects. The central effects may be mediated by the vagus nerve. The direct smooth muscle relaxation and the increased local cholinergic transmission can be partly reversed by naloxone. This decreased motility is the basis of several over-the-counter antidiarrheal preparations including diphenoxylate, a μ-agonist that does not cross the blood-brain barrier and thus acts as a peripheral opioid agonist. Morphine also causes an increase in biliary tract tone, which may cause biliary colic, as well as increased tone in the bladder detrusor muscle and vesical sphincter. Urinary retention is common with opioids and occurs in 55% of children receiving spinally administered opioid and 20% receiving intravenous (IV) opioid.[23]

Morphine has been studied extensively in term and preterm neonates. Glucuronidation is present in term babies and in many preterm ones. The half-life of morphine, however, is 2 hours in children, 6.5 hours in term neonates, and 9 hours in the preterm child because of reduced clearance. Volume of distribution did not vary with age.[24] Morphine causes histamine release and can cause peripheral vasodilatation. Infused at analgesic doses, it has little effect on the cardiovascular system, but skin flushing is not uncommon with rapid IV administration. The histamine-releasing potential should be considered in patients with asthma, especially during an acute exacerbation, and in patients with unstable cardiovascular systems for whom safer alternatives, such as fentanyl, exist.

Dosing recommendations in the ICU include a bolus dose of 0.05 to 0.1 mg/kg and an infusion of 0 to 30 μg/kg/h. Fifty percent of these doses should be used if the patient is younger than 3 months of age. The pharmacokinetics of various opiates is outlined in Table 123-4. All opiates are weak bases and are moderately ionized at pH 7.4. Oral morphine is effective but undergoes hepatic first-pass metabolism, which is variable among patients. The oral dose for acute pain is two to five times the IV dose, while with long-term use the oral dose is 1.5 to 2.5 times the IV dose.

Table 123–4 Opiate Pharmacokinetics

Drug	Elimination Half-Life (hr)	Volume Distribution (SS) (L/kg)	Clearance (mL/kg/min)	Protein Binding (%)
Morphine	2.2	3.3	15	30
Meperidine	3.2	2.8	5	58
Fentanyl	3.1	3.2	8	79
Sufentanil	2.7	1.7	13	92
Alfentanil	1.2	0.3	2.8	89

SS, Steady state.
Modified from Baresh PG, Cullen BF, Stoelting RK et al, editors: *Clinical anesthesia*, ed 2, Philadelphia, 1992, JB Lippincott.

Morphine is metabolized to morphine-3-glucuronide (M3G) and M6G in the liver. M3G is the major metabolite and has little morphine-like activity, although some research has suggested that M3G may be associated with an antinociceptive effect, accounting for failure of analgesia during long-term use.[25] In contrast, M6G is many times more potent than morphine itself.

Morphine undergoes significant first-pass hepatic metabolism, whereby after a single parenteral dose, only morphine is initially active. After a single dose by mouth (PO), both morphine and M6G are active. With long-term oral use, M6G accumulates until its analgesic effect is greater than that of morphine. A similar effect can be anticipated with long-term morphine infusion in the patient in the PICU. The glucuronides are excreted by the kidney, together with only a small amount of free morphine. Ninety percent of total urinary excretion occurs within 24 hours.

Tolerance, defined as an increase in the dose required to create the same response, is a potential problem with all opiates. Tolerance is mainly limited to the depressant actions of morphine, including analgesia, respiratory depression, anxiolysis, and drowsiness. Tolerance of morphine's inhibition of bowel motility and pupillary constriction is minimal. The mechanism of tolerance appears to involve the degree and duration of both μ- and κ-receptor occupancy. It appears more rapidly after continuous infusion, and cross-tolerance to other opiates is common, although anecdotal evidence suggests that when opioids are switched, a dose reduction may be possible because cross-tolerance sometimes appears incomplete.[26] Receptor downregulation also may occur, as well as altered metabolism with an increased M3G/M6G ratio. Simultaneous blockade of *N*-methyl-D-aspartate receptors has been shown to be effective in reducing the development of tolerance.[27] Clinical tolerance appears uncommon with an exposure of less than 3 days, but after prolonged administration, doses 10 to 20 times that which would cause respiratory arrest in nontolerant patients may be tolerated.

Meperidine

Meperidine has one tenth the potency of morphine. Compared with other common opioids, meperidine has more CNS excitatory effects including tremors, muscle spasm, myoclonus,

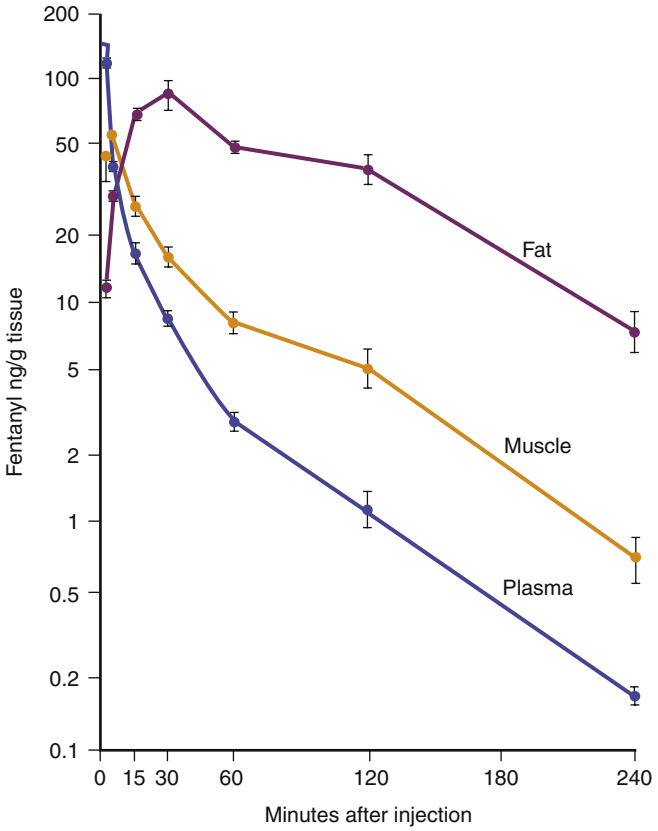

Figure 123–2. Initial fentanyl redistribution.

psychiatric changes, and seizures. These effects may be due to a central serotoninergic effect.[28] It is metabolized by the liver to normeperidine, which is twice as toxic as meperidine and has a longer half-life (15 hours). Normeperidine accumulation is enhanced in patients with an induced cytochrome P450 system. Meperidine has a shorter duration of action (2 to 3 hours) and has a more rapid onset because of its increased lipid solubility compared with morphine. Meperidine is unique among opioids because of its local anesthetic properties, which are capable of providing surgical spinal analgesia.[29] A small dose (0.125 to 0.25 mg/kg) of meperidine may be used to treat postoperative shivering.

Fentanyl

Fentanyl is one of the most commonly used opiates in the ICU. It is a synthetic derivative of meperidine without many of its unwanted side effects. It is a potent μ-agonist and is 100 times more potent than morphine. It has a rapid onset and cessation because of its high lipid solubility (Figure 123-2). Fentanyl may be administered by several routes, including IV, intramuscular (IM), transmucosal,[30] and subcutaneous (SC) when venous access is inadequate. Skeletal muscle rigidity (which can occur with all synthetic opiates) is well described in the literature. It is mediated through the CNS and is an idiopathic response usually associated with a large bolus dose (≥5 μg/kg). It improves with the administration of NMBAs and is reversible with naloxone. Fentanyl has limited cardiovascular effects. Moderate bradycardia is the most common hemodynamic effect. Fentanyl does not cause histamine release. Dosing in the ICU is either by bolus (1 to 2 μg/kg) or infusion (1 to 4 μg/kg/h with higher doses as tolerance develops). The short duration of effect of a single dose of fentanyl is not due to metabolism but rather to rapid redistribution. Maximum brain concentration after a bolus is achieved within 90 seconds. Then, because of rapid redistribution, the plasma level falls by 50% in 30 minutes, and the result is a clinical duration of effect of a single dose of approximately 30 minutes. Fentanyl then accumulates in fat, where it is stored and slowly released with a longer elimination half-life of about 4 hours (longer than morphine). Marked respiratory depression occurs within 120 seconds, and a single dose of 5 μg/kg will cause apnea in 50% of patients. Also, fentanyl is metabolized by the liver to nor-fentanyl and hydroxy fentanyl derivatives, both of which are thought to be inactive. In the operating room, high-dose fentanyl is commonly used for cardiac anesthesia and for anesthetization of other unstable patients. A loading dose of 50 μg/kg, followed by 0.5 μg/kg/min, will occupy all opioid receptors and produce a state of anesthesia. Many cases of awareness with patients under anesthesia have been documented, however, even when these high doses of fentanyl were used.

Sufentanil

Sufentanil is another synthetic opiate that has actions and therapeutic effects that are similar to those of fentanyl. It is five to ten times more potent than fentanyl and is the most potent opioid in clinical practice, posing a high risk of apnea with bolus administration. Dosing recommendations include bolus dosing of 0.2 to 0.4 μg/kg or an infusion of 0.2 to 1 μg/kg/h.

After a single bolus, sufentanil has kinetics similar to that of fentanyl with a short duration of clinical effect of approximately 30 minutes. However, with prolonged use, sufentanil accumulates less and is associated with a more rapid recovery after infusion because of its smaller volume of distribution and similar clearance. When the patient is receiving high doses of fentanyl, sufentanil is useful to conserve infusion volume.

Alfentanil

Alfentanil is another synthetic opiate with a rapid onset. It is five times less potent than fentanyl. Although it is less lipid soluble than fentanyl because of its low pKa (negative logarithm of the acid ionization constant), a higher percentage of the drug is present in the active unionized form, which results in a rapid onset. Because of its low volume of distribution, alfentanil has a short elimination half-life, which results in a short duration of action (5 to 10 minutes). Dosing regimens include boluses of 5 to 10 μg/kg if there is spontaneous respiration or 20 to 50 μg/kg if the patient's lungs are ventilated. Alfentanil is a useful agent for preventing the hypertensive or increased intracranial pressure (ICP) response to intubation. As with all synthetic opiates, there is a risk of muscle rigidity with the higher dosing. Infusion dosing includes 0.2 to 1 μg/kg/min for patients receiving mechanical ventilation. Postinfusion recovery is quicker with alfentanil than with fentanyl. It is useful by infusion and safe to use in patients with hepatic or renal failure.

Codeine

Codeine has a chemical structure and effects that are similar to those of morphine and is commonly used as an oral medication for cough suppression or mild to moderate pain relief. A

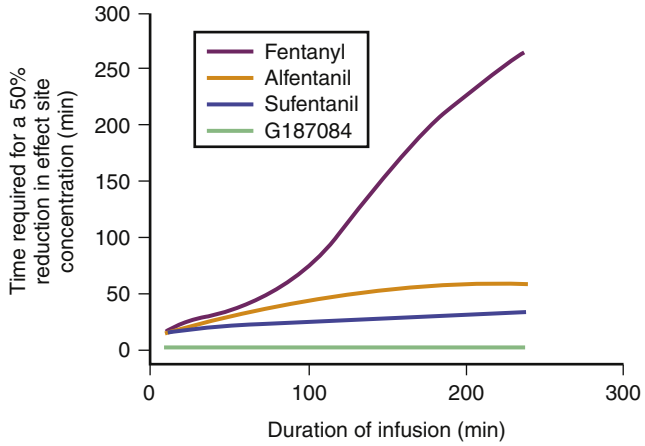

Figure 123–3. Context-sensitive half-life.

large part of its effects are due to the metabolism of codeine to morphine. Ten to twenty percent of patients lack a metabolic pathway to convert codeine to morphine, which results in an unpredictable effect. Dosing is 0.5 to 1 mg/kg. Constipation is a major adverse effect, and some patients report having a vague peculiar or unpleasant feeling when they take codeine. This drug can be habit-forming. It can be given orally, IM, or rectally. Rapid IV use may result in cardiovascular collapse. Rectally administered codeine has been shown to have as rapid an onset as IM codeine, but it yields lower peak levels in children.[31] Codeine has been the analgesic of choice by neurosurgeons because of the belief that pupillary signs are maintained with use of this drug. Morphine has been shown to be a more effective analgesic, however, in patients with head injuries.[32]

Remifentanil

Remifentanil is one of the newest synthetic opiates available. It was designed to be metabolized by plasma esterases to provide a short half-life. It is a potent μ-agonist with mild κ and δ effects. It is substantially more potent than fentanyl. It is supplied as a white lyophilized powder that contains glycine (it should not be used for epidural or spinal analgesia). The metabolism is by nonspecific esterases not affected by pseudocholinesterase deficiency. The metabolite, a weak μ-agonist, is excreted by the kidney. The kinetics of remifentanil is different from those of most opiates used in the ICU. It has a short half-life that is due to metabolism rather than to redistribution. Therefore remifentanil has what is known as a context-sensitive half-life. The elimination half-life for remifentanil is about 8 minutes. With an infusion of remifentanil, the half-life does not increase but remains constant. With opiates such as fentanyl and alfentanil (Figure 123-3), the clinical effect half-life increases with time until it reflects the elimination half-life of between 2 and 4 hours.

Kinetics reported for neonates are similar to those reported for adults. The continuous infusion rate depends on the degree of sedation/analgesia required (0.1 to 0.5 μg/kg/min for sedation; 0.75 to 2 μg/kg/min for balanced anesthesia; 4 μg/kg/min for loss of consciousness). Remifentanil has effects on the cardiovascular system that are similar to those of fentanyl. Remifentanil causes a mild bradycardia and a slight decrease in blood pressure,[33] which may be prevented with glycopyrrolate. No histamine release occurs. Remifentanil is a potent respiratory depressant. For spontaneous respiration, a low continuous infusion dose (without a bolus) should be used (0.1 μg/kg/min). Sedation can be effectively managed by continuous infusion without the need for a bolus because of the short half-life. An increase or decrease of infusion rate is rapidly reflected by a change in the degree of sedation, which is important to note. Most other opiate sedatives require bolus dosing to achieve a rapid change in effect. This type of dosing is neither appropriate nor needed for remifentanil.

Remifentanil has the usual opiate adverse effects; however, because of the short half-life, they have only brief clinical effect. Remifentanil may prove to be a safe and effective choice for PICU sedation in patients with severe renal or hepatic disease; however, the potential exists for glycine accumulation in patients with renal failure. It is an option only for those who require overnight ventilation or for those patients in whom a rapid awakening may be required for neurologic assessment. Remifentanil has been shown to reduce cerebral oxygen use and reduce cerebral blood flow if the CO_2 is maintained in a normal range.[34] Remifentanil is currently an expensive option and should not be considered for every patient. Also, because of its short duration, the postoperative patient may need an alternative analgesic after extubation. Rapid development of opiate tolerance with remifentanil has been described in healthy volunteers[35] and also when used in the ICU setting. This rapid tolerance has also been described in postoperative scoliosis patients[36]; however, the increased morphine requirements described probably reflect the initial postoperative need to achieve an adequate morphine blood level rather than any acute tolerance.

Hydromorphone

Hydromorphone is a hydrogenated ketone of morphine. It is seven times as potent as morphine with a similar onset and duration of action. It causes less histamine release than morphine and may be used in patients who report pruritus due to morphine. Like morphine, hydromorphone undergoes hepatic metabolism; however, there are no active metabolites that are dependent on renal excretion. As such, it may be an effective alternative in patients with renal insufficiency or failure.

Tramadol

Tramadol is an opiate analgesic that relieves pain by binding to opiate receptors and by inhibiting the reuptake in the CNS and spinal cord of norepinephrine and serotonin, two pain-modifying neurotransmitters. Tramadol does not have antiinflammatory effects. Its use is indicated in cases of moderate to severe pain.[37] Despite being a narcotic-like agent, the Food and Drug Administration (FDA) has not classified tramadol as a controlled substance. Dosage (not FDA approved for patients younger than 16 years) is an initial oral dose of 1 to 2 mg/kg every 6 hours and should not exceed 6 mg/kg/day. An IV preparation is available outside of the United States. Patients with a creatinine clearance less than 30 mL/min should not receive a dose more often than once every 12 hours, with a maximum dose of 3 mg/kg/day. The dose for patients with cirrhosis or hepatic dysfunction is 1 mg/kg every 12 hours. Patients undergoing dialysis can receive their dose on the day of dialysis because only 7% of the drug is

removed by the process. The adverse effects of tramadol most often involve the CNS and the GI tract. Patients may become dependent on tramadol. Abuse is possible, and it should not be given to opiate-dependent patients. Seizures have been seen in patients receiving high single oral doses of 10 mg/kg; this danger is even greater in patients with epilepsy and in anyone taking monoamine oxidase inhibitors and neuroleptic agents that lower the seizure threshold. Respiratory depression may occur if the recommended dosage is consistently exceeded or if another centrally acting depressant drug (e.g., alcohol) or an anesthetic is given concurrently. Because of the possibility of withdrawal symptoms, patients should not abruptly discontinue use of tramadol. Tramadol is not a useful drug for sedative action.

Table 123-5 provides conversion doses for some commonly used oral opiates. A summary of IV doses of different opiates is provided in Table 123-6.

Opiate Antagonists

Several opiate antagonists are available. The most commonly used is naloxone, which is a specific and sensitive receptor antagonist of all opiate receptors. Dosing can be either low dose (1 μg/kg) or high dose in an emergency situation (10 μg/kg). If the drug cannot be administered intravenously, then it can be given intramuscularly, intranasally, or into the midventral surface of the tongue. When naloxone is being used for a long-acting agonist, an infusion may be necessary because its half-life is only 30 to 81 minutes (mean of 64 ± 12 minutes). In neonates, the half-life has been reported as 3.1 ± 0.5 hours; however, this prolonged effect is likely to be offset by a concomitant increase in the duration of action of the opioid for which the naloxone is given. No effect is seen in the healthy patient in the absence of administered opioids; however, in the setting of sepsis in the ICU, a vasopressor effect may occur, presumably because of an interaction with endogenous opioids released in response to stress. Nalmefene, a longer-acting antagonist, can be given through IV, IM, and SC routes. It has a redistribution half-life of 41 minutes and a terminal half-life of 10.8 hours in adults and somewhat less in children. Thus reappearance of the antagonized opioid is unlikely if it is given in an adequate dose.[38]

Table 123–5 Dose Equivalents: Short Acting

Drug	Oral	Parenteral
Morphine	0.5 mg/kg q4h	0.15 mg/kg q3h
Hydromorphone	0.1 mg/kg q4h	0.02 mg/kg q4h
Codeine	4 mg/kg q3h	
Hydrocodone	0.5 mg/kg q3h	
Oxycodone	0.5 mg/kg q3h	
Meperidine	5 μg/kg q2h	1.5 mg/kg q2h
Fentanyl		1.5 μg/kg q2h

Incidental Pain Syndromes in the Pediatric Intensive Care Unit

In addition to the techniques used to sedate children to facilitate their PICU management, many children will have pain related to their underlying condition. Many different options are available for controlling pain in the pediatric patient (Box 123-1). The pharmacologic management of pain should follow the traditional World Health Organization analgesic ladder, which begins with a nonopioid analgesic such as a nonsteroidal antiinflammatory drug or acetaminophen, followed by a weak opioid such as hydrocodone added to the nonopioid, and then moves on to a strong opioid such as morphine or hydromorphone as needed. When taken orally, a sustained-release preparation is often useful once the dose requirement has been determined. The dose requirement of a strong opioid is variable in the patient taking opioids for a prolonged period, and failure to appreciate this variability is a common cause for therapeutic failure. In addition, once a dose requirement is known, the analgesic should be given to preempt pain rather than to relieve pain as required. At each level of analgesic use, the addition of adjuvant medications should be considered. Adjuvant drugs fall into six groups: antidepressant, anticonvulsant, neuroleptic, steroid, stimulant, and local anesthetic. Of the tricyclic antidepressants, nortriptyline is available in a liquid form. The tricyclic antidepressants are indicated for neuropathic pain, particularly when the patient describes a burning pain. Also useful for neuropathic pain are the anticonvulsant agents gabapentin, pregabalin, and carbamazepine. These drugs often work best when the pain is described as shooting or lancinating. Neuropathic pain may result from tumor invasion, vincristine therapy, cytomegalovirus

Table 123–6 Summary of Opiate Dosing

Drug	Relative Potency	Bolus Dose	Initial Infusion Rate	Active Metabolites
Morphine	1	0.1 mg/kg	0.04 mg/kg/h	M6G
Meperidine	0.1	1 mg/kg	NA	Normeperidine
Fentanyl	100	1 μg/kg	1 μg/kg/h	None
Hydromorphone	7	0.015 mg/kg	0.005 mg/kg/h	None
Sufentanil	500	0.2 μg/kg	0.2 μg/kg/h	None
Remifentanil	NA	NA	0.1 μg/kg/min	None
Alfentanil	10	10 μg/kg	10 μg/kg/h	None
Methadone	1	0.1 mg/kg	NA	None

M6G, Morphine-6-glucuronide; *NA*, not applicable.

Box 123–1 Options for Controlling a Child's Pain

Analgesics
Opioids—weak, potent
NSAIDs
Nonopioids

Anesthetics
Regional block
Epidural anesthesia
Topical anesthesia

Physical
Thermal
Massage
Physical therapy
TENS

Cognitive
Imagery
Distraction
Hypnosis
Choices and control
Information
Role play

Behavioral
Biofeedback
Relaxation therapy

NSAIDs, Nonsteroidal antiinflammatory drugs; *TENS*, transcutaneous electrical nerve stimulation.

infection, or human immunodeficiency infection. Neuroleptic drugs, including chlorpromazine and trimeprazine, may be useful in the management of nausea, anxiety, and pruritus. Steroids benefit mood, inflammation, nausea, appetite, nerve swelling/entrapment, and vasculitis. When opioid sedation is interfering with quality of life, a stimulant such as an amphetamine may restore energy and alertness while allowing ongoing analgesia from the opioid. Sometimes pain can be managed by local anesthetic, placed by peripheral nerve block, topically, or as a neuraxial block.

Patient controlled analgesia (PCA) has become the mainstay of postoperative pain relief in children because of its efficacy and safety. However, its use is limited by the child's ability to understand how to use the PCA pump. Proxy PCA (PCA-P) has been used for younger children or those with cognitive impairment.[39] The use of the PCA by the nurse or the caregiver may override the "safety net" that the PCA has. The use of PCA-P has been associated with greater need for rescue interventions; however, it is often used in sicker children. When PCA-P is used, careful evaluation and rigorous monitoring is needed.

Sickle Cell Crisis

Sickle cell disease differs from cancer and acquired immune deficiency syndrome in that intermittent episodes of severe pain occur, requiring urgent intensive treatment. A good review of this subject has been published.[40] Chronic pain also may be present because of long-term tissue and bone damage from periods of ischemia during past crises, including persisting myocardial ischemia. Patients may be receiving long-acting opioids or may have had repeated exposure to opioids with past crises. Patients with a sickle cell disease crisis that involves the chest or brain are likely to be admitted to the PICU. Chest crises result from the sickling of erythrocytes in the pulmonary vasculature and result in hypoxia to the rest of the body and local lung damage. The systemic hypoxia worsens the crisis and is thus self-perpetuating. Chest radiograph changes may be late, and an associated paralytic ileus may be present. Poor pulmonary function may discourage the practitioner from using adequate opioid analgesics out of concern for worsening the hypoxia. However, it is important not to underestimate the need for pain relief and to appreciate that past opioid exposure may have resulted in tolerance to opioids. If IV access is difficult to obtain, morphine may be given subcutaneously or orally. Anecdotal success also has been reported with nebulized morphine.[41]

Opiate Tolerance

The use of opiate infusions in the ICU is associated with the potential for the development of tolerance or dependence.[42] Iatrogenic withdrawal symptoms can occur if the opiates are discontinued abruptly. These effects have been shown to be related to the total dose and duration of fentanyl infusion. A fentanyl infusion of 5 days or a total cumulative dose of 1.6 mg/kg during the hospital stay was associated with a 50% chance of the development of narcotic withdrawal, whereas a fentanyl infusion of 9 days or longer or a total cumulative fentanyl dose of 2.5 mg/kg or more during the hospital stay had a 100% incidence of withdrawal.[43] The rising plasma fentanyl levels caused by increased dosing suggested that increased metabolism or clearance was not responsible for the development of tolerance. A study of patients in a PICU to determine the degree of opiate tolerance has shown a significant increase in opiate dosing required for adequate sedation.[44] The opiate infusion increased by about 80% per week for the first 3 weeks of opiate use. No difference in the rate of opiate increase was found with respect to age of the patient, postoperative status, mode of ventilation, and paralysis.

For patients considered to be at risk of withdrawal, several options are available. If circumstances allow, it is better to start the treatment for withdrawal prevention before the patient has symptoms and signs of withdrawal. Opiate withdrawal is not usually a serious medical problem; it is rarely life-threatening and is self-limited. However, treatment should be started early if possible for patient comfort. In a few circumstances the associated hypersympathetic state may not be good for the patient. The signs and symptoms of withdrawal are nonspecific, and other causes, such as infection, hypoglycemia, hypocalcemia, hyperthyroidism, and hypoxia, should be excluded. Because of the nonspecific nature of the symptoms of opiate withdrawal, several scoring systems have been described to aid with the diagnostic process. The Finnegan score is based on 31 variables and is lengthy. The Lipsitz score is shorter and easier to use than the Finnegan score. Both of these scoring systems, however, were devised for use with neonates, and several of the measurements are not appropriate for patients in the PICU. Currently no validated scoring system exists for assessing opiate withdrawal in the pediatric patient. In the limited number of articles in which opiate withdrawal in the PICU is evaluated, the authors have modified these scores (Table 123-7) in an attempt to provide an objective assessment of the patient.

Recently the assessment of a new score based on a similar set of signs and symptoms, the Withdrawal Assessment Tool,[45] has been proposed. The bedside nurse reviews the patient's chart for the previous 12 hours and performs a short assessment of the child's level of agitation, as well as other signs/symptoms. This review is then followed by an assessment of the response to stimulus and also how quickly the child settles down after the stimulus. A score of 1 is assigned to each assessment (maximum, 12). A score of greater than 3 was associated with a greater likelihood of drug withdrawal. Although this score is new and has limited verification, it probably provides

Table 123–7 Signs and Symptoms of Opiate Withdrawal

Sign/Symptom	Examples
Neurologic excitability	Sleep disturbances
	Agitation
	Tremors
	Seizures
	Choreoathetoid movements
GI disturbances	Vomiting
	Diarrhea
	Autonomic dysfunction
Hypertension (>150 mm Hg)	Tachycardia (>150 mm Hg)
	Tachypnea (>40 beats/min)
	Fever (>38.58° C)
	Frequent yawning
	Sweating
	Goose flesh
	Mottling

GI, Gastrointestinal.

a better evaluation than just the clinician's "bedside" opinion, especially in complex cases in which both opiate and BDZ withdrawal may occur together.

Several therapeutic options are available for the prevention and treatment of opiate withdrawal. Drugs from the same class are preferable. The FDA has approved methadone for opiate withdrawal. Other agents that may be useful include morphine, clonidine, dexmedetomidine, phenobarbital, paregoric, chlorpromazine, transdermal clonidine patch,[46] and SC fentanyl. Paregoric contains morphine plus papaverine, noscapine, camphor (a CNS stimulant), ethanol (45%), benzoic acid (which competes with bilirubin-binding sites), and glycerin (which causes diarrhea). Paregoric has been used for neonatal withdrawal, but because of its composition, it may cause adverse effects. Chlorpromazine may be useful for GI adverse effects, but hypothermia and hypotension may occur. Haloperidol also may be of use, having minimal respiratory depression and no active metabolites. It also offers cardiovascular stability. Phenobarbital has been used for hyperactive behavior; however, it can cause significant CNS depression, it induces drug metabolism, and it is tolerance/dependence forming.

Methadone seems to be the most suitable agent for treating opiate withdrawal. It has an oral bioavailability of 80% to 90% and an elimination half-life of 12 to 24 hours. It is equipotent to morphine. Methadone has inactive metabolites and is less sedating than morphine while remaining an effective analgesic. Because of its higher bioavailability and reduced first-pass metabolism, the effect of oral doses is more predictable than that of morphine. Methadone has been extensively used in the outpatient management of patients addicted to opiates.

The convenience of the oral route, the less-frequent dosing because of its longer half-life, and the ease of calculating doses because of its equal potency to morphine make methadone attractive for use in the management of opiate withdrawal in children. However, a huge variability exists in recommendations regarding the methadone dose that should be used to prevent opiate withdrawal in children. Several factors are important in the dosing of methadone for conversion from fentanyl. After prolonged IV administration, fentanyl has a potency 100 times that of methadone; it has a metabolic half-life approximately one quarter that of methadone; and if given intravenously, it has a bioavailability 20% greater than orally administered methadone. In a study in which the effectiveness of a fentanyl-methadone conversion protocol was assessed, researchers found that giving 2.4 times the daily fentanyl dose as methadone prevented withdrawal symptoms.[42] The methadone was given intravenously for 24 hours, and the fentanyl dose decreased by 50% on day 1 and by another 50% on day 2, and then it was discontinued. On day 3, the methadone was converted to oral dosing. The methadone was given intravenously initially. Because of its long half-life, oral dosing could take up to 5 days to reach a steady state. The duration of methadone requirement varied from 1 to 4 weeks, depending on the duration of opiate infusion. Methadone was being weaned by 3% to 15% per day with no signs of withdrawal. To date, there have been no published cases of respiratory arrest when methadone has been used for opiate weaning. However, it would appear prudent to initiate the conversion from fentanyl to methadone in the ICU environment in the event that problems arise and to ensure that an adequate dose is given. Once stabilized, the patient may be transferred to the floor and ultimately home, with a clearly described plan for decreasing the methadone dose over time. The weaning plan also should involve the home pediatrician so that patients have access to someone who is familiar with the process. In a follow-up of patients who had received methadone while in the ICU, 38% of patients were discharged home during the weaning process. No problems were associated with the weaning of methadone at home. Stigma regarding methadone use was not expressed by any of the parents.

The use of a clonidine patch also has been evaluated in the PICU. Clonidine has been shown to be effective in the management of nicotine, opiate, and alcohol withdrawal. It decreases sympathetic outflow from the CNS and has a synergistic effect for analgesia, both at the central and spinal level. In one report, eight patients were described after tracheal reconstructive operations. They required postoperative sedation and ventilation for 7 days, which put them at high risk for withdrawal.[20] A clonidine patch was applied 12 hours before extubation, and the patients were weaned off the opiate. The dose used was approximately 6 μg/kg/day of clonidine, and the patch was left on for 7 days. One patch had to be removed because of hypotension. The patch seemed to be effective in preventing withdrawal. Use of the clonidine patch is attractive because of its noninvasive approach, which is desired. However, the use of a transdermal patch prevents titration of effect, and problems with bradycardia, hypotension, hypothermia, sedation, and dysrhythmia may occur.

A confounding issue in many publications and in the clinical management of opiate withdrawal is the potential for simultaneous BZD withdrawal. Most researchers have not been able to separate these two issues. The symptoms of BZD withdrawal differ from those of opiate withdrawal because the BZD symptoms generally include less sympathetic activation. BZD withdrawal symptoms are characterized by agitation and a movement disorder. If BZD withdrawal is a concern, low-dose lorazepam or diazepam may be added to the withdrawal

Table 123–8 Pharmacokinetics of Benzodiazepines

Drug	Elimination Half-Life (hr)	Volume Distribution (SS) (L/kg)	Clearance (mL/kg/min)	Protein Binding (%)
Diazepam	46.6	1.13	0.4	97.8
Midazolam	3.0	1.09	7.5	94
Lorazepam	14.5	1.1	1.1	91
Flumazenil	0.67	1.2	15.3	50

SS, Steady state.

management strategy (Table 123-8). A prospective study of BZD withdrawal[47] following lorazepam infusion (up to 0.3 mg/kg/h) documented BZD withdrawal syndrome in approximately 25% of the children. This withdrawal occurred even when using a 6-day tapering of the lorazepam dose. All the children had been previously weaned off fentanyl infusions. No predisposing risk factors were found for BZD withdrawal with respect to BZD or opiate dosing or duration.

Rapid Opiate Detoxification

Reports have been made of rapid opiate detoxification in the ICU. These procedures have used a form of deep sedation (often with use of propofol or another anesthetic agent) to facilitate opioid withdrawal in patients addicted to the recreational use of opiates.[48] The patients are given high doses of opiate antagonists to displace all opiates from the receptors and then heavy sedation is initiated to reduce the occurrence and effects of the sympathetic stimulation observed with short-term opiate withdrawal. These procedures have been safely performed in the ICU; however, there have been several reports of complications[49] when these procedures were not performed with full ICU support. Currently the effectiveness and safety of 1-day opiate detoxification is still an area of debate.[50] If used, however, it should be combined with an established long-term support plan to optimize long-term success.

In the PICU, deep sedation with propofol has been used to facilitate rapid opiate weaning of ventilator-dependent patients.[51] The use of propofol for up to 3 days allowed a reduction of fentanyl dosing from 24 to 9 μg/kg/h (a 65% reduction). No signs or symptoms of opiate withdrawal were noted, and metabolic acidosis did not develop. Opiate antagonists were not used for this rapid weaning process. However, concern has been raised regarding the long-term administration of propofol, especially in the PICU patient, given the development of the propofol infusion syndrome.

Benzodiazepines

BZDs are among the most commonly used agents for sedation in the ICU. They augment the function of the GABA type A ($GABA_A$) receptor at the postsynaptic membrane. This pentameric protein controls a chloride channel, the opening of which leads to an inhibitory effect due to hyperpolarization of the cell membrane.[52,53] Benzodiazepines bind to BZD receptors, which in the CNS are usually found as part of the $GABA_A$ receptor, enhancing the effect of endogenous GABA.[54] Peripheral BZD receptors[55] are not usually associated with the $GABA_A$ receptor but are a binding site for diazepam and midazolam. These 18-kDa proteins are associated with regulation of cellular proliferation, immunomodulation, porphyrin transport, heme biosynthesis, and anion transport. In particular, they seem important in the regulation of steroid synthesis and apoptosis, and they have a significant effect on the hypothalamic-pituitary-adrenal axis.[56] These latter effects may be pertinent to the physiologic care of patients in the ICU.

BZD receptors are bound by a family of endogenous peptides called endozepines, which have similar effects to the BZDs.[57,58] The expression of this diazepam-binding inhibitor may be relevant to the development of dependence not only on BZDs but also on alcohol and opioids[59] and may therefore be relevant in the drug dependence commonly seen in patients in the PICU who are given these agents continuously. Naturally occurring BZDs have been detected with structures similar to those used clinically.[60] Subsets of $GABA_A$ receptors have been shown to have different effects. Type 1 receptors were responsible for sedation and anterograde amnesia, whereas type 2 receptors mediated anxiolysis. It may be possible to develop selective subtype receptor agonists to provide anxiolysis without sedation, amnesia, or dependence.

The general pharmacologic effects of BZDs are sedation, anxiolysis, euphoria (limbic system), reduced skeletal muscle tone (through spinal BZD receptors), anticonvulsant properties, and neuroendocrine effects. They impair acquisition and encoding of new information, providing anterograde amnesia. They do not have any analgesic properties. They have little direct effect on ICP. Their effects are dose dependent. Patient cofactors including age, concurrent disease, and any cosedation therapy influence responses to BZDs. Paradoxical reactions are reported in which agitation rather than calming is observed.[61] In healthy patients, BZDs have few cardiovascular adverse effects, but in a sick, intensive care population, profound cardiovascular depression may be observed occasionally. BZDs should be used judiciously until the patient response is known.[62] Midazolam has been most often associated with this effect,[63] and research in dogs has shown both negative inotropy and chronotropy, especially when the sympathetic response has been abolished.[64] Clinical use is largely encompassed by discussion of the pharmacologic properties of diazepam, midazolam, and lorazepam.

Specific Benzodiazepines

Diazepam

The first widely used BZD in the ICU was diazepam. Because of its low solubility in water, it is available in the IV or IM form dissolved in propylene glycol. This formulation causes a significant amount of pain and thrombophlebitis with peripheral IV use. A lipid emulsion that has fewer adverse effects is available in the United Kingdom. Diazepam is inexpensive and is effective for short-term sedation; in such cases, accumulation is less of a concern. Diazepam may be given orally because it has good absorption, but absorption tends to be erratic when it is given rectally or intramuscularly. It is highly lipid soluble with a long half-life (24 hours). Metabolism by oxidative biotransformation generates several hypnotically active metabolites with an elimination half-life that may be longer than diazepam, including oxazepam (half-life, 10 hours) and n-dimethyldiazepam (half-life, 93 hours). Delayed recovery has been reported in neonates after they received diazepam,

possibly because of the long half-life of dimethyldiazepam.[65] Prolongation of effects occurs in patients when clearance is reduced because of hepatic dysfunction and when metabolism is inhibited by drugs such as cimetidine and omeprazole.

Midazolam

Midazolam is an imidazobenzodiazepine. It has a short elimination half-life of 2 hours and is water soluble, which means that IV injection is nonirritating. Because of these factors, it has become popular in ICUs for sedation by infusion. Intranasally (0.2 mg/kg), midazolam has proven to be as effective at controlling febrile seizures as IV diazepam (0.3 mg/kg).[66] It has extensive first-pass metabolism and provides less reliable results when given PO, although this route is often successfully used for premedication of children before general anesthesia in doses of 0.5 to 0.75 mg/kg (maximum, 20 mg). It is available in a pleasant-tasting cherry syrup and is effective in 10 to 15 minutes, providing up to 1 hour of adequate anxiolysis, although residual hangover effects may persist.[67] Rectal and sublingual administration has been described.

Midazolam is about eight times more potent than diazepam, with starting dose recommendations of a bolus dose of 0.05 to 0.1 mg/kg[68] and an infusion of 1 to 6 μg/kg/min. Midazolam is metabolized by the cytochrome P450 system subfamily IIIA (nifedipine oxidase), polypeptide 4 (CYP3A4),[69] to hydroxymidazolam (63% potency) and hydroxymidazolam glucuronide (9% potency). Because of the high degree of protein binding (94% protein bound), the free level can be significantly changed with interactions because of the protein binding, which also may occur with heparin. Hepatic or renal failure increases the free fraction by two to three times, and its effect also can be prolonged by the accumulation of active metabolites.[70] The half-life of midazolam in patients in the ICU may be prolonged compared with that in healthy patients.[71] With short-term infusions (<12 hours), it retains a rapid recovery; however, with increased duration of use, the recovery becomes prolonged. Its clearance may be reduced by several commonly used ICU drugs, including calcium channel blockers, erythromycin, and triazole antifungal agents.[72]

Lorazepam

Lorazepam is an alternative water-soluble agent that is well absorbed after both oral and IM administration.[73] It produces sedation for 4 to 8 hours after a single dose. Lorazepam has a slower onset than does midazolam. The elimination half-life is about 14 hours. Metabolism is by glucuronyl transferase, not the cytochrome P450, and there are no active metabolites. This metabolism is unaffected by cimetidine or phenobarbital, which only affects oxidative metabolic pathways. Sodium valproate may inhibit its metabolism.[74] In persons with advanced liver disease, these phase II glucuronidation reactions are better preserved, and the increased half-life seen is due to increases in the volume of distribution rather than to reduced clearance. In patients with renal failure, prolonged half-life is also due to reduced protein binding because clearance is unchanged. No change in metabolism occurs with aging or critical illness. In a comparison of infusions of midazolam and lorazepam, the recovery characteristics were found to be significantly different. In patients receiving lorazepam, it took an average of 260 minutes to return to baseline, whereas in patients receiving midazolam, it took more than six times longer to return to baseline. Lorazepam may be administered by bolus (0.05 to 0.1 mg/kg every 2 to 4 hours) or by infusion (0.05 mg/kg/h). Lorazepam is slightly less expensive than is midazolam.[75] It has been recommended as the BZD of choice for long-term sedation because of its more predictable recovery profile in sick patients in the ICU. Lorazepam for IV use has propylene glycol as a carrier. Risk of a metabolic lactic acidosis exists because of the metabolism of this carrier. Cases of fatal metabolic acidosis from propylene glycol have been reported in neonates taking a particular vitamin preparation. Several other potential ICU drugs may use propylene glycol as a carrier, including some IV preparations of phenytoin and phenobarbital, nitroglycerin, digoxin, and etomidate. Reports of propylene glycol toxicity in adults who received multiple propylene glycol infusions have been made.[76] Care should be taken when lorazepam is infused in patients who receive these other medications. In patients in the PICU, propylene glycol levels have been shown to correlate with the dose of lorazepam received; however, no metabolic abnormalities were detected.[77] Hemodialysis has been used successfully in the management of the lorazepam-associated propylene glycol toxicity.[78]

The metabolisms of different BZDs are intertwined with each other. Most of the agents require an oxidative process first with potentially active compounds before glucuronidation and excretion. The pharmacokinetics for different BZDs is shown in Table 123-8.

Tolerance and Dependence to the Benzodiazepines

Tolerance for and dependence on BZDs can occur as with opiates in the PICU.[79] This effect is not all due to receptor number downregulation.[80] Withdrawal symptoms may be avoided with a slow taper of the medication of 10% per day or by substituting a long-acting oral agent such as diazepam. Acute withdrawal symptoms may include anxiety, insomnia, nightmares, seizures, psychosis, and hyperpyrexia. A postmidazolam infusion phenomenon has been described that includes poor social interaction, decreased eye contact, and a decreased interest in the surroundings. The patient may exhibit choreoathetotic movements with dystonic posturing that can persist for 2 to 4 weeks but will resolve with no sequelae.

Flumazenil

Flumazenil is an imidazobenzodiazepine and is a specific competitive antagonist of the BZD receptor. It has no effect on other drugs such as barbiturates, ethanol, or other GABA-mimetic agents. Flumazenil reverses the hypnotic and sedative effects of BZDs. It has a half-life of approximately 1 hour after a single IV bolus. In patients with hepatic impairment, its half-life and clearance are prolonged, and a significant increase (>50%) of free drug occurs because of reduced plasma protein binding. Renal failure has little effect on the pharmacokinetics of flumazenil. It is indicated for the complete or partial reversal of the central sedative effects of BZDs. Contraindications include patients who have a known hypersensitivity to BZDs, patients with epilepsy who are receiving treatment with BZDs, and persons who have overdosed with a tricyclic antidepressant. The use of flumazenil is often associated with mild to moderate tachycardia and hypertension.

In cases of multiple drug overdose, the use of flumazenil remains controversial. It often is overused in the emergency setting without due concern for potential adverse reactions[81] because of the potential toxic effects (e.g., cardiac arrhythmias or convulsions) of other psychotropic drugs ingested. The toxicity of tricyclic antidepressants becomes apparent as the effects of BZDs are antagonized. Patients should be evaluated for the signs and symptoms of a tricyclic antidepressant overdose; an electrocardiogram (ECG) may be helpful in determining the risks involved.

The dosing information for pediatric patients is limited. The initial suggested dose is 0.01 mg/kg (maximum, 0.2 mg) with incremental doses of 0.005 to 0.01 mg/kg (maximum, 0.2 mg) given every minute up to a maximum cumulative dose of 1 mg. The lower doses are suggested for sedation reversal and the higher doses for BZD overdose. Infusions at 0.05 to 0.01 mg/kg/h have been used.[82] The use of flumazenil in sedated patients in the ICU should be tempered by the potential for an unrecognized BZD dependence, which would increase the risks of adverse effects. If its use is required, then a carefully titrated dose would be appropriate. The half-life of flumazenil is much shorter than that of some of the BZDs it may be counteracting (see Table 123-8). The use of an infusion may be necessary because resedation has been reported after single-bolus use.[83] However, this requirement should not preclude the use of flumazenil in an ICU setting.[84] Flumazenil has been used for the reversal of moderate sedation. In the pediatric population, although it was well tolerated, it was not shown to significantly reduce recovery time.[85] Because flumazenil has a limited duration with the potential for resedation after discharge from medical care, an appropriate period of observation is required before discharge. A study in which researchers monitored the effects of flumazenil after sedation indicated that some of the residual effects of midazolam were still present after reversal.[86] Flumazenil also has been used to treat a paradoxical midazolam reaction[87] and has been shown to be effective in the management of hepatic encephalopathy or hyperammoneamia.[88] A Cochrane Collaboration review of articles pertaining to flumazenil use demonstrated a short-term improvement in hepatic encephalopathy. However, no improvement in recovery or survival was documented. No serious adverse effects were noted.

Chloral Hydrate

Chloral hydrate is a widely used oral hypnotic/sedative agent. It has been used for sedation for radiographic procedures, for EEGs, and in many different health care locations. It was first synthesized in 1832 and used in 1869 as a hypnotic agent. Shortly after, reports of acute and chronic toxicity were published.[89] In 1910, it was labeled as the most dangerous of hypnotics even though heroin and opium were in common use at that time. The addition of ethanol potentiates its effect (street name "Mickey Finn"). It has been used to control agitation in the intensive care nursery and to treat sleep difficulties in older patients.

Chloral hydrate is rapidly and completely absorbed from the GI tract and is immediately converted into the active component, trichloroethanol (TCE), by alcohol dehydrogenase.[90] The plasma levels peaks at 30 to 60 minutes. TCE is 45% protein bound. TCE undergoes glucuronidation with some oxidation to trichloroacetate (TCA). The half-life of TCE is 8 to 12 hours, while that of TCA is 67 hours. In infants and neonates this may be increased by a magnitude of three to four. With multiple dosing, a significant potential exists for accumulation. TCA can displace bound bilirubin from albumin. Its actions include CNS depression with drowsiness and sleep in less than an hour. With an overdose, the patient falls into a deep stupor or coma, and the pupils change from contracted to dilated. At therapeutic levels, the blood pressure and respiratory rate are unaffected. Chloral hydrate has little hangover effect. It has several effects on the cardiovascular system including decreased myocardial contractility, a shortened refractory period, and an increased sensitivity of the heart to catecholamines. It also has effects on mucous membranes. Irritation can cause gastritis, nausea, and vomiting. With overdose, a severe hemorrhagic gastritis with gastric necrosis and esophagitis has been described. Chloral hydrate and ethanol interfere with one another's metabolism through competition for alcohol dehydrogenase. Also, ethanol inhibits the conjugation of TCE, and TCE inhibits the oxidation of ethanol. Coumadin activity may be increased by chloral hydrate. Chloral hydrate is synergistic with other sedative agents. In children receiving amphetamine-based medication, chloral hydrate is contraindicated because there have been rare reports of arrhythmias. The reversal of chloral hydrate with flumazenil has been described; however, a report of ventricular tachycardia with this combination also has been made.

Chloral hydrate is available as capsules, syrup (50 mg/mL), and suppositories. The sedative dose is 25 to 50 mg/kg (PO/by way of the rectum), while up to 100 mg/kg can be safely used in children younger than 5 years with a maximum dose of 1 g. Because of an increased half-life, neonatal dosing should be lower (25 mg/kg). In preterm babies, toxicity resulted when chloral hydrate was used for 3 days; in term babies toxicity resulted when it was used for 7 days. The therapeutic level for TCE is 2 to 12 μg/L; toxicity occurs when the level is more than 25 μg/L. Chloral hydrate provides successful moderate sedation in approximately 90% of patients, but it appears to be less effective in patients older than 2 years. A higher risk of failure with excessive effect can be seen in patients with a history of obstructive sleep apnea or encephalopathy.

Signs of toxicity are usually noted within 3 hours of dosing. Paradoxical excitement also has been described in 6% of patients. There is some evidence that chloral hydrate may be genotoxic and carcinogenic. Mice studies have shown that a single-dose exposure can result in an increased risk of hepatic carcinomas and adenomas.[91] Chloral hydrate overdose produces a clinical picture that is similar to acute barbiturate poisoning. Ataxia, lethargy, and coma occur within 1 to 2 hours. Also, a pearlike odor may be noted. Cardiovascular instability poses the main threat to life. Severe arrhythmias including atrial fibrillation, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, torsades de pointes, and ventricular fibrillation have been described. Chronic use can cause a dependence syndrome. Also, chloral hydrate is not detectable in the blood. TCE levels are measurable, but they are not useful for clinical management, although they can be helpful for retrospective diagnosis. The management of toxicity includes evaluation and monitoring at a medical facility if an amount greater than 50 mg/kg or an unknown amount has been ingested. Two capsules may cause significant toxicity in a toddler, so there is little room for error in the history. Charcoal with intubation should be considered if significant

toxicity is suspected. Standard antiarrhythmic management is often unsuccessful, although esmolol, overdrive pacing, and hemoperfusion have been tried.

Other Agents for Sedation in the PICU Patient

Butyrophenones and Phenothiazines

Haloperidol

Butyrophenones belong to the group of major tranquilizers. Haloperidol is a potent antipsychotic agent with nonspecific dopamine antagonist action. It has little effect on the cardiovascular or respiratory systems. It produces the appearance of calm with minimal hypnotic effect and reduces operant behavior (purposeful movement). The patient appears tranquil and dissociated from surroundings but is readily accessible if spoken to. Haloperidol may mask actual feelings of mental restlessness. It is a potent antiemetic agent (action at the chemotrigger zone) and has no appreciable effect on the EEG. It potentiates analgesics and other sedative agents. Compared with less potent butyrophenones, it has fewer adverse effects. Neuroleptanalgesia, a dissociative form of anesthesia, can be induced when haloperidol is combined with high-dose opiates. This anesthetic state is useful for certain cardiac and neurosurgical procedures that require cardiovascular stability and a responsive patient. It is metabolized to inactive compounds with a half-life of 15 to 25 hours. It is highly protein bound. Hepatic dysfunction increases the half-life because of reduced clearance. Adverse effects include extrapyramidal signs, although acute dystonia is rare. Prolongation of the QT interval is possible with the subsequent risk of ventricular tachycardia.[92] Hepatic toxicity can occur but is rare. Haloperidol is indicated for the treatment of psychoses, Tourette's disorder, and severe behavioral problems in children. In the PICU it is used as a treatment for agitation in patients who are often unresponsive to other more commonly used agents. It also has proved to be effective as part of a sedative withdrawal strategy. Haloperidol is available as syrup, tablets, and an IM preparation. The usual dosage for agitation in children younger than 3 years is 0.01 to 0.03 mg/kg every 4 hours. The maximum daily dose is 0.15 mg/kg/day. Two IM preparations are available: the lactate is for repeated use, and the decanoate is a slow-release monthly formulation. Although not approved by the FDA, the IM lactate form has been given intravenously without problems.

Droperidol

Droperidol is faster acting than haloperidol with a shorter duration of action and a half-life of 2 hours. It is available as an approved IV formulation. With an IV bolus, mild hypotension occurs because of mild α-adrenergic receptor blockade. Droperidol is more sedating than haloperidol and may be used as a sedation adjunct to general anesthesia. It also is used in low doses (0.05 mg/kg) as an antiemetic agent. Concerns exist about the potential for droperidol to cause prolongation of the QT interval and result in ventricular tachycardia.[93]

Chlorpromazine

Chlorpromazine is a weaker antipsychotic agent with general CNS depressant activity. It has an antidopaminergic effect including extrapyramidal adverse effects, lethargy, and apathy with an EEG similar to that of normal sleep. It also causes a decrease in the body's ability to maintain temperature control, shivering is reduced, and it can be useful in patients in hypothermic-induced states. Cardiovascular effects include α-adrenergic receptor blockade with hypotension and postural hypotension, but no effect is seen on the ECG. Respiratory drive and depth are unaffected; however, some dryness of the mucosa may be noted. In the GI tract, its anticholinergic effect causes a decrease in secretions and motility. Liver effects include jaundice, which occurs in 0.5% (recurrence rate, 40%), independent of dose or duration of therapy, and is associated with a rash, fever, and eosinophilia. This syndrome has a low mortality rate and usually resolves quickly upon discontinuation of chlorpromazine. Other effects include antihistamine-like action; local analgesia; a temporary leukopenia; and, rarely, agranulocytosis. Chlorpromazine also has antiemetic properties. Indications include premedication, sedation as part of the lytic cocktail catheterization mixture number 3 (CM3),[94] intractable pain, antipsychosis, treatment of hiccoughs, prevention of succinylcholine pain, and induction of hypothermia (with other active measures). Dosing (0.05-1 mg/kg every 6 hours) may be via the PO, IM, IV, or rectal routes. Chlorpromazine is metabolized both in the gut wall and by the liver. It yields more than 50 metabolites, most of which are inactive.

Other phenothiazine derivatives include prochlorperazine, which has mainly antiemetic properties. Extrapyramidal adverse effects are more common in children younger than 5 years. Dosage is a PO or rectal dose of 0.4 mg/kg every 8 hours and an IM or IV dose of 0.15 mg/kg.

The Lytic Cocktail

The lytic cocktail (CM3) is a mixture of 25 mg/mL of meperidine, 6.5 mg/mL of promethazine, and 6.5 mg/mL of chlorpromazine. Its recommended dose is 0.1 mL/kg of body weight, but significant institutional variations exist. The CM3 was popular as sedation for cardiac catheterization. However, CM3 has been reported to have a high failure rate and lacks several important characteristics of an ideal sedative for children. Dosing cannot be titrated easily and individually. Onset of action is delayed (30 minutes), and duration of effect is protracted (5 to 20 hours). CM3 has no anxiolytic or amnestic properties. Additional caution should also be exercised when this cocktail is used in children with seizure disorders. The metabolite of meperidine and the lowered seizure threshold from the chlorpromazine put the patient at risk. Patients with congenital heart disease with physiologic conditions such as a tetralogy of Fallot or left ventricular outflow obstruction may be put at risk because of systemic vasodilation that causes altered blood flow through shunts, a hypercyanotic spell, or decreased coronary blood flow due to diastolic hypotension.

Neuroleptic Malignant Syndrome

Both the butyrophenones and the phenothiazines have a rare but well-described adverse effect called the neuroleptic malignant syndrome. It is a cluster of adverse effects of antipsychotic medications first described in 1968. It involves the development of hypertonicity with autonomic instability, fever, and cognitive disturbance. The incidence is 0.5% to 1.4% of patients exposed to neuroleptic agents. The true

incidence in children is unknown, however. Several different diagnostic criteria are available. Fever and rigidity present in all cases; other symptoms are shown in Box 123-2. A variety of therapies have been described (Table 123-9).

Baclofen

Baclofen is a p-chlorophenol derivative of GABA analog that has specific agonist activity at the $GABA_B$ receptor. It has a half-life of 2 to 6 hours. Baclofen has inhibitory effects on the brain and spinal cord. At the spinal cord level it suppresses spinal reflexes to result in muscle relaxation. It is widely used as a skeletal muscle relaxant in patients with spasticity, such as cerebral palsy, spinal cord injury, and multiple sclerosis. It is most frequently given PO. Adverse effects include urinary retention, sedation, bradycardia, hypotension, respiratory depression, and apnea. Weakness may limit patient compliance. These side effects are sedative-like characteristics of the drug, which are not useful in clinical practice. Therefore abrupt cessation of long-term baclofen therapy resembles, in part, short-term sedative withdrawal.

Recently, intrathecal baclofen (ITB) has been used with increasing frequency in children to treat spasticity. ITB was first introduced in 1984[95] with a pump delivery system that was available in 1992 for adults. This system allows delivery of the drug to the spinal cord and reduces the dose significantly (1% of oral requirements), limiting systemic adverse effects.[96] Baclofen inhibits the release of serotonin in the brainstem. After long-term use there is accommodation of the serotonin pathways to this long-term inhibition that is consistent with the usually observed increasing doses required for ITB during the first 12 to 18 months of treatment. When this inhibition is abruptly removed, sudden excess release of serotonin occurs. Acute overload of serotonin transmission, such as an overdose of serotonin reuptake inhibitors, can result in confusion, hyperthermia, myoclonus, and autonomic instability. It also has anticholinergic and antihistamine effects that may result in drowsiness; paradoxical excitation has been reported in children. More than 25 case reports[97] of ITB withdrawal have now been reported. ITB withdrawal seems to be more severe if the ITB treatment was for more than 1 year. A review of ITB pumps in 100 patients at a single center[98] has shown that problems with the delivery system are fairly common. Twenty-four percent of patients experienced a problem, with a follow-up period for a maximum of 5.6 years. An average of two problems per patient was reported. Disconnection of the catheter from the implanted pump was the most common problem. Access ports on the pump seemed to increase the risk of problems (16% compared with a 2% disconnection rate); however, these ports make troubleshooting easier. Causes of difficulty with ITB delivery are shown in Box 123-3.

The ITB withdrawal syndrome is interesting because it appears to have many similarities with the neuroleptic malignant syndrome. Prolonged muscle contraction caused by rebound spasticity results in thermogenesis, hyperthermia, and rhabdomyolysis.[99] Patients with ITB withdrawal often are managed initially with broad-spectrum antibiotics as if they have sepsis and multisystem organ failure, with no improvement in

Box 123–2 Signs and Symptoms of Neuroleptic Malignant Syndrome

Elevated creatine phosphokinase (97%)
Tachycardia (75%)
Altered consciousness (75%)
Tachypnea
Hypertension
Diaphoresis
Leucocytosis

Table 123–9 Treatment Described in the Case Reports of Neuroleptic Malignant Syndrome

	Supportive Treatment	Neuroleptics Discontinued	Anticholinergics/ Amantadine	Bromocriptine	Dantrolene	L-dopa	ECT
Frequency*	35	50	17	18	19	8	9
Total (N)†	55	55	48	57	58	58	59
Percent	63.6	90.9	35.4	31.6	32.8	13.8	15.3
Sequelae (n)	7	15	3	7	5	3	4
Deaths (n)	2	3	0	0	1	1	0
DURATION OF NMS‡							
Median	12	12.5	14	13	15	32	19.5
Mean	14.9	19.2	19.9	25.7	21.3	35	24.1
(SD)	(14.8)	(21.6)	(29.3)	(29.5)	(17.9)	(20.3)	(22.2)
NMS SEVERITY SCORE							
Median	8	7	7.5	7	—	—	—
Mean	7.2	6.8	7.1	7.6	–.6	7.4	5.6
(SD)	(2.1)	(2.1)	(2.5)	(1.3)	(1.4)	(2.1)	(2.1)

ECT, Electroconvulsive therapy; *NMS,* neuroleptic malignant syndrome; SD, standard deviation.
*Number of reports in which the treatment was administered.
†Number of reports in which the treatment was mentioned.
‡Duration in days.

the clinical situation.[100] This treatment results in a delay of the diagnosis of ITB withdrawal. The differential diagnosis of the hypermetabolic state is listed in Box 123-4. The symptoms of ITB withdrawal can be classified into three categories (Table 123-10). Often the first clinical signs are the development of itching and some increase in spasticity. If replacement baclofen is not given, then the symptoms may progress to a severe hypermetabolic state that can be fatal if the cause is not recognized and treated. Of 27 patients reported to the FDA, six deaths were documented.[101] The management of ITB withdrawal requires early diagnosis. It involves supportive ICU care and the onset of baclofen replacement therapy as soon as possible. Box 123-5 provides a guideline for the evaluation of the patient with suspected baclofen withdrawal. A definitive diagnosis may be obtained with measurement of cerebrospinal fluid baclofen levels, but the results probably are not going to be available in the time course of treatment initiation. Although the primary aim should be to replace baclofen, rapid replacement of ITB may not be possible. The required oral baclofen replacement dose may be 50 to 100 times the intrathecal dose, and this dose often is not well tolerated by patients because of adverse effects. IV administration of a BZD should be the initial step in the treatment of baclofen withdrawal. Dantrolene has been used as an adjunct therapy for the increased spasticity.

The use of the potent serotonin antagonist cyproheptadine has been proposed as an alternative treatment adjunct.[102] It improved fever, spasticity, and itching in adult patients with gout who had ITB withdrawal. Dosages of cyproheptadine were in the range of 0.25 mg/kg/day every 6 hours, either PO or IM. In some patients the ITB withdrawal is an elective management problem due to pump removal for infection. In these patients, if a replacement pump cannot be placed, the patient needs to be observed and managed in the ICU to recognize and treat the withdrawal syndrome. The monitoring of creatine phosphokinase (CPK) levels may be helpful in managing withdrawal. In the reported cases of ITB withdrawal, CPK levels have been in the range of 1800 to more than 40,000.[103] Mild elevations in CPK (300 to 500) may be an early marker of inadequate treatment.

Box 123–3 Causes of Interrupted Intrathecal Baclofen Delivery

Pump malfunction
Pump failure
Battery failure
Infections necessitating pump removal
Catheter problems (e.g., kinks, holes, tears, dislodgement, disconnection, migration)

Box 123–4 Differential Diagnosis of Intrathecal Baclofen Withdrawal

Autonomic dysreflexia
Neuroleptic malignant syndrome
Malignant hyperthermia
Sepsis
Status epilepticus
Toxic
Metabolic
Immune-mediated disorders

Dexmedetomidine

Dexmedetomidine (Precedex) is a selective α_2 adrenergic agonist. It has an effect at receptors in the CNS and peripheral nervous system, as well as in autonomic ganglia. Stimulation of the α_2 receptor decreases the release of norepinephrine, inhibits sympathetic activity, and produces sedation, anxiolysis, and analgesia. It is 1600 times more active at the α_2 receptor than at the α_1 receptor and is thus eight times more selective than clonidine. It is available as a white water-soluble powder in a 100-μg vial. In adults it has a redistribution phase of 6 minutes and an elimination half-life of 2 hours. The pharmacokinetics appears to be similar in the pediatric patient, even after a 24-hour infusion.[104] It is almost completely metabolized in the liver by glucuronidation and P450 pathways to inactive metabolites. In patients with renal failure the pharmacokinetics did not show any prolongation of the terminal half-life; however, these patients were sedated for longer after the infusion was terminated compared with the control group.[105] The prolonged sedation may be related to reduced protein binding of this normally highly protein-bound drug (94%) and thus higher free drug levels in the patient with renal failure. In patients with hepatic dysfunction, reduced clearance has been reported. With patients in severe hepatic failure, a prolongation of the half-life almost three times longer than normal was reported.[106]

Dexmedetomidine has proved to be effective for sedation in the adult intensive care setting.[107] Currently it is only licensed for 24 hours of sedation, although approval for more

Table 123–10 Severity of ITB Withdrawal

Designation	Description
Mild	Pruritic symptoms and increased spasticity
Moderate	High fever, altered mental status, seizures and profound rigidity, autonomic instability
Severe	Rhabdomyolysis, hepatic, renal failure, DIC brain injury, death

DIC, Disseminated intravascular coagulation; *ITB*, intrathecal baclofen.

Box 123–5 Management of Suspected Baclofen Withdrawal

Suspicion in at-risk patients
Administer antipyretics and other cooling techniques for fever
Administer benzodiazepines for seizures or spasticity
Rule out medical causes
Oral baclofen therapy
Contact patient's ITB pump specialist to interrogate the pump and check the reservoir
Abdominal radiographs (anteroposterior/lateral) to check for catheter integrity
Neurosurgical consultation for possible surgical exploration and repair
If catheter appears intact on plain radiographs, consider performing a contrast catheter study to check for catheter integrity
If problem is unresolved, contact manufacturer

ITB, Intrathecal baclofen.
Modified from Kao LW, Amin Y, Kirk MA et al: Intrathecal baclofen withdrawal mimicking sepsis, *J Emerg Med* 24:423-427, 2003.

prolonged use is pending. The recommended dosage for dexmedetomidine is a loading dose of 1 μg/kg over 10 minutes followed by an infusion of 0.2 to 0.7 μg/kg/h. It appears that in pediatric patients, the higher end of the dose range is required. Doses higher than 1.5 μg/kg/h have not been shown to provide any further sedative action. Advantages of dexmedetomidine include minimal respiratory depression and predictable hemodynamic effects. Because of the reduced sympathetic activity, blood pressure and heart rate fall slightly. Clinical sedation trials have shown a decrease in heart rate of 7% and blood pressure by 10%. It has been infused before, during, and after the extubation process. Hypotension and bradycardia are more likely to occur during the loading phase, which may need to be prolonged or interrupted. Dexmedetomidine cannot be given by rapid IV bolus because hypertension may occur as a result of direct stimulation of α_1-adrenergic receptors. Mild transient hypertension is sometimes noted in adults during the loading phase, although this effect was not noticed in pediatric patients. Long-term use of dexmedetomidine (160 hours) also has now been reported,[108] with no evidence of accumulation. The concern about rebound hypertension after long-term α_2-adrenergic agonist treatment, such as that occurring with clonidine, has not been reported; however, anecdotal reports exist regarding withdrawal phenomena, including hypertension after prolonged infusions.

Sedation from dexmedetomidine often results in a patient who is tranquil yet easily aroused. Reduced analgesic requirements have been reported with its use. The easy arousal may make it a useful agent for when repeat neurologic examinations are required. Several articles concerning the use of dexmedetomidine in the PICU have recently been published. In a retrospective review of 121 patients from a mixed medical and surgical population in the PICU, a decrease of 20% in the dose of BDZ and/or opiates was documented in 80% of the children who received dexmedetomidine.[109] Bradycardia (12%) and hypotension (16%) requiring intervention was described. Another retrospective review of dexmedetomidine use (infused >36 hours) in 35 postoperative pediatric cardiac patients did not show any significant changes in cardiovascular parameters, but a reduction in the postoperative opiate requirements occurred with an equal level of sedation.[109a] At present, a pharmacokinetic phase 2 trial is in progress and a prospective phase 3 study is planned in the near future. These studies should help answer the questions regarding the metabolism, efficacy, and adverse effects of dexmedetomidine in the PICU population. This agent also has been safely used for a variety of noninvasive sedation procedures such as magnetic resonance imaging (MRI), and several cases have been reported of its use as an adjunct to general anesthesia for pediatric patients. It appears to be a useful agent in the management of opiate withdrawal. Furthermore, dexmedetomidine is useful for patients who are difficult to sedate, for treatment of postoperative shivering, and for postanesthesia agitation. Procedural sedation with intranasal (IN) dexmedetomidine also has been reported (dexmedetomidine, 2 μg/kg IN, along with IN sufentanil, 1 μg/kg). Twenty children sedated with IN dexmedetomidine underwent dental restorative treatment without any complications. Sedation onset took approximately 45 minutes with a recovery time of about 1 hour.

Dexmedetomidine is not without adverse effects. It is contraindicated in patients with heart block, and bradycardia has been reported in an infant treated with digoxin who received dexmedetomidine during the infusion phase.[110] It also would appear prudent to avoid its use with other drugs that can reduce arteriovenous node function such as β-blockers and calcium channel blockers, as well as with patients who have severe ventricular dysfunction or hypovolemia, because reduction in sympathetic tone may cause a profound decrease in blood pressure.

Table 123–11 Pharmacokinetics of Intravenous Anesthetic Agents

Drug	Elimination Half-Life (hr)	Volume Distribution (SS) (L/kg)	Clearance (mL/kg/min)	Protein Binding (%)
Etomidate	2.9	2.52	17.9	76.9
Ketamine	3.1	3.1	19.1	12
Propofol	1.9	2.3	30	96.8

SS, Steady state.

Propofol

Propofol is a rapid-acting IV anesthetic agent. As a highly lipid-soluble 2,6-diisopropylphenol, it is an oil and is insoluble in water. It is formulated as a 1% aqueous emulsion (1.2% egg phosphatide, 10% soyabean oil, 2.25% glycerol) with a propofol concentration of 10 mg/mL. A water-soluble prodrug form of propofol has been released recently, although no data are available regarding its use in children. Recovery from propofol is rapid because of its short redistribution half-life (α), and it is rapidly cleared by hepatic metabolism in healthy patients after short infusions, making it ideal for short procedures. The elimination half-life is 2 hours (Table 123-11), but the half-life is context sensitive and has been reported to be between 1 and 3 days after a 10-day infusion because of significant body accumulation. The kinetics follows a three-compartment model. The dose for induction of anesthesia in children is 2.5 mg/kg to 3.5 mg/kg; higher doses are required for infants and toddlers. Anesthesia also can be maintained by an infusion. The depth of sedation/anesthesia can be easily titrated, and an infusion rate of 25 to 150 μg/kg/min usually provides adequate sedation.

As with most sedative agents, propofol has adverse effects that may be a concern for the intensivist. It often causes hypotension in the sick child, and in patients dependent on high sympathetic tone to maintain normal blood pressure, even small doses of propofol may result in a significant decrease in blood pressure. The hypotension is mainly caused by vasodilatation, and there is little direct myocardial depressant. Bradycardia also can occur upon the induction of anesthesia. Propofol increases atrial conduction time for neonatal rabbits and prolongs the refractory period. Propofol anesthesia can prevent the induction of known atrial tachycardias in the electrophysiology laboratory, and cases have been reported of conversion of atrial tachycardia to sinus rhythm upon induction of propofol anesthesia. Propofol is a potent respiratory depressant, and it has a useful depressant effect on airway reflexes, which may facilitate endotracheal intubation. The injection of propofol often causes pain, and in the alert patient, strategies to minimize this effect are useful. Most commonly, lidocaine, either mixed with the propofol or injected before the injection of propofol, will markedly reduce the pain.

Propofol sedation in the ICU has several advantages. It acts rapidly and produces an easily controllable level of sedation. Unlike the barbiturates, it provides rapid clinical recovery, even after prolonged infusion. It has antiemetic properties and can provide transient deep sedation if required for procedures. It also has been shown to facilitate sedative synergy with BZDs.[111] In the adult ICU population, propofol has been compared with midazolam for long-term sedation. Both agents provide good sedation, but propofol has the advantage of being more titratable with a faster recovery.[112] Despite the increased drug cost, the use of propofol can reduce overall ICU costs because of a reduction in ventilator weaning time.[113]

Propofol has been used in the ICU as an anticonvulsant for patients with refractory status epilepticus.[114] In a comparison with pentobarbital to provide burst suppression, both drugs were equally effective. Propofol was much more rapid in effect; no difference was found in outcome or ICU support measurements or length of stay.[115] In patients with raised ICP, propofol has the same effects on ICP and cerebral blood flow (CBF) and cerebral metabolic rate of oxygen as barbiturates. It also requires a similar level of hemodynamic support to maintain appropriate blood pressure and cerebral perfusion pressure (CPP). It can produce the same degree of burst suppression that may be required for uncontrolled intracranial hypertension. It also allows rapid changes in the level of sedation, to facilitate neurologic examination. In this regard it is a superior agent. As described later, however, the use of large doses of propofol in the ICU setting may be associated with worsened outcomes.

Special Issue Regarding Long-Term Infusion of Propofol

Several important problems may occur when propofol is used in the PICU. With long-term propofol infusions, a significant amount of lipid may be infused into the patient, with the same consequences as lipid infusions used for hyperalimentation. Hyperlipidemia and triglyceridemia have been reported in up to 10% of patients receiving propofol in the ICU. Pseudohyponatremia or the inability to do routine plasma electrolyte analysis has been described. It is important that the propofol calorie (20 mL/h = 528 kcal/day)[116] and lipid load be included in the nutrition plan for the patient. It may be necessary to reduce enteral feeds or avoid intralipids in selected patients. With high propofol dosing, respiratory acidosis has been reported.[117] The emulsion used for propofol administration is an excellent culture medium at room temperature; cases have been reported of patients with systemic infection caused by propofol during operative procedures.[118] This infection is due to poor aseptic technique in the preparation and use of the propofol syringes and infusion lines. Unusual infective organisms were detected in several patients, and an epidemiological study by the Centers for Disease Control and Prevention found propofol to be the common element.[119] Certain precautions should be followed when propofol is used in the PICU. The staff should be educated to the potential dangers of infection from propofol. The ampule neck should be wiped with alcohol. There are no multidose vials of propofol. Syringes should be disposed of when they are more than 6 hours old, and lines should be changed every 12 hours. Filters are available that can remove many of the potential pathogens, and they are compatible with the lipid-based propofol infusion.

A few episodes of allergy to propofol have been reported; immune reactions, involve both anaphylactic and anaphylactoid types of reactions, are estimated at 1:45,000.[120] Although clinically indistinguishable, the anaphylactic response involves prior exposure to a component of the propofol suspension. Egg allergy has been considered a contraindication to its use. However, the egg phosphatide component found in propofol is not related to the major egg allergen protein ovalbumin.[121] In fact, intradermal testing with propofol in 25 patients allergic to eggs was negative; therefore, current evidence suggest that anaphylaxis is not more likely to develop in patients who are allergic to eggs when they are exposed to propofol. Propofol does not release histamine and is an acceptable agent for use in patients with asthma.

Several new generic formulations of propofol are available. These formulations include different antioxidants, such as metabisulfites, which may have an increased risk of allergic reaction. However, this increased risk has not been borne out.[122] They appear to be equal in efficacy and adverse effects to the propofol solution known by the brand name Diprivan. A new water-soluble prodrug, fos-propofol, has been approved by the FDA and is due for release soon. The onset of action of fos-propofol is significantly slower than for propofol (5 minutes), which may reduce the incidence of hypotension and respiratory depression. A few patients who receive propofol may have dark-green urine due to phenol metabolites; this effect is not a clinical concern.[123]

Propofol Infusion Syndrome

One of the most important concerns is the development of a refractory metabolic acidosis in children who had received propofol sedation in the ICU. This effect was first described in 1992 as a series of five cases[124] with fatal myocardial failure in children with respiratory illnesses requiring ventilation and sedation. Five young patients from different ICUs had croup and went on to have a refractory cardiac failure, bradycardia, and acidosis. A lipemic serum had developed in all patients. They had all received propofol at an average rate of about 8 mg/kg/h for more than 70 hours.

In review, the case reports were not as simple or as complete in their reporting, with several published letters[125] from physicians involved with these patients showing incomplete data in the reporting. Several other case reports of an apparently similar clinical course were then subsequently described in the literature, which was enough evidence for the Committee on Safety of Medicines in the United Kingdom to issue a warning on propofol and its use in pediatric patients. At that time the FDA could not find a causal link between propofol and the deaths in children and did not issue a warning.

This reaction to propofol came to be known as the propofol infusion syndrome (PRIS).[126] It is the sudden or relatively sudden onset of a marked bradycardia resistant to treatment with a least one of the following signs: lipemia, enlarged liver, severe metabolic acidosis, or rhabdomyolysis.

PRIS is unlikely to be due to the carrier emulsion because intralipid has been used extensively in severely ill patients without problems. The propofol metabolites are acidic, highly water soluble, and have a short half-life.

A steady number of case reports of this syndrome have appeared in the literature since the initial description, as well as a couple of studies involving several hundred patients[127,128]

who have not shown any problem with propofol in the PICU. In these studies, lower doses of propofol (4 mg/kg/h) were used, with regular monitoring of the acid base status and triglyceride levels. "Propofol bashing" became popular.[129] There are few drugs that are licensed specifically for the PICU, however, and proper trials are needed to avoid drugs being condemned as hearsay. Subsequently, a randomized, controlled trial of propofol was begun, and after its use in 327 patients, it was reviewed by the FDA.[130] The study was never published, but researchers found that, despite similar pediatric risk of mortality scores, patients who had received either 1% or 2% propofol preparations had a two to three times greater risk of death compared with the control sedative group. This finding led to a letter from AstraZeneca reminding health care workers that propofol was not approved for sedation of pediatric patients.[131]

Much debate still occurs regarding whether there is a safe infusion rate or duration of infusion for propofol in the PICU setting. It has been estimated that a study to show a significant increase in death would require 7000 patients, which would be difficult to accomplish.

PRIS has also now been described in adult patients.[132] These patients had similar cardiac and metabolic findings, often associated with the management of intracranial hypertension. PRIS appeared to be a higher risk if the 2% formulation was used. Patients with raised ICP require deeper levels of sedation and require higher doses of propofol; they also are receiving vasopressor support to maintain the CPP, which puts a further stress on a myocardium that is already failing.

The pathophysiologic cause of PRIS is still poorly understood, but it appears to mimic mitochondrial myopathies. Such patients are generally well until stressed. Rhabdomyolysis and cardiac and hepatic failure then develop in these patients.[133] Case reports have shown some metabolic abnormalities that may be the cause of the cardiac failure and acidosis. One report describes a 10-month-old child who had the syndrome and was successfully treated with hemofiltration and plasmapheresis.[134] Muscle and liver biopsy specimens showed changes consistent with a toxic insult. Analysis also showed a reduction in the cytochrome C oxidase activity in the muscle, with a normal activity in skin fibroblasts, excluding an underlying respiratory chain defect. Profound acidosis with lactic acidosis is found in different types of genetically acquired cytochrome oxidase deficiency. It was postulated that the hemofiltration removed a water-soluble metabolite of propofol that had caused a reversible reduction in the oxidase activity. A second case report[135] also showed a metabolic abnormality. Elevated levels of malonylcarnitine and C5-acyl carnitine were found in a patient with PRIS. This patient was also treated successfully with hemofiltration. These findings are consistent with impaired fatty acid oxidation due to impaired entry of long chain fatty acids into the mitochondria and a failure of the respiratory chain. A review of the pathophysiologic function of the syndrome[136] suggested that propofol increases the activity of malonyl coenzyme A, which inhibits the carnitine palmityl transferase I, so long chain fatty acids cannot enter the mitochondria. Propofol also uncouples oxidation, so the short and medium chain fatty acids cannot be used, even though they have entered the mitochondria and also may inhibit the respiratory chain. Low energy production leads to cardiac and peripheral muscle necrosis.

In pediatric patients it has been suggested that an inadequate calorific intake coupled with a high metabolic demand requires a fully active fatty acid oxidation capacity. Propofol may inhibit this pathway and cause a cellular metabolic failure syndrome to develop. Children have lower glycogen stores and often require higher doses of sedative agents; thus the syndrome is more likely to occur in pediatric patients. A carbohydrate intake of 6 to 8 mg/kg/min should be enough to suppress fat metabolism in the critically ill child. Also, concerns have been raised about the influence of catecholamines and steroids in the development of the syndrome, especially in the adult population.

Propofol is still frequently used for procedural and short-term sedation,[137] but in a recent case report, researchers describe a patient who had PRIS.[138] The patient had received a propofol infusion for 15 hours at 20 mg/kg/h. After a 13-hour propofol-free period, an 8-hour infusion of propofol at 4 mg/kg/h was given, after which the patient had intractable bradycardia and acidosis. This report raises concerns about high-dose, short-term propofol use in the PICU.

In a report on the use of propofol for two cases of refractory status epilepticus, patients aged 7 and 17 years had features similar to the PRIS.[139] Status epilepticus itself can result in neurologic deficit, hypoxia, rhabdomyolysis, cardiac arrhythmias, hyperthermia, metabolic acidosis, acute renal failure, and death. However, these patients received high doses of propofol (18 to 27 mg/kg/h) to achieve burst suppression for more than 48 hours. Rhabdomyolysis and cardiac failure developed in both patients. No monitoring of lipid status or acid base was performed, and propofol was used as the sole agent by practitioners with limited experience with this drug. In light of the reports now appearing in the adult neurointensive care literature with the development of a propofol infusionlike syndrome in adult neurosurgical patients,[140] it would appear that propofol is not the best choice for prolonged sedation for patients with intracranial hypertension. An early indicator of the cardiac instability from PRIS may be changes in the ECG. It has been reported that the development of a right bundle-branch block with convex ST elevation was an early sign of this syndrome.[141]

Propofol remains a useful agent for procedural sedation in the PICU. When compared with midazolam and ketamine, propofol resulted in safe, effective sedation. The patients sedated with propofol awakened almost twice as fast; thus the efficiency of the sedation service was also improved.[142] Propofol is also probably appropriate for overnight sedation, and higher doses should be avoided. It probably should not be used as a solo agent because in those cases tolerance appears to develop more rapidly. If its use is required for a prolonged period, then careful consideration should be given to its risks and benefits. A recent study showed that staff members of some PICUs are still using long-term high doses despite the potential risks involved.[143] Prevention of PRIS could include adequate calorific intake. The dose and duration of propofol should be carefully managed to minimize its use. It would appear from the reports of PRIS in the neurosurgical population that the desire for rapid awakening has propagated the use of propofol coma, rather than using barbiturates. Regular monitoring of the cardiac function, ECG, and CPK are warranted; lipid profile and acid base status may help in early detection. However, these steps may not necessarily prevent mortality from the syndrome.[144] Treatment should

Table 123–12 Features Reported for PRIS, Incidence, and Score

Feature	% Incidence	Score
Cardiac	44	1
Hypotension	34	0
Rhabdomyolysis	27	1
Hepatic failure	24	0
Renal failure	24	1
Metabolic acidosis	20	1
Dyslipidemias	5	0
Rhabdomyolysis and hypotension		1
Age <18 y and renal failure		–1
Rhabdomyolysis and renal failure		–1

Table 123–13 Predicted Outcome from PRIS

Score	Predicted Mortality Rate (%)
0	10
1	25
2	50
3	75
4	90

be immediate cessation of propofol. Cardiac support may be difficult because of unresponsiveness to conventional circulatory support. The use of pacing and extracorporeal membrane oxygenation has been reported. Hemodialysis or hemofiltration have been reported as having some success.

An outcome prediction table has been developed for PRIS based on more than 1000 reports from the FDA's Medwatch program, of which 20% were pediatric patients.[145] The features associated with PRIS are shown in Table 123-12. In addition to the individual features, there were several additional scores depending on a combination of features (see Table 123-12). The predicted outcome from these scores is shown in Table 123-13. These predicted outcomes were very close to the actual reported mortality of the analyzed cohort. No independent verification exists at present. However, this article does highlight the variability in features of the PRIS and accounts for the differences in the reported mortality.

Sedation and Analgesia for Procedures

Many procedures performed on children involve pain and anxiety. In many hospitals the administration of sedation and analgesia falls to the pediatric intensive care physician.[146] The pediatric intensive care physician needs to be familiar with guidelines and protocols that are used for moderate sedation outside the ICU setting. Procedural pain accounts for most of the pain experienced by children with malignancies,[147] and many pediatric patients with trauma will require sedation for procedures such as correction in the emergency department of fractured limbs and lacerations.

Table 123–14 States of Altered Consciousness

Designation	Description
1	Minimal sedation (anxiolysis)
2	Moderate sedation/analgesia ("conscious sedation")
3	Deep sedation/analgesia
	General anesthesia

Conscious sedation, now commonly called moderate sedation or more appropriately procedural sedation, is a medically controlled state of depressed consciousness whereby the patient remains responsive to verbal stimuli or, at most, a gentle shaking of the shoulder.[148] It anticipates that protective reflexes will be maintained and that the patient retains a patent airway independently. Neither airway patency nor airway protection should be taken for granted because patients with conditions such as obstructive sleep apnea may obstruct their airway with little sedation and aspiration of food can occur even without sedation. Before moderate sedation is further explored, the insightful words spoken by Burton Epstein, in his "40th Rovenstine Lecture of the ASA" in the fall of 2002, should be considered: "The myth . . . of the achievability of a state of conscious sedation in which pediatric patients are simultaneously responsive to voice stimulus while immobile in the face of pain is just that—a myth."[149] A little consideration will reveal that for painless procedures, anxiolysis will most likely suffice, whereas for painful procedures, pharmacologic elimination of the response to pain will result in a need for general anesthesia. Between these two extremes, the use of local anesthetic agents may modify the response so as to allow potentially painful procedures to be performed during moderate sedation. Another factor to consider is the effect of variation in the level of stimulation, whereby sedation titrated to effect during a painful stimulus becomes excessive once the stimulus is completed. Thus the practitioner treads on a narrow and sometimes impossible pathway when giving moderate sedation. The state of moderate sedation is part of a continuum (Table 123-14) defined by the working groups of the American Academy of Pediatrics (AAP) and the American Society of Anesthesiology (ASA),[150] which encompasses a range from anxiolysis to general anesthesia that is appropriate for surgery. This continuum is difficult to control, and staff administering moderate sedation must be able to appropriately manage any patients who enter a deeper level of sedation than that planned. The goals of sedation are shown in Box 123-6. It is helpful to think of moderate sedation as consisting of several components. A balanced sedation technique will involve amnesia, analgesia, relaxation, and inattention. Different procedures require different degrees of these components (Table 123-15).

Types of Procedures and Preprocedure Evaluation

In many instances sedation may be beneficial in the PICU, such as for the placement of central lines and centesis tubes and during dressing changes. Sedation facilitates the procedure in uncooperative patients and allows long or uncomfortable procedures to be performed. Outside the ICU, both

Box 123–6 Goals of Sedation

Guard the patient's safety and welfare
Minimize physical discomfort or pain
Minimize negative psychological responses to treatment
Control behavior
Return patient to a state in which safe discharge is possible

Table 123–15 Suggested Sedation Quality for Different Procedures

	Amnesia	Analgesia	Relaxation	Inattention
MRI	0	0	1	4
Endoscopy	1	3	2	2
Paracentesis	1	3	0	2
Burn dressing	2	4	0	2
Local anesthesia	3	2	2	3

MRI, Magnetic resonance imaging.

Box 123–7 Non-ICU Procedures Requiring Sedation

Cardiac catheterization—diagnostic, angioplasty, stents, valvuloplasty, closure devices
Neuroradiology—angiograms, stents, embolization
Ultrasound—TEE, drainage procedures
CT scan–guided abscess drainage

CT, Computed tomography; *ICU*, intensive care unit; *TEE*, transesophageal echocardiography.

noninvasive and invasive radiologic examinations[151,152] often require sedation (Box 123-7).

Safety with moderate sedation is largely determined by careful assessment and management of the airway, together with precautions to prevent aspiration of gastric contents. Adequacy of sedation largely depends on appropriate patient selection, the combination of the patients' known medical conditions, past sedation experience, and the nature (particularly pain) of the patients' procedures, coupled with appropriate drug selection. Moderate sedation may be better tolerated than deep sedation or general anesthesia when hemodynamic stability is compromised because many sedative and anesthesia agents induce cardiovascular instability such as vasodilation or myocardial depression. Furthermore, the ability to monitor the patient's neurologic status during the procedure through conversation or instruction may be helpful, especially during invasive neuroradiologic procedures. Moderate sedation may allow an earlier discharge because less sedative is being used and may make the procedure, which would usually require the full operating room environment, possible outside of the operating room.

All patients should be assessed before moderate sedation. Box 123-8 lists the elements that should be included in the assessment. The medical history should include evaluation of the cardiorespiratory system, any history of gastroesophageal reflux, and any previous sedation attempt that failed or any abnormal reaction to sedation. A recent asthmatic attack or

Box 123–8 Presedation Assessment

History
Medications
Allergies
Previous experience with sedation, anesthesia
Alcohol, tobacco, illicit substance abuse
Fasting

Examination
Head extension and neck flexion
Mouth opening, jaw size
Body habitus

Documentation
Informed consent
Instructions and information to responsible person

Table 123–16 American Society of Anesthesiology Classification

Class	Description
I	A normally healthy patient
II	A patient with mild or well-controlled disease state
III	A patient with severe or poorly controlled disease state
IV	A patient with severe disease state that is a constant threat to life
V	A moribund patient who is not expected to survive without surgery

respiratory tract infection, poorly controlled seizure disorder, or diabetes may require a change or postponement of the sedation plan. It is recommended that patients be classified according to the ASA preoperative patient classification (Table 123-16). In most circumstances it is generally recommended that patients in ASA class VI and some in class III are not suitable for moderate sedation.

It is prudent to adopt the same guidelines that are used before general anesthesia is administered, in case sedation that is deeper than anticipated occurs. These guidelines are age dependent, and current recommendations are shown in Table 123-17. Despite this, less caution is often reported regarding fasting, without any apparent worsening of outcome. For example, in a survey of 450 radiology departments, 35% had no nothing by mouth (NPO) status requirement for neonates, and 17% used a 2-hour NPO status requirement for infants. For oral contrast studies, most departments sedated the patient within 1 hour of the contrast being swallowed.[153] Consent should be obtained as with any medically indicated procedure or intervention. It should include discussion about the risks and benefits of the procedure and the sedation technique, as well as expectations of outcome and alternatives to the procedure and sedation.

The presedation interview for outpatients or non-ICU patients also should involve giving instructions and information to a responsible person, including postsedation instructions, a 24-hour phone contact phone number, guidelines concerning limitations of activity, and expected postsedation behavior. If moderate sedation is provided for nonscheduled patients, a review of several aspects is important (Box 123-9).

Table 123–17 Presedation NPO Guidelines

	Solids/Nonclear Liquids*	Clear Liquids†
Adults	6 h	3 h
Children	6 h	3 h
Neonates (<3 mo)	4 h	2 h

NPO, Nothing by mouth.
*Milk, breast milk, pulp fruit juices.
†Clear fruit juices, water.

Box 123–9 Preparing for Moderate Sedation

Consider airway
Assess airway
Preexisting risk factors
Trauma-induced risk factors

Circulation
Correct hypovolemia
Hypovolemia is manifest when sympathetic tone is decreased

Fasting
Time of last meal
Trauma-induced delay in gastric emptying
Drug-induced delay in gastric emptying

Monitoring During the Procedure

Sedation provided outside the ICU should be performed in a facility/area with the appropriately trained support staff. The staff should have had appropriate training with respect to pharmacology, monitoring, resuscitation (basic and advanced life support), emergency drugs, and cardiac arrest protocols and medications. Advanced cardiac life support and pediatric advanced life support recommendations should be available to be followed.

Monitoring of patients undergoing moderate sedation is an important component of safe, effective sedation. Several different recommendations have been made by the Joint Commission on Accreditation of Healthcare Organizations,[154] the American Board of Anesthesiology, and the AAP. These recommendations have not yet been fully followed by persons providing sedation for children.[155] A study of pediatric dentists after publication by the AAP of its new recommendations found minimal monitoring and documentation of the sedation procedure. Obtaining baseline vital signs is important. Because of the possibility of oversedation, the level of consciousness should be assessed frequently, especially during titration of effect. This level of consciousness is best assessed with the Ramsay scale (see Table 123-1). A sedation record is important for documentation of the drugs used with times and doses and for the monitored measurements that are charted on a time-based record. Monitoring should include pulse oximetry for assessment of the degree of oxygenation and heart rate. The saturation should be maintained by supplemental oxygen. Breathing can be assessed either by monitoring the respiratory rate or by capnography. The blood pressure should be checked at regular intervals during the procedure. A study of 85 pediatric patients with complications after sedation showed that most severe complications resulted from a common pathway involving respiratory depression

Box 123–10 Causes of Sedation Complications

Drug overdose
Inadequate monitoring—during and after
Lack of appropriate skills by staff administering the sedation
Lack of appropriate pharmacology knowledge

leading to respiratory arrest, cardiac arrest, and subsequent severe neurologic devastation. The most common causes for these complications are summarized in Box 123-10. There is no particular drug that is more likely to cause problems. Polypharmacy, especially with three or more drugs, has been shown to be a risk factor for pediatric sedation complications.[156] Dentists using nitrous oxide in combination with other agents appeared to have a higher incidence of problems. If long-acting drugs are used, the patient must be observed for an appropriate length of time. Several reports have been made of respiratory arrest occurring while the child was in the car seat on the way home. Any health care worker providing moderate sedation should be familiar with an emergency algorithm in case problems arise (Figure 123-4).

Many different pharmacologic options are available for moderate sedation in children. The oral route is commonly used in children; it has a slow onset time that avoids a rapid peak effect, but it also gives an unpredictable degree of sedation, which is not easy to titrate. IM administration is painful; however, it is useful in uncooperative patients. The rectal route is nearly always available and has found favor in the past for barbiturate sedation. More contemporaneously, rectal diazepam at 0.2 to 0.5 mg/kg has proved useful in the control of seizures when IV access is not available.[157] Onset can be fairly slow and the duration prolonged. The IV route offers a titratable effect but also adds the danger of acute overdose. The use of intranasal sedation administration has been reported for a variety of drugs. A disposable device such as the Mucosal Aerosol Device can be used. The Mucosal Aerosol Device attaches to a Luer lock syringe and has a soft cone insert for placement in the nares. It creates a fine spray that improves drug delivery and deposition onto the nasal mucosa. Another route of administration is transmucosal administration, such as the fentanyl "lollipop" (ACTIQ). Dosing recommendations are shown in Table 123-18. One must always keep in mind that BZD-opiate or barbiturate-opiate combinations are potent causes of respiratory depression, and extra monitoring and vigilance should be used. With IM and oral medications, adequate time should elapse to allow absorption before a further dose is given to avoid accidental overdose.

As noted in Table 123-15, different procedures require different qualities of sedation. These qualities are found in the array of drugs available to the intensivist (Table 123-19). It may be useful to choose the sedative agent or agents that best fit the particular requirements for the procedure being performed.

Opiate and BZD antagonists should be readily available wherever moderate sedation is being performed. Staff caring for these patients should understand the drug indications and dosing of these medications to reduce any potential delay in their appropriate use. They can quickly and effectively reverse the respiratory depression from excessive doses of sedation.

In some circumstances the services of the anesthesia department may be useful. The anesthesia department has access to other pharmacologic agents such as propofol and nitrous

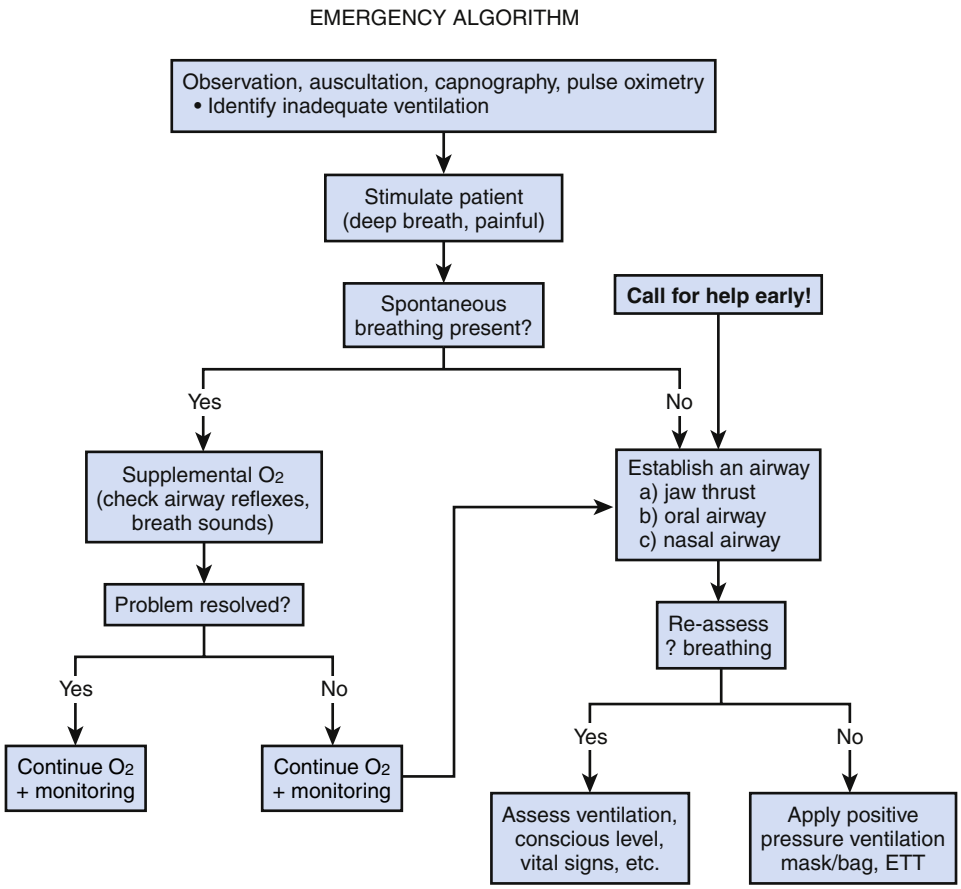

Figure 123–4. Sedation emergency airway algorithm. *ETT,* Endotracheal tube.

Table 123–18 Drug Dose Guidelines for Moderate Sedation

Route	Drug	Dose
PO	Chloral hydrate	50–75 mg/kg (repeat 25 mg/kg)
	Diazepam (Valium)	0.2–0.4 mg/kg (max, 20 mg)
	Midazolam (Versed)	0.5–0.75 mg/kg (max, 20 mg)
IM	Pentobarbital (Nembutal)	4–6 mg/kg (max, 100 mg)
	Fentanyl (Sublimaze)	1–3 μg/kg
	CM3	0.08–0.1 mL/kg (max, 2 mL)
IV	Morphine	0.1 mg/kg
	Meperidine (Demerol)	1–2 mg/kg (max, 75 mg)
	Fentanyl (Sublimaze)	1–2 μg/kg (max, 5 μg/kg)
	Midazolam (Versed)	0.05–0.1 mg/kg
	Diazepam (Valium)	0.05–0.1 mg/kg

CM3, Catheterization mixture number 3; *IM*, intramuscular; *IV*, intravenous; *PO*, by mouth.

Table 123–19 Sedation Quality: Different Drugs

	Amnesia	Analgesia	Relaxation	Inattention
Barbiturates	0	0*	0	4
BZDs	4	0	2	4
Antihista-mines	1	0	0	2
Opioids	0	2	0*	2
Chloral hydrate	0	0	0	4
Ketamine	2	4	0*	4
Nitrous oxide	3	3	1	3

BZD, Benzodiazepine; *0,* possible effect.
*May antagonize other drugs having this effect.

oxide, as well as the inhalational agents. The ability to use a deeper level of sedation if required is easily obtained with these rapidly acting, short-acting agents. In emergency procedures where the patient's NPO status is unsafe or unknown, patients may need to undergo intubation to protect the airway.

Anesthesiologists have the ability to perform a "needle-less" sedation technique using a gas induction with anesthetic agents; an IV drip may be placed if required when the patient is asleep. This technique is especially useful for repeat procedures in oncology patients. Also, anesthesia personnel are better able to sedate patients whose illness may contraindicate routine moderate sedation protocols (Box 123-11).

Box 123–11 Patients Unsuitable for Moderate Sedation

Premature (<60 weeks' gestation)
Apnea, respiratory, or cardiac monitor at home
Airway obstruction
BPD, COPD, recent pneumonia, or croup
Uncontrolled seizures or multiple medications
Multiple psychotropic medications
Poorly controlled asthma
Vomiting
GERD
Raised ICP
History of difficult sedation

BPD, Bronchopulmonary dysplasia; *COPD*, chronic obstructive pulmonary disease; *GERD*, gastroesophageal reflux disease; *ICP*, intracranial pressure.

Postprocedure Care and Monitoring

Care of the patient during the recovery period after moderate sedation is important. The patients must be monitored during recovery to ensure adverse events are rapidly recognized and treated. The recovery area should be equipped with appropriate monitors and resuscitation equipment and have a trained individual in attendance. The monitoring should be performed to the same degree as during the actual procedure. Level of consciousness and vital signs should be recorded at regular intervals. A physician who is responsible for the patient must be identifiable and must be easy to contact if required urgently. Patients may be discharged home when they are alert and orientated or when they have returned to baseline if baseline initial mental status was abnormal. Vital signs should be stable and within acceptable limits. A sufficient time should have elapsed if a reversal agent was used (2 hours). Patients should be discharged in the presence of a responsible adult to accompany them home and report any complications. Written instructions should be given to the parent concerning diet, medications, and activities, and a 24-hour contact telephone number also should be given to the parent.

Moderate sedation is safe and frequently used; unconscious sedation is potentially hazardous, and patients who undergo it require careful monitoring. Hospital protocols are useful for a smoothly run, safe sedation policy.[158] Staff should be appropriately trained in sedation and resuscitation basic and advanced life support. When the ASA/AAP recommendations are followed, the risks of a sedation-related complication can be reduced.[159] Individual risk factors include deep sedation and the use of chloral hydrate. When all the recommendations for moderate sedation, including NPO, ASA class, avoidance of deep sedation, sedation level monitoring, and drug use were followed, the adverse event rate was zero.

Sedation for Magnetic Resonance Imaging

The PICU physician is often called upon to provide sedation for a patient in the ICU who is undergoing MRI. Also, many institutions rely on the PICU team to provide a sedation service for other inpatients or outpatients undergoing MRI. Deep sedation is often required for effective sedation of younger children undergoing an MRI scan. The same standards should be adhered to as with any other child undergoing sedation[160] with respect to patient selection, monitoring, and postimaging care.

Box 123–12 Indications for Sedation for Magnetic Resonance Imaging

Very young or agitated patient
A prolonged study (multiple scans)
Anxiety
Claustrophobia
Intensive care patient

Not a complete list.

Box 123–13 Contraindications to MRI

Cardiac pacemaker
Aneurysm clips
Automatic implanted cardiac defibrillator
Neurostimulator
Pacing wires
Cochlear implant
Implanted insulin pump
Penile prosthesis
History of ocular injury involving metal object
History of vascular surgery <3 mo
History of soft tissue metal foreign body <3 mo
History of orthopedic hardware <3 mo

Not a complete list.

MRI is an imaging modality that is being increasingly used to aid in the diagnosis of neuroanatomic disorders. The patient is required to lie still within a small space while multiple images are obtained. MRI scanning is performed less rapidly than computed tomography (CT) scanning. Movement by the patient causes degradation of the image quality, and a change in the patient's position may affect the homogeneity of the magnetic field, which is optimized at the beginning of the scan. Studies can take from 45 minutes to more than 2 hours, with individual sequences taking 3 to 10 minutes. The scanner is noisy and the restriction on space and movement can induce claustrophobia in some patients. The patient also may experience a slight increase in temperature. Most adults and older children (older than 6 years) are capable of lying still for the scan. With the use of earplugs and music it is well tolerated. Several groups of patients, however, may require sedation[161] for the scan to be performed (Box 123-12).

Because of the large magnetic field, several unique problems[162] can occur during a scan. These problems include the potential risk of the magnet causing a ferromagnetic object to move or heat up or the induction of an electric current from the radio frequency pulses and switching magnetic gradients used in generating the images. This potential risk results in a significant list of contraindications to MRI (Box 123-13). Sedating these patients also entails several risk factors. The patient is in a remote location, with limited access to and visibility of the airway. Several equipment issues exist as well (Box 123-14). The monitors used must be suitable for use in the MRI suite.[163] They should be nonferromagnetic; the cables should be screened from electromagnetic interference (fiberoptic is ideal); and the signal should be filtered to avoid radio

Box 123–14 Potential Difficulties in MRI

Malfunction of anesthesia or sedation equipment
Malfunction of monitoring
Anesthesia or sedation equipment causing interference with image quality
High-velocity ferromagnetic projectile from loose object
Disruption of electronic devices

frequency interference (which interferes with image quality). Despite the specialized technology that is available, several problems remain. The ECG waveform is frequently altered, and analog information is often lacking during a scanning cycle. The ECG cables may cause burn injury, and special ECG electrodes are required to avoid burn injury. For pulse oximetry to be performed, a special probe is required. Heating of the usual probe may cause burn injury. Fiberoptic connection to the patient is best. Capnography requires long tubing, which results in a prolonged upsweep and delay in displaying real-time measurements. The respiratory rate and trends can still be useful. Any battery-powered monitor requires a nonmagnetic lithium battery. Exposure to the MRI shortens battery life. Most ICU ventilators are not MRI compatible (Servo *i* is available as an MRI compatible model). Some specialized MRI-safe anesthesia machines have a ventilator; however, their use should be restricted to the anesthesia staff who are familiar with the equipment. The IV poles and the equipment carts also should be nonferromagnetic. Any equipment with a transformer (e.g., syringe pumps and IV pumps) must be kept out of the magnetic field. Gas cylinders must be aluminum. The area around any magnet that generates a magnetic field stronger than 5 G should not contain any ferromagnetic items.

Any staff entering the MRI suite should remember to remove any ferromagnetic objects, including keys, watches, pens, and credit cards. Stethoscopes and laryngoscopes also are ferromagnetic. Infusion pumps should be outside the magnetic field, that is, outside the 5-G line. The electric motor in infusion pumps emits electromagnetic radiation and may run at an abnormal speed in the presence of a strong magnetic field. The pump is also a projectile risk. IV infusions through long tubing from outside the scanner can be useful so that the depth of anesthesia can be altered without having to enter the MRI suite. MRI-compatible infusion pumps are now also available. Some of these pumps allow changing infusion rates via electronic hand-held devices without entering the scanning room The ICU patient's infusions can be changed over to these infusion devices while the patient is still in the ICU and then transported to the scanner.

The use of a cuffed endotracheal tube may affect the quality of the MRI image because of metal in the valve of the pilot balloon and reinforcement of the mask airway. With the patient in the ICU, special care must be taken to ensure that all cables and transducers that may be carefully screened and all ferromagnetic objects are removed ("hiding in the sheets"). For invasive vascular pressure to be measured, the transducer should be as far from the patient as is practically possible and separated with a saline-filled pressure line. If cardiac arrest occurs, the patient should be removed from the magnetic field. The defibrillator should be kept outside the magnetic field and checked regularly. A nonferromagnetic code cart is also advisable. It is essential that the code team follow the rules about removing any loose magnetic items before entering the MRI suite or else a lethal projectile may be released. Ventilating the lungs of the ICU patient is often performed by hand ventilation by ICU staff in the MRI suite. The sedation technique is often a continuation of that used in the ICU, especially for a patient who undergoes intubation. In some children single doses of fentanyl or midazolam may be sufficient for a adequate sedation. If deeper sedation is required for patient comfort/cooperation, then IV sedation with supplemental oxygen with propofol is useful. A bolus of 2 mg/kg and an infusion of 100 μg/kg/min is a good method for patients with few medical problems and an easily maintained airway. It results in a rapid recovery with little nausea or vomiting.

Specific Drugs for Sedation

Ketamine

Ketamine is a phencyclidine derivative that provides sedation and analgesia. It results in a state of dissociative (trancelike) anesthesia. It is available in a variety of different dilutions, such as 10 mg, 50 mg, and 100 mg/mL. The latter is the most useful for IM use and the preparation of infusions. For a state of general anesthesia to be induced, a dose of 2 mg/kg IV is required. Onset takes 1 to 2 minutes with anesthesia lasting 10 to 15 minutes. Lower doses may be used for sedation. Anesthesia also can be induced by the IM route with a dose of 10 mg/kg, although onset is slower (5 to 10 minutes) and duration of prolonged effect is 45 to 60 minutes. It is metabolized by the liver and excreted by the kidneys. The half-life is 3.1 hours (see Table 123-11).

The adverse effects of ketamine include hypertension, tachycardia, increased intracranial pressure, and bronchodilation. The bronchodilation is probably due to its sympathomimetic action. It is a direct myocardial depressant, but blood pressure is usually maintained by the sympathetic stimulation that ketamine causes. In critically ill patients who already are using their maximum sympathetic drive, ketamine may cause a decrease in cardiac output or even cardiac arrest. Hallucinations and other psychiatric symptoms are often reported during and after its use in adults, but they occur less frequently in children. Ketamine is a potent sialogogue, and the use of an anticholinergic agent such as glycopyrrolate may be helpful. Its use is contraindicated in patients who cannot tolerate hypertension,[164] have a history of cerebrovascular hemorrhage, have psychiatric disturbances, and have raised ICP. It is a useful agent for sedation for procedures, especially if there is no IV access. It has been used in patients with status asthmaticus as an adjunct bronchodilator both in intubated and nonintubated patients at an infusion rate of 0.5 to 2 mg/kg/h. After discontinuing its use, the patient should receive BZDs to minimize the likelihood of hallucinations and be nursed in a quiet environment. Ketamine cannot be assumed to preserve pharyngeal reflexes any better than other sedatives agents, and apnea and airway obstruction can still occur.[165] NPO guidelines should still be observed.

Etomidate

Etomidate is a carboxylated imidazole that is unrelated to other anesthetic agents. It is a rapidly acting IV anesthetic agent, which, like other rapid-onset anesthetic agents, partitions into the brain within one circulation time and redistributes out of

the brain over the next few minutes. It is available dissolved in 30% propylene glycol as a 2 mg/mL solution. Like propofol, it causes pain on injection. The anesthetic dose is 0.2 to 0.3 mg/kg. It has a favorable adverse effect profile with minimal cardiovascular and respiratory depression. Etomidate is associated with a high incidence of nausea and vomiting after emergence from anesthesia. Its pharmacokinetics are shown in Table 123-11. The greatest disadvantage of etomidate in the intensive care setting is adrenocortical depression due to inhibition of adrenocortical mitochondrial 11-β-hydroxylase.[166] This effect is present in neonates and in adults.[167] The outcome of patients sedated with etomidate is worse than in those using alternative sedation, and steroid deficiency is thought to be the cause.[168]

In the CNS, etomidate suppresses seizure activity, although patients may show excitatory movements not associated with cortical EEG changes suggestive of seizures. The intracranial and intraocular pressures are lowered. It is the drug of choice for patients who are undergoing emergency intubation, those who have head injuries, and those who have a compromised cardiovascular system, and it is safe for use in patients with asthma because there is no histamine release. Etomidate has the highest therapeutic index of any anesthetic agent.

Several case reports of the satisfactory use of etomidate for controlling refractory intracranial hypertension have been published; it is associated with fewer cardiovascular problems than are barbiturates. Nevertheless, caution must be taken concerning the development of a lactic acidosis due to the metabolism of propylene glycol.

Inhalational Anesthetic Agents

The inhalational agents remain the most widely used anesthetics in the operating room, although their mechanism of action is still poorly understood. The following agents are currently in clinical use: enflurane, isoflurane, sevoflurane, and desflurane. Sevoflurane and desflurane are newer agents that currently have limited use in the ICU. Isoflurane remains the most logical choice of inhalational anesthetic in the ICU based on its cost/benefit ratio. As with any drug used in the ICU, it is important to understand the pharmacology, the adverse effect profile, and, in this case, the technical aspects of delivering these agents to the patient. These drugs are all fluorinated hydrocarbons (Figure 123-5). Except for halothane, which is no longer in common clinical use, they are ethyl-methyl esters. Each agent has different physicochemical properties that are important to its properties (Table 123-20).

Nitrous oxide is frequently used by anesthesia personnel as an adjunct. In some institutions it is used as the basis of a hospital pediatric procedural sedation service for children. Patients on the hospital floor undergoing minor to moderately painful procedures are mildly sedated with 50% nitrous oxide (as routinely used in pediatric dentistry); this technique has a good safety profile. A newer anesthetic agent in use in Europe is xenon. This gas has anesthetic properties with very few cardiac adverse effects. It is very expensive to use and requires a specialized fully closed breathing circuit to minimize the amount of gas used. The rate at which a change in inspired concentration is reflected in the brain is determined mainly by the blood/gas solubility. The more soluble the gas is in blood, the slower is the change due to the gas dissolving into the blood and reducing the partial pressure available to equilibrate with the brain. Sevoflurane and desflurane are the least soluble and therefore have the most rapid onset and offset; halothane has the slowest onset. The potency of the agents is represented by the minimal alveolar concentration (MAC). The MAC is the percent of inhaled anesthesia agent required to prevent 50% of anesthetized patients from responding to a surgical incision. The lower the MAC, the more potent the agent is. Halothane is the most potent of the agents used and desflurane is the least potent. The MAC of anesthetic agents is not constant with age. For all the agents it is highest for those aged 1 to 12 months, and the MAC falls throughout childhood to reach adult levels. Neonates show a slightly reduced MAC compared with infants. The oil/water solubility determines the degree of accumulation of the agent within the body fat stores. A highly fat-soluble agent will have larger body stores; therefore recovery from the agent is delayed.

These agents all have significant effects on the cardiorespiratory systems. Although respiration can be controlled, the negative inotropic and vasodilator effects are pronounced and limit the concentrations that can be used. Halothane, the oldest of these agents, has the greatest degree of cardiac depression. Sevoflurane and desflurane have an adverse effect profile similar to that of isoflurane, except that sevoflurane is partly metabolized to a potentially toxic metabolite, compound A, from a reaction with the soda lime used in anesthesia circle systems. For accumulation of compound A to be minimized in the circuit, a fresh gas flow of greater than 2 L/m should be used. Thus sevoflurane is may not be not a good choice for prolonged ICU treatment with this type of circuit. Desflurane has some sympathomimetic effect, especially when the concentration is abruptly increased, and significant tachycardia and hypertension can occur.

Adverse effects of halothane include hypotension, which is due to direct myocardial depression. It also causes bradycardia

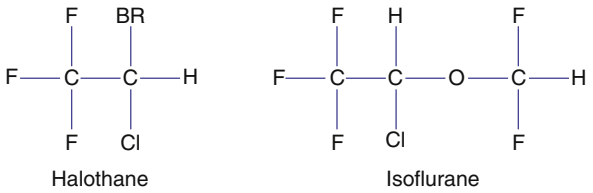

Figure 123–5. Structures of inhalational agents.

Table 123–20 Vapor Characteristics

	Halothane	Isoflurane	Sevoflurane	Desflurane
MW	197.4	184.5	200	168
SVP (mm Hg)	243	240	157	700
Boiling point (8° C)	50.2	48.5	58.5	22.8
MAC (%)	0.75–1.2	1.3–1.85	2.5–3.0	8.0–10
Blood/gas solubility	2.3	1.4	0.68	0.42
Oil/w% metabolized	20	0.2	3.3	0.02

MAC, Minimal alveolar concentration; *MW*, molecular weight; *SVP*, saturated vapor pressure.

because of effects on the sinoatrial node and vagal stimulation. Cardiac arrhythmias may occur, most commonly junctional rhythm. Halothane also sensitizes the myocardium to catecholamines, especially when the patient is hypercapnic or hypoxic. Because these physiologic changes are common in the intensive care patient, the potential for serious interactions with halothane abound. Halothane is metabolized approximately 20% by the liver, and a trifluoroacetic metabolite may cause an immune-mediated fatal hepatitis.[169] Isoflurane causes hypotension mainly because of vasodilation, while maintaining cardiac output. Concern has been expressed about a coronary steal phenomenon occurring in which blood is diverted from a partially obstructed coronary bed served by collateral arteries, due to vasodilation. The evidence for this phenomenon is weak, however, and ischemia is probably due to hypotension rather than a true steal phenomena. Isoflurane vapor is pungent and may cause airway irritation, coughing, and laryngospasm if the patient is not adequately sedated before its use. It is only minimally metabolized (0.2%), and a hepatitis reaction is extremely unlikely.

Malignant hyperthermia is a rare reaction that may occur whenever the halogenated inhalational anesthetics or succinylcholine is given to a patient. It involves the unrestrained entry of calcium into myocytes and consequential consumption of adenosine triphosphate, resulting in metabolic failure. Hypermetabolism, manifested by increased CO_2 production, and acidosis occur. Later the body temperature rises and death from hyperkalemia occurs. Correction of blood chemistry, aggressive cooling, and the administration of dantrolene are urgently indicated.

The metabolism of all the anesthesia agents can result in the production of free fluoride ions. Concentrations of fluoride greater than 50 μmol/L can cause renal dysfunction and a reduced concentrating capacity. This risk would appear to be higher for both halothane and sevoflurane because of their more extensive metabolism. It also may be exaggerated by patients who are prescribed drugs that induce the cytochrome P450 enzyme complex.

Inhalational agents may cause hepatotoxicity in two ways: (1) by metabolism to reactive intermediates that are directly hepatotoxic or (2) through the intermediates that form adducts to hepatic proteins. These new proteins are then recognized as foreign, and an immune response that causes hepatic injury occurs. This is thought to be the mechanism of halothane hepatitis. This form of hepatitis is most common after halothane use; even then it is rare, occurring in 1 of 100,000 cases. It is less common with isoflurane, sevoflurane, or desflurane, which are much less metabolized. This fulminant hepatic failure, which may be fatal, is most common after repeated administrations of halothane in older obese patients. The predominance of reductive halothane pathway metabolism results in a trifluoroacetic acid metabolite that forms a hapten. Halothane hepatitis is also less common in children.

All of the inhalational agents cause cerebral vasodilation, which results in an increase in CBF (because of decoupling of the demand/flow ratio) and ICP. In pediatric patients with raised ICP, there was no difference among isoflurane, desflurane, and sevoflurane with respect to the increase in ICP and CBF.[170] In contrast, IV anesthetics maintain the demand/flow ratio, and CBF and ICP fall, with the exception of ketamine. In addition to an effect of CBF, the arterial blood pressure typically will decrease with anesthesia, and the effect of this on the CPP must be accounted for. In one study, the effect of the decrease in arterial pressure on CPP exceeded the effect of increasing ICP by a factor of 3.[171] With these potential effects on CBF, the use of isoflurane should be carefully considered in patients who have or are at risk of raised ICP. Nevertheless, isoflurane has been safely used in neuroanesthesia with controlled ventilation to a normal $Paco_2$ and an inspired concentration not exceeding 1 MAC.[172]

Isoflurane has two main applications in the PICU: sedation and the management of refractory asthma. Only a few reports have been made of long-term sedative use of isoflurane in the ICU. In an adult study, 40 patients[173] who received an average of 96 MAC hours of isoflurane showed hemodynamic stability, less tachyphylaxis compared with other sedative agents, and a more rapid wean from the ventilator. No evidence was found of renal or hepatic dysfunction with serum fluorides less than 50 μmol/L. In a pediatric study, 10 patients[174] who had been receiving large doses of opiates or BZDs received an average of 130 MAC hours of isoflurane. The range of use was from 1 to 30 days. Fifty percent of the patients experienced a withdrawal-like phenomenon—most commonly, those who had received more than 70 MAC hours of isoflurane. Fluoride levels also were measured, and although they were correlated with the duration of treatment, none was greater than 30 μmol/L. The highest levels were in a patient who was taking both phenytoin and phenobarbitone. Hypotension only occurred in one patient. No hepatic or renal dysfunction occurred. The withdrawal was treated with a combination of BZDs and haloperidol with good effect. Isoflurane also has been used in patients with renal dysfunction, and fluoride levels were not elevated.[175] The starting dose for sedation should be 0.5%; this dose can then be titrated to effect by the ICU team. At levels above 1.5%, other sedative agents and paralytics often are not required.

Multiple case reports of the use of inhalational agents for status asthmaticus in both adults and children have been made. Because of its speed of onset and its bronchodilation effects, isoflurane is a useful adjunct to β_2-adrenergic agonists. If no improvement occurs, or if unacceptable adverse effects occur, then its effects rapidly wane on discontinuation. Isoflurane is recommended for use because of its safer adverse effect profile. No reports of renal or hepatic dysfunction have been made despite its use for often prolonged periods. Hypotension seems to be more common in patients sedated with isoflurane; it is possibly related to increased intrathoracic pressure and the potential for greater preload reduction with vasodilation. Fluid boluses and occasionally vasopressors are often required. Because isoflurane is not an analgesic agent, opiates may be needed for painful or uncomfortable procedures. Also, when the patient is weaned off the isoflurane, additional sedatives will be required. The isoflurane should be started at 0.5% and titrated for effect; doses of up to 2.5% have been reported as safely used.[176]

The inhalational anesthetic agents are liquids at room temperature. A special delivery device called a vaporizer is required to deliver an accurate supply of the vapor. All vaporizers have several features in common. They provide a reservoir of the inhalational liquid with a level indicator and are capable of delivering a constant level of vaporization. Most newer vaporizers also have a color-coded keyed filler (e.g., purple for isoflurane and yellow for sevoflurane) that prevents the accidental filling of the vaporizer with the wrong agent.

This error could result in overdosing the patient because the vaporizer calibration is drug specific. If two vaporizers are accommodated in series on the anesthesia machine back bar, then an interlocking system should be used to prevent the accidental use of both vaporizers. Otherwise, the results would be contamination of the second vaporizer by gas from the first vaporizer and an uncontrolled excess delivery of gas to the patient.

One of the main problems with using these inhalational agents in the PICU is how to deliver them to the patient. One technique is to use an anesthesia machine to deliver the gas to an ICU ventilator with the correct oxygen percentage and inhalational agent. This mixture is delivered from the fresh gas outlet of the anesthesia machine. It is selected by adjustment of the flow rotameters on the anesthesia machine to give the desired oxygen concentration and then selection of the desired inspired concentration of inhalational agent on the vaporizer. Unfortunately, most ICU ventilators will not accept this low-pressure gas supply as their driving gas. The Servo 900C is an exception because it has a low pressure inlet option for the driving gas. High flow rates are required to maintain filling of the bellows of the ventilator; the flow rates must be higher than the minute ventilation. This requirement sometimes results in a limitation of inspired oxygen because the maximum flow of oxygen from the rotameters of the anesthesia machine is 10 to 12 L/m. Also, this process consumes a lot of vapor.

Also available is another Servo ventilator, the 900D, that has a custom-fit vaporizer on the normal high-pressure input. This machine is similar to the 900C, but it has been modified for anesthesia use and also allows hand ventilation with inhalational agents. Often the only alternative is to deliver anesthetic with an anesthesia machine. Anesthesia machine ventilators are not as sophisticated as ICU ventilators, may not be able to deliver appropriate volumes for pediatric patients, and often have limited positive end-expiratory pressure capabilities. The anesthesia machine needs to be checked before use and its correct function should be continually assessed during its use, which requires an understanding of the setup and alarms on the machine and an understanding of the procedures of the appropriate tests. This understanding usually is not within the confines of a pediatric intensivist's scope of practice, and an anesthesiologist should be involved to ensure the safe and effective use of this apparatus.

Whenever inhalational agents are used, the waste gases from the expiratory limb of the ventilator should be scavenged to avoid prolonged exposure of the health care worker to these agents. The Occupational Safety and Health Administration limits occupational exposure to 2 ppm halothane for health care workers.[177] The worker is at risk of becoming sedated, and potential teratogenic effects also exist. Several large studies about prolonged exposure to these agents have not shown any increase in risks for anesthesia personnel with respect to hepatic disease, teratogenesis, spontaneous abortions, psychological difficulties, infertility, neuropathy, or bone marrow depression.[178] Caution also should be taken when filling the vaporizer to avoid spilling the liquid during the process.[179] Two forms of scavenging are available. A passive system involves simply a tube connected to the expiratory limb connected to the outside. This system is at risk of occlusion because of kinking or someone standing inadvertently on the tubing, which will then occlude the expiratory limb of the ventilator. An active system involves an active suction to the expiratory limb, with a safety reservoir bag in series to prevent excess suction pressure from being exposed to the patient.

In the operating room it is routine to monitor the levels of anesthesia agents given with a gas analyzer. This monitoring provides an inspired and expired inhalational agent concentration and is helpful to ensure that the vaporizer is functioning correctly, that the vaporizer has not emptied without being detected, and that the concentration dialed on the vaporizer has reached its effect. When the end-tidal inhalational agent concentration equals the inspired agent, then steady state has been achieved. This steady state normally occurs rapidly with isoflurane, but in a patient with severe asthma due to the severe limitation in airflow gas exchange, achievement of steady state may be delayed.

If the PICU staff is unfamiliar with the delivery system being used for the isoflurane, then it would be appropriate to have staff from the anesthesiology department set up the equipment and ensure that it functions correctly. Failure to configure the delivery system correctly has the potential to cause considerable harm or death. Once the situation has stabilized, an anesthesiologist may not be required at the bedside. However, an anesthesiologist should be available by pager to help troubleshoot any difficulties. In these cases the inspired agent should be monitored continually.

The use of inhalational agents in the PICU involves the use of equipment that may be unfamiliar to pediatric intensive care physicians. Isoflurane appears to be the best choice,[180] and it offers several useful advantages, including the ability to deeply sedate patients (especially those difficult to sedate) without polypharmacy.[181] Although they are currently poorly defined,[182] tolerance and a withdrawal-like syndrome have been described; however, they appear to occur more slowly than with other sedative agents. It may be helpful to have a set of guidelines available for isoflurane use to facilitate its use in the PICU. These guidelines could include equipment use, monitoring requirements, dosing, and treatment of complications.[183] Caution should be used in patients who may have raised ICP because isoflurane may increase CBF. Isoflurane does allow for rapid arousal if neurologic examinations are required.

The Anaesthetic Conserving Device (AnaConDa) is a modified heat moisture exchanger that has been developed to allow the use of inhalational agents in the ICU without requiring high fresh gas flows or specialized ventilators.[184] It is placed in the breathing circuit between the ventilator Y circuit and the endotracheal tube. The liquid anesthesia agent is injected directly into the device using a syringe pump. The device membrane allows for the inhalational agent to be taken up by the inspired gas. On expiration much of the inhalational agent is deposited on the membrane, allowing for an efficient inhalational rebreathing technique. The inspired concentration of the inhalational agent is monitored from the device using a routine gas analyzer. It has been used in several adult ICU trials as well as in a series of three children. Some problems due to excess dosing have been experienced, and the 100 mL dead space of the device, as well as resistance to gas flow, may make its use inappropriate in children. Compared with an inhalational agent vaporizer, there is no percentage inhalational agent dial. The rate on syringe injection determines the percentage of the inhalational agent. This infusion rate is set according at a pre-recommended rate. Initially the inspired concentration is low because of dilution. Differences in minute

ventilation and gas flows may make this pre-recommended rate inaccurate. The injection rate needs to be titrated to the monitored percent of the inspired inhalational agent, which can increase significantly with time, especially until equilibrium is reached. The AnaConDA device is not approved for use in the United States.

Apoptosis

Recent evidence from rodents suggests that most general anesthetics and sedatives, which are either *N*-methyl-D-aspartate receptor antagonists or $GABA_A$ agonists, trigger apoptosis or programmed cell death. Those incriminated include inhalational anesthetic agents (including nitrous oxide), propofol, benzodiazepines, and ketamine. Adjuvants that do not trigger apoptosis include dexmedetomidine, melatonin, and possibly xenon. Interestingly, lithium has been shown to exert an antiapoptotic effect. Massive apoptosis occurs in vulnerable regions of the brain that are responsible for learning and cognition (e.g., the hippocampus, caudate/putamen, thalamus, and others) when these proapoptotic anesthetics are administered during the period of synaptogenesis or the rapid brain growth spurt in young rodents, most notably, during the seventh postnatal day. The severity of the apoptosis depends on the dose of anesthetic and duration of administration. In addition to histologic changes associated with apoptosis (as evidenced by caspases-3 staining), long-term memory loss and cognitive impairment have been demonstrated.

Whether these data are directly applicable to humans has not been established. Primate research suggests that ketamine[185] induces apoptosis in vulnerable young monkeys, although an exposure to ketamine of less than 3 hours duration does not induce significant injury. To date, the studies in humans have been retrospective in design. Four studies have demonstrated conflicting findings on the effects of anesthetics on cognitive function in young children. The most impressive of these retrospective studies is from the twin registry in Denmark[186] in which monozygote twins concordant or discordant for anesthetic exposure before the age of 4 years failed to demonstrate any differences in educational achievement or cognitive impairment years later. A prospective randomized study of general anesthesia versus regional anesthesia for lower abdominal surgery with long-term evaluation of cognitive function in children is currently under way (expected conclusion in 2013) and may help us to understand the risk, if any, of administering these general anesthetics to vulnerable human infants and young children.

Pharmacoeconomics

In today's economical climate it is important to consider the cost of the different sedation options available to the pediatric intensivist (Table 123-21). Most PICUs use a low-cost sedative regimen for the bulk of the sedations required and keep the more expensive options for selected circumstances. Table 123-21 shows the different costs of some of the available agents in the PICU as well as the 24-hour cost for a child weighing 20 kg. They are presented as the cost per kilogram per hour of sedation at equipotent doses. The costs are the lowest hospital drug cost (at the Women's and Children's Hospital of Buffalo) for each agent in its most inexpensive form and exclude preparation, delivery, and equipment issues related to each drug. Fentanyl is inexpensive. For a 20-kg child, it costs $7.49 per day. Midazolam is now a more inexpensive option than is lorazepam. The other synthetic opiates are more expensive to use, and consideration should be given to appropriate indications for their use. A rapid recovery, however, with as quick an extubation as may be possible with remifentanil and early ICU discharge is also a considerable cost factor to be considered. Propofol (which is now available in a generic form) and ketamine are both relatively inexpensive options for ICU sedation, if they are deemed clinically appropriate. The drug costs of isoflurane and sevoflurane are comparable to those of the BZDs; however, they require the availability of a specialized delivery system, which could increase the cost. If a device were available that could deliver these agents at low flows with most of the available ICU ventilators, then inhalational sedation would be a more attractive option.

Table 123–21 Relative Drug Costs of Different ICU Sedative Agents

Drug	Dose	Cost/kg/hr ($)	24-Hour Cost for 20-kg Child ($)
Morphine	50 μg/kg/h	0.002	1.15
Fentanyl	4 μg/kg/h	0.016	7.49
Sufentanil	0.8 μg/kg/h	0.058	27.80
Remifentanil	0.4 μg/kg/min	0.253	121.31
Midazolam	0.1 mg/kg/h	0.02	9.38
Lorazepam	0.1 mg/kg/h	0.028	13.51
Propofol	5 mg/kg/h	0.043	20.87
Ketamine	1 mg/kg/h	0.008	3.89
Dexmedetomidine	0.5 μg/kg/h	0.15	70.62
Isoflurane	0.5% (@ 61 L/min)	0.93	22.30
Desflurane	3% (@ 61 L/min)	29.92	717.79
Sevoflurane	1% (@ 61 L/min)	1.36	32.74
Xenon	30% (proprietary closed circuit)		404.76

References are available online at http://www.expertconsult.com.

VII Chapter 124

Malignant Hyperthermia

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PEARLS

- Malignant hyperthermia (MH) is a muscle disorder first recognized as a complication of general anesthesia with the potent inhalational anesthetic agents.
- The initial signs of MH can also occur postoperatively as fever with excessive metabolic rate and muscle injury.
- Myoglobinuria produces renal injury in about 10% of MH cases. Renal failure is more likely when treatment with dantrolene is delayed.
- Disseminated intravascular coagulation and cerebral edema may complicate fulminant MH.
- After initial treatment with 2.5 to 10 mg/kg of dantrolene, at least 1 mg/kg of dantrolene should be given every 6 hours for four doses because 20% of patients experience an exacerbation or recrudescence of MH within 24 hours after the acute episode.

The physician in the pediatric intensive care unit (PICU) may first encounter a patient with malignant hyperthermia (MH) in transfer from the operating room or from an outpatient facility where general anesthesia was given and treatment for acute MH was begun. Because 20% of patients experience a recurrence of MH in the 24 hours after the initial episode, close observation for a relapse of MH is warranted and administration of dantrolene for at least 24 hours after the initial episode is recommended. Alternatively, the ICU physician may be the first to entertain the diagnosis of MH in a patient admitted to the ICU for medical care or postoperative management.

MH is characterized by hypermetabolism, but there are many causes of fever and muscle injury that are not MH. Regardless of the underlying cause, ICU management should be directed to control critical temperature and complications of rhabdomyolysis. The ICU physician should pursue common diagnoses while directing diagnostic workup for the rare syndrome of MH.

Pathophysiology

In fulminant MH, a dramatic increase in the metabolic rate of genetically abnormal muscle results in muscle injury and multiorgan system failure. The underlying biochemical defect is a sudden, sustained increase in the concentration of calcium ion in the sarcoplasm.[1] Carbon dioxide (CO_2) production increases severalfold. Even with increased minute ventilation, it may not be feasible to maintain normocarbia. Lactic acid production overwhelms the body's buffering capacity. Increased O_2 demand and the concomitant sympathetic response stress the cardiovascular system. High circulating catecholamines may stimulate muscle metabolism and hasten fulminant MH, but MH can occur in the presence of total sympathetic blockade and normal plasma catecholamines. Conversely, dantrolene, which can prevent MH in the susceptible patient, has no effect on stress-induced increases in catecholamines.[2]

MH can progress rapidly to severe mixed acidosis, hyperkalemia, elevated temperature as in heatstroke,[3] and rhabdomyolysis. Renal failure, disseminated intravascular coagulation, cerebral edema, pulmonary edema, dysrhythmias, and cardiovascular collapse are potential consequences of fulminant MH. Even with aggressive treatment, death may ensue. Before dantrolene, the mortality rate of MH was 70%. Symptomatic therapy including mechanical ventilation, active cooling, administration of bicarbonate, expansion of the intravascular volume, and treatment of dysrhythmias can prolong life during an episode of fulminant MH. However, the most effective therapy is intravenous dantrolene.[4]

In the majority of MH-susceptible (MHS) humans, there is a defect in the ryanodine receptor channel (RYR1).[5] Normally, depolarization of the sarcolemma is propagated through the transverse tubule system. There, the dihydropyridine receptor (DHPR), the skeletal muscle L-type calcium channel, undergoes conformational change in response to depolarization. This is coupled to opening of RYR1 through which calcium flows out of the sarcoplasmic reticulum (SR) into the myoplasm. The interaction between DHPR and RYR1 also activates entry of extracellular calcium (ECCE) into the myoplasm. The $\alpha_2\delta_1$ subunit of the DHPR is necessary for sustaining calcium transients in response to repeated action potentials.[6] MHS RYR1 has increased sensitivity to agonists that open the channel[7,8] and decreased sensitivity to inhibitors of RYR1 channel opening. Furthermore, ECCE is greater than normal in myotubes expressing MHS RYR1.[9] Dantrolene inhibits ECCE in both MHS and normal muscle. Store-operated calcium entry (SOCE) is another process, occurring after depletion of SR calcium, that moves extracellular calcium into the myoplasm. SOCE is coupled to RYR1 and decreased by dantrolene.[10]

Genetics

MHS has been described as a syndrome with autosomal dominant inheritance, incomplete penetrance, and variable expressivity. The first-degree relatives of an individual that

has had fulminant MH are considered potentially MHS until they have normal results of in vitro muscle contracture testing with halothane and caffeine (CHCT). Incomplete penetrance means that a person with a MHS mutation may not experience MH during the first or subsequent exposures to MH trigger agents. Multifactorial inheritance may be relevant.[11,12] Variable expressivity means that clinical symptoms of MH vary from minor to fulminant depending on factors such as the anesthetic agents, genetics, and temperature.[13] MHS episodes are more often observed in males.[14,15]

The primary genetic locus of MH (MHS1) is the ryanodine receptor gene (*RYR1*) on chromosome 19q13.1. Variants associated with MHS are found throughout *RYR1*. Fewer than 30 of these met the rigorous criteria (see www.emhg.org) that prove causation of MH. In families with an MH-causative *RYR1* mutation, genetic analysis is a useful initial step in the diagnosis of MHS.[16,17] See www.mhaus.org for addresses of clinical diagnostic testing laboratories in the United States. This pathologic test has been useful to document MH susceptibility in postmortem muscle.

Several different genetic abnormalities are associated with MH. A variant associated with MH susceptibility was found in the α-1 subunit of the DHPR gene (CACNA1S) on chromosome 1q32.[18] This is the MHS 5 locus. It is associated with MH in only a few families as of 2009. Other loci associated with MH susceptibility, MHS 2, MHS 3, and MHS 6, have been identified on chromosomes 17q11-24,19 7q22-24, and 5p respectively. There are not obvious candidate genes at these sites other than the DHPR α_2/δ_1 subunit in 7q22-24, but extensive examination of MHS families has not identified a variant there. It has been suggested that two different genetic loci may be required to produce the MH phenotype in some families.[11,20] Although factors that modify the expression of MHS are not completely determined, active cysteines contribute to redox modulation and nitrosylation of RYR1.[21,22]

Clinical Recognition of a Malignant Hyperthermia Episode in Humans

The initial signs of acute MH are nonspecific (Box 124-1).[23] The first or only MH signs reported to the North American MH Registry in 286 cases were hypercarbia (38%), sinus tachycardia (31%), or masseter spasm (21%).[14] Inappropriately elevated (>38.8° C) or rapidly increasing temperature was one of the first signs in 8.2% and the only initial sign in 3.9%.[14]

However, high temperature was one of the first three signs in 63.5% of cases, with median maximum temperature of 39.1° C. The skin may be mottled and cyanotic and muscles rigid enough to extend the legs. Other signs include tachypnea, sweating, arrhythmias (ventricular tachycardia, ventricular fibrillation), dark urine, and excessive bleeding. Mixed respiratory and metabolic acidosis, hyperkalemia, myoglobinemia, myoglobinuria, and increased serum creatine kinase can be noted. However, rhabdomyolysis does not always occur during acute MH.[24]

In the ICU, a septic patient with kidney disease or chronic lung disease may exhibit fever, tachycardia, mixed respiratory and metabolic acidosis and hyperkalemia. If sepsis, cardiovascular failure, central nervous system injury, heat stroke, or other medical or surgical conditions could have produced the abnormal vital signs, then these other diagnoses must be pursued and treated. MH may not be the most likely diagnosis in general, but recognition of recent exposure to volatile anesthetic agents and/or succinylcholine in a patient with a family history of problems after general anesthesia or muscular diseases associated with MH supports the presumptive diagnosis of MH.

Box 124–1 Positive Findings Consistent with MH

History of recent exposure to trigger agent, including volatile anesthetic agents or succinylcholine
Family or personal history of MH susceptibility
Total body rigidity
Masseter spasm
Inappropriately elevated (38.8° C) or rapidly increasing temperature (>1.5° C over 5 min)
Inappropriate tachypnea
Profuse sweating
Mottled, cyanotic skin
Dark urine, urine dipstick testing shows a positive result from blood without red cells in the sediment and no hemolysis
Unexplained, excessive bleeding
Unexplained ventricular tachycardia or fibrillation
Inappropriate hypercarbia (venous $PaCO_2$ >65 mm Hg, arterial Pa CO_2 >55 mm Hg) if the patient is receiving positive-pressure ventilation or is spontaneously breathing with greater than normal minute ventilation
Arterial base excess more negative than −8 mEq/L
Arterial pH <7.25
Potassium concentration >6 mEq/L
Creatine kinase >10,000 IU/L

MH episodes can be fulminant or abortive. In the operating room, MH can develop rapidly after the administration of succinylcholine in the presence of volatile anesthetic agents, or insidiously during a long anesthetic.[25] When the nonspecific early signs of MH are noted during induction of anesthesia, the potent inhalation anesthetics should be discontinued. This patient is considered to be MH-susceptible until proven otherwise and this episode is called abortive MH. Early termination of inhalation anesthetic agents in the presence of abortive MH may allow spontaneous resolution of the syndrome. On the other hand, there have been cases in which only mild signs of abortive MH occurred intraoperatively, but renal failure, hyperthermia, and death occurred postoperatively with no explanation other than MH.[26]

In a retrospective Danish study of 386,250 anesthesias that occurred over 6.5 years in 87 hospitals, the incidence of fulminant MH was 1 in 250,000 general anesthesias.[27] In this series, there were no cases of fulminant MH during regional anesthesia or "nontriggering" general anesthesia. When only anesthesias that included the administration of succinylcholine and potent inhalational anesthetic agents, such as halothane, isoflurane, and enflurane, were considered, the incidence of abortive MH was 1 in 4200 cases. In this study, abortive MH was defined as a masseter spasm or moderate changes in vital signs with slight metabolic or respiratory acidosis.[27] These clinical signs are not specific for MH.[28] No deaths occurred in the patients with abortive MH in this series.

The fiftyfold difference in incidence between fulminant and abortive MH can be explained by early termination of anesthesia in the presence of abortive MH with resolution of the

syndrome, and perhaps by the fact that although the episode was classified as abortive MH, the patient may not in fact be MH-susceptible. Because MH is a potentially fatal condition that may progress rapidly, the anesthesiologist may be inclined to overdiagnose episodes of abortive MH.

In this retrospective series,[27] there was no information about further anesthetic experience or other pathologic evaluation of MH susceptibility, specifically the results of in vitro caffeine-halothane contracture testing, in those patients who had experienced abortive MH.

A person may have fulminant MH during one anesthesia and no symptoms at all during other similar anesthesias. A patient who survived an episode of fulminant MH is considered capable of having another episode, although he or she may have undergone many anesthesias uneventfully before the first episode of MH. Larach et al. reported that 77 of 152 patients who experienced serious MH episodes had two or more prior unremarkable general anesthesias.[14] Patients with the MH trait are often symptom-free until exposed to the most common triggering agents, the volatile anesthetic agents such as sevoflurane, isoflurane, desflurane, and halothane and the depolarizing neuromuscular blocking agent, succinylcholine. If the pharmacologic triggering agent is eliminated from the patient before the development of profoundly decreased pH in the muscle, rapidly increasing temperature, and shock, the metabolic abnormalities may resolve readily. This sequence of events could be termed abortive MH.

Potential Systemic Complications

Complications were noted in approximately 35% of 181 MH events reported to the North American MH Registry. These included changes in level of consciousness or coma in 9.4%, cardiac dysfunction in 9.4%, pulmonary edema in 8.4%, renal dysfunction in 7.3%, disseminated intravascular coagulation in 7.2%, and hepatic dysfunction in 5.6%.[14] Disseminated intravascular coagulation was associated with a 50-fold increased likelihood of cardiac arrest and an 89-fold likelihood of death.[29] The likelihood of any complication increased 2.9 times for every 2° C increase in maximum temperature and 1.6 times for every 30 minutes of time between the appearance of the first clinical sign of MH and the beginning of dantrolene administration.[14] Other complications reported were compartment syndrome, stroke after cardiac arrest, bilateral brachial plexopathy, generalized muscle weakness, significant muscle loss, and prolonged intubation.[14]

Cerebral edema and coma have been reported in episodes of fulminant MH. Although normal metabolism of the brain was described during episodes of MH, O_2 supply to the central nervous system may be inadequate. Therefore supportive care to the patient during and after an episode of fulminant MH should include measures to document cerebral function and maximize cerebral perfusion.

Ventilatory failure may occur early in an episode of fulminant MH. During a MH episode, desaturation can be also secondary to increased oxygen extraction. The workload of the respiratory system may be further increased by the occurrence of pulmonary edema. Pulmonary edema may be the result of capillary leak. It may be worsened by impaired cardiac contractility in the presence of acidemia. Cardiac dysrhythmias may occur in the presence of marked electrolyte abnormalities. In older patients, there may be foci of myocardial fibrosis as well. It has been hypothesized that such areas of fibrosis are the result of subclinical episodes of MH that produced increased levels of circulating catecholamines.[30] Cardiac contractility can be impaired.

Rhabdomyolysis will occur when the energy supply of the muscle is exhausted. Clinical manifestations include myalgias, swollen extremities, red-to-brown urine due to myoglobinuria, and elevated muscle enzymes. It is noteworthy that enzymes commonly elevated in the blood during hepatic injury including LDH and SGOT will also be released from muscle when creatine kinase (CK) is markedly elevated. Rhabdomyolysis can produce electrolyte imbalance (hyperkalemia, hyperphosphatemia, hypocalcemia), metabolic acidosis, severe hyperuricemia, acute renal failure,[31] and compartment syndrome. Melli et al. reported that the incidence of acute renal failure associated with myoglobinuria was 46%.[32] Massive rhabdomyolysis, producing CK of greater than 20,000 IU/L, may occur in patients with underlying muscular diseases not necessarily related to MH. Thus rhabdomyolysis in the absence of increased metabolic rate, hypercarbia, and metabolic acidosis should not be assumed to be MH. However, the same treatment, including administration of dantrolene acutely, may be helpful to the myopathic patient who experiences rhabdomyolysis in the ICU. It will be helpful to the patient and his or her family if the underlying cause of rhabdomyolysis is determined, because the implications for medical care of relatives differ depending on the pathologic diagnosis (e.g., dystrophinopathy vs. MH).

Hyperthermia in the Pediatric Intensive Care Unit

In the PICU, the most likely cause of fever is a bacterial infection,[33] but elevated temperature can also be the result of trauma, viral infection, lymphoma, and leukemia. Inadequate fluid replacement predisposes to increased core temperature in children.[34] Excessive environmental heat with inadequate opportunity for evaporative heat loss can result in temperature elevation. In some cases increased core temperature can be associated with tachycardia, increased expired CO_2, and metabolic acidosis, which are consistent with the expected increase in metabolic demand produced by fever. This can be so extreme as to mimic MH.

When hyperthermia occurs in a child with history of exposure to succinylcholine or volatile anesthetic agents, MH should be considered in the differential diagnosis. In a retrospective cohort study, conducted to analyze and identify the causes of hyperthermia in the PICU over a 9-year period, Schleelein et al. noted that the incidence of clinically diagnosed MH was low (0.4%).[35] These cases were classified as "definite " or "probable" MH[23] by a Malignant Hyperthermia Association of the United States (MHAUS) hotline consultant.[35] No information about CHCT or other pathologic tests that could support the diagnosis of MH for these patients is available.

Postoperative Fever

Postoperative fever (>38° C, >100.4° F) is common after surgery and usually resolves spontaneously. In establishing a differential diagnosis, it is very helpful to consider the timing of fever onset: immediate, acute, subacute, or delayed. The causes may be infectious or noninfectious. The most common noninfectious cause is a medication reaction, followed

by blood transfusion and by trauma suffered prior to surgery or as part of surgery. The fever due to MH usually starts within 30 minutes after administration of the triggering agent, but has also been reported up to several hours later, after the anesthesia was discontinued.

Some clinical states, such as the increased temperature that accompanies improved circulation after cardiac surgery, share some of the features of MH.[36] These situations may even include rhabdomyolysis, but it is the result of muscular injury from impaired circulation, not usually from a primary muscular disease.

Abortive Malignant Hyperthermia Episodes and Isolated Masseter Spasm

There is controversy about evaluation of the individual who has experienced abortive MH or isolated masseter spasm. Abortive MH could be relatively slowly evolving MH or a group of signs produced by processes completely unrelated to MH. Increased stiffness of the masseter muscles, even to the degree that endotracheal intubation is precluded, can be a normal response to succinylcholine.[37-39] Because MH could develop some minutes to hours after an occurrence of masseter spasm, some anesthesiologists recommend cancellation of an anesthesia after such an occurrence and evaluation of the CK levels at 12 and 24 hours after the incident. Neurologic evaluation and muscle biopsy to rule out susceptibility to MH have also been recommended. Neurologic evaluation is relevant after abnormal intraoperative muscle tension because myotonia may be the underlying diagnosis. A mutation in the muscle sodium channel has been noted in one family evaluated after severe rigidity followed succinylcholine administration.[40] Others recommend discontinuing the triggering agents of MH, careful evaluation of acid-base status, and continuation of the anesthetic and surgical procedure if no further problems are identified. Urine should be checked for the presence of myoglobin. If masseter spasm occurs without significant metabolic or cardiovascular changes, it is unlikely to be followed by fulminant MH.[41] Similarly, the low specificity of the contracture test for MH may produce many false-positive results in such patients.[42]

Rhabdomyolysis

Rhabdomyolysis is characterized by muscle necrosis and the release of intracellular muscle constituents including CK, myoglobin, calcium, and potassium. CK levels greater than five times baseline are a sensitive definition of rhabdomyolysis. Rhabdomyolysis can be due to inherited or acquired causes, and the severity of clinical consequences ranges from asymptomatic increase of serum muscle enzymes to life-threatening hyperkalemia. The most frequent causes are trauma, overexertion, immobilization, alcoholism, vascular insufficiency, and orthopedic surgery. Grand mal seizures, delirium tremens, psychotic agitation, and amphetamine overdose can lead to rhabdomyolysis in individuals with normal muscles.[32] Some drugs such as HMG-CoA reductase inhibitors (statins) and colchicine are directly myotoxic.[32] Rhabdomyolysis may occur in patients with metabolic myopathies such as carnitine palmitoyltransferase deficiency, myophosphorylase deficiency (PYGM) or McArdle disease, myoadenylate deaminase deficiency (AMPD1), mitochondrial myopathy, or malignant hyperthermia susceptibility. Occasionally, patients with structural myopathies can develop acute rhabdomyolysis after strenuous exercise, after exposure to potent inhalation anesthetics, after exposure to other myotoxic drugs, or after a viral infection.

Treatment of an Episode of Malignant Hyperthermia

Remove Trigger Agents

When an episode of MH is suspected, it is prudent to alter, as soon as possible, the anesthetic technique with elimination of all triggering agents. In the operating room, if potent inhalation anesthetic agents were administered, these should be discontinued immediately and a nontriggering anesthetic technique administered. High fresh gas flows of 10 L/min or more, or charcoal filters, are needed to eliminate residual potent inhalational anesthetic agents from modern anesthesia machines. If the physician suspects MH, and especially if blood gas analysis has proven the presence of significant respiratory and metabolic acidosis, dantrolene should be administered immediately and supportive treatment should be started as soon as possible (Box 124-2). Treatment of the life-threatening complications should not detract from the need to continue monitoring the metabolic status and the continued administration of dantrolene, in increasing doses if necessary, until the metabolic state is normal. Resolution of some of these complications may take longer than the adequate treatment of the acute episode of MH.

Administer Dantrolene

Dantrolene, a hydantoin with muscle relaxant properties, has greatly changed the treatment of and risk of death from MH. Before the introduction of dantrolene, Brit and Kalow reported a 36% MH survival rate with symptomatic treatment only.[43] It was thought that dantrolene decreased calcium release from the SR by decreasing the mobility of a calcium ionophore that transports calcium across membranes. Although dantrolene interacts with amino acids 590-609 in the N-terminal fragment of the RYR144, its analog, azumolene, does not alter calcium release from the SR. Dantrolene does decrease both excitation-coupled calcium entry into muscle cells and store-operated calcium entry coupled to RYR1.[9,10] It does not act on the neuromuscular junction or on the passive or active electrical properties of the surface membranes of muscle fibers. Therefore patients given effective doses of dantrolene have normal electromyograms and depressed force of muscle contraction.[45]

Dantrolene for intravenous administration (Dantrium) is supplied in 70 mL vials, containing 20 mg dantrolene sodium and 3 g mannitol. It must be diluted with 60 mL of sterile, preservative-free, distilled water. Dantrolene should be available in all locations where general anesthesia is administered. It should be immediately supplied to other areas of the hospital by the pharmacy. If dantrolene has to be obtained from a central location, such as the pharmacy, it must be stressed that the need for the initial and subsequent doses of drug is urgent. The initial dose of intravenous dantrolene for treatment of MH is 2.5 to 3 mg/kg.[46] More than 10 mg/kg has sometimes been required to return metabolism to normal. As soon as dantrolene is ordered to treat fulminant MH, replacements

Box 124–2 Management of an Acute MH Episode in the ICU

1. Administer high-flow 100% oxygen via a nonrebreathing mask and consider endotracheal intubation.
2. For ventilated patients, administer an Fio_2 of 1.0 and increase minute ventilation to control $Paco_2$.
3. Administer dantrolene (2.5 mg/kg intravenously) over 10 minutes and repeat, until acidosis and muscle rigidity have resolved. Repeat dantrolene (1 mg/kg) every 6 hours.
4. Initiate cooling with ice packs in the axillae and groin, decrease room temperature, use hypothermia blankets, iced intravenous saline solution (10 mL/kg over 10 min, repeated as needed), and lavage body cavities with cold saline solution if temperature is greater than 39° C. Stop cooling when core temperature falls to 38° C.
5. Correct metabolic acidosis with sodium bicarbonate (1–2 mEq/kg initially) and give subsequent doses based on base excess and body weight.
6. Administer calcium chloride (10 mg/kg) or calcium gluconate (100–200 mg/kg) to cardiotoxicity associated with hyperkalemia.
7. Give regular insulin (0.1 U/kg) and glucose (0.3–0.5 g/kg) to correct hyperkalemia.
8. Administer lidocaine (1 mg/kg) to treat ventricular arrhythmias. Consider amiodarone (5 mg/kg IV) for refractory, stable ventricular tachycardia. Do not delay defibrillation or cardiopulmonary resuscitation if indicated by cardiovascular instability.
9. Maintain urine output of 2 mL/kg/hr with aggressive cold fluid administration, furosemide (0.5–1 mg/kg), and additional mannitol (0.25–0.3 g/kg) if needed.
10. Consider quantitative end-tidal CO_2 monitoring.
11. Monitor core temperature (pulmonary artery, esophageal temperature probe, rectal probe).
12. Place arterial catheter for invasive blood pressure monitoring and frequent blood sampling. Consider central venous catheter and/or pulmonary artery catheter if indicated by cardiovascular instability.
13. Repeat venous blood gas and electrolytes analysis until these normalize. Repeat CK at least every 6 hours while the patient is in ICU and then daily until CK returns to normal. Assess glucose, clotting function, hepatic and renal functions, and treat symptomatically. Repeat lactic acid measurement after each dantrolene administration.
14. Consider hemodialysis if indicated.
15. Consider intensive care monitoring for at least 24 hours after MH episode or after recrudescence of MH.
16. Refer the patient for muscle caffeine-halothane contracture testing and consider exam of *RYR1*. Pursue a pathologic diagnosis for other occult myopathies.

should be obtained by the pharmacy. In children, the intravenous infusion of dantrolene, 2.4 mg/kg IV over 10 to 12 minutes, produced stable blood levels of about 3.5 μg/mL for 4 hours, after which a slow decline in plasma concentration occurred (Figure 124-1).[47] It appears that the half-life of dantrolene in the plasma of children is somewhat shorter than in adults: 7 to 10 hours compared with 12 hours, respectively.[45] This is consistent with the recommendation to repeat dantrolene (1 mg/kg) every 6 hours for prophylaxis against recurrence of MH in a child. Immediately after the administration of intravenous dantrolene, one may note a dramatic decrease in heart rate. This is the result of an effect on the underlying hypermetabolic state and is generally a reassuring sign that dantrolene is effectively controlling the episode of MH. However, a modest decrease in heart rate after the administration of intravenous dantrolene may be caused by increased intravascular volume. The other goals of the treatment with dantrolene are complete cessation of tachypnea and muscle rigidity, correction of hypercarbia, hyperthermia, electrolyte disturbances, and blood gas abnormalities. Also, urinary output should be increased and mental status should improve. A flow sheet recording heart rate and rhythm, arterial blood pressure, central venous pressure, minute ventilation, core temperature, urine output, mixed venous blood gas tensions, serum electrolytes, serum glucose, and total fluid intake is useful.

The major side effect of dantrolene is muscle weakness.[45] Muscle weakness is noted in approximately 25% of patients after an acute episode of MH treated with dantrolene. The effects of dantrolene on strength may persist for more than 8 to 12 hours. Severe muscle weakness of variable duration can also be the result of an MH episode and muscle injury. It is likely that when the plasma concentration of dantrolene is sufficient to inhibit an episode of MH, the patient will experience weakness and possibly disequilibrium. The ability to swallow could be compromised. The patient with MH may require intubation and artificial ventilation anyway because of respiratory failure or pulmonary edema. Phlebitis is a common side effect of dantrolene administration, noted in approximately 10% of patients. Giving dantrolene by intermittent bolus rather than by continuous infusion may lessen the incidence of phlebitis noted after dantrolene administration.

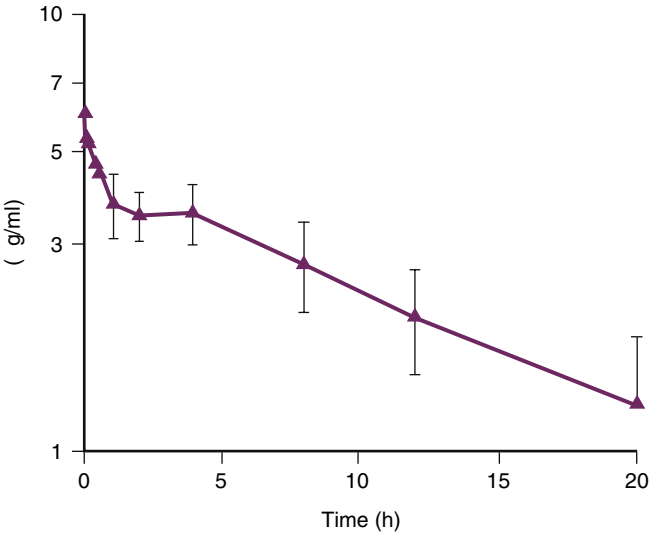

Figure 124–1. Whole blood concentration of dantrolene vs. time in a cohort of children. *(Modified from Lerman J, McLeod ME, Strong HA: Anesthesiology 70:625,1989.)*

If no recurrence is noted in the 24 hours following treatment of MH, the patient is metabolically stable, and weakness is marked, dantrolene administration may be withheld and weaning from supportive therapy begun. If dantrolene must be administered to a patient who is also receiving calcium

channel antagonists, invasive hemodynamic monitoring is necessary. Serum potassium should be closely monitored. Dantrolene may be useful in the treatment of fever and muscle spasticity not associated with MH. Therefore if fever diminishes and abnormal vital signs associated with fever resolve after the administration of dantrolene, the patient did not necessarily have MH.

Symptomatic Treatment

Adjunctive treatment in MH correlates with the severity of abnormal findings. Because pulmonary and cardiovascular compromise is a result of fulminant MH and because the major side effect of dantrolene is muscular weakness, endotracheal intubation and controlled ventilation may be useful in the treatment of an episode of fulminant MH. When calculation of O_2 consumption and CO_2 production is simplified by mechanical ventilation, these values serve as the most appropriate monitor of the adequacy of treatment of an episode of fulminant MH. Minute ventilation should be increased severalfold and O_2 provided as needed. When repeated assessment of blood gases indicates resolution of acidosis, minute ventilation can be normalized. Sodium bicarbonate should be administered liberally to treat metabolic acidosis.

If the core body temperature is elevated, active measures should be taken to cool the patient. In the operating room, drapes should be removed. A water mattress should be placed under the patient and turned to cooling temperatures. Room temperature should be decreased. The most effective means of cooling is the intravenous administration of cold normal saline through a peripheral or central vein. The stomach can be lavaged with iced saline. Ice packs may be placed on the groin and the axillae. Wet cloths and a fan can be used to promote surface evaporation. Active cooling should be stopped when core temperature falls below 38.8° C, to prevent inadvertent hypothermia.

Cardiac dysrhythmias usually stop when the episode is adequately treated with dantrolene. Lidocaine (1 mg/kg) is recommended for treatment of arrhythmias in MH. Amiodarone (5 mg/kg) can be administered for refractory ventricular tachycardia.[48] Hyperkalemia may require aggressive treatment, especially if arrhythmias have occurred or myoglobinuria has compromised renal function.

Administration of calcium gluconate or calcium chloride is an effective initial measure to reverse the cardiotoxicity of hyperkalemia. To produce an intracellular shift of potassium, and also to correct respiratory acidosis, hyperventilation should be initiated as soon as possible. Sodium bicarbonate should be administered, not only to correct metabolic acidosis but also to decrease plasma potassium. Glucose (0.3 to 0.5 g/kg), preferably as a 10% glucose solution with insulin (1 unit per 4 to 5 g glucose[49] or 0.1 unit/kg), will decrease plasma potassium. If hyperglycemia exists, the dose of dextrose should be reduced. Albuterol can be administered to reduce life-threatening hyperkalemia, in the same doses used to treat bronchoconstriction. Alternatively, intravenous β-adrenergic agonists (terbutaline, isoproproterenol, or epinephrine) may also be administered. Furosemide can be used to promote diuresis and treat high serum potassium. Dialysis (hemodialysis and peritoneal dialysis) can treat hyperkalemia, acidosis, and volume overload. Conventional hemodialysis does not remove myoglobin effectively, due to the size of this protein.[50] The use of antioxidants and free radical scavengers such as pentoxifylline, vitamin E, and vitamin C may be justified in the treatment or prevention of myoglobinuric acute renal injury,[51] but more controlled studies are needed. Early hypocalcemia secondary to rhabdomyolysis-induced acute kidney injury should not be treated unless it is symptomatic or severe hyperkalemia is present.[50]

Large losses of intravascular volume may occur, because evaporative loss may be great, edema formation may occur in muscle and other tissues, and mannitol given as part of the formulation of dantrolene may induce significant diuresis. Hypovolemia should be avoided because even mild hypovolemia impairs dissipation of heat produced by increased metabolism.[34] If diuresis is not occurring, additional mannitol should be administered to protect the kidneys from the effects of high concentrations of myoglobin in the urine. Cardiovascular support, in the form of isotonic fluid administration as well as vasopressor and inotropic drugs (epinephrine, phenylephrine, norepinephrine, dopamine) should be administered as soon as possible if indicated.

Urine and Blood Tests in Malignant Hyperthermia

Myoglobin, a heme-containing respiratory protein, is released from damaged muscle and rapidly excreted in the urine. In the presence of inhalation anesthetic agents in healthy children, myoglobinemia occurs within minutes of exposure to succinylcholine. Myoglobinuria occurs when the renal threshold of 0.5 to 1.5 mg/dL is exceeded. Myoglobinuria is suggested by persistent red to reddish-brown urine. At myoglobin levels of 100 mg/dL, urine tests positive for heme by dipstick after centrifugation, whereas the sediment has normal color and tests negative for heme. The dipstick test has a sensitivity of 80% for detection of rhabdomyolysis.[31] Renal injury is frequent when urine myoglobin is more than 1 g/mL. Because the half-life of myoglobin in the plasma is approximately 12 hours, less than the half-life of CK,[52] persistence of myoglobinuria for more than several days suggests that muscle cell integrity continues to be impaired. Patients with chronic myopathies may have moderately raised concentration of plasma myoglobin but not overt myoglobinuria.[52] Patients with chronic myopathies such as muscular dystrophy and inflammatory dystrophies seldom develop acute kidney injury, unless a superimposed event is present.

Marked elevation of CK (typically >10,000 U/L) and other muscle enzymes confirm the diagnosis of rhabdomyolysis. CK increases in the plasma with a slower time course than myoglobin does. There is no defined threshold value of serum CK above which the risk of acute kidney injury is increased. Usually the risk is low when the CK level is less than 15,000 to 20,000 U/L.[53] When coexisting conditions such as sepsis, dehydration, and acidosis are present, acute kidney injury may be associated with CK values as low as 5000 U/L. Serum myoglobin level peaks before serum CK and myoglobin is cleared from plasma more rapidly than CK. Thus it is not unusual to have increased CK without myoglobinuria.

When further evaluation is required to assess for the presence of MH, the test most likely to be helpful is venous blood gas analysis. Oxygen desaturation, hypercarbia, and lactic acidemia in mixed venous blood are the results of the hypermetabolism of MH. Elevated $PaCO_2$ is apparent in mixed venous

blood before it is abnormal in arterial blood during an episode of MH.[4] There is an increase in lactate release from muscle before a decrease in the partial pressure of oxygen in venous blood during an episode of MH.[54] If venous blood indicates significant acidosis, with $PaCO_2$ greater than 60 mm Hg and bicarbonate less than 19 mEq/L,[4] and the history of the patient is consistent with MH, the physician should assume that the patient is experiencing an episode of MH and treat accordingly.

The Course of a Clinical Episode of Malignant Hyperthermia

The case fatality for MH was about 70% to 80% in the 1970s. In 2009, estimates for MH mortality were less than 10%. The initial clinical signs of an impending episode of MH are nonspecific. When MH is fulminant, metabolic and respiratory acidosis, tachycardia with dysrhythmias, a rapid increase in body temperature to 39.5° C or greater, hyperkalemia, myoglobinuria, and a marked increase in serum CK are observed. The patient's medical history and clinical course usually help to differentiate fulminant MH from other medical, metabolic, or endocrinologic crises such as sepsis, porphyria, thyroid storm,[55] and untreated pheochromocytoma (see Box 124-3).

If the triggering agent is removed before the syndrome becomes self-perpetuating, abortive MH could be said to have occurred. In this case, there are only mild signs suggestive of MH: moderate increases in heart rate, blood pressure, and temperature along with a slight respiratory acidosis. Mild metabolic acidosis and moderate increases in serum myoglobin and CK may or may not be present. Masseter spasm may occur.[28] As previously suggested (see "Clinical Recognition of an Episode in Humans"), differentiating an abortive episode of MH from an anesthesia complicated by other factors can be difficult.

Recrudescence

There are cases in which a patient was symptomatically treated for MH with dantrolene, appeared to recover, and then some hours later had another episode of increased metabolic rate. This second episode was sometimes accompanied by remarkable stiffness of the muscles. It is difficult to explain how these episodes occur in the apparent absence of a pharmacologic trigger. Perhaps metabolic derangements in the muscle can become self-perpetuating.

Recrudescence of MH was reported in 20% of cases reported to the MH Registry[56] after initial treatment appeared to be successful. Muscular body type, the presence of temperature increase during the MH episode, and a longer time between the induction of inhalation anesthesia and the first sign of MH were associated with a greater risk of recrudescence.[56] There is no definite or guaranteed time course for these events in the human. Some suggest observing a patient closely for 24 hours after the apparent end of an episode of fulminant MH to allow for the early recognition and treatment of recrudescence. Such patients should be monitored in an ICU setting because of the utility of invasive cardiovascular monitoring in documenting the course of an episode of MH. Recrudescence of MH can progress into fulminant MH and therefore warrants aggressive treatment with dantrolene and supportive therapy.

Box 124–3 Differential Diagnosis of MH in the ICU

Neuroleptic malignant syndrome
Exertional hyperthermia and heat stroke
Serotonin syndrome
Sepsis associated with renal and respiratory failure
Central nervous system injury
Postoperative fever
Thyrotoxicosis
Rhabdomyolysis
Pheochromocytoma
Porphyria
Allergic reaction secondary to medications
Blood transfusion reactions
Administration of hypertonic dye such as diatrizoate
Drug abuse (cocaine, amphetamines, ecstasy)
Drug withdrawal
Iatrogenic overheating
Delirium tremens

Factors that "Trigger" Malignant Hyperthermia

MH is the result of acutely increased intracellular calcium concentrations in muscle. Excitation of the sarcolemma activates the voltage-sensitive dihydropyridine receptor that results in release of calcium through the RYR157 into the cytosol. There are at least two other processes, excitation-coupled calcium release and store-operated calcium release, that also produce increased intracellular calcium. The SR Ca^{2+}-ATPase pumps calcium back into the SR. Theoretically, factors that increase calcium release or impair the removal of calcium out of the sarcoplasm could facilitate the appearance of MH. Because removal of calcium from the sarcoplasm requires ATP, any factor that impairs the formation of ATP could similarly facilitate the appearance of MH.

Potent inhalational anesthetic agents such as sevoflurane, halothane, enflurane, isoflurane, and desflurane have been identified as triggering agents of MH in humans. Depolarizing neuromuscular blocking agents are also potent triggers of MH in humans. Succinylcholine is the only drug of this type currently in common use. Different anesthetics may trigger MH at different rates depending on the combination of agents used. The combination of succinylcholine and potent inhalation anesthetic agents produces more episodes of MH than do potent inhalation anesthetic agents administered without succinylcholine or succinylcholine administered in the presence of nitrous oxide and intravenous anesthetic agents.[27] A number of drugs, such as amide local anesthetics, droperidol, ketamine, calcium, digitalis, methylxanthines, anticholinergics, anticholinesterases, and sympathomimetic drugs, had in the past been considered to be potential triggers of MH in humans, primarily on theoretical grounds. Review of clinical and laboratory[58,59] experience suggests that these drugs are not triggers of MH; however, on rare occasions, MH may occur during an anesthesia in which no trigger agents were administered.

In general, MH in humans differs from porcine MH in that a pharmacologic trigger is usually required for the syndrome to develop. However, there is the possibility that a MH-like syndrome can occur without exposure to anesthesia.[60] This is very rare in humans, but has been observed repeatedly in MH-susceptible animals.[61] In a large, well-investigated human

kindred, two young patients who had the familial mutation associated with MH susceptibility died unexpectedly during febrile illnesses.[20] An athletic adolescent who had an *RYR1* mutation associated with MH died after strenuous exercise.[62] Of 12 unrelated patients with exercise-induced rhabdomyolysis, 10 had in vitro contracture tests that were positive for MH and 3 of these had RYR1 mutations.[63] Others have also reported recurrent myoglobinuria associated with exercise in patients with MH-positive in vitro muscle contracture studies and mutations in the RYR1 gene.[64]

Muscular Diseases Associated with Malignant Hyperthermia

There are a limited number of relatively rare muscular diseases that are closely linked with MH susceptibility. These include central core disease, multiminicore and nemaline rod myopathies,[65] and King-Denborough syndrome.[66] Central core disease (CCD) is a relatively mild congenital myopathy, characterized by motor developmental delay and signs of mild proximal weakness, most pronounced in the hip and girdle musculature. CCD and other congenital myopathies are characterized by early onset and by the presence of chronic, subclinical myopathy. Late onset of symptoms, in the seventh to eighth decade of life, has been reported with some of these conditions.[67] A patient with dystrophinopathy (Duchenne or Becker muscular dystrophy) can develop a hyperkalemic cardiac arrest and exacerbation of rhabdomyolysis after administration of the potent inhalation anesthetic agents. Succinylcholine is expected to elicit hyperkalemic cardiac arrest in such patients through a mechanism unrelated to MH. During initial treatment, such cases can be difficult to differentiate clinically from MH. Indeed, calcium is not handled normally in dystrophic muscle, and RYR1 channels may be part of the problem.[68] In the presence of neuromuscular disease, myoglobinuria may occur after exposure to potent inhalation anesthetics alone [52,69] and is to be expected after succinylcholine administration in patients with muscular dystrophy.[52] A child with myopathy who receives potent inhalation anesthetic agents can develop an increase in postoperative serum CK and potassium concentrations as well as myoglobinuria. These findings are due to the myopathy, not to MH.

Myotonias are a class of inherited skeletal muscle diseases characterized by impaired relaxation after sudden voluntary muscle contraction. There are defects in the chloride, sodium, and calcium channels in the different types of myotonia. The risk for MH is not greater than that of the general population, with the possible exception of hypokalemic periodic paralysis. Many cases of hypokalemic periodic paralysis are associated with variants in the CACNA1S, which codes for the DHPR, the voltage gate of the RYR1. Thus there is a theoretical association between MH and hypokalemic periodic paralysis, which has not been clearly confirmed.[13] To prevent episodes of myotonic contractures, depolarizing neuromuscular blocking agents such as succinylcholine should not be given to patients with myotonia. Other details of preventive management may differ between different forms of myotonia. In general myotonic patients should be maintained normothermic, episodes of anxiety should be avoided, and serum potassium should be documented. If nondepolarizing neuromuscular blocking agents (NMBAs) must be used, a drug with short duration is best and neuromuscular function should be monitored. The use of anticholinesterase drugs has been reported to precipitate myotonia. Neither nondepolarizing NMBAs nor dantrolene will counteract myotonic rigidity. Lidocaine, a sodium channel blocker, may decrease myotonic rigidity.

Exertional heat illness (EHI), exertional rhabdomyolysis (ER), and malignant hyperthermia are all hypermetabolic states, and can have similar manifestations. EHI is a disorder caused by excessive heat production, coupled with insufficient heat dissipation. It can progress to exertional heat stroke (EHS), which includes extreme hyperthermia (core body temperature higher than 40° C or 104° F) associated with central nervous abnormalities (delirium, coma, seizure). EHS can progress to multiorgan failure[70] with rhabdomyolysis. The CHCT can confirm the diagnosis of MHS, but it cannot be used to diagnose the potential for EHI or ER. Because there is a subset of patients who present with heat stroke that are also susceptible to MH, Grogan and Hopkins[71] suggested that these patients undergo testing for MH susceptibility. However, the majority of ER and EHS cases do not have a subclinical myopathy such as MH susceptibility.[71,72]

Patients with mitochondrial disease may develop acidosis and fever and even rhabdomyolysis. All anesthetics depress mitochondrial function, but there is no clear relationship between MH and mitochondrial myopathy.

Evaluation of Patients at Risk

The most efficient way to evaluate a family for MH susceptibility is to first evaluate the index patient with a caffeine-halothane contracture test of living muscle.[73] First-degree relatives of an individual with positive contracture results are assumed to have a 50% probability of also being MH susceptible. This assumption allows definition of the positive predictive value of the contracture test. Elements of the history and physical examination that could strengthen the suggestion that an individual may be susceptible to MH are a history of muscle cramping, heatstroke, hernias, clubfeet, scoliosis, spontaneous dislocation of the hip, eye muscle imbalance, or other minor muscular abnormalities. It must be acknowledged that these findings are nonspecific, but they may occur with greater frequency in individuals susceptible to MH than in the population at large. Similarly, resting CK concentrations may be elevated in MH-susceptible individuals. CK levels, at rest, are of no predictive value in the general population.[74,75] In some populations, more than 25% of the patients with elevated CK levels were not susceptible to MH on in vitro testing.[76] However, if a relative of a patient known to be susceptible to MH has an elevated CK level, that individual has an increased likelihood of being susceptible as well.[75]

Asymptomatic Elevation of Creatine Kinase Values

Nontraumatic exertional rhabdomyolysis (subclinical myoglobinemia, myoglobinuria, and elevation of CK) can be found after physical exertion when energy supply to muscle is insufficient to meet demands. Reasons for an exaggerated response include genetic factors,[77] fiber type, underlying occult myopathy,[78] environmental or behavioral factors such as exertion in humid conditions, and history of sickle cell trait.[79] The many potential causes of an elevated CK concentration should be evaluated by a neurologist.

CK, which is abundant in skeletal muscle, has a key role in energy metabolism. One isoenzyme of CK, the muscle specific CK (CK-MM), attempts to maintain energy homeostasis by providing a steady supply of creatine phosphate, which is critical for sustaining the Ca^{2+}-ATPase of the sarcoplasmic reticulum and other energy dependent enzymes.[80] Heled et al.[78] reported that the genotype of the CK-MM NcoI polymorphism was associated with the risk of having an exaggerated CK response to exercise. The location of the gene encoding this enzyme (chromosome 19q13.2-13.3) is in the same region where *RYR1* is located (19 q13.1)[81] The similar locations of these two genes, the possible association of RYR1 and exertional rhabdomyolysis, and the exaggerated response of CK-MM NcoI polymorphism genotype with exercise suggests a possible association between mechanical work and metabolic stress.

The "Safe" Anesthesia

An anesthesia designed for an individual who is or is suspected of being MH susceptible avoids drugs known to be triggers of MH, including depolarizing neuromuscular blocking agents such as succinylcholine and the potent inhalational anesthetic agents (sevoflurane, halothane, enflurane, desflurane, and isoflurane). Anesthetic regimens considered to be "nontriggering" include any regional anesthetic technique as well as intravenous drugs such as narcotics, barbiturates, benzodiazepines, propofol; nitrous oxide; and nondepolarizing neuromuscular blocking agents. Some intravenous anesthetic agents (e.g., thiopental and althesin) may attenuate or even prevent the initiation of MH in response to halothane. In general, drugs should be selected that have the least potential to increase heart rate (because tachycardia is an early sign of MH) and the least need for pharmacologic antagonism. Although anticholinesterase medications with anticholinergic agents can be administered to patients with susceptibility to MH, it is advisable to avoid drugs that may affect temperature regulation and sympathetic tone to such an extent that it might be difficult to distinguish drug effects from early signs of MH. Despite these concerns, ketamine has been safely administered to MHS patients. No anesthetic regimen is guaranteed to preclude the development of MH in a susceptible individual. There have been case reports of MH in patients who received regional anesthesia or general anesthesia with nontriggering drugs. However, it is to be expected that the incidence of MH will be much lower during the use of anesthetic agents that do not include the "triggering" agents of MH.[27] All anesthetic records should carefully document minute ventilation, core temperature, and fluid therapy. Point-of-care devices should be available to measure blood gases and electrolytes. Drugs and equipment necessary to treat MH should be immediately available.

Testing for Malignant Hyperthermia Susceptibility

In Vitro Caffeine-Halothane Contracture Testing

In vitro caffeine-halothane contracture testing (CHCT) is the only specific lab test of MH susceptibility other than identification of a *RYR1* mutation. At least 2 to 3 months should pass between an episode of suspected MH and the date of muscle biopsy.[82] This test has been described in detail, and the standards for its performance have been accepted by the specialized centers in North America and Europe that perform it.[83,84] The addresses of centers where muscle biopsy and contracture testing can be done can be found at www.mhaus.org and www.emhg.org.

CHCT has a sensitivity of 97% and a specificity of 78%.[85] It was designed to decrease the rate of false negatives. Therefore, it may produce false-positive results. For the in vitro test to be performed according to the North American standards, a sample of skeletal muscle is obtained from the quadriceps. In a test chamber where pH, oxygen tension, and temperature are controlled, the muscle is exposed to 3% halothane for 10 minutes or to caffeine given incrementally to 32 mmol/L. Muscle strips are stimulated supramaximally at 0.2 Hz, and tension is measured with a strain gauge. A video of this procedure can be seen at www.mhaus.org.

A positive result of the halothane contracture test is defined as a contracture of any one of the four to eight muscle strips prepared of greater than 0.2 to 0.7 g in the presence of 3% halothane. (The exact range of abnormal force is determined by each testing site after evaluation of at least 30 healthy controls.) A positive caffeine contracture test is defined as the observation of greater than 0.2 g tension in the presence of 2 mM caffeine, more than 1 g contracture at less than 4 mM caffeine, or an increase in maximal tension of more than 7% above baseline at 2 mM caffeine.

Results may be reported in terms of the caffeine-specific concentration, the concentration of caffeine at which muscle produces a contracture equal to 1 g of tension. As noted, a caffeine-specific concentration of less than 4 mM caffeine is a positive caffeine contracture test.

Reexamination of the results of the caffeine-halothane contracture test produced a statement of the operating characteristics of the test.[83,84] Its negative predictive value is high, but because the specificity of the in vitro test is only 85% at best, the positive predictive value of this test varies greatly depending on the prior probability of the individual being susceptible to MH.[42] As much clinical and laboratory evidence as can be obtained should be used to interpret the results of the muscle biopsy specimen. Many months can be required to confirm a diagnosis of MH susceptibility. Genetic analysis may be helpful if several generations of one family can be examined.

Less Invasive Tests of Malignant Hyperthermia Susceptibility

None of the relatively noninvasive tests of MH susceptibility have proved as sensitive and as specific as the in vitro caffeine-halothane contracture test. Tests that have been evaluated in the past include calcium uptake into frozen muscle, skinned fiber testing, platelet nucleotide depletion, ionized calcium concentration in lymphocytes, force of contracture, and phosphorus nuclear magnetic resonance spectroscopy. Recently, other tests based on RYR1 function in lymphocytes,[86,87] pharmacologic response in muscle cell cultures,[88-90] and microdialysis study of in situ muscle[91] have been proposed. None of these are usefully clinically in 2010.

An alternate to the caffeine-halothane contracture test for confirmation of MH susceptibility is a genetic test of *RYR1*. This was developed by genetic analysis of families in which

several individuals had undergone caffeine halothane contracture tests. Patients who had very strong contracture test results underwent characterization of *RYR1*. The exons in which variants are most commonly found were studied first (the hot spots). Biophysical properties of variants were studied in vitro to confirm that they altered calcium in a manner consistent with causing MH. At the present, more than 300 *RYR1* variants have been documented; of these, only 30 have been formally accepted as causative MH mutations (see www.emhg.org). Therefore the sensitivity of the clinical *RYR1* exam which sequences only the exons in which known causative MH mutations are located is at best 30%. The entire *RYR1* can be sequenced in a CLIA-approved laboratory. Sequencing of the entire gene may detect a variant in 50% to 70% of people who would have positive CHCT results. However, it is difficult to interpret the medical implications of the variants of unknown significance that may be identified. We suggest that professional genetic counseling is appropriate, in concert with consultation with a neurologist, when genetic testing of MH susceptibility is considered. Genetic testing has been useful post-mortem when the clinical circumstances were consistent with fulminant MH. Addresses of the laboratories can be found at www.mhaus.org. Patients with strong contractures in the presence of 3% halothane and no findings on *RYR1* may have a defect in a different protein. If *RYR1* screening fails to identify an MH-causative mutation, that patient should undergo muscle contracture testing to further evaluate MH susceptibility. A normal result on the CHCT is the only method that can currently prove that an individual is not MH-susceptible. Many months can be required to confirm a diagnosis of MH susceptibility.

Neuroleptic Malignant Syndrome and Serotonin Syndrome

NMS has been reported within 7 days after administration of antipsychotic drugs given to treat psychiatric disorders. NMS may occur 2 to 4 weeks after administration of depot neuroleptics and days after intravenous administration of various antipsychotic and antiemetic medications of the phenothiazine and butyrophenone classes.[92] Surgical patients may have received neuroleptics as antiemetics or sedatives. NMS can occur at any age. Silva et al.[93] reviewed the literature on NMS in children. They found 77 cases in patients ranging in age from 0.9 to 18 years, with only 10 patients younger than 10 years of age. NMS can be fatal. It develops insidiously over days. Initial signs include changes in mental status and extrapyramidal function. Sinus tachycardia or oscillation of blood pressure is very common. Muscle rigidity that can be described as "lead pipe," hyperthermia, and increased CK are major manifestations of NMS. Myoglobinuric renal failure due to rhabdomyolysis and respiratory distress are serious complications of NMS.

The treatment of NMS starts with discontinuation of neuroleptic agents as well as institution of supportive treatment to control hyperthermia, sustain vital functions, and prevent renal failure. There is evidence that NMS results from an acute reduction in dopaminergic function in the brain. Medications such as amantadine, bromocriptine, and levodopa have been used in treatment of NMS. Dantrolene, which inhibits muscle contraction and heat production, was reported to be effective in 81% of patients with NMS.[94] Electroconvulsive therapy (ECT) has also been suggested to be therapeutic.

NMS and MH are both drug-induced hypermetabolic syndromes. In the perioperative setting where both anesthetic agents and neuroleptic agents have been used, NMS should also be considered in the differential diagnosis of hyperthermia with rigidity. In contrast to MH, NMS does not appear to occur intraoperatively, because anesthetic agents and neuromuscular blocking agents may inhibit or mask the features of NMS. Both disorders may respond to dantrolene, but only NMS responds to nondepolarizing neuromuscular blocking agents and dopamine agonists.

The potential for susceptibility or cross-reactivity to both MH and NMS in the same patient is unproven. However, five of seven NMS patients who underwent muscle biopsy for in vitro halothane contracture testing had significantly abnormal results. Therefore the recommendation has been made to treat NMS patients as MH-susceptible until proven otherwise. Unfortunately, this can pose anesthetic difficulties during ECT. Succinylcholine, a potent trigger of MH, is a useful drug for lessening the force of the convulsions that accompany ECT. One patient who had experienced NMS did later receive succinylcholine repeatedly for ECT without complications.[95] Therefore it is unclear whether patients who have had NMS should be prevented from receiving anesthetic agents capable of triggering MH when these drugs are otherwise indicated. On the other hand, neuroleptic agents have been considered safe to administer to MHS patients, but there is some risk of hyperthermic reactions.[96]

There is evidence that patients with proximal myotonic dystrophy may be at increased risk for muscular complications after receiving neuroleptic drugs. Schneider et al. reported a patient with this disease who developed muscle stiffness, oculogyric dystonias, and elevated CK after administration of neuroleptic. This patient had a positive contracture test for MH susceptibility.[96]

Serotonin syndrome (SS) is another potentially life-threatening condition associated with increased serotonergic activity in the central nervous system, as a result of stimulation of postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors.[97] It may result from any combination of drugs that increase serotonergic activity, such as amphetamine, cocaine, selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, triptans, lithium, dextromethorphan, and ondansetron. The diagnosis of SS in the pediatric population can be difficult. Clinical manifestations include autonomic changes such as tachycardia, hyperthermia, hypertension, diaphoresis, and diarrhea, and increased neuromuscular activity with tremor, muscle rigidity, hyperreflexia, and clonus. In SS, neuromuscular findings are typically more pronounced in the lower extremity,[98] compared with MH where there is a rigor-mortis–like rigidity. When compared with NMS, the distinguishing features of SS, besides the different causative agents, are a rapid onset (within 24 hours),[98] hyperreactivity (tremor, clonus, increase in reflexes), and rapid resolution.[97]

Although there may be similarities in the presentation of MH, NMS, and the SS, they have pathophysiologic differences. Nevertheless, there is experimental evidence in animals that stress-induced MH, more than anesthetic-induced MH, may be mediated in part by 5-HT.[99]

The Malignant Hyperthermia Assocation

The Malignant Hyperthermia Association of the United States (MHAUS, 11 East State Street, Box 1069, Sherburne, NY, 13460-1069; fax 607-674-7910) is a valuable resource for families affected by MH, NMS, or SS and for their physicians. This organization offers information, expert consultation, and referral. MHAUS maintains a 24-hour, professionally staffed telephone line to assist physicians and patients in dealing with MH (1-800-644-9737). All cases of suspected MH and similar heat-related disorders should be reported to the North American Malignant Hyperthermia Registry (telephone 888-274-7899; Web site, www.mhaus.org, MH Registry) to support the continued epidemiologic study of MH.

References are available online at http://www.expertconsult.com.

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